OK, good afternoon everyone it’s 12:00 PM on this beautiful Friday and today is the next session and our yield.

So as you can see on the agenda in the last few weeks, we covered multiple myeloma, lymphoid malignancies, myeloid malignancies, and pediatric leukemia and hematology.

And today we will be discussing classical or B9, but not so benign hematology.
So as usual, many abstracts are presented in about classical hematology in the ASH mythology meeting. However, due to time limitations the focus will be on the most prominent abstracts, and the ones that have the highest clinical relevance to practice on a day-to-day basis. The abstracts will be grouped in areas of clinical need and there are many other abstracts of course that are very good that we do not have the time to cover today. Important to note that these abstracts represent.
Often preliminary presentations and data that has not been yet completely vetted or peer reviewed or finalized. So we have to take that into consideration. As we discussed the data we like to thank the authors who shared their presentations with us and the recording of this session and the other sessions will be available. Over the next week or so, for those who cannot attend the live sessions and the CME credit will be available after filling up receive feedback on the seminars and how we can improve him going forward. So today it’s a pleasure to be joined
by my colleagues Sabrina Browning, who's our instructor in medicine and section of Hematology who will be covering bleeding and hemostasis. Sam Alexander Pienaar, associate professor of medicine. Who will be covering from bosses an antithrombotic therapy? Advances from ash and then our bright fellow George Joshua will finish their presentations, covering other important and relevant classical hematology topics. At the end we will have Professor of Medicine Doctor Robert Bona,
and our Associate Professor of Medicine, Doctor Alfred Lee, who will moderate your questions and also be available to help the speakers in answering. Any of the questions that are relevant to the abstracts presented, or any other abstracts from the meeting that are important. So it’s my pleasure to present our first speaker, doctor Sabrina Browning, who will discuss bleeding and hemostasis without so Sabrina. Feel free to share your screen. Thank you Doctor Zayden and welcome everyone. For those interested,
we’ve included QR codes throughout our presentation that will link you directly to the ASH abstracts. You can access these by using your smartphone camera.

I have no disclosures to report.

So this slide outlines the abstracts that I will cover today which span disorders of platelet number or function disorders of coagulation and fibrinolysis and von Willebrand disease and at the end I will briefly touch upon abstracts that were presented at ASH on the role of convalescent plasma therapy.
in the management of COVID-19 and provide an update on where we stand with this treatment currently.

So to begin, doctor Charlotte Bradbury from the University of Bristol in the United Kingdom presented a late breaking abstract on the flight trial, which is a multicenter randomized trial evaluating the addition of mycophenolate to standard of care. This study was developed due to the heterogeneous responses in ITP to corticosteroids in the management of patients with newly diagnosed immune thrombocytopenia.
first line steroids and concerns regarding their long term side effects. Evidence for mycophenolate or MF and treatment and beyond really comes only from Russia’s retrospective studies at this time. This study recruited adult patients with ITP and a platelet count of less than 30,000 who were requiring therapy. Subjects were then randomized to standard corticosteroids, which could be in the form of dexamethasone, pulsed, at 40 milligrams daily for four days, up to three cycles, or Prednisolone 1 milligram.
per kilogram daily,
NOTE Confidence: 0.8116819
followed by a taper or
NOTE Confidence: 0.8116819
corticosteroids plus MMF,
NOTE Confidence: 0.8116819
which was initially dosed at 500
NOTE Confidence: 0.8116819
twice daily and then
NOTE Confidence: 0.8116819
escalated to a Max dose of 1 gram
NOTE Confidence: 0.8116819
daily with a plan to taper and then
NOTE Confidence: 0.8116819
stop after six months of treatment.
NOTE Confidence: 0.8116819
The investigators from this
NOTE Confidence: 0.8116819
trial hypothesize that MF,
NOTE Confidence: 0.8116819
combined with steroids,
NOTE Confidence: 0.8116819
would be more effective than steroids alone,
NOTE Confidence: 0.8116819
and the primary outcome measured was time
NOTE Confidence: 0.8116819
from randomization to treatment failure,
NOTE Confidence: 0.8116819
defined as a platelet count
NOTE Confidence: 0.8116819
less than 30 and a clinical need
Secondary outcomes are outlined here and included bleeding events, side effects, and patient reported outcomes both at baseline and AT246 and 12 months as measured by validated questionnaires. 120 patients were included in this study, with 59 on the MF ARM and 61 patients receiving steroids alone. The median follow-up was 18 months. 52.4% of patients were male with a median age of 54, so it was noted that more than 1/4 of patients enrolled in the
study were over the age of 70.

The primary outcome of proportion of patients without treatment failure is illustrated in the Kaplan Meier curve.

Here on the left of the slide and favored the MF arm with an adjusted hazard ratio of 0.41.

Interesting Lee.

Similar responses were observed in the two groups at 2 weeks, despite the less refractoriness that was seen in the MF cohort and a statistically significant increase in plate in patients who reached a platelet count greater than 100 before they required in second line treatment.
There were no differences observed in bleeding events or hospitalizations, and there were comparable rates of treatment side effects in both groups. However, there were some aspects on quality of life questionnaires that were observed to be worse in the MF arm, including both physical function and fatigue scores. So to summarize this abstract, this is the first randomized control trial using MF to treat ITP, and it illustrated good overall efficacy and tolerability when added.
to first line corticosteroids,

including in a cohort of patients that had included elderly patients.

