But it’s 1202 an Why don’t we get started ‘cause I want to make sure everyone has time.

This is actually our last Cancer Center grand rounds of calendar year 2020 and what a year it has been. A lot of things have happened, a lot of great work and it seems almost fitting that actually theme for our last grand rounds is our division of hematology. And which we are extremely proud. And among the highlights of all the many
accomplishments in the division was actually the results of our search for our new division chief. As, as you've heard, we had a national search and without question. There was one person that the committee felt very strongly rose to the top, and that is Doctor Stephanie Allyne, a recognized. Physician scientists, clinician educator, leader, and which is so pleased to have Stephanie now in that role in the really extraordinary legacy.
of accomplishment in hematology
00:01:10.686 --> 00:01:12.498 So I’m going to turn it
00:01:12.500 --> 00:01:15.680 detail. So I’m going to turn it
00:01:15.680 --> 00:01:17.952 over to Stephanie to introduce
00:01:17.952 --> 00:01:19.768 our esteemed 2 speakers.
00:01:20.910 --> 00:01:23.976 Like Italian, thank you for this honor.
00:01:23.980 --> 00:01:26.710 So I’m really honored to introduce two
00:01:26.710 --> 00:01:30.109 over my dear dear colleagues and friends,
00:01:30.110 --> 00:01:32.826 and our first speaker of the day
00:01:32.826 --> 00:01:34.930 is Doctor Nikolai productive.
00:01:34.930 --> 00:01:36.244 He’s associate professor,
00:01:36.244 --> 00:01:38.353 internal medicine, hematology, and Sir.
00:01:38.353 --> 00:01:40.819 Just as the associate director of
00:01:40.819 --> 00:01:43.068 Hematology Oncology Fellowship program,
00:01:43.070 --> 00:01:45.478 he is also the from T for
00:01:45.478 --> 00:01:47.749 education on the Duffy service.
00:01:47.750 --> 00:01:50.024 Nicolai received his MD and PhD
from Saint Peters Burg State, Pablo Medical University and completed his fellowship at Yale in hematology oncology, after which we get to keep him and Nikolai Nikolai’s clinical practice and research are focused on my light neoplasms, including acute minor. Kenya models plastic syndromes and in particular my lucrative neoplasms in which he really is an expert. Nikolai serves as a Pi for a number of clinical studies. Their industry sponsored cooperative group investigator initiated and his clinical care and his trials.
He really makes a difference for his patience. So nicholi, we look forward to your time. Thank you Stephanie, I'll be talking about polycythemia Vera today. Are these are my disclosures? So, first of all, polycythemia Vera belongs to the Group of Milo proliferative neoplasms based on W2 2016 classification mpanza divided into
pH positive or BCR ABL positive? Or also known as chronic myeloid leukemia as well as BCR, ABL negative Milo proliferative neoplasms, and among them there are classical mpanza including polycythemia vera we’re discussing today. Also essential thrombocythemia. And primary myelofibrosis so the definition is based on WTO 2016 criteria represented on the slide. To diagnose the very you have to have three major criteria on the left or two first major criteria and then minor criterion on the right.
The major criteria include elevation of hemoglobin. This is the hallmark feature, and that’s what makes it different from other classical Milo proliferative neoplasms. The bone marrow biopsy is necessary and usually shows up on my loses. Excessive presence of red blood cells and myeloid precursors, as well as megakaryocytes and then. Finally, there is one of two Jack two mutations, Jack 2V617F mutation or Jack. Two exon 12 mutation in very rare
In certain circumstances, about 2% or less. When this mutations are not present, you need lower throughput and level to diagnose polycythemia Vera. So the history of Mila proliferate diseases is interesting if at first they were described as a group by Doctor William Damashek, working in Tufts when he described myeloproliferative diseases. This group of conditions became reportable to seer the lodge.
Registry of cancer patients in the United States in 2001 and in 2008 show renamed MP dies to MPs, so from Milo proliferative diseases, they became I’ll of proliferative neoplasms in Part B, cause in 2005, Jack 2V617F mutation was identified as a driver mutation in majority of patients with PD ET an Milo fibrosis in 2006 nipple exam 10 mutation another. Driver mutational Jack Stat pathway which was discovered and then in 2007, two exon 12 mutation was described. Finally in 2013 call reticular
mutation was described and if you look at polycythemia Vera which is the subject of my presentation today, most of the patients will have Jack 2V617F mutation 97 percent 1%. 2% of patients will have other drivers. So the polycythemia Vera Epidemiology was recently summarized in our review. As you can see the patients with this diagnosis are older, median age of diagnosis is 65 years. It’s not the most common malignancy. The incidence is only .5 to 400,000 person years.
Estimated prevalence in the USA is 25 to 57 per 100,000 persons. Median overall survival is 12 to 14 years, which is less than expected in age and gender matched population. 5 year relative survival is 84 to 89%. Males diagnosed with this condition are little bit more common than females. This condition is extremely divided in different age groups.
rarely diagnosed in younger patients.

Those who look way younger than 40. So this is one of the large cohort studies in one institution and Mayo Clinic, which looked at survival of.

Patients with classical Milo proliferative neoplasms and here you can appreciate that 80 survival yellow line is less than survival of general population. The dark blue line and polycythemia is worse survival than ET. So the etiology of Milo prolifer.

Trackmania plasma goes beyond driver mutations.

We know the driver mutations.
We also just figured out that they may occur many, many years before MPN diagnosis. During this ash meeting a week ago, there was a presentation which showed that these mutations may develop in neutral, but factors leading to the acquisition and development of MPN are much less clear. So in fact, MPM doesn’t develop in everyone who has Jack two mutations. The other interesting observation is that there is higher incidence of mpanza in first degree relatives. It’s actually 7 times more likely. The patients that first degree relatives...
are seven times more likely to develop MPs and German driver mutations. It is felt that congenital predisposition due to certain polymorphisms help to acquire MPM and families overall within 5 to 10% of MPN patients. So we started the extrinsic factors influencing on the development of polycythemia Vera, among other myeloproliferative neoplasm’s, and for that we used in HRP, diet and health study cohort with more than 450,000 participants.
Median follow-up was 15 1/2 years.

490 ampion cases were discovered among them 190 PV cases.

So it is well known that tobacco is a bad carcinogen, and we were able to show that there is increased risk of MPs velopment one smoking women.

