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 preective 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important to remember that a lot of the abstracts contain preliminary information and preliminary data, and they have not been peer reviewed or finalize or published.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. With us for this presentation at the end of the entire Series A recording.
NOTE Confidence: 0.8444918
00:01:41.830 --> 00:01:44.216 of this session and the other sessions
NOTE Confidence: 0.8444918
00:01:44.216 --> 00:01:46.806 will be available on the subsequent week.
NOTE Confidence: 0.8444918
00:01:46.810 --> 00:01:49.386 An slice of each presentation that will
NOTE Confidence: 0.8444918
00:01:49.386 --> 00:01:51.844 also be available for your review and
NOTE Confidence: 0.8444918
00:01:51.844 --> 00:01:54.560 for people who cannot make the live event.
NOTE Confidence: 0.8444918
00:01:54.560 --> 00:01:57.264 At the end of the six session series,
NOTE Confidence: 0.8444918
00:01:57.270 --> 00:01:58.965 CME Credit will be provided
NOTE Confidence: 0.8444918
00:01:58.965 --> 00:02:00.660 for those who claim it.
NOTE Confidence: 0.8444918
00:02:00.660 --> 00:02:05.079 You will have to fill a quick form and.
NOTE Confidence: 0.8444918
00:02:05.080 --> 00:02:07.660 Supply some feedback to claim the
NOTE Confidence: 0.8444918
00:02:07.660 --> 00:02:10.990 CME credit at the end of the series.
NOTE Confidence: 0.8444918
00:02:10.990 --> 00:02:12.630 So today we’ll be covering
NOTE Confidence: 0.8444918
00:02:12.630 --> 00:02:13.614 the myeloid neoplasms.
NOTE Confidence: 0.8444918
00:02:13.620 --> 00:02:15.270 As you can see here,
NOTE Confidence: 0.8444918
00:02:15.270 --> 00:02:17.573 I will be updating you for Milo
NOTE Confidence: 0.8444918
00:02:17.573 --> 00:02:18.560 dysplastic syndromes then,
NOTE Confidence: 0.8444918
00:02:18.560 --> 00:02:20.786 Doctor Orish Alice will update us on
NOTE Confidence: 0.8444918
00:02:20.786 --> 00:02:22.829 acute myeloid leukemia and finally doctor,
NOTE Confidence: 0.8444918
00:02:22.830 --> 00:02:24.480 but also full update us
NOTE Confidence: 0.8444918
00:02:24.480 --> 00:02:25.140 on myeloproliferative.
NOTE Confidence: 0.8444918
00:02:25.140 --> 00:02:27.156 Neoplasm’s will try to stick to
NOTE Confidence: 0.8444918
00:02:27.156 --> 00:02:29.727 the times that you can see here so
NOTE Confidence: 0.8444918
00:02:29.727 --> 00:02:31.886 that we can allow some time for
NOTE Confidence: 0.8444918
00:02:31.886 --> 00:02:34.016 questions in the last 10 minutes.
NOTE Confidence: 0.8444918
00:02:34.020 --> 00:02:36.644 We can stay a few minutes beyond one.
NOTE Confidence: 0.8444918
00:02:36.650 --> 00:02:39.922 For those of you who can stay if
NOTE Confidence: 0.8444918
00:02:39.922 --> 00:02:43.090 there are many questions as well.
NOTE Confidence: 0.8444918
00:02:43.090 --> 00:02:45.118 So I'll start with the updates
NOTE Confidence: 0.8444918
00:02:45.118 --> 00:02:47.220 on my latest ostick syndromes.
NOTE Confidence: 0.8444918
00:02:47.220 --> 00:02:50.410 So these are my disclosures.
NOTE Confidence: 0.8444918
00:02:50.410 --> 00:02:53.226 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, 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,
this is actually a schema from 2013,
and the reason I'm showing you this one.
From seven or eight years ago is because.
Not much really has changed in
the schema in the management of
Andy as until last year until 2020
and in 2020 we have the first 2
approvers basically since
so we had 14 years without any
approvals for Andy's until 2020 when we
have two drugs that have been approved.
One of them is last battleship which
is a transforming growth factor beta,
an inhibitor disinhibits. Elegant and.
This is recommended for patients who
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, 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.