However, there were some negative affects on quality of life that were observed in the treatment arm and the investigator suggested that this regimen could be considered in some, but not necessarily all, patients with newly diagnosed ITP. The next abstract I'd like to share was presented by Doctor David Kuter from Massachusetts General Hospital and highlights the clinically active and the durable...
platelet response that were observed with the oral BTK inhibitor ibrutinib in patients with heavily pretreated ITP as illustrated in the figure here. On the left, ibrutinib is a reversible and selective inhibitor of BTK that aims to target the disease mechanisms leading to platelet destruction in ITP, though it’s without the effects on platelet aggregation that we often see. In the drug ibrutinib trial, this trial of Phase 1 two open label trial was a dose finding study and
that enrolled adult patients with relapsed or refractory ITP who had responded to at least one prior line of ITP therapy and had more platelet counts that were less than 30 at the time of study entry. Subjects could be on stable doses of concomitant corticosteroids and or thrombopoietin receptor agonist during this trial. The dose escalation phase of this study was previously reported at ASH with a minimum effective dose of 400 milligrams twice daily. The primary endpoint of this part of the study was achieving two or more
NOTE Confidence: 0.8653912
00:08:41.393 --> 00:08:43.113 consecutive platelet counts that
NOTE Confidence: 0.8653912
00:08:43.113 --> 00:08:45.398 were greater than 50,000 with an
NOTE Confidence: 0.8653912
00:08:45.398 --> 00:08:47.869 increase of more than 20,000 from the
NOTE Confidence: 0.8653912
00:08:47.869 --> 00:08:49.585 patients baseline without requiring
NOTE Confidence: 0.8653912
00:08:49.585 --> 00:08:51.730 any rescue or additional medications.
NOTE Confidence: 0.8653912
00:08:51.730 --> 00:08:54.050 The investigators also performed subgroup
NOTE Confidence: 0.8653912
00:08:54.050 --> 00:08:56.370 analysis to determine the impact
NOTE Confidence: 0.875766
00:08:56.435 --> 00:08:58.095 of certain prior treatments
NOTE Confidence: 0.875766
00:08:58.095 --> 00:08:59.755 on this primary endpoint.
NOTE Confidence: 0.875766
00:08:59.760 --> 00:09:01.972 A long term extension study was also
NOTE Confidence: 0.875766
00:09:01.972 --> 00:09:03.737 conducted to further assess safety
NOTE Confidence: 0.875766
00:09:03.737 --> 00:09:05.637 and durability of this medication,
NOTE Confidence: 0.875766
00:09:05.640 --> 00:09:07.390 and so this specific abstract
NOTE Confidence: 0.875766
00:09:07.390 --> 00:09:09.140 presented on 38 patients who
NOTE Confidence: 0.875766
00:09:09.201 --> 00:09:11.187 had received the dose of 400
NOTE Confidence: 0.875766
milligrams twice daily and the patients who entered the long term extension study at this same dose.

So patients in the 400 milligram twice daily cohort had a median duration of ITP of six years and had received a median of six prior lines of therapy. Their median age was 50, with a little more than half of patients being female. At the time of data cutoff, which was July of 2020, forty 2% of patients had achieved the primary endpoint. Furthermore, responses were relatively similar whether or not these patients had responded to prior therapy.
00:09:48.762 --> 00:09:50.338 including thrombopoietin receptor agonist, 
00:09:50.340 --> 00:09:51.525 rituximab, or fostamatinib, 
00:09:51.525 --> 00:09:53.895 and notably responses were quite rapid, 
00:09:53.900 --> 00:09:56.702 with 53% of patients achieving a 
00:09:56.702 --> 00:10:00.109 platelet count of more than 30 by day 8. 
00:10:00.110 --> 00:10:02.145 And responses were also 
00:10:02.145 --> 00:10:03.366 durable in nature. 
00:10:03.370 --> 00:10:05.730 A real rose alot nib was generally well 
00:10:05.730 --> 00:10:08.109 tolerated in all portions of the trial 
00:10:08.109 --> 00:10:09.839 with approximately half of patients 
00:10:09.900 --> 00:10:12.364 experiencing grade one or two side effects 
00:10:12.364 --> 00:10:14.428 that were transient and mostly GI. 
00:10:14.428 --> 00:10:15.100 In nature, 
00:10:15.100 --> 00:10:17.158 though there were no serious adverse 
00:10:17.158 --> 00:10:19.430 events or treatment related bleeding or 
00:10:19.430 --> 00:10:21.805
thrombotic complications during this study.

So, in conclusion,

reels reels of Bruton AB therapy at a dose of 400 milligrams twice daily achieved significant rapid and long lasting platelet responses in about a slightly under half a percent percentage of this patient population with heavily treated pretreated ITP, and this was observed irrespective of the response to prior lines of treatment rules. Ibrutinib was granted fast track designation by the FDA in October designation by the FDA in October and further clinical trials with this drug. That drug is current.
Currently on going.

In the plenary session,

Doctor Terry Gurne Shime are from the University of Washington School of Medicine,

presented the results of the American trial using tranexamic acid and thrombocytopenia or the a treat trial.

This study specifically examined the effects of tranexamic acid or txa prophylaxis on bleeding outcomes in individuals with hematologic malignancy undergoing treatment therapy.