So the other interesting finding of this study was identification of coffee intake as protective against development of polycythemia Vera.

You can see that high versus low consumption of decaffeinated coffee was associated with decreased incidence of that diagnosis.
00:09:26.696 --> 00:09:28.966 did not have protective effect.

00:09:28.970 --> 00:09:35.066 We also looked at different micronutrients.

00:09:35.070 --> 00:09:37.025 And food groups and identified

00:09:37.025 --> 00:09:39.392 food consumption is one of the

00:09:39.392 --> 00:09:41.450 risks of the development of PV.

00:09:45.420 --> 00:09:47.676 He as well as sugar intake,

00:09:47.680 --> 00:09:49.570 which is also associated navaira.

00:09:49.570 --> 00:09:51.957 So to conclude, it’s good to have

00:09:51.957 --> 00:09:54.847 a Cup of coffee in the morning,

00:09:54.850 --> 00:09:57.858 but not with sugar and without a cigarette.

00:10:00.110 --> 00:10:02.850 Of polycythemia Vera include microvascular

00:10:00.110 --> 00:10:02.850 complications like headache,

00:10:04.500 --> 00:10:06.144 aerothermal, alja dizziness,

00:10:06.144 --> 00:10:08.336 paresthesias and blurred vision
microvascular complications,

including heart attacks,

strokes and venous thrombotic events.

Patients with PD may suffer from constitutional symptoms,

including fatigue, night sweats, weight loss, and teaching.

Specifically aquagenic parictis.

Splenomegaly occurs in less than half of the patients and patients with PD may have splenomegaly associated symptoms as well.

Most of morbidity and mortality in this group of patients comes from thrombo SIS, arterial and venous thrombosis occur in about 20%.
Of patience and you can see that this is the data from cohort of more than 1500 patients with them in follow up of 6.9 years, but not only promote transposes, the danger that these patients can also develop major hemorrhage, and it is known that polycythemia V era is strong, but humor odijk disorder. So what is feared most is disease progression, and patients with polycythemia may progress to post PV myelofibrosis about 10% of patients in 10 years. But even more scary with progression to.
As you can see, 4% of the patients will develop AML after 10 years of follow up. It is a little bit more than 80 but much less than the primary myelofibrosis. So also we sometimes can observe evolution of essential thrombocythemia and/or polycythemia Vera. Can we predict the risk of disease evolution? Can we predict progression to Milo fibrosis or acute myeloid leukemia?
US based PV data set.

We contributed 100 patients to this 500 patient cohort and what looked at is Lucas Cytosis over year and its Association with disease evolution and thrombo SIS. It turns out that this. White cell count trajectory did not associate with thrombosis, but was associated with increased risk of transformation to post TV Milo fibrosis, as well as MPs. Unlike my with leukemia, this study used very interesting statistical approach,
so-called group based trajectory modeling which is usually used in social and behavioral Sciences and this allowed to capture infrequent or delayed phenomena from the landmark start point. Over the course of the disease, as opposed to other studies which looked at Lucas Cytosis at one time point. So is WBC increases surrogate marker or of disease evolution potential or is a prompt for cytoreduction, allowing us to prevent it? This particular question is not answered yet. I am privileged to represent our Cancer Center 1 NCM guideline,
panel developing guidelines for Milo

proliferative neoplasm and I’m going to.

I show you the section which is related
to management of polycythemia Vera.

So the goals of management is to
reduce the risk of thrombosis
and hemorrhage control.
The symptoms and try to prevent
and delay disease transformation.
Everyone with a diagnosis of PV
should be receiving low dose
aspirin as well as be phlebotomist.
Two hematocrit goal of less than
54.5% cardiovascular risk factors have
to be managed as well as this as
Cardiovascular mobility and mortality is common among these patients, so the evidence behind aspirin in polycythemia Vera comes from this study which was published in 2004. This so-called The CLAP study evaluation of aspirin in polycythemia and it looked at probability of survival free of marker. Users had 60% risk. Reduction of adverse events and
incidents of major bleeding episodes was not significantly different in this low dose aspirin group.

So the next recommendation in the guidelines is to keep him at ecrit below 45%.

The study which was published in New England Journal of Medicine in 2013, confirmed this goal, which we actually. Using practice for many years, even before this article was published, it turns out that this stricter control of hematocrit using Phlebotomies as well as cytoreductive therapies is associated with four times decreased risk of traumatic events.
So in regards to management of cardiovascular risk factors. Our group looked at use of statins and survival among older patients with polycythemia Vera using serum Medicaid and Medicare data set, so we identified 721 polycythemia Vera patients. Half of them use statins after diagnosis. Using univariate analysis on the left, we showed that starting users had improved survival. In multivariate analysis, we also showed that proportion of these covered.
By 10% increase of proportion of discovered by 10% led to reduction of risk of death by 18%. So status is certainly beneficial for this group of patients. All the patients with polycythemia Vera, so the center of the algorithm of management of patients with polycythemia is there risk risk stratification based on 11 criteria. So patients are considered high risk for traumatic events, arterial and venous. If they are older than 60, or if they had history of Trumbo.
SIS so this patient is beyond

aspirin phlebotomy to America,

lesson 45 and modification of cardiovascular risk factors should be on site to re directed therapy and

frontline therapy recommended to this patience is either hydroxyurea or interferon.

So of course if patients are not high risk and they developed worsening of symptoms, they have new traumatic events or bleeding events.

They do not tolerate phlebotomy, which they continuously require, which they continuously require, or they have elevated white cell count as well as platelet count.

Cytoreductive therapy may be used as well,
so there are no randomized studies looking at hydroxyurea in patients with polycythemia Vera. The reason why we’re using it is mostly extrapolation from the studies, which were done for essential thrombocythemia patients, so we looked at 820 older patients with TV, once again using CR Medicee. Medicare data set and found out that about 40% of those patients who are high risk under did that, and looking at the treatment with everybody and specifically with hydroxyurea, we found out that every 1010% increase
In proportion of days covered by hydroxyurea led to decrease risk of death by 8%.

Similarly, increase of PTC by 10% lead to decrease of trim bushes by 8%, so this is certainly an effective treatment which are not only helps to prevent traumatic events but also improves survival in older patients with polycythemia Vera.

