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

NOTE Confidence: 0.86493784
of accomplishment in hematology.

So I’m going to turn it over to Stephanie to introduce our esteemed 2 speakers.

Like Italian, thank you for this honor.

So I’m really honored to introduce two over my dear dear colleagues and friends,

and our first speaker of the day is Doctor Nikolai productive.

He’s associate professor,

internal medicine, hematology, and Sir.

Just as the associate director of

Hematology Oncology Fellowship program,

he is also the from T for education on the Duffy service.

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. Nikolai 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, for this kind introduction.

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 thrombocytopenia.

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
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, he immigrated with his family from Russia to Massachusetts at the age of three and then stayed in Massachusetts, was 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. 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% will have Jack to exam 12 and then. 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. And 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 a little bit more common than females. This is divided in different age groups. One other thing you can appreciate here is that this condition is extremely...
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 Both in red is worse survival than ET. So the etiology of Milo proliferata. 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

00:08:10.987 --> 00:08:13.767 to color it economical genes uncommon.

It is felt that congenital predisposition
due to certain polymorphisms help
to acquire MPM and families overall
within 5 to 10% of MPN patients
have germline predisposition.
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,

we were able to show that there is increased risk of MPs development one smoking women.

coffee intake as protective against development of polycythemia Vera.

You can see that high versus low coffee intake was associated with decreased incidence of that diagnosis.

Consumption of decaffeinated coffee
did not have protective effect.

We also looked at different microminerals.

And food groups and identified food consumption is one of the risks of the development of PV.

He as well as sugar intake, which is also associated navaira.

So to conclude, it’s good to have a Cup of coffee in the morning, but not with sugar and without a cigarette.

So the common clinical features.

Of polycythemia Vera include microvascular complications like headache,
aerothermal, alja dizziness, 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.
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 vera 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
last phase of Milo proliferative neoplasm

or secondary acute myeloid leukemia.

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

Jack Two V 617 mutation positive two polycythemia Vera.

Can we predict the risk of disease evolution?

Can we predict progression to Milo fibrosis or acute myeloid leukemia?

So we participated in this multicenter study, which looked at the largest
00:12:03.475 --> 00:12:05.860 US based PV data set.

00:12:05.860 --> 00:12:08.275 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.

00:12:11.187 --> 00:12:13.635 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,

00:12:16.162 --> 00:12:19.197 It turns out that this.

00:12:23.220 --> 00:12:25.495 White cell count trajectory did not associate with thrombosis,

00:12:25.495 --> 00:12:27.315 but was associated with increased risk of transformation to post TV Milo fibrosis,

00:12:27.320 --> 00:12:30.554 but was associated with increased risk of transformation to post TV Milo fibrosis,

00:12:30.554 --> 00:12:33.248 transformation to post TV Milo fibrosis,

00:12:33.250 --> 00:12:35.074 as well as MPs.

00:12:35.074 --> 00:12:36.898 Unlike my with leukemia,

00:12:36.900 --> 00:12:39.175 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,
00:13:18.350 --> 00:13:20.675 panel developing guidelines for Milo

00:13:20.675 --> 00:13:23.260 proliferative neoplasm and I’m going to.

00:13:23.260 --> 00:13:26.164 I show you the section which is related


00:13:28.400 --> 00:13:30.710 So the goals of management is to

00:13:30.710 --> 00:13:32.791 reduce the risk of thrombosis

00:13:32.791 --> 00:13:34.318 and hemorrhage control.

00:13:34.320 --> 00:13:36.690 The symptoms and try to prevent

00:13:36.690 --> 00:13:38.270 and delay disease transformation.

00:13:38.270 --> 00:13:40.580 Everyone with a diagnosis of PV

00:13:40.580 --> 00:13:42.590 should be receiving low dose

00:13:42.590 --> 00:13:44.990 aspirin as well as be phlebotomist.

00:13:44.990 --> 00:13:47.755 Two hematic rate goal of less than

00:13:47.755 --> 00:13:49.586 545% cardiovascular risk factors have

00:13:49.586 --> 00:13:52.767 to be managed as well as this as

00:13:52.767 --> 00:13:54.995
cardiovascular mobility and mortality.

NOTE Confidence: 0.817933

Is common among these patients,

NOTE Confidence: 0.817933

so the evidence behind aspirin in

NOTE Confidence: 0.817933

polycythemia Vera comes from this

NOTE Confidence: 0.817933

study which was published in 2004

NOTE Confidence: 0.817933


NOTE Confidence: 0.817933

Is this so called?