And it was supported by understanding the high incidence of bleeding in this patient population,
even despite our evidence based use of platelet transfusions prophylactically and while anti fibrinolytic therapy has certainly been used with pain in patients with hematologic malignancy undergoing treatment evidence, evidence of its benefit has really been lacking. So the Atria trial was a multi center, double blinded, placebo controlled trial aimed to assess the safety and efficacy of prophylactic transit tranexamic acid. Which is seen in this schematic, here included on the left of the slide block slicing binding site on
plasminogen an inhibits and its activation, thus halting fibrinolysis. And the train exam IC acid was used as an adjunct to routine platelet transfusions. As was previously studied. Patients undergoing therapy for hematologic malignancy whom were expected to have platelet counts less than 10,000 for five or more days were eligible to be enrolled in the study and were randomized to receive either tranexamic acid at a dose of 1 gram Ivy or 1.3 grams opeo every eight hours or placebo with the start of the study drug after a
00:12:29.880 --> 00:12:32.229 platelet count had dropped below 30.
NOTE Confidence: 0.8092774
00:12:32.230 --> 00:12:33.990 Tranexamic acid or placebo was
NOTE Confidence: 0.8092774
00:12:33.990 --> 00:12:36.157 discontinued after 30 days or when
NOTE Confidence: 0.8092774
00:12:36.157 --> 00:12:38.233 platelet counts had re platelet count
NOTE Confidence: 0.8092774
00:12:38.233 --> 00:12:40.477 had recovered to more than 30,000
NOTE Confidence: 0.8092774
00:12:40.477 --> 00:12:42.382 and the trans transfusion thresholds
NOTE Confidence: 0.8092774
00:12:42.382 --> 00:12:44.614 used during the study where per
NOTE Confidence: 0.8092774
00:12:44.614 --> 00:12:46.810 standard of care the primary endpoint
NOTE Confidence: 0.8092774
00:12:46.876 --> 00:12:48.880 was the proportion of patients with
NOTE Confidence: 0.8092774
00:12:48.880 --> 00:12:51.417 WHO grade two or above bleeding with
NOTE Confidence: 0.8092774
00:12:51.417 --> 00:12:53.691 Grade 2 being moderate bleeding Grade
NOTE Confidence: 0.8092774
00:12:53.691 --> 00:12:55.538 3 being severe bleeding requiring
NOTE Confidence: 0.8092774
00:12:55.538 --> 00:12:57.740 transfusion of red blood cells or
NOTE Confidence: 0.8092774
00:12:57.806 --> 00:13:00.212 other intervention and grade for being
NOTE Confidence: 0.8092774
00:13:00.212 --> 00:13:02.559 life threatening or debilitating bleed bleed.
NOTE Confidence: 0.8092774
00:13:02.560 --> 00:13:04.144 Additional secondary and safety
endpoints are outlined on the slide and include rate of thrombosis, vino occlusive disease and mortality. There were 330 patients, a valuable in the study with 165 on each arm, and the two groups were well balanced by age, gender, and type of therapy. Only 9% of the patients actually completed 30 days on drug, with an average of 12 days on train exam. IC acid or placebo. And as you can see in the table here on the left, the primary outcome of proportion of WHL grade two or higher bleeding was
no different between the tranexamic acid and placebo, placebo arms, and this was also true irrespective of. The pre specified treatment subgroups that included allogeneic stencel stem cell transplant, autologous transplant, and chemotherapy alone. The time to 1st WH O2 or more two or higher bleeding or death was also remarkably similar, with the lines overlying each other in the graph, seen here on the right. Mean platelet transfusion mean days alive with WHO two or more bleeding an mean red blood cell
transfusion per thrombocytopenia.

Cdai were also not impacted by the use of tranexamic acid.

There was, however, a statistically significant increase in the overall thrombotic events on the tranexamic acid arm, though this primarily was made up of line occlusions with a trend that was actually fewer in non catheter thrombotic events in the treatment arm.