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.

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 side 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, have refer patients for us, 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.
NOTE Confidence: 0.8306338
00:07:26.614 --> 00:07:28.726 of best response was 12 months.
NOTE Confidence: 0.8306338
00:07:28.730 --> 00:07:31.350 So I think well.
NOTE Confidence: 0.8306338
00:07:31.350 --> 00:07:33.966 The follow up still needs to be longer.
NOTE Confidence: 0.8306338
00:07:33.970 --> 00:07:36.546 It’s important to know that for now it
NOTE Confidence: 0.8306338
00:07:36.546 --> 00:07:38.974 seems that oral version of Decitabine is
NOTE Confidence: 0.8306338
00:07:38.974 --> 00:07:41.808 very similar to how we decide to be in,
NOTE Confidence: 0.8306338
00:07:41.810 --> 00:07:43.916 and I think we have a lot of data
NOTE Confidence: 0.8306338
00:07:43.916 --> 00:07:46.090 now suggesting that it can be
NOTE Confidence: 0.8306338
00:07:46.090 --> 00:07:47.960 completely replacing the IBD side
NOTE Confidence: 0.8306338
00:07:48.024 --> 00:07:49.989 been as monotherapy for Andy’s.
NOTE Confidence: 0.8306338
00:07:49.990 --> 00:07:52.662 And on this note also I like to
NOTE Confidence: 0.8306338
00:07:52.662 --> 00:07:54.965 highlight that many of you are aware
NOTE Confidence: 0.8306338
00:07:54.965 --> 00:07:57.560 that there is an oral version of is
NOTE Confidence: 0.8306338
00:07:57.560 --> 00:08:00.210 cited in the CC-486 or on your leg.
NOTE Confidence: 0.8306338
00:08:00.210 --> 00:08:01.850 That has been approved,
but this 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.

I'm sorry.