NOTE Confidence: 0.817933

The CLAP study evaluation of aspirin

NOTE Confidence: 0.817933

in polycytemia and it looked at

NOTE Confidence: 0.817933

probability of survival free of marker.

NOTE Confidence: 0.8374873

Action and stroke and death from

NOTE Confidence: 0.8374873

cardiovascular causes as well as P and DVT.

NOTE Confidence: 0.8374873

That was the combined endpoint the

NOTE Confidence: 0.8374873

aspirin uses as opposed to placebo.

NOTE Confidence: 0.8374873

Users had 60% risk.

NOTE Confidence: 0.8374873

Reduction of adverse events and
00:14:31.729 --> 00:14:33.663 incidents of major bleeding episodes

00:14:33.663 --> 00:14:35.183 was not significantly different

00:14:35.183 --> 00:14:37.328 in this low dose aspirin group.

00:14:37.330 --> 00:14:39.997 So the next recommendation in the guidelines

00:14:39.997 --> 00:14:42.810 is to keep him at ecrit below 45%.

00:14:42.810 --> 00:14:45.309 The study which was published in New

00:14:45.309 --> 00:14:47.550 England Journal of Medicine in 2013,

00:14:47.550 --> 00:14:49.890 confirmed this goal, which we actually.

00:14:49.890 --> 00:14:52.070 Using practice for many years,

00:14:52.070 --> 00:14:54.680 even before this article was published,

00:14:54.680 --> 00:14:57.662 it turns out that this stricter control

00:14:57.662 --> 00:14:59.528 of hematocrit using Phlebotomies

00:14:59.528 --> 00:15:02.093 as well as cytoreductive therapies

00:15:02.093 --> 00:15:04.711 is associated with four times

00:15:04.711 --> 00:15:07.176 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. Little bit more. 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 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 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 Thrombo.
00:16:18.901 --> 00:16:21.074 SIS so this patients beyond
NOTE Confidence: 0.8374873
00:16:21.074 --> 00:16:23.326 aspirin phlebotomy to America,
NOTE Confidence: 0.8374873
00:16:23.330 --> 00:16:25.435 lesson 45 and modification of
NOTE Confidence: 0.8374873
00:16:25.435 --> 00:16:27.540 cardiovascular risk factors should be
NOTE Confidence: 0.8374873
00:16:27.607 --> 00:16:30.421 on site to re directed therapy and
NOTE Confidence: 0.8374873
00:16:30.421 --> 00:16:32.528 frontline therapy recommended to this
NOTE Confidence: 0.8374873
00:16:32.528 --> 00:16:35.024 patience is either hydroxyurea or interferon.
NOTE Confidence: 0.8374873
00:16:35.030 --> 00:16:38.117 So of course if patients are not high risk
NOTE Confidence: 0.8374873
00:16:38.117 --> 00:16:41.298 and they developed worsening of symptoms,
NOTE Confidence: 0.8374873
00:16:41.300 --> 00:16:43.120 they have new traumatic
NOTE Confidence: 0.8374873
00:16:43.120 --> 00:16:44.940 events or bleeding events.
NOTE Confidence: 0.8374873
00:16:44.940 --> 00:16:47.030 They do not tolerate phlebotomy,
NOTE Confidence: 0.8374873
00:16:47.030 --> 00:16:48.802 which they continuously require,
NOTE Confidence: 0.8374873
00:16:48.802 --> 00:16:51.460 or they have elevated white cell
NOTE Confidence: 0.8374873
00:16:51.536 --> 00:16:53.720 count as well as platelet count.
NOTE Confidence: 0.8374873
00:16:53.720 --> 00:16:56.639 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,
and among patients with hematological malignancies. Majority developed AML and MD S 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 metalogic 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, have an option of second line 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 Jak2V617F 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 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
interferon can be effective and safe.

One term in P.  Vera patients.

So this is the response study which led to have the approval of Jack inhibitor rock solid Nip for second line treatment in patients with Vera with primary endpoint being composite reduction of spleen volume and hematocrit control.

As you can see it was accomplished in 21% of patients separately.