As you can see, the benefit of lobotomy was also confirmed in this study.

So why hydroxyurea works for PV patients? It’s an oral chemotherapeutic agent that inhibits ribonucleotide reductase and interferes with the
process of DNA synthesis and repair.

It is cheap and has a reasonably favorable toxicity profile as well as long term safety data, including in children with sickle cell disease.

Its mechanism of action in PV is debated but may include impact on blood counts.

Ability to reduce neutrophil activity.

Decreased expression of the filial adhesion molecules and in use of nitric oxide generation.

Side effects occur and the drug is not tolerated by about 20% of patients.

The side effects include mild suppression, mucocutaneous ulcers,
non Melanoma skin cancers.

It is also teratogenic.

So the big question, which is still debated during MPM meetings and on the pages of publications, is hydroxyurea relationship with second malignancies, that hydroxyurea increase risk of 2nd malignancies. We again use your Medicare data set to look at second malignancies and one MPN patients. As you can see we started more than 3000 patients and. About 40% of them had polycythemia Vera. This patients were followed up to 10 years. Median follow-up was 2.67 years and
NOTE Confidence: 0.80290896
00:19:37.260 --> 00:19:39.878 median age of diagnosis was 77 years,
NOTE Confidence: 0.80290896
00:19:39.880 --> 00:19:42.624 so it’s a little bit older than
NOTE Confidence: 0.80290896
00:19:42.624 --> 00:19:44.866 General PD population because of
NOTE Confidence: 0.80290896
00:19:44.866 --> 00:19:47.346 Medicare requirement for this study.
NOTE Confidence: 0.80290896
00:19:47.350 --> 00:19:50.176 So 65% of patients used hydroxyurea,
NOTE Confidence: 0.80290896
00:19:50.180 --> 00:19:53.484 allowing us to look at two groups,
NOTE Confidence: 0.80290896
00:19:53.490 --> 00:19:55.378 hydroxyurea users and nonusers.
NOTE Confidence: 0.80290896
00:19:55.378 --> 00:19:58.210 It is well known that second
NOTE Confidence: 0.80290896
00:19:58.291 --> 00:20:00.179 malignancy is common in.
NOTE Confidence: 0.80290896
00:20:00.180 --> 00:20:02.430 Patients with mild proliferative neoplasms,
NOTE Confidence: 0.80290896
00:20:02.430 --> 00:20:06.462 it is not really clear exactly why that is,
NOTE Confidence: 0.80290896
00:20:06.470 --> 00:20:09.613 but you can see that in our
NOTE Confidence: 0.80290896
00:20:09.613 --> 00:20:10.960 cohort of patients,
NOTE Confidence: 0.80290896
00:20:10.960 --> 00:20:13.200 about 8.8% developed second malignancy,
NOTE Confidence: 0.80290896
00:20:13.200 --> 00:20:15.900 more than half solid second malignancies,
NOTE Confidence: 0.80290896
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and among patients with hematological malignancies. Majority developed AML and MD as expected in this group of patients with myeloid neoplasms.

So when we compare two groups, hydroxyurea users and non users using univariate analysis, we found no difference in incidence of 2nd malignancies.

In the multivariable analysis of hydroxyurea use and type of 2nd malignancies we found no difference in occurrence of all second malignancies, solid second malignancies and he etal logic non myeloid second malignancy’s.
We also did an analysis specifically aimed at my Lloyd second malignancies and there was no difference here either. So moving on this algorithm, if cytoreductive therapy stops working or is not tolerated, there is an option of second line sector reduction with ruxolitinib, which is the only FDA approved drug by the way, in polycythemia Vera neither hydroxyurea nor interferon I approved at this time in the United States by the FDA. So the interferon is used in Milo proliferative neoplasms for many years,
and it is associated with decently high rates of haematological response reduction and independence form. Phlebotomies improvement of symptoms, and in some patients up to 30% significant reduction and disappearance of Jack 2V617F positive cells. Side effects include flu like symptoms. Psychiatric conditions and that’s why this drug is not given to patients with psychiatric disorders as well as autoimmune side effects. Side effects are better with regulated preparations, which can be given once a week. One other thing which is quite important,
this drug is not teratogenic and is preferred for younger patients with PV. So it has potential for disease modification by targeting the malignant clone, which is evidenced by disappearance of Jack 2V617F positive cells and some of those patients. This meta analysis of 41 studies, including 12181 patients, more than 500 of them had PV. The overall response rate was 75% with complete haematological response of 50. He presented in meta regression analysis. There was no different from between. No difference between Montag later than...
pig related interference in regards to response rates and thrombo embolic events and treatment discontinuation due to adverse events were not frequent. 5% and 6.5% per year, respectively.
Molecular responses, which is certainly interesting because we hope that this drug is disease. Modifying could not be analyzed in this particular meta analysis. You took heterogeneity. Of definition and outcome assessments. In conclusion, we thought that both regulated interference and non regulated...
00:23:17.677 --> 00:23:20.017 interferon can be effective and safe.

00:23:20.020 --> 00:23:22.092 One term in P.

00:23:22.092 --> 00:23:23.128 Vera patients.

00:23:23.130 --> 00:23:25.140 So this is the response study

00:23:25.140 --> 00:23:27.752 which led to have the approval of

00:23:27.752 --> 00:23:30.146 Jack inhibitor rock solid Nip for

00:23:30.146 --> 00:23:32.447 second line treatment in patients

00:23:32.447 --> 00:23:34.727 with Vera with primary endpoint

00:23:34.727 --> 00:23:36.798 being composite reduction of spleen

00:23:36.798 --> 00:23:38.406 volume and hematocrit control.

00:23:38.410 --> 00:23:41.217 As you can see it was accomplished

00:23:41.217 --> 00:23:43.226 in 21% of patients separately.

00:23:43.226 --> 00:23:45.638 Reduction of spleen volume by 35%

00:23:45.640 --> 00:23:48.482 was seen in almost 40% of patients

00:23:48.482 --> 00:23:50.978 and 60% of patients could accomplish

00:23:50.978 --> 00:23:50.994

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schematic control with this treatment.

This is important anti-inflammatory medication and one of the side effects may be infections including herpes Auster.

So we recommend Shingrix vaccine to all of our patients on rock solid net.