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 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
transfusion independence of.
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.
NOTE Confidence: 0.8676015
00:10:50.467 --> 00:10:52.507 in the typical refractory relapsed MD
NOTE Confidence: 0.8676015
00:10:52.573 --> 00:10:54.624 S setting and even patients who have
NOTE Confidence: 0.8676015
00:10:54.624 --> 00:10:56.162 more OCR have significant survival.
NOTE Confidence: 0.8676015
00:10:56.162 --> 00:10:58.444 As you can see with 15 months.
NOTE Confidence: 0.8676015
00:10:58.450 --> 00:10:58.778 Again,
NOTE Confidence: 0.8676015
00:10:58.778 --> 00:11:00.418 this is single ARM study,
NOTE Confidence: 0.8676015
00:11:00.420 --> 00:11:01.056 not randomized,
NOTE Confidence: 0.8676015
00:11:01.056 --> 00:11:04.030 and I think we need more data before this
NOTE Confidence: 0.8676015
00:11:04.030 --> 00:11:06.599 could be used in routine clinical practice.
NOTE Confidence: 0.8676015
00:11:06.600 --> 00:11:07.988 There are important differences
NOTE Confidence: 0.8676015
00:11:07.988 --> 00:11:09.723 in how financial classes used
NOTE Confidence: 0.8676015
00:11:09.723 --> 00:11:11.689 in real life setting or for Andy
NOTE Confidence: 0.8676015
00:11:11.689 --> 00:11:13.439 as compared to AML for example.
NOTE Confidence: 0.8676015
00:11:13.440 --> 00:11:15.000 And both of those studies,
NOTE Confidence: 0.8676015
00:11:15.000 --> 00:11:17.488 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, 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.
00:14:05.998 --> 00:14:07.888 volume app which is approved for
00:14:07.955 --> 00:14:10.337 several solid tumors did not improve
00:14:10.337 --> 00:14:12.444 outcomes compared to other sighting.
00:14:12.444 --> 00:14:15.528 However I think this is probably
00:14:15.528 --> 00:14:17.690 just related to PD L1.
00:14:17.690 --> 00:14:20.266 And does not extend necessarily to other
00:14:20.266 --> 00:14:22.830 classes of immune checkpoint inhibitors.
00:14:22.830 --> 00:14:25.086 And on that note,
00:14:25.086 --> 00:14:27.342 another immune checkpoint inhibitor
00:14:27.342 --> 00:14:29.759 called sabatella mob or MPG 453.
00:14:29.760 --> 00:14:31.630 Is basically being studied in
00:14:31.630 --> 00:14:33.126 combination with hypomethylating agents,
00:14:33.130 --> 00:14:35.368 not only for high risk MD’s,
00:14:35.370 --> 00:14:37.918 but also for AML patients and the
00:14:37.918 --> 00:14:40.183 data from what was presented in
00:14:40.183 --> 00:14:43.191 in ash this year showed this is a
NOTE Confidence: 0.8049437
00:14:43.191 --> 00:14:45.465 single arm again phase one study,
NOTE Confidence: 0.8049437
00:14:45.470 --> 00:14:48.454 but it showed the CR rate of 23%
NOTE Confidence: 0.8049437
00:14:48.460 --> 00:14:50.330 which is slightly higher than
NOTE Confidence: 0.8049437
00:14:50.330 --> 00:14:52.200 what you expect with monotherapy,
NOTE Confidence: 0.8049437
00:14:52.200 --> 00:14:54.818 but the overall response rate was 64%,
NOTE Confidence: 0.8049437
00:14:54.820 --> 00:14:57.457 and what you can see on the right hand
NOTE Confidence: 0.8049437
00:14:57.457 --> 00:15:00.538 is that there was encouraging durability.
NOTE Confidence: 0.8049437
00:15:00.540 --> 00:15:01.653 Of the combination,
NOTE Confidence: 0.8049437
00:15:01.653 --> 00:15:03.508 especially with patients who have
NOTE Confidence: 0.8049437
00:15:03.508 --> 00:15:05.718 long or very high risk disease,
NOTE Confidence: 0.8049437
00:15:05.720 --> 00:15:07.988 and I would note the side effect
NOTE Confidence: 0.8049437
00:15:07.988 --> 00:15:11.021 profile here it does not seem to add
NOTE Confidence: 0.8049437
00:15:11.021 --> 00:15:13.490 myelosuppression to the exercise again alone,
NOTE Confidence: 0.8049437
00:15:13.490 --> 00:15:14.756 and also importantly,
NOTE Confidence: 0.8049437
00:15:14.756 --> 00:15:16.866 the incidence of immune related
effects seems to be low with this.
With this particular agent, so appears on this data.
There are ongoing several study.
We just completed a cruel to a randomized phase two study in higher risk MD S of.
Is there with the battle map versus is alone and this study is completed accrual and we expect the results in the next one to two years.
There’s another face retrial that will open here as well.
Called the stimulus MD S2, which is a randomized phase three combination is with
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.
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 well as transplant consideration in the last couple of minutes. I will talk about lower risk MD’s partnerships have been approved after ESA failure. For patients who have RingCentral plastic anemia from lower risk MD’s now, 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 is 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

that we did 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 an 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 setting about what is the right cut off for transfusions in, especially in the outpatient setting. For patients with ambius 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?

Every seeing a full slide who sees 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 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.
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 reaction.
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.
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 rates of mortality.