There was no increase in Vino occlusive, disease, or all cause mortality.
at either 30 or 20 days, and no deaths were observed as the result of thrombosis. So based on all of this, train exam IC acid administered prophylactically, in addition to routine platelet transfusion did not seem to increase, decrease the rate of WHL grade 2 plus or bleeding in patients who are severely thrombocytopenia as a result of treatment for their hematologic malignancy. It also did not seem to alter transfusion requirements and actually resulted in an increased rate
NOTE Confidence: 0.85934526
00:15:06.651 --> 00:15:08.659 of central line occlusion events,
NOTE Confidence: 0.85934526
00:15:08.660 --> 00:15:10.400 and so the authors emphasize,
NOTE Confidence: 0.85934526
00:15:10.400 --> 00:15:11.372 despite these findings,
NOTE Confidence: 0.85934526
00:15:11.372 --> 00:15:12.992 that the utility of tranexamic
NOTE Confidence: 0.85934526
00:15:12.992 --> 00:15:14.947 acid in other settings with
NOTE Confidence: 0.85934526
00:15:14.947 --> 00:15:16.619 thrombocytopenia cannot be excluded.
NOTE Confidence: 0.85934526
00:15:16.620 --> 00:15:18.068 By this study alone.
NOTE Confidence: 0.8342403
00:15:20.300 --> 00:15:23.023 So moving on to an abstract presented
NOTE Confidence: 0.8342403
00:15:23.023 --> 00:15:25.433 by Doctor Steven Pipe from the
NOTE Confidence: 0.8342403
00:15:25.433 --> 00:15:28.156 University of Michigan on the long term,
NOTE Confidence: 0.8342403
00:15:28.160 --> 00:15:28.944 durability, safety,
NOTE Confidence: 0.8342403
00:15:28.944 --> 00:15:31.296 and efficacy of fat userin prophylaxis,
NOTE Confidence: 0.8342403
00:15:31.300 --> 00:15:32.828 prophylaxis in patients with
NOTE Confidence: 0.8342403
00:15:32.828 --> 00:15:35.592 hemophilia A or B with or without
NOTE Confidence: 0.8342403
00:15:35.592 --> 00:15:38.378 inhibitors as seen on the slide here.
NOTE Confidence: 0.8342403
So for twos are in is a small interfering RNA that as described in the schematic, blocks the production of anti thrombin and as a result increases or improves thrombin generation and.
Remote team of stasis and individuals with hemophilia of phase one. Study of monthly subcutaneous photographer to Sarandos ING was previously reported in the New England Journal of Medicine in 2017 and demonstrated that this drug was well tolerated and also reliably lowered antithrombin in a dose dependent manner resulting in decreased bleeding frequency.
NOTE Confidence: 0.8342403
00:16:13.582 --> 00:16:15.154 with moderate severe haemophilia
NOTE Confidence: 0.8342403
00:16:15.154 --> 00:16:17.374 moderate or severe hemophilia A or
NOTE Confidence: 0.8342403
00:16:17.374 --> 00:16:19.924 B who had tolerated for chooser in
NOTE Confidence: 0.8342403
00:16:19.924 --> 00:16:22.368 in the Phase one study were eligible
NOTE Confidence: 0.8342403
00:16:22.368 --> 00:16:24.258 to continue into this phase.
NOTE Confidence: 0.8342403
00:16:24.260 --> 00:16:24.966 A2 cohort,
NOTE Confidence: 0.8342403
00:16:24.966 --> 00:16:27.084 which was an open label extension
NOTE Confidence: 0.8342403
00:16:27.084 --> 00:16:29.118 portion and they receive photos,
NOTE Confidence: 0.8342403
00:16:29.120 --> 00:16:31.703 are in at a dose of 50 or 80
NOTE Confidence: 0.8342403
00:16:31.703 --> 00:16:33.610 milligrams subcutaneous monthly.
NOTE Confidence: 0.8342403
00:16:33.610 --> 00:16:35.102 The primary endpoints were
NOTE Confidence: 0.8342403
00:16:35.102 --> 00:16:36.594 safety and adverse events,
NOTE Confidence: 0.8342403
00:16:36.600 --> 00:16:38.796 and there were key secondary endpoints
NOTE Confidence: 0.8342403
00:16:38.796 --> 00:16:40.720 that included a calculated median.
NOTE Confidence: 0.8342403
00:16:40.720 --> 00:16:42.800 Analyze the annualized bleed rate
NOTE Confidence: 0.8342403
Pharmacokinetics in quality of life in the patient cohort.

34 patients were included in this portion of the study with a median age of 35.4 years. And this included 27 individuals with hemophilia A, 7 individuals with hemophilia B and 15 out of the group had inhibitors with 19 individuals. Patients received a median of 3.1 years of a tutor inducing as of the data cut off, which was September of 2020 and 12 individuals were on the 50 milligram dose, 22 being on the 80 milligram dose. But users and were noted in this study to decrease antithrombin levels quickly.
NOTE Confidence: 0.9159124
00:17:24.442 --> 00:17:26.854 with sustained levels that remained at
NOTE Confidence: 0.9159124
00:17:26.854 --> 00:17:29.096 or below 20% in individuals who remained
NOTE Confidence: 0.9159124
00:17:29.096 --> 00:17:31.909 on the drug and so this was confirmed.
NOTE Confidence: 0.9159124
00:17:31.910 --> 00:17:34.724 The findings of the Phase one portion
NOTE Confidence: 0.9159124
00:17:34.724 --> 00:17:35.930 of the study.
NOTE Confidence: 0.9159124
00:17:35.930 --> 00:17:37.910 Immediate analyzed bleed rate was
NOTE Confidence: 0.9159124
00:17:37.910 --> 00:17:39.890 calculated for this cohort after
NOTE Confidence: 0.9159124
00:17:39.954 --> 00:17:41.634 achieving antithrombin knockdown an
NOTE Confidence: 0.9159124
00:17:41.634 --> 00:17:44.154 was zero for treated bleeds during
NOTE Confidence: 0.9159124
00:17:44.219 --> 00:17:45.479 the follow up period.
NOTE Confidence: 0.9159124
00:17:45.480 --> 00:17:48.091 The figure included here on this slide
NOTE Confidence: 0.9159124
00:17:48.091 --> 00:17:51.124 is a result from a post hoc analysis
NOTE Confidence: 0.9159124
00:17:51.124 --> 00:17:53.929 of 258 treated bleeds in 15 subjects,
NOTE Confidence: 0.9159124
00:17:53.930 --> 00:17:56.228 with each separate graph showing data
NOTE Confidence: 0.9159124
00:17:56.228 --> 00:17:58.090 on bleed causality, bleed location,
NOTE Confidence: 0.9159124
an bleeds severity and from left to right in patients with hemophilia. A patients with an inhibitor hemophilia. A patients without an inhibitor and hemophilia B patients with an inhibitor. So while this is a bit of a busy figure, the takeaway is really that breakthrough bleeds occurred mostly in the joints or mild in nature, and tended to be more spontaneous in those individuals with inhibitors. These breakthrough bleeds were managed with factor replacement or bypassing agent per the study management guidelines with a focus on reduced doses to try.
and minimize the potential thrombotic risk. However, in the safety analysis of this study, 97% of patients experienced at least one adverse event with 38% having a serious adverse event which included the events such as an arterial thrombosis in one patient and a death that actually occurred in 2017 as a result of a cerebral vein thrombosis. So in October of 2020, Sanofi voluntarily paused enrollment, inducing with Catoosa, to further investigate these adverse events and the rate of thrombotic
events in the clinical trials,

these trials have now resumed with reduced dosing of Fatou Suran,

initially at 50 milligrams every other month in order to target and antithrombin level of 15 to 35%, which was found to be less associated with the thrombotic events.