Another side effect can be non-Melanoma skin cancers which has increased incidence in Brooklyn of users but also in hydroxyurea users.

So I refer all my patients for German irregular dermatological evaluations. So we looked at 5 year relative survival probability for PV patients in the United States. Patients who are diagnosed between
2001 and 2011 with end of observation in 2016 and as you can see this five year relative survival unfortunately is not getting better, so we need new drugs which may improve survival by modifying the disease. So this study looked at GNU interference formulation so called role peg interferon. This is a European study phase three trial comparing group peginterferon. This is a European study phase three trial comparing group peginterferon. Against hydroxyurea in high risk TV patient frontline treatment. The goal of the study was to show Noninferiority of Ro peg. to hydroxyurea an at one year.
Interestingly enough, they did not accomplish that primary endpoint of the hydroxyurea was superior from the standpoint of inducing complete haematological responses as well as you can see here, molecular responses at six months were higher among patients treated with hydroxyurea. So interferon in general takes time to work, and that’s what we observed over the course of this study. So this is the publication which shows data up to three years of follow-up data, and you can see that in the second part of the study interferon did better from the
NOTE Confidence: 0.854975
00:25:49.308 --> 00:25:51.510 standpoint of haematological responses,
NOTE Confidence: 0.854975
00:25:51.510 --> 00:25:53.274 which were statistically significantly
NOTE Confidence: 0.854975
00:25:53.274 --> 00:25:55.479 better than among patients taking
NOTE Confidence: 0.854975
00:25:55.479 --> 00:25:57.598 hydroxyurea as well as molecular responses,
NOTE Confidence: 0.854975
00:25:57.600 --> 00:26:00.570 and you can see that.
NOTE Confidence: 0.854975
00:26:00.570 --> 00:26:02.830 This is actually improving overtime.
NOTE Confidence: 0.854975
00:26:02.830 --> 00:26:05.662 This ash the follow up of the study
NOTE Confidence: 0.854975
00:26:05.662 --> 00:26:08.712 five year follow up was presented
NOTE Confidence: 0.854975
00:26:08.712 --> 00:26:11.542 showing continues that this translate
NOTE Confidence: 0.854975
00:26:11.542 --> 00:26:14.271 continuing as well as there are
NOTE Confidence: 0.854975
00:26:14.271 --> 00:26:16.351 no significant new side effects.
NOTE Confidence: 0.854975
00:26:16.360 --> 00:26:19.078 So this new formulation of the
NOTE Confidence: 0.854975
00:26:19.078 --> 00:26:21.838 interferon can be given once every
NOTE Confidence: 0.854975
00:26:21.838 --> 00:26:24.834 three to four weeks after the first
NOTE Confidence: 0.854975
00:26:24.834 --> 00:26:28.070 year of treatment and is now approved
NOTE Confidence: 0.854975
42
The company making this medication is bringing up to the US market and it is likely that this medication will become available for our patients next year. So there are few new treatments I wanted to mention before I end. Is giving ability to all patients to enroll on this study is offering new treatments, some of them? Maybe this is modifying so. First of all, this is the given a staff the age Deccan hitter,
so leading to a situation of the histone.

That transcriptions of genes responsible for cell growth, arrest, differentiation, apoptosis.

This drug is wanna be started in the phase three trial against hydroxyurea for the frontline treatment of PV patients with high risk disease.

So the other class of drugs which may be interesting is MDM. Two inhibitors.

As you know MDM two inhibits TP53 function, and by inhibiting MDM two way allowing TP 53 to perform.

It’s wrong,
not in the malignant cell,

by the way,

interfere on one of the mechanisms

be activations of genes,

increasing transcription of TP 53

so the last study I want to mention

phase two trial of hepcidin analog.

It’s nice to see after discovery of

hepcidin 20 years ago that we have

an analog and you know we now have

a test we can check for hepcidin.

Very expensive.

I never was able to do it but

now we also have a drug.

Which basically shuts down transport
00:28:18.060 --> 00:28:21.394 of iron and locks it in the cells

00:28:21.394 --> 00:28:23.907 and this drug is used for patients with severe who need phlebotomies

00:28:23.989 --> 00:28:26.054 in an attempt to avoid iron deficiency which may have detrimental effects on quality of life.

00:28:26.054 --> 00:28:28.984 and in an attempt to avoid iron deficiency which may have detrimental effects on quality of life.

00:28:28.984 --> 00:28:31.144 The preliminary results which office to study, which were presented at Ash week ago, were quite promising.

00:28:31.144 --> 00:28:33.020 The preliminary results which office to study, which were presented at Ash week ago, were quite promising.

00:28:33.020 --> 00:28:34.241 The preliminary results which office to study, which were presented at Ash week ago, were quite promising.

00:28:34.241 --> 00:28:35.869 No side effects and pretty much everyone on this drug does not require phlebotomist.

00:28:35.870 --> 00:28:38.726 which were presented at Ash week ago, were quite promising.

00:28:38.730 --> 00:28:39.963 which were presented at Ash week ago, were quite promising.

00:28:39.963 --> 00:28:43.322 No side effects and pretty much everyone on this drug does not require phlebotomist.

00:28:43.322 --> 00:28:45.770 this drug does not require phlebotomist.

00:28:45.770 --> 00:28:46.248 Anymore.

00:28:46.248 --> 00:28:49.116 So I’d like to conclude that polycythemia Vera is driven by Jack.
2V617F mutation in the majority of cases in 97% sugar intake increases and coffee intake decreases the risk of polycythemia Vera development. In fact, consumption of coffee moderate amounts can be considered part of normal lifestyle. Increased white cell count is associated with PV evolution. To post PD, Mila, fibrosis, MD, SNL user status should be considered in PV patients for. Cardiovascular disease risk reduction, hydroxyurea safe and effective, but interference holds promise to be disease.

Modifying and normal treatments to
prevent or delay disease transformation.

I need it.

At the end I would like to acknowledge funding from the Frederick Dilucca Foundation Yellow Corporate Center, allowing us to conduct the studies and my collaborators thank you very much.

Nikolai absolute proof.

So you can’t see my coffee tears. It was coffee right now.

Getting my very soon.

Yeah, I think we just have.

It may be time for just one or two questions because we want to give him his time.
So are you thinking right?

So for example in the other matters.

Order in chronic malaria leukemia.