Reduction of spleen volume by 35% was seen in almost 40% of patients and 60% of patients could accomplish
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
00:24:28.260 --> 00:24:31.470 2001 and 2011 with end of observation
00:24:31.470 --> 00:24:35.193 in 2016 and as you can see this five
00:24:35.193 --> 00:24:37.549 year relative survival unfortunately
00:24:37.549 --> 00:24:39.905 is not getting better,
00:24:39.910 --> 00:24:43.350 so we need new drugs which may improve
00:24:43.350 --> 00:24:46.190 survival by modifying the disease.
00:24:46.190 --> 00:24:49.473 So this study looked at GNU interference
00:24:49.473 --> 00:24:52.469 formulation so called role peg interferon.
00:24:52.470 --> 00:24:55.550 This is a European study phase three
00:24:55.550 --> 00:25:00.275 trial comparing group peginterferon.
00:25:00.275 --> 00:25:02.087 TV patient frontline treatment.
00:25:02.090 --> 00:25:05.359 The goal of the study was to
00:25:05.359 --> 00:25:07.698 show Noninferiority of Ro peg
00:25:07.698 --> 00:25:10.236 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
in Europe by European Medicines Agency.

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 this talk and few clinical trials we’re planning to participate in. 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
interfere on one of the mechanisms by action of interferon would 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 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
of iron and locks it in the cells and this drug is used for patients with severe who need phlebotomies

in an attempt to avoid iron deficiency which may have detrimental effects on quality of life.

The preliminary results which were presented at Ash week ago, were quite promising.

No side effects and pretty much everyone on this drug does not require phlebotomist.

Anymore.

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, cardiovascular disease risk reduction, hydroxyurea safe and effective, but interference holds promise to be disease. Modifying and normal treatments to
00:29:26.065 --> 00:29:28.160 prevent or delay disease transformation.

00:29:28.160 --> 00:29:28.877 I need it.

00:29:28.877 --> 00:29:31.151 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.

00:29:31.151 --> 00:29:33.801

00:29:33.801 --> 00:29:35.921 Foundation Yellow Corporate Center,

00:29:35.930 --> 00:29:38.464 allowing us to conduct the studies and

00:29:38.464 --> 00:29:40.440 my collaborators thank you very much.

00:29:31.151 --> 00:29:33.801 funding from the Frederick Dilucca Foundation Yellow Corporate Center,

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00:29:33.801 --> 00:29:35.921 Foundation Yellow Corporate Center,

00:29:35.930 --> 00:29:38.464 allowing us to conduct the studies and

00:29:38.464 --> 00:29:40.440 my collaborators thank you very much.
So are you thinking right? 
So for example in the other matters. 
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. So that was thank you Emerson.
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 he malignancy service through the 1st surge of Covid an 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, 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 again on pilot malignancy’s leukemia, and I think his talk will speak for his amazing expertise in treating these diseases and taking care of patients.

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.
Anne. So here are my disclosures.

An ad to start wanted just to

do a really quick reminder

on my love dysplastic syndrome.

Stressing that we have with this disease,

Arelia turgeon’s group of

clonal bone marrow neoplasms,

we have the cytopenias due to the

ineffective in multiple years is

we have abnormal blood and bone

marrow cell morphology and the risk

of clonal evolution and progression

to acute myeloid leukemia.

From a molecular standpoint,

these diseases are extremely generous with
some main driver spliceosome mutation, such as the three one mutation epigenetic targeted mutation such as at T ed 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 dysplastic syndrome in clinic, we can see someone who has a median overall survival of more than eight years,
00:34:28.570 --> 00:34:30.830 as well as people that.

00:34:30.830 --> 00:34:33.530 In the worst case scenario,

00:34:33.530 --> 00:34:36.230 can progress to leukemia and

00:34:36.230 --> 00:34:38.390 die within a year,

00:34:38.390 --> 00:34:41.090 and so addressing this eternity

00:34:41.090 --> 00:34:44.870 is something that is on your mind.

00:34:44.870 --> 00:34:47.570 Each time we’re seeing patient

00:34:47.570 --> 00:34:49.730 from the treatment standpoint,

00:34:49.730 --> 00:34:53.160 we can go from a pure observation

00:34:53.160 --> 00:34:55.973 for patients without any symptoms

00:34:55.973 --> 00:34:59.103 or significant cytopenia to some

00:34:59.103 --> 00:35:01.800 low intensity treatment such as.