So in summary, for chooser and is an investigational small interfering RNA therapeutic and it has the potential use as a prophylactic treatment in patients with hemophilia A or B with or without inhibitors in order to try and reestablish hemostatic balance.
However, further evaluation of its safety is imperative, and phase three trials of this drug are now ongoing.

And so I'll switch gears a bit with this abstract that was presented by Doctor Brooks Sadler from Washington University School of Medicine on Genotype analysis of adolescents with low. One von Willebrand factor, she noted that heavy menstrual bleeding occurs in about 1/3 of adolescents and accounts for 2/3 of patients.
who require hysterectomy and the prevalence of bleeding disorders, including von Willebrand disease in this cohort is higher than the general population. However, no one has looked or evaluated at other genetic hemostatic risk factors that may play a role here. So in this study, 86 adolescent patients who met criteria for heavy menstrual bleeding and had von Willebrand activity between 30 and 50% were enrolled in the study and underwent whole exome sequencing that was compared to 600 unrelated in-house controls. The sequencing interesting Lee revealed...
00:20:43.625 --> 00:20:46.767 in excess of rare stop gain and stop

00:20:46.767 --> 00:20:48.692 loss mutations in genes associated

00:20:48.692 --> 00:20:50.662 with bleeding or haematologic diseases

00:20:50.662 --> 00:20:52.936 as outlined in the slide here.

00:20:52.940 --> 00:20:55.677 There was also an excess of rare

00:20:55.677 --> 00:20:57.317 pathogenic variants that were

00:20:57.317 --> 00:20:59.663 observed in jeans that cause anemia

00:20:59.663 --> 00:21:02.408 or cause disease with anemia as a

00:21:02.408 --> 00:21:04.278 major symptoms of major symptom.

00:21:04.280 --> 00:21:07.017 This included variance in Adams TS 13,

00:21:07.020 --> 00:21:07.435 Fink,

00:21:07.435 --> 00:21:10.340 CA and G6PD and the other jeans

00:21:10.340 --> 00:21:12.350 that are listed here.

00:21:12.350 --> 00:21:14.360 There was analysis Additionally for

00:21:14.360 --> 00:21:15.968 common single nucleotide polymorphism's

NOTE Confidence: 0.85483044

38
or snips that were that identified, -

3 common snips infirm too, -

and this past genome wide significance as -

This was the first whole exome sequencing study in patients with heavy menstrual bleeding and suggest there may be some Association in this group.