We're thinking about Q or we want to get people off these long years of medication?

Do you foresee something like that for polycythemia? You know you would hope that there is known driver and inhibiting it will cure this patience.

But unfortunately, like now, with rooks Lid NAP, which is in an incubator of Jack two, we don't really see that.

In fact it is not disease modifying
if you ask me that you know so. Unfortunately, the successes we’ve had in CML did not translate to pH negative MPs, but you know, we have promising future medications. Or perhaps we’ll have something which is going to decrease or eliminate that difference in survival. Our PV patients have when compared to regular population. OK, I see we have a comment from armor, great talk and many new exciting options available for these patients.
I share you enthusiasm.

It is actually very challenging to do study for those patients because they have such a good prognosis comparing to all other cancer patients.

So really have to have drugs which are not only working well but also well tolerated.

Well hematology is going to be around for many many more years.

So thank you, Nicola.

I think we should move on with Tama talk, so let me introduce Doctor to Microbee.

He’s associate Professor of Medicine and the medical director informed Chief of Operations and Quality.
And I think everybody knows that tomorrow with the entire Smilow team has gotten the malignancy service through the 1st surge of Covid and now the second surge. So thank you so much for that tomorrow also serves as the disease aligned research team or direct leader from my light malignancies. And tomorrow completed his doctorate in hematology oncology in Lyon, France, and then joined the Institute Power Lee comment in Marseille, France, and he completed a fellowship at Johns
Hopkins University as a Fulbright alumnus, and I think that’s how eventually we got tomorrow to join us here.

So Demott is focused on again pilot malignancy’s leukemia, and I think his top will speak for his amazing expertise in treating these diseases and taking care of patients.

So. To my valuers.

Hope that everybody is seeing my screen now. OK so for today I want to focus my presentation and one on the topic of Milo dysplastic syndrome and more precisely, on the patient exposed, hyperventilating agent and we experience hyper mediating agent failure.
NOTE Confidence: 0.30600467
00:32:52.640 --> 00:32:57.230 Anne. So here are my disclosures.
NOTE Confidence: 0.7758981
00:33:00.920 --> 00:33:03.237 An ad to start wanted just to
NOTE Confidence: 0.7758981
00:33:03.237 --> 00:33:06.102 to do a really quick reminder
NOTE Confidence: 0.7758981
00:33:06.102 --> 00:33:09.067 on my love dysplastic syndrome.
NOTE Confidence: 0.7758981
00:33:09.070 --> 00:33:12.647 Stressing that we have with this disease,
NOTE Confidence: 0.7758981
00:33:12.650 --> 00:33:14.698 Arelia turgeon’s group of
NOTE Confidence: 0.7758981
00:33:14.698 --> 00:33:16.746 clonal bone marrow neoplasms,
NOTE Confidence: 0.7758981
00:33:16.750 --> 00:33:20.292 we have the cytopenias due to the
NOTE Confidence: 0.7758981
00:33:20.292 --> 00:33:22.822 ineffective in multiple years is
NOTE Confidence: 0.7758981
00:33:22.822 --> 00:33:25.588 we have abnormal blood and bone
NOTE Confidence: 0.7758981
00:33:25.588 --> 00:33:28.805 marrow cell morphology and the risk
NOTE Confidence: 0.7758981
00:33:28.805 --> 00:33:31.555 of clonal evolution and progression
NOTE Confidence: 0.7758981
00:33:31.555 --> 00:33:33.649 to acute myeloid leukemia.
NOTE Confidence: 0.73165816
00:33:36.610 --> 00:33:39.122 From a molecular standpoint,
NOTE Confidence: 0.73165816
00:33:39.122 --> 00:33:42.890 these diseases are extremely generous with
NOTE Confidence: 0.73165816
some main driver spliceosome mutation,

such as the three one mutation

epigenetic targeted mutation such as

at Ted 2 for example, and EMT 3A and.

This eternity is also something

we see in the prognosis.

I’m not going to go in the
details of the risk stratification

of Milo dysplastic syndrome,

but I just want you to focus your
attention on the right side of

the panel where you would see that
when we see a patient with mild
when we see a patient with mild dysplastic syndrome in clinic,

we can see someone who has a median

overall survival of more than eight years,
as well as people that. In the worst case scenario, can progress to leukemia and die within a year, and so addressing this eternity is something that is on your mind. Each time we’re seeing patient from the treatment standpoint, we can go from a pure observation for patients without any symptoms or significant cytopenia to some low intensity treatment such as. Activating stimulating agent for patients with anemia, but in the context of the
higher risk disease,

the mainstay of treatment as being

namely as cited in or decide to be in.

Over the last few years and for the

few patient eligible allogeneic stem

cell transplantation is obviously

something that we would consider frontline.

That’s a pretty classic for all NDS talk.

That’s basically the registration

study of as a sighted in MD’s,

showing that with Asia we are able

to prolong the median overall

survival of probably nine months in

median as compared to conventional.

Care we definitely have evidences
00:35:54.530 --> 00:35:57.615 that the 24 months of median overall
survival that we see in this study
are probably a bit overestimated as
compared to what we see in real life. Probably around 18 months.

And that’s many works from basically
the registry studies such as the group
Uncle Phone, Digital Displays E,
but also some really nice work of
Stephen Armor. For example on CS.

What do we call activating agent failure?
Because we know that at the end 90
percent of the patient that we start
mediating
agent will experience on the real failure.

We classically defined that as a lack of response or progression after at least four to six cycles of iPod mediating agent,

there's no difference between as cited in or decided in from this standpoint and.

One of the main features that we see is really limited overall survival for patients experiencing failure after average four to six months median survival, and that's something that we initially described almost 10 years ago and that has been since.
reproduced in many different studies.

So Interestingly, we have many reason why this hyper mitigating agent resistant can develop, but so far we can say that we have a home run we don’t consider that we have a unifying theory to explain why we have this failure of this iPod engagement. We see phenomenon of clonal selection and clonal evolution, maybe potentially with some difference of profiling between the patient that are completely refractory to the disease. In the patient that.
Response and then progress after treatment.

But many other mechanisms have been potentially put on the table as explaining what we see or to fatty affect change in nucleotide analogue transporter expression of immune checkpoint inhibitors and regulators and we will circle back on that later in the presentation.