So this is the actual trial. This scheme is a little complex, but essentially like I mentioned, newly diagnosed patients with AML received clad plus ldac with van.
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 know how to use a
NOTE Confidence: 0.77116615
00:27:59.334 --> 00:28:00.319 highlighter or whatever,
NOTE Confidence: 0.77116615
00:28:00.320 --> 00:28:02.318 but patients received a * 2 then
NOTE Confidence: 0.77116615
00:28:02.318 --> 00:28:05.304 B * 2 and then back and forth back
NOTE Confidence: 0.77116615
00:28:05.304 --> 00:28:07.978 and forth for up to 18 cycles.
NOTE Confidence: 0.77116615
00:28:07.980 --> 00:28:10.225 So here the patient characteristics
NOTE Confidence: 0.77116615
00:28:10.225 --> 00:28:13.440 as of the first day to cut of
NOTE Confidence: 0.77116615
00:28:13.440 --> 00:28:15.638 note 40% of patients for older.
NOTE Confidence: 0.77116615
00:28:15.638 --> 00:28:17.648 Sorry older than 70 years,
NOTE Confidence: 0.77116615
00:28:17.650 --> 00:28:19.665 25% were had disease characterized
NOTE Confidence: 0.77116615
00:28:19.665 --> 00:28:20.874 by porous I,
NOTE Confidence: 0.77116615
00:28:20.880 --> 00:28:23.100 genetics ANAN would be would be
NOTE Confidence: 0.77116615
00:28:23.100 --> 00:28:25.310 generally expected given this population,
NOTE Confidence: 0.77116615
00:28:25.310 --> 00:28:27.675 although nearly half were ellenor
NOTE Confidence: 0.77116615
00:28:27.675 --> 00:28:30.040 European leukemia net poor risk
NOTE Confidence: 0.77116615
00:28:30.121 --> 00:28:32.381 after accounting for the relevant
NOTE Confidence: 0.77116615
50
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.

MRD 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 median 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

However, this is just some.

You know, some smaller kind

You can see that when accounting for

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
00:30:07.878 --> 00:30:09.634 folks not getting to transform
00:30:09.634 --> 00:30:11.339 with 69% but a difference,
00:30:11.339 --> 00:30:13.054 did not reach statistical significance.
00:30:13.060 --> 00:30:15.118 Likely in the setting of just,
00:30:15.120 --> 00:30:15.806 you know,
00:30:15.806 --> 00:30:17.864 obviously a small early phase study.
00:30:20.240 --> 00:30:21.825 So just going to switch
00:30:21.825 --> 00:30:23.750 gears a little bit with AML,
00:30:23.750 --> 00:30:25.750 one of the first decision we have to
00:30:25.750 --> 00:30:28.217 make is whether patient is quote unquote
00:30:28.218 --> 00:30:30.123 intensive therapy eligible or not.
00:30:30.130 --> 00:30:32.062 The first 2 trials I mentioned were
00:30:32.062 --> 00:30:33.707 really geared towards patients that
00:30:33.707 --> 00:30:35.227 are intensive therapy ineligible.
00:30:35.230 --> 00:30:36.980 But what about patients receiving
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. 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.
be considering with concurrency 3A

four inhibition as well as toxicities

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 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.

So a complex slide,

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
expect with intensive therapy and addition of class including based on what I just presented. For C PX351.

CRC is 90% and in the newly diagnosed cohort 60 to 75% in the roaster factory cohorts. So and fairly good rates of MRD negativity. And this is essentially just looking at at. Based on their their disease, the disease cohort specifically. So I’ll just kind of wrap it up with just promise two more slides. So those updates for therapies we already had. But what about just one update? on an agent or regimen?
We do not yet really have. This is Google Map or the this is the humanized anti CD. 

47 IgG, four monoclonal antibody product from Gilead Sciences, relevant as tumor expression of CD 47 prompts evasion from an 80 minute surveillance. 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

00:35:51.199 --> 00:35:54.837 MD S but I’ll just focus on the AML cohort.

00:35:54.840 --> 00:35:56.400 Specifically,

00:35:56.400 --> 00:35:58.550 90% porous surgeon attics 70% P

00:35:58.550 --> 00:36:00.310 three mutations with a robust

00:36:00.371 --> 00:36:02.466 median vaf which would otherwise

00:36:02.466 --> 00:36:04.561 predict biallelic loss of function.