With both rare and common variants in hemostasis and anemia, genes that warrant further validation in larger studies.
And Lastly, I wanted to touch upon the abstracts that presented data on the use of kobid 19 convalescent plasma, which is collected from individuals who have recovered from infection, is a therapeutic modality that’s actually been used for over a century with the aim to transfer virus neutralizing antibodies to patients who have active infection. However, data on its use in COVID-19 has been limited and quite mixed. And so I’ll highlight here again, the five abstracts that presented...
So in our institutional experience with 105 patients with severe or life threatening COVID-19 who were transfused one unit of convalescent plasma through the national Expanded Access program, we saw that 42.9% of patients had improvement in their WHO ordinal scale, which is a score comprised of functional status, level of care, and oxygen supplement. Interestingly, we observed a correlation between D dimer level more than five at 2448 and 72 hours after transfusion.
Ibrahim and colleagues shared data on 17 patients, six of whom were being treated for a hematologic malignancy, and these individuals were transfused one to two units of COVID-19 convalescent plasma that had confirmed positive antibody titer, and they also observed a decrease in the mean WHO ordinal score by two points at the time of discharge of a multicenter phase two trial presented by Doctor Al Hashmi compared 178 COVID-19 convalescent plasma recipients to 391 matched controls.
Is a significant reduction in 30-day mortality in the treatment arm. In this study, though Interestingly they observed that the hospital and ICU length of stay as well as duration of intubation was longer and that was actually longer in the convalescent Plasma Group. Another phase, two matched case control study looked at a smaller number of hospitalized COVID-19 patients who received 2 units of transfusion and there was a trend in this group towards improved survival, though this was not statistically significant,
NOTE Confidence: 0.8524265
00:23:59.800 --> 00:24:02.128 it was noted in this study that the
NOTE Confidence: 0.8524265
00:24:02.128 --> 00:24:04.238 donor plasma was quite heterogeneous,
NOTE Confidence: 0.8524265
00:24:04.240 --> 00:24:05.950 with an increase in antibody
NOTE Confidence: 0.8524265
00:24:05.950 --> 00:24:07.318 activity observed in some,
NOTE Confidence: 0.8524265
00:24:07.320 --> 00:24:08.346 but not all,
NOTE Confidence: 0.8524265
00:24:08.346 --> 00:24:10.740 of the patients included in the study,
NOTE Confidence: 0.8524265
00:24:10.740 --> 00:24:11.721 and interesting Lee,
NOTE Confidence: 0.8524265
00:24:11.721 --> 00:24:14.010 those who had undergone anti CD 20
NOTE Confidence: 0.8524265
00:24:14.069 --> 00:24:16.589 treatment in the last year had a demo
NOTE Confidence: 0.8524265
00:24:16.589 --> 00:24:18.350 demonstrated an impaired response.
NOTE Confidence: 0.8524265
00:24:18.350 --> 00:24:20.200 In regards to antibody activity
NOTE Confidence: 0.8524265
00:24:20.200 --> 00:24:22.754 and Lastly a multi center Phase 1
NOTE Confidence: 0.8524265
00:24:22.754 --> 00:24:24.980 two trial of 70 patients who had
NOTE Confidence: 0.8524265
00:24:24.980 --> 00:24:26.237 received COVID-19 convalescent
NOTE Confidence: 0.8524265
00:24:26.237 --> 00:24:28.847 plasma found that 30 day overall
NOTE Confidence: 0.8524265
survival was improved in those patients who had severe acute respiratory distress syndrome as a part of their COVID-19 infection, though there was an adverse event rate of 3.65% and there was one patient who was observed to have transfusion, associated circulatory overload and a venous thromboembolic event. So the QR code included here on this slide links to a section of our available evidence on COVID-19. Convalescent Plasma provides a summary.
the data presented today, information on its effectiveness has been somewhat mixed and we’re really awaiting data from larger randomized control trials. There are some themes that have emerged, and they include the importance of both antibody titer, but more notably neutralizing function in the donor COVID-19 convalescent plasma. As well as the benefit of providing this treatment earlier in disease course, there has been concern raised by our group and others regarding whether COVID-19 convalescent plasma may
00:25:35.756 --> 00:25:37.544 actually potentiates the already
NOTE Confidence: 0.8445773
00:25:37.607 --> 00:25:39.008 increased thrombotic risk.
NOTE Confidence: 0.8445773
00:25:39.010 --> 00:25:41.514 An end to Ophelia Opathy that we now
NOTE Confidence: 0.8445773
00:25:41.514 --> 00:25:44.041 know occurs with COVID-19 and further
NOTE Confidence: 0.8445773
00:25:44.041 --> 00:25:46.326 investigation into this is warranted.
NOTE Confidence: 0.8445773
00:25:46.330 --> 00:25:48.610 So taking this all into account
NOTE Confidence: 0.8445773
00:25:48.610 --> 00:25:50.949 as of just actually last week,
NOTE Confidence: 0.8445773
00:25:50.950 --> 00:25:53.194 the FDA has updated their emergency
NOTE Confidence: 0.8445773
00:25:53.194 --> 00:25:54.690 use authorization for COVID-19
NOTE Confidence: 0.8445773
00:25:54.747 --> 00:25:55.879 convalescent plasma.
NOTE Confidence: 0.8445773
00:25:55.880 --> 00:25:57.819 Really limiting it to use of high
NOTE Confidence: 0.8445773
00:25:57.819 --> 00:25:59.067 titer plasma for hospitalized
NOTE Confidence: 0.8445773
00:25:59.067 --> 00:26:01.197 patients that are early in their
NOTE Confidence: 0.8445773
00:26:01.197 --> 00:26:03.392 disease course and those who may
NOTE Confidence: 0.8445773
00:26:03.392 --> 00:26:04.820 have impaired humoral immunity.
NOTE Confidence: 0.8751028
00:26:07.060 --> 00:26:10.000 Thank you and I’ll turn it over to Alex now.
Thank you Sabrina. I'm just.

OK, hopefully everybody can see the screen.

Alright, wanted to say thank you to decide and Megadeth for putting all this together and everybody who's contributed else.

Um, exciting, serious, and learning a lot.

So I am going to see if I can move the slides. Yes.

I'm just going to touch upon a few guests. 3.

The abstracts that that and identified, and specifically about cancer, associated venous thromboembolism and one of the new exciting agent for reversal of anticoagulation.

And then I'm going to touch
00:27:21.980 --> 00:27:25.180 base and our own work.


00:27:27.250 --> 00:27:31.780 How it actually. Informed us about

00:27:31.780 --> 00:27:35.060 in conditions beyond COVID-19.

00:27:35.060 --> 00:27:37.830 No disclosures on my end.

00:27:37.830 --> 00:27:39.267 Um, so the.

00:27:39.267 --> 00:27:42.141 One of the first highlight the

00:27:42.141 --> 00:27:44.912 this abstract about machine

00:27:44.912 --> 00:27:48.547 learning for prediction of cancer.

00:27:48.550 --> 00:27:49.578 Social verbalism,

00:27:49.578 --> 00:27:52.662 especially in the setting of new

00:27:52.662 --> 00:27:54.805 guidelines that ash guidelines

00:27:54.805 --> 00:27:57.375 that have been just released

00:27:57.375 --> 00:27:59.550 about cancer regarding cancer.