So for the moment there’s still a lot of open questions on explaining this hypomethylating agent failure. There’s obviously also something that is pretty clear which is the role of the stem cell. Quiescence and resistance MD’s are stamps,
00:38:33.680 --> 00:38:35.186 stem cell diseases, and even in responding patients.

00:38:35.186 --> 00:38:38.638 For example, correct there IMO globin and that have a decrease in their blast counts,

00:38:41.452 --> 00:38:45.229 like here in there in the blue line, we can still detect cytogenetics abnormalities.

00:38:45.230 --> 00:38:49.246 And more Interestingly, we can still detect stem cells like L TC IC’s for example, that harbors marker of the minor dysplastic syndrome, important when it comes to the
way we’re considering treatment, not only for relapse, but on a more general basis from the get go on the diagnosis of this patient.

Let’s talk about the treatment now. We reviewed a few years ago. What were the option for this patient with some health care treatment? And let’s say that nothing is really satisfying with the exception of the few patient that can potentially transition to an allogeneic stem cell transplantation, either directly after relapse, or, for example, after intensive cytoreduction. With chemotherapy,
so there’s been a lot of basically investigation around what we can do when it comes to intensive treatment. Brute force approaches for HMA failure. We try to dig deeper, a bit on the data that. We initially generated. On induction, as we may have a lot of different type of induction, Conventional 7 + 3 regimen like we would be doing in newly diagnosed AML Internet to hide those site arabien regimen. And that’s something we’re doing, mostly on the European side as well as pure in analog based regimen.
such as flag or flag idea that.

We see on both side of the Atlantic, and so we gather basically group of 15 different.

Investigator you ran in the US and put together basically a data set of 307 patient with maladies plastic syndrome treated with induction chemotherapy. We found that roughly 41% of the patient will achieve a complete remission with only a median overall survival of 11 months.

The two take home message from this work that we developed at here with Brian Bowl a few years ago was one that we do not so any real significant
difference between the conventional 7
+ 3 the intensive hydac regimen or the.
Genopro, Fabian based regimen and I think also
pretty importantly that all patient
did not have a chance to bridge to
analogy in transplantation died within
a year of the initiation of treatment.
So that’s pretty telling on the
fact that we definitely need to
develop more option for this patient,
including from the initiation of response,
but also on the transplant to make
sure that we can maximize access.
Uh, to transplant for all of these patients.
One of the extension and one of the.

Development following this initial study was to maybe try to use a better drug for induction chemotherapy for this patient, and we had CP351D liposomal formulation of Donna Mycin and Sitara been that was approved two years ago three years ago now for acute myeloid leukemia arising from Milo dysplastic syndrome. And so we're thinking about this internally approaches that was kind of a natural conclusion to basically try to use. Pretty similar drug to achieve response in HMA resistant BI lo dysplastic syndrome. That's a phase two study that we
developed with Prajwal Bodo at Yale as a multicenter IIT, the plan is basically to give two cycles of induction with two days of CPX in acute myeloid leukemia. We usually use three days of CPX, but there's some data showing that from a safety standpoint, especially in elderly patient two days, maybe probably more appropriate, and the patient that are responding, we can continue for six cycle of maintenance with one day of civics or transition to bone marrow transplantation.
The study is open to accrual after the Covid adventures that we had over the last year and we open running. So all these non selected approach, induction chemotherapy but also basically non targeted agent that we have developed over the years. For the moment, let’s say that we have not found any real good candidate to be a standard of care option, especially for patients that are not eligible for aggressive chemo. I’ve just listed here a few of the studies but as you can see, in lots of these general studies.
without any real targeting,
when situation where the response rates are low and more importantly,
the overall survival seems still stuck below below one year,
so we definitely need to do better.
And that goes back to the way we considering the pathophysiology of this disease,
and acknowledge that this HMA failure or not,
and imaginas situation,
just to give an example.
We see that from just a clinical standpoint we see different outcome
in patients at our primary refractory
and really do not respond at all to hyper mediating agent in patients with relapsing disease. That basically seems to have a bit more favorable. Outcome in this context so still a lot of work to do on the translational and basic science side. One way we’ve tried to tackle this difference of outcome based on this clinical finding was to deal with the stable disease with a slightly different term than just using. Regular treatment by adding on the hyperventilating agent, potentially drug that may be
00:45:30.945 --> 00:45:34.152 synergistic based on their mode of
action or based on in vitro studies.

00:45:34.152 --> 00:45:37.197 We had several attempts at this
over the last years.

00:45:37.200 --> 00:45:40.176 An easy combination and logical
combination was to add on the
almighty engage in the second
epigenetic targeted agent.

00:45:40.176 --> 00:45:44.600 As such, as H.

00:45:44.600 --> 00:45:47.705 then we treated 19 patient with vorinostat,
which is one of the first in
Class Age document or with,
unfortunately,

00:45:47.705 --> 00:45:50.560 almighty engage in the second
epigenetic targeted agent.

00:45:50.560 --> 00:45:52.273 As such, as H.

00:45:52.280 --> 00:45:54.224 then we treated 19 patient with vorinostat,
which is one of the first in
Class Age document or with,
unfortunately,

00:45:54.224 --> 00:45:55.196 Dark inhibitor,

00:45:55.200 --> 00:45:58.595 unfortunately,

00:45:58.600 --> 00:46:02.023 pretty limited outcome really

72
knows how that rate of only 10%, but the median survival of 12 months in potentially a pretty selected population. We also tried to use a bit more recently, and that’s not a fully public published yet. The addition of a smooth and inhibitor to try to use really work on the stem cell component. There’s some individual data showing that this moves on emitter can potentially. Abrogates the resistance to hypomethylating agent, but so far the results were pretty disappointing too. Well not to be completely gloom. There’s end at the probably
00:46:46.895 --> 00:46:49.969 light at the end of the tunnel.

00:46:49.970 --> 00:46:52.150 I need to highlight the work presented by armor.

00:46:52.150 --> 00:46:53.894 If you have a year ago.

00:46:53.900 --> 00:46:58.245 Basically at the ash meeting on the add on of venetoclax in maybe less selected population.

00:47:01.205 --> 00:47:03.509 24 patient is. Resistance with this edition of the BCL, two inhibitor or some real complete remission and some marrow.

00:47:03.510 --> 00:47:06.288 Chimia Free State with a six months program.