00:35:01.800 --> 00:35:02.943 Activating stimulating agent

00:35:02.943 --> 00:35:04.467 for patients with anemia,

00:35:04.470 --> 00:35:06.762 but in the context of the
higher risk disease, the mainstay of treatment as being to use iPod mitigating agent, namely as cited in or decide to be in. Over the last few years and for the 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
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% of the patient that we start treating with this iPod 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 treatment within average four to six months median survival, and that's something that, as that we initially described almost 10 years ago and that has been since.
reproduced in many different studies. So Interestingly, we have many reasons 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,
stem cell diseases, and even in responding patients. For example, correct there IM0 globin and that have a decrease in their blast counts, like here in there in the blue line, we can still detect cytogenetics abnormalities. And more Interestingly, we can still detect stem cells like LTC IC’s for example, that harbors marker of the minor dysplastic syndrome, and so that’s something that is important when it comes to the
way we’re considering treatment, not only for relapse, but on a more general basis from 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,
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, we can potentially use in this context. 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 that 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 Donaur Mycin and Sitara been that was approved two years ago three years ago now for acute myeloid leukemia arising from Miio 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 MIlo dysplastic syndrome. That’s a phase two study that we
developed with Prajwal Bodo at Yale as a multicenter IIT, and 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 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
synergistic based on their mode of action or based on in vitro studies.

We had several attempts at this over the last years.

An easy combination and logical combination was to add on the epigenetic targeted agent.

As such, as H. Dark inhibitor, then we treated 19 patient with vorinostat, which is one of the first in Class Age document or with, unfortunately, pretty limited outcome really
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 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 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.

00:46:56.520 --> 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 76% that from our standard is pretty pretty promising.

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.

00:47:17.630 --> 00:47:20.535 So statue and we will have more information,

00:47:20.535 --> 00:47:23.069 but that’s one of the Avenue that

00:47:23.070 --> 00:47:26.686
we are currently investigating. Stop. That’s. Pretty good,
that’s basically based on a combination of mode of action. 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 patient, 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 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 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.
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 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 patient
00:52:16.681 --> 00:52:19.375 in acute myeloid leukemia and maladies

00:52:19.375 --> 00:52:21.583 plastic syndrome that were already

00:52:21.583 --> 00:52:24.103 exposed to IDH inhibitor in the

00:52:24.110 --> 00:52:26.987 patient that are naive of IDH inhibitor.

00:52:26.990 --> 00:52:29.606 We have an early response assessments

00:52:29.606 --> 00:52:32.927 after one cycle and if we do not

00:52:32.927 --> 00:52:34.797 see any clear clinical benefit,

00:52:34.800 --> 00:52:36.850 this patient are usually discontinued.

00:52:36.850 --> 00:52:38.562 An transition classical IDH

00:52:38.562 --> 00:52:41.130 inhibitor for the patient that are

00:52:41.209 --> 00:52:44.197 responding to the patient that were

00:52:44.197 --> 00:52:46.189 previously exposed to accommodating.

00:52:46.190 --> 00:52:47.986 Agent and IDH numitor.

00:52:47.986 --> 00:52:50.680 We are reassessing response after three,
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 patienten 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 starting to work with winning Wong from the West Campus. On single cell sequencing for this. Specific samples an studies, as we definitely think that we
will have some clonal selection as potentially one of the mechanism of resistance in this context. So stay tuned. That’s a bit early to make any conclusion. We just have a few patients in a few months on treatment, but that’s a developing story. As I was saying earlier, one of the things that has also been mentioned as a mechanism of resistance, and I try to go fast on that. Is uh, even though logic escape of the matter. Dysplastic syndrome.
We have an over expression of PD,

One PD L1 and C A4 in.

Patient with hypomethylating agent

failure and that’s led to several

several studies I’m mentioning here.

Studies with basically ipis,

nivo or Pam bro.

I also need obviously to 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 email of idea 2012 plus nivolumab in Phase one pilot study for 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 where aggressive management for transplant 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,
NOTE Confidence: 0.83678097
00:57:33.260 --> 00:57:35.265 for example in Milo dysplastic syndrome is definitely different.
NOTE Confidence: 0.83678097
00:57:35.265 --> 00:57:36.869 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.
NOTE Confidence: 0.83678097
00:57:39.600 --> 00:57:41.766 That’s something that we need to work on and so.
NOTE Confidence: 0.83678097
00:57:44.520 --> 00:57:47.807 The best way we have to deal with this HTML file is ready to try to avoid it and optimize the frontline treatment.
NOTE Confidence: 0.83678097
00:58:00.258 and optimize the frontline treatment.
NOTE Confidence: 0.83678097
00:58:00.260 --> 00:58:02.330 We have lots of currently really exciting drugs in the pipeline.
NOTE Confidence: 0.83678097
00:58:04.350 --> 00:58:07.275 Lots of data that we presented at the Ash team.
NOTE Confidence: 0.83678097
00:58:07.275 --> 00:58:10.295 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 a 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 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.

Participate to this effort for sure.

The Yellow Cancer Center group alphabetically.

My mentor Stephanie for lot of collaboration.

Steve Gore.

Nicolai, Rory and armor for being such trooper an 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 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.