00:27:59.550 --> 00:28:01.236 Associated venous thromboembolism

00:28:01.236 --> 00:28:05.777 just the other day and as you all
NOTE Confidence: 0.6899577
00:28:05.777 --> 00:28:08.879 know we there are several clinical
NOTE Confidence: 0.6899577
00:28:08.879 --> 00:28:12.129 prediction rules of which comma score.
NOTE Confidence: 0.6899577
00:28:12.130 --> 00:28:15.406 Is most validated and had been.
NOTE Confidence: 0.6899577
00:28:15.410 --> 00:28:21.218 Used to stratify the risk in multiple trials,
NOTE Confidence: 0.6899577
00:28:21.220 --> 00:28:25.000 including most recently a PERT and
NOTE Confidence: 0.6899577
00:28:25.000 --> 00:28:28.499 Cassini RCT S42 Deluxe prophylactic
NOTE Confidence: 0.6899577
00:28:28.499 --> 00:28:32.829 regimen versus placebo and recall.
NOTE Confidence: 0.6899577
00:28:32.830 --> 00:28:37.345 It’s pretty simple score to
NOTE Confidence: 0.6899577
00:28:37.345 --> 00:28:40.957 to use the questions.
NOTE Confidence: 0.6899577
00:28:40.960 --> 00:28:43.634 We have been raised over the over
NOTE Confidence: 0.6899577
00:28:43.634 --> 00:28:45.960 over the years is exactly where
NOTE Confidence: 0.6899577
00:28:45.960 --> 00:28:48.522 the draw the line in terms of
NOTE Confidence: 0.6899577
00:28:48.606 --> 00:28:52.044 prophylaxis versus which group to sort
NOTE Confidence: 0.6899577
00:28:52.044 --> 00:28:54.336 of start prophylactic production,
NOTE Confidence: 0.6899577
00:28:54.340 --> 00:28:55.678 if at all.
NOTE Confidence: 0.6899577
And Furthermore, since Corona score as anybody know, several other scores have been released that had also been addressing certain features that had not been including current score. But unfortunately all of them have been. Not so useful in terms of prediction because their predicted power was not was in moderate mild to moderate sort of territory with statistics between .6 and .7. So for Corona score itself, there’s a three categories so long to medium, high and specifically in high in the original.
00:29:41.490 --> 00:29:44.778 An original paper by Doctor Corona.

00:29:44.780 --> 00:29:49.172 We know that the rate of DTE was about 7% in high risk cohort,

00:29:49.172 --> 00:29:56.713 so the authors of this app start from Libor Sloan, Kettering, US Sameta and.

00:29:56.713 --> 00:30:02.720 Microsoft Group they sought to use to utilize the machine learning algorithms to inform about the which features actually would be more productive in there for create a score or update the current score that potentially could increase its predictive power.

00:30:02.807 --> 00:30:05.711 to to utilize the machine learning

00:30:05.711 --> 00:30:08.701 to use known predictors.

00:30:08.701 --> 00:30:11.121 features actually would be more productive in there for create a score or update the current score that potentially could increase its predictive power.

00:30:11.121 --> 00:30:13.765 So they positive that they would use known predictors.
00:30:26.680 --> 00:30:28.364 It from Corona score.
NOTE Confidence: 0.6899577
00:30:28.364 --> 00:30:30.469 They would utilize too much
NOTE Confidence: 0.6899577
00:30:30.469 --> 00:30:32.809 genomic information that they they
NOTE Confidence: 0.6899577
00:30:32.809 --> 00:30:35.563 collect it in their preferred their
NOTE Confidence: 0.6899577
00:30:35.637 --> 00:30:38.433 profiling assay with 341 uncle gene
NOTE Confidence: 0.6899577
00:30:38.433 --> 00:30:40.297 and tumor suppressor genes.
NOTE Confidence: 0.6899577
00:30:40.300 --> 00:30:40.897 Overall,
NOTE Confidence: 0.6899577
00:30:40.897 --> 00:30:45.076 they had a significant number of patients
NOTE Confidence: 0.6899577
00:30:45.076 --> 00:30:49.559 at 12,000 out of those they had about 850.
NOTE Confidence: 0.6899577
00:30:49.560 --> 00:30:52.152 It’s something about like events in
NOTE Confidence: 0.6899577
00:30:52.152 --> 00:30:55.679 the span of six months from from
NOTE Confidence: 0.6899577
00:30:55.679 --> 00:30:57.955 the diagnosis from enrollment,
NOTE Confidence: 0.6899577
00:30:57.960 --> 00:31:00.430 and most frequent cancer along
NOTE Confidence: 0.6899577
00:31:00.430 --> 00:31:01.418 Bryson colorectal.
NOTE Confidence: 0.6899577
00:31:01.420 --> 00:31:04.384 They did not include upper extremity
NOTE Confidence: 0.6899577
00:31:04.384 --> 00:31:06.360 DVT’s and their collected.
This is amazing that they collected all these events from clinic review of clinical notes, radiology reports and text search, which itself is very valiant effort knowing. From now, from my own experience doing similar work. So as far as the predictors that they put that they use in the model, which was not really clear how they selected it, but it seemed like it was some sort of manual selection. Not unbiased informed selection, at least based on their abstract and presentation.
So the tumor type status of metastases, age, cytotoxic chemotherapy time since cancer diagnosis, tumor sampling, and they included interesting without the blood counts. In the prior three months. Indices of calculation be my end. Of course. Those somatic genetic alterations on the jeans in tumor suppression genes, of which they include 56. And so when they put it all together and they used this fancy math, the random survival forest basically to create a model to fit the model using all of these. Various sets of permutations of the features,
the predictors and what they come up with. It came up with basically that if you include all of it, that gives usage statistics of .7 is just the kind of worry and people here. If it’s insisted 6.5 is a coin toss, so basically it doesn’t predict anything and see statistics of one. It’s the perfect sensitivity, specificity of 5%, of course is unreachable. So somewhere in between that, the higher the better. But .7 ISM is it. Legitimate number, and as I would like to remind everybody,
the original credit score
NOTE Confidence: 0.750427
system tistic was also .7.
NOTE Confidence: 0.750427
They also then separated their
population into five groups,
although how they get it not
clearly was outlined as well,
and it’s five risk groups based on the.
Incidence of VTE I presume,
clearly was outlined as well,
and it’s five risk groups based on the.
Per their validation metric that was
validated, model was performed well.
and so then they validated this with
the model in the said that that is.
Per their validation metric that was
validated, model was performed well.
With, Interestingly enough,
when they looked at which
predictors had been most predictive
of the venous thromboembolism,
they found that it’s a cancer type came,
whether patient received chemotherapy,
platelet count.
PT White count and so on was interesting.
This is out of these features.
Where this is not a selection,
so these features were determined.
The importance of these features was
determined in sort of post hoc.
These are not the features that
were selected to go into the model.
That’s it, that’s a key issue,
because in my opinion, because.
If the if you if the features
are included in a biased way,
the prediction of course would potentially suffer as well. And so out of all the genes that they pulled. As you can see this STK 11 was found to be significant and only one of them based on value of false detection rate. So every other one gene was not considered significant. And as people probably know, STK 11 is actually tumor suppressor gene out of all possible jeans. So question on my end that I sort of would like to one of wanted to clarify was unclear how initial features were selected, and again that’s important because the
NOTE Confidence: 0.78821117
00:35:41.722 --> 00:35:45.172 biased it will be by a set of features
NOTE Confidence: 0.78821117
00:35:45.172 --> 00:35:47.511 if it manually manually selected and
NOTE Confidence: 0.78821117
00:35:47.511 --> 00:35:50.115 similar to other clinical scoring tools.
NOTE Confidence: 0.78821117
00:35:50.120 --> 00:35:52.538 So there are some robust methods
NOTE Confidence: 0.78821117
00:35:52.538 --> 00:35:54.630 exist that feature feature selection
NOTE Confidence: 0.78821117
00:35:54.630 --> 00:35:57.048 algorithm that you know existed prior
NOTE Confidence: 0.78821117
00:35:57.048 --> 00:36:00.179 that can be used to to select features
NOTE Confidence: 0.78821117
00:36:00.179 --> 00:36:02.420 prior to including into the model.
NOTE Confidence: 0.78821117
00:36:02.420 --> 00:36:03.980 That would be very,
NOTE Confidence: 0.78821117
00:36:03.980 --> 00:36:05.420 very helpful in China.
NOTE Confidence: 0.79679555
00:36:09.630 --> 00:36:11.534 Something something like this.
NOTE Confidence: 0.79679555
00:36:11.534 --> 00:36:14.889 We were actually thinking of doing the
NOTE Confidence: 0.79679555
00:36:14.889 --> 00:36:16.979 VA and another interesting component
NOTE Confidence: 0.79679555
00:36:16.979 --> 00:36:20.001 was prior vtu is not included although
NOTE Confidence: 0.79679555
00:36:20.001 --> 00:36:22.976 has it has a racial quoted somewhere
NOTE Confidence: 0.79679555