00:36:04.570 --> 00:36:06.122 So essentially a very,

00:36:06.122 --> 00:36:09.210 very poorest population and not the

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

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

00:36:14.026 --> 00:36:16.506 other than I’d say a mild transient

00:36:16.506 --> 00:36:18.595 on targeting me that was reversible.
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 65.
00:36:51.025 --> 00:36:55.947 18.9 months and even after isolating 18.9 months and even after isolating
NOTE Confidence: 0.79211825

00:36:55.947 --> 00:36:59.781 patients that had a P3 mutation. patients that had a P3 mutation.
NOTE Confidence: 0.79211825

00:36:59.781 --> 00:37:03.097 And we still 12.9 months, And we still 12.9 months,
NOTE Confidence: 0.79211825

00:37:03.097 --> 00:37:07.274 which to be honest is the longest which to be honest is the longest
NOTE Confidence: 0.79211825

00:37:07.274 --> 00:37:10.143 median OS I believe ever reported median OS I believe ever reported
NOTE Confidence: 0.79211825

00:37:10.143 --> 00:37:12.674 for this population, for this population,
NOTE Confidence: 0.79211825

00:37:12.674 --> 00:37:14.090 so quite striking as you can see, so quite striking as you can see,
NOTE Confidence: 0.79211825

00:37:14.090 --> 00:37:17.060 four or five patients are still four or five patients are still
NOTE Confidence: 0.79211825

00:37:17.060 --> 00:37:20.674 alive more than two years out, alive more than two years out,
NOTE Confidence: 0.79211825

00:37:20.674 --> 00:37:24.000 so quite impressive. so quite impressive.
NOTE Confidence: 0.79211825

00:37:24.000 --> 00:37:26.740 So I am a little bit over and So I am a little bit over and
NOTE Confidence: 0.79211825

00:37:26.740 --> 00:37:30.097 I apologize to Nikolai. I apologize to Nikolai.
NOTE Confidence: 0.79211825

00:37:30.097 --> 00:37:33.413 Mostly this is raw, Mostly this is raw,
NOTE Confidence: 0.79211825

00:37:33.413 --> 00:37:37.067 conclude my section and look conclude my section and look
NOTE Confidence: 0.79211825

00:37:37.067 --> 00:37:39.929 forward any questions at the end. forward any questions at the end.
NOTE Confidence: 0.79211825
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,
00:38:50.110 --> 00:38:51.940 acquisition in pH, negative MPs,
NOTE Confidence: 0.71176875
00:38:51.940 --> 00:38:54.716 and this study managed to show that this
NOTE Confidence: 0.71176875
00:38:54.716 --> 00:38:57.676 mutations are quite as early as in utero
NOTE Confidence: 0.71176875
00:38:57.676 --> 00:38:59.600 until disease develops decades later.
NOTE Confidence: 0.71176875
00:38:59.600 --> 00:39:02.155 So the goal of the study was
NOTE Confidence: 0.71176875
00:39:02.155 --> 00:39:03.705 timing of driver, mutation,
NOTE Confidence: 0.71176875
00:39:03.705 --> 00:39:04.160 acquisition,
NOTE Confidence: 0.71176875
00:39:04.160 --> 00:39:05.980 and clonal expansion evolution
NOTE Confidence: 0.71176875
00:39:05.980 --> 00:39:07.800 dynamics of the clones.
NOTE Confidence: 0.71176875
00:39:07.800 --> 00:39:10.494 The methods used by UK investigators
NOTE Confidence: 0.71176875
00:39:10.494 --> 00:39:13.039 included studying 10 patients with Jack.
NOTE Confidence: 0.71176875
00:39:13.040 --> 00:39:15.662 Two mutations of this is Jack
NOTE Confidence: 0.71176875
00:39:15.662 --> 00:39:17.410 two mutation for Stevens.
NOTE Confidence: 0.71176875
00:39:17.410 --> 00:39:20.469 This patients were between H20 and 76.
NOTE Confidence: 0.71176875
00:39:20.470 --> 00:39:22.142 The single cell derived
NOTE Confidence: 0.71176875
00:39:22.142 --> 00:39:23.814 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 Belmira stole pork it so its allosteric BSL, one 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
results with this medication.

There is Mr Lated and terminal

an with BCR ABL translocation.

This N terminal piece of.