00:47:06.288 --> 00:47:10.488 edition of the BCL, two inhibitor or some real complete remission and some marrow.

00:47:10.488 --> 00:47:14.010 Chimia Free State with a six months program.

00:47:14.010 --> 00:47:17.626 French fries survival 76% that from our standard is pretty pretty promising.

00:47:14.010 --> 00:47:17.626 French fries survival 76% that from our standard is pretty pretty promising.

00:47:17.630 --> 00:47:20.535 So statue and we will have more information, but that’s one of the Avenue that
we are currently investigating.

Stop. That’s. Pretty good,

That’s still not something that really

address the specificity of the clone

of the Milo dysplastic syndrome,

and maybe instead of using brute

force to try to induce a response,

we can maybe try to outsmart the

disease rather than just using those

intensity or non selected approaches

in the context of Milo dysplastic.

Syndrome,

where a bit less fortunate that

in the acute model in the world,
as we don’t have so many targeted agents that we can use at the majority of the patients, we will have as a freebie wanted two SS two mutations that are for the moment at least non-targetable, even if there’s some basically development on the side and I’m going to take the example of some product we have done in the IDH world. And that can potentially be avenues that we are going to explore in the future to try to get a better outcome for these patients.
inhibitors from IDH two and IDH one. I did too. That’s in a Sydney IDs, one that’s evil. Setting it in both of the phase. One study of this compounds model, spastic syndrome patient were allowed after at least one line of treatment. 76% of the patient seems to be able to respond with the IDH two sorry 559% of the patient seems to be able to respond to IDH, two inhibitor and maybe a bit more in the IDH one subclone with a 71% response rate. As you can see, that’s pretty small samples of patient. There’s ongoing investigation with this IDH inhibitor,
single agent or combination.
The one thing that is pretty striking, the fact that we’re probably in a situation where the duration of response is still pretty limited, so. Potentially we can try to find some alternatives to IDH inhibitor on this context, and that’s potentially when I was mentioning outsmarting the disease. I’m not that smart guy, but I had the chance and that will work with really intelligent people branded Bindra Stephanie Allen,
for example, and you may know the story that was developed by Ranjit over the last years about the fact that when you have an IDH mutation that was initially basically. Developed and found in gliomas the fact of having these two hydroxy glutarate will basically impair the activity of the X Rays in the cell, decrease malicious recommendation, repair and create a braknis phenotype. That obviously is interesting as a potentially chemo radio sensitizer, but from all standpoints were especially interested in our.
Potentially, we can use pop emitters to create synthetic lethality with this agent, and when we tested, basically when we move from gliomas to leukemias and Milo dysplastic syndromes, indeed, that’s what we found that we were able to potentially. Induce apoptosis in samples of patient that were exposed to hyperventilate. Engagement that were exposed to IDH inhibitor an that I came to development with NCI study right now of the olaparib. The 1st in Class I DH pop inhibitor for patient offering IDH mutation. So that’s patient that as a diagnosis of.
Acute myeloid leukemia or marriages.
Plastic syndrome with an IDH one or IDH two mutation and at least one prior line of treatment, including in lot of this patient's permitting.
Agent there are four cohorts that are currently investigated.
One for patients with IDH, one IDH, two mutant email without prior exposure to IDH.
And if it or one with my dysplastic syndrome without.
Exposure to ideas, debit, or an arm two and four are for patient
NOTE Confidence: 0.7622402
00:52:16.681 --> 00:52:19.375 in acute myeloid leukemia and maladies
NOTE Confidence: 0.7622402
00:52:19.375 --> 00:52:21.583 plastic syndrome that were already
NOTE Confidence: 0.7622402
00:52:21.583 --> 00:52:24.103 exposed to IDH inhibitor in the
NOTE Confidence: 0.7622402
00:52:24.110 --> 00:52:26.987 patient that are naive of IDH inhibitor.
NOTE Confidence: 0.7622402
00:52:26.990 --> 00:52:29.606 We have an early response assessments
NOTE Confidence: 0.7622402
00:52:29.606 --> 00:52:32.927 after one cycle and if we do not
NOTE Confidence: 0.7622402
00:52:32.927 --> 00:52:34.797 see any clear clinical benefit,
NOTE Confidence: 0.7622402
00:52:34.800 --> 00:52:36.850 this patient are usually discontinued.
NOTE Confidence: 0.7622402
00:52:36.850 --> 00:52:38.562 An transition classical IDH
NOTE Confidence: 0.7622402
00:52:38.562 --> 00:52:41.130 inhibitor for the patient that are
NOTE Confidence: 0.7622402
00:52:41.209 --> 00:52:44.197 responding to the patient that were
NOTE Confidence: 0.7622402
00:52:44.197 --> 00:52:46.189 previously exposed to accommodating.
NOTE Confidence: 0.7622402
00:52:46.190 --> 00:52:47.986 Agent and IDH numitor.
NOTE Confidence: 0.7622402
00:52:47.986 --> 00:52:50.680 We are reassessing response after three,
NOTE Confidence: 0.7622402
00:52:50.680 --> 00:52:52.472 69 and 12 cycles,
continuing the treatment until progression.

The study has been activated this year and we’re pretty happy to have over the last few months.

Three patient included an in treatment an three patient screening right now.

One of the big interest of this work is also to see the pretty extensive collaboration we have.

From a translational standpoint, that’s collaboration with the NCI through more calf or what exam sequencing and sequencing.

That’s a lot of study done in hours.