Peace is gone,

so you have PCR and now 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
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, 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 GIS used before and patients have to change treatment either because they were intolerant or resistant to treatment and so
00:43:18.530 --> 00:43:21.212 the patients was 2315 I mutation
NOTE Confidence: 0.78682363
00:43:21.212 --> 00:43:23.737 or V299L mutations were excluded
NOTE Confidence: 0.78682363
00:43:23.737 --> 00:43:26.160 because pursuit Nip is not.
NOTE Confidence: 0.78682363
00:43:26.160 --> 00:43:27.900 Active against this mutation.
NOTE Confidence: 0.78682363
00:43:27.900 --> 00:43:31.094 So this is specifically the study which
NOTE Confidence: 0.78682363
00:43:31.094 --> 00:43:33.629 didn’t include T315I mutated patients.
NOTE Confidence: 0.78682363
00:43:33.630 --> 00:43:36.546 This particular group of patients was
NOTE Confidence: 0.78682363
00:43:36.546 --> 00:43:39.745 addressed by the Phase One study and
NOTE Confidence: 0.78682363
00:43:39.745 --> 00:43:42.468 the drug is active against the BCR
NOTE Confidence: 0.78682363
00:43:42.552 --> 00:43:45.307 ABL with this particular mutation,
NOTE Confidence: 0.78682363
00:43:45.310 --> 00:43:47.146 so patients were randomized.
NOTE Confidence: 0.78682363
00:43:47.146 --> 00:43:51.380 As you can see in two to one fashion,
NOTE Confidence: 0.78682363
00:43:51.380 --> 00:43:53.530 and the demographics were slightly
NOTE Confidence: 0.78682363
00:43:53.530 --> 00:43:56.620 different in two groups I highlighted.
NOTE Confidence: 0.78682363
00:43:56.620 --> 00:43:59.350 In yellow here that a similar patients
NOTE Confidence: 0.78682363
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
groups was twelve point 2%. So taking into consideration the differences between two groups I 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. 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.
comparing tiks for treatment.

Assistant Intolerant CML

population and assimilate,

which is first class stamp inhibitor,

showed superior efficacy compared with

bosutinib with favorable side effect profile,

so this is upcoming hopefully.

Approved in the near future

treatment option for CML patients,

particularly with resistant and

intolerant disease.

After treatment with two different guys.

Also, the drug is effective in

treating patients with T315I mutation,

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, 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.

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
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%. 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 72% for intermediate 160. 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
00:50:03.055 --> 00:50:05.370 hemoglobin more than 10 and less than 10,
NOTE Confidence: 0.8362344
00:50:05.370 --> 00:50:06.698 but didn’t require transfusions.
NOTE Confidence: 0.8362344
00:50:06.698 --> 00:50:08.358 And as you can see,
NOTE Confidence: 0.8362344
00:50:08.360 --> 00:50:10.565 after initial small dip there is improvement
NOTE Confidence: 0.8362344
00:50:10.565 --> 00:50:13.007 in anemia in this subgroup of patients,
NOTE Confidence: 0.8362344
00:50:13.010 --> 00:50:14.334 which is quite impressive.
NOTE Confidence: 0.8362344
00:50:14.334 --> 00:50:15.658 So one other thing,
NOTE Confidence: 0.8362344
00:50:15.660 --> 00:50:16.904 at the bone marrow’s,
NOTE Confidence: 0.8362344
00:50:16.904 --> 00:50:18.770 their biopsies were done at the
NOTE Confidence: 0.8362344
00:50:18.834 --> 00:50:20.927 beginning as well as during the study
NOTE Confidence: 0.8362344
00:50:20.927 --> 00:50:23.300 and there was improvement in fibrosis.
NOTE Confidence: 0.8362344
00:50:23.300 --> 00:50:25.844 Great in 1/3 of patients and most of
NOTE Confidence: 0.8362344
00:50:25.844 --> 00:50:27.704 the improvements observed were observed
NOTE Confidence: 0.8362344
00:50:27.704 --> 00:50:30.399 during the first six months of treatment.
NOTE Confidence: 0.8362344
00:50:30.400 --> 00:50:32.764 Only two patients get worsening of
NOTE Confidence: 0.8362344
00:50:32.764 --> 00:50:35.338 fibrosis and you can see that there
00:50:35.338 --> 00:50:38.292 is also a sign that there is improved air throughout differentiation and normalization of megakaryocytic histopathology.

00:50:44.090 --> 00:50:47.418 So the side effects the CPI 16 in combination with Link was generally well tolerated.

00:50:51.170 --> 00:50:54.002 So 87% reported at least one treatment emergent adverse event.

00:51:00.490 --> 00:51:04.025 haematological and now this was an email from both cytopenia.

00:51:05.580 --> 00:51:07.488 Of course this may be manifestations of the most common ones were.
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.
plus placebo,
which allows crossover down the road.
We are planning to open it at Yale this year.
So the final study I want to present is PG
hepcidin was discovered about 20 years ago,
master regulator why and metabolism
with high hepcidin level shutting down
for a port and transport of ferritin.
And so the reason to use it in polycythemia
Vera is of course this patient need
phlebotomies as the main part of their
treatment which lead to iron deficiency.
Perhaps keep citing analog PG 300?
Can do this instead by shutting down
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 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, 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,
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 deficiency can cause the symptoms as well was well tolerated.

More than 90% had drug related adverse events, but all of them were sorry,

so I would like to conclude by summarizing this study.

It was PG 300 subcutaneously
00:54:55.015 --> 00:54:56.419 administered once a week,
NOTE Confidence: 0.7385071

00:54:56.420 --> 00:54:59.509 was safe and well tolerated, no Grade 3/4.
NOTE Confidence: 0.7385071

00:54:59.509 --> 00:55:01.724 Adverse events related to treatment.
NOTE Confidence: 0.7385071

00:55:01.730 --> 00:55:04.145 It was effective in eliminating
NOTE Confidence: 0.7385071

00:55:04.145 --> 00:55:06.077 the therapeutic phlebotomy’s and
NOTE Confidence: 0.7385071

00:55:06.077 --> 00:55:08.405 reversing iron deficiency impact on
NOTE Confidence: 0.7385071

00:55:08.405 --> 00:55:10.620 previous symptoms is being studied,
NOTE Confidence: 0.7385071

00:55:10.620 --> 00:55:13.380 and this study is also planned
NOTE Confidence: 0.7385071

00:55:13.380 --> 00:55:16.239 for opening at Yell this year.
NOTE Confidence: 0.7385071

NOTE Confidence: 0.8375762

00:55:19.670 --> 00:55:21.806 Thank you Nikolaj and Rory great
NOTE Confidence: 0.8375762

00:55:21.806 --> 00:55:24.299 talks and I think very important
NOTE Confidence: 0.8375762

00:55:24.300 --> 00:55:26.232 updates from from the meeting
NOTE Confidence: 0.8375762

00:55:26.232 --> 00:55:28.548 since we’re a little bit overtime,
NOTE Confidence: 0.8375762

00:55:28.550 --> 00:55:30.300 will actually take 10 minutes
NOTE Confidence: 0.8375762
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 day 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.
NOTE Confidence: 0.7818602

Those are not germline mutations.
NOTE Confidence: 0.7818602

This is somatic mutations which acquired.
NOTE Confidence: 0.8318645

So Doctor God actually follows up on the CML presentation and he’s asking if this drug is actually approved.
NOTE Confidence: 0.8318645

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?
NOTE Confidence: 0.8318645

Like would you put this drug ahead of assertive in your kind of lines of therapy?
NOTE Confidence: 0.8318645

If the drug is approved?
NOTE Confidence: 0.8318645

Or how would you approach it?
NOTE Confidence: 0.8318645

Yeah, so you know.
NOTE Confidence: 0.8318645

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
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

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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 single arm studies and needing to know more data so CD 47 is actually expressed in most of their cells in 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. There’s some element of specificity for those cells on which CD 47 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

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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.