At Yale with Ranjit and Stephanie to explore from ex vivo samples.
DNA damage.
Response, but also all these cells will behave put in the Mr Jimmys model that Stephanie is developing. We have collaboration with Domino’s thanks to Pat Larusso and that collaboration with Jiggly to assess the evolution of the two hydroxy glutarate and some metabolomics marker Anne. Right now we are starting to work with winning Wong from the West Campus. On single cell sequencing for this. Specific samples and studies, as we definitely think that we
00:54:18.520 --> 00:54:20.722 will have some clonal selection as 
NOTE Confidence: 0.7622402
00:54:20.722 --> 00:54:22.690 potentially one of the mechanism 
NOTE Confidence: 0.7622402
00:54:22.690 --> 00:54:24.840 of resistance in this context. 
NOTE Confidence: 0.7622402
00:54:24.840 --> 00:54:25.881 So stay tuned. 
NOTE Confidence: 0.7622402
00:54:25.881 --> 00:54:28.310 That’s a bit early to make any 
NOTE Confidence: 0.7622402
00:54:28.392 --> 00:54:29.550 any conclusion. 
NOTE Confidence: 0.7622402
00:54:29.550 --> 00:54:31.674 We just have a few patients 
NOTE Confidence: 0.7622402
00:54:31.674 --> 00:54:34.250 in a few months on treatment, 
NOTE Confidence: 0.7622402
00:54:34.250 --> 00:54:37.730 but that’s a developing story. 
NOTE Confidence: 0.7622402
00:54:37.730 --> 00:54:39.440 As I was saying earlier, 
NOTE Confidence: 0.7622402
00:54:39.440 --> 00:54:41.904 one of the things that has also been 
NOTE Confidence: 0.7622402
00:54:41.904 --> 00:54:44.227 mentioned as a mechanism of resistance, 
NOTE Confidence: 0.7622402
00:54:44.230 --> 00:54:47.598 and I try to go fast on that. 
NOTE Confidence: 0.7622402
00:54:47.600 --> 00:54:48.452 Is uh, 
NOTE Confidence: 0.7622402
00:54:48.452 --> 00:54:51.434 even though logic escape of the matter. 
NOTE Confidence: 0.72344524
00:54:51.440 --> 00:54:52.294 Dysplastic syndrome.
We have an over expression of PD, One PD L1 and CA4 in. Patient with hypomethylating agent failure and that’s led to several studies I’m mentioning here. Studies with basically ipis, nivo or Pam bro. I also need obviously to mention that the study led by armor with basically edge darkening bitters plus checkpoint blockade inhibitors that was recently published. For the moment, let’s say that we are not at the point where. It’s a game changer.
There may be some kind of response, but for the moment, nothing that is really perfect. So still a lot of work to do. One way we thought about that is potentially to try to bring this. Potentially checkpoint inhibitor earlier in the development, and for instance, we’re currently developing a study in an MD's an email of idea 2012 plus patients that were already exposed to chemotherapy or iPod mediating agent. Another study has been on all and has to be restructured because of covid.
but we’re back in business and open to accrual oor.

Since basically lost last week.

Once again translation and collective studies are really important and we have some ongoing collaboration with Stephanie and will in one so.

If I need to to summarize a bit where we are really quickly for the moment for this patient with permitting agent failure with Steven situation agent failure with Steven situation transplanta allogeneic transplant candidate makes sense as we don’t have any really reliable other
option besides maybe some targeted therapy on small number of patients, we do not have a reliable standard of care for patients and fit for treatment. Maybe even eight o’clock, maybe some other drug will come and will be confirmed as option, but for the moment that’s still pretty struggling. The way the field is moving is interesting and we are learning a lot from the email world. At the same time, we probably cannot really completely extrapolate everything we do from the email side, we know that the microenvironment,
for example in Milo dysplastic syndrome is definitely different. We know that the ability of this patient to sustain any aggressive treatment is definitely less than what we see in AML on other malignancy so. That’s something that we need to work on and so. The best way we have to deal with this HTML file is ready to try to avoid it and optimize the frontline treatment. We have lots of currently really exciting drugs in the pipeline. Lots of data that we presented at the Ash this year on Venetoclax Magnolia Map team.
Three BitTorrent.

Amar has been part of some of these studies, so statue MBS Field is really moving and we hope to see the type of change in landscape that we have seen over at the last year in acute myeloid leukemia. So in conclusion, this situation of hyper mediating agent failure really represent some academic challenges we need to improve our understanding of the Physiology.

Pathophysiology of this situation to be able to help us to better define the standard of care for this patient, we need to build resources we need to build, represent repository and logical.
Follow up for this patient which is sometimes challenging. In the context of a disease that is treated in both small and big centers, we need to collaborate around academics to be able to really have significant number of patients to be able to answer the right question. I also think that it’s important to keep in mind that there are some clinical care challenges for that. The access to innovation to Center of excellence is not something that is a modulus in the country or
just a modulus in Connecticut.

And that’s definitely one of the mission.

I think we have at scale to be able to promote the access to innovation and promote the access to the Center of excellence that that we have.

We know that patients in Connecticut without snowstorm like tomorrow will have potentially some issues limiting the ability to basically get to academic centers, get to clinical trial, and so I think that one of the mission that we have as academics is also to make sure that we can potentially bring research.
Bring basically knew therapy and exciting therapy to the different sites where the patients are treated close to their home. With that I would like to thanks everyone. Right? Participate to this effort for sure. The Yellow Cancer Center group alphabetically. Steve Gore. My mentor Stephanie for lot of collaboration. Nicolai, Rory and armor for being such a great group to work with my dear colleagues, colleagues from the group Francophone.
the Mirror Displays E, as well as collaborators in US, Europe. And now I should say, knew K should probably split. You can Europe now two weeks anyway. On that I'll take any questions I would like to thank you for your attention. Thanks so much. Sounds fantastic to my thank you so much. Really true for some, and MD’s and AML and. You know, as we are presenting, you’ve actually answered like my burning questions. We just get rid of a society in, you know, and use it for salvage after everything else. And that is certainly very exciting
to see how you and the whole team are going to come up with exciting trials. I think we’re a little bit after the hour, but maybe. Say something sad, or Nickelodeon request and then we have to let people go for two or getting kicked out of the room. Which is correct? No, I think that’s definitely the HMA is a sign of care, but that’s not a perfect one. So developing new agents or new formulation, for example, we have now access to oral formulation of these hypomethylating agent.
That’s definitely something that we want to continue to develop with the idea that even if it may not improve the response rate or the overall survival and that may be something we can discuss as the way we can. I use this medication is a bit different than conventional accommodating age and we can discuss as the way we can. I use this medication is a bit different than conventional accommodating age and we can improve quality of life of the. And access to care, so that’s definitely something that is important for sure. Yeah, fantastic so Charlie, do you want to tell me? We probably have to break.
No thank you tomorrow and
Nikolai for two superb talks
really as two to four’s on two
important areas of human logic.
Malignancy’s, thank you.
Thank you alright.
Well thank you so much and look forward
to tackling these problems over
the years. Thank you.
Thanks everyone. Alright bye.