60
in between two to three which is not insignificant risk factor and of course. Current score is not the dynamic score and would be interested to know how variability of the features, specifically of CBC features assessed. So overall it’s I think it’s important work and I think it’s interesting how the field of all because again, even the guidelines have been released, their sort of, they still leave a lot of uncertainty into who which group needs to be anticoagulated versus whether it’s intermediate group versus high Group. Um patients for should be inside quite late.
It’s still not clear. I think uncertainties still exist, and so the better we have, the better method we have in terms of determining which features are important, I think that’s going to be very helpful. Alright, so moving on are also an interesting abstract about than you. A reversal agent for anticoagulation. This is really interesting. Abstract the work has been going on for quite awhile and I found references going quite badly. Even just doesn’t 14 but essentially
pseudoprime tag is a small molecule that was initially designed through very rational design to reversibly bind to fractionated heparin low molecular weight heparin through noncovalent charge charge interaction. It was interesting that they unexpectedly found that it also binds the DOAX, which prevents their Association with factor 10 factor to rain, but it doesn’t bind to a lot of things at a lot of drugs. It doesn’t bind to albumin and doesn’t bind to actual factors, and so they say uh-huh.
Let’s try to reverse. Let’s try to use their parents like to reverse do act like apixaban oral molecular weight heparin so they. They’ve done that in animals and in humans. So here you can see that for instance on the left. After the silicone flag was administered, there was a very rapid. Reversal a curd that actually stayed. Plateaued for a number of hours and then on the right side the same
idea with low molecular weights
00:39:17.746 in same sort of data that,
00:39:22.118 with different doses of Sopron tags.
00:39:24.640 The universal was fairly complete.
00:39:26.644 Below 10% of baseline.
00:39:29.749 to determine this is a whole
00:39:32.725 blood clotting time,
00:39:34.220 and that’s actually important,
00:39:37.240 because apparently I cannot activity
00:39:39.760 of Sharon Cycle rather reversal.
00:39:44.600 Enter calculation cannot be determined
00:39:46.900 using regular typical methods.
00:39:48.740 For instance using PT PTT
00:39:51.470 because your parent act would be
00:39:54.655 in in the in the tube,
00:39:57.480 --> 00:40:00.480 in the inner tube of blood.

00:40:00.480 --> 00:40:02.900 It would be pulled competitively

00:40:02.900 --> 00:40:04.836 inhibited by like say,

00:40:04.840 --> 00:40:07.255 citrate or ETA that already

00:40:07.255 --> 00:40:09.187 present in the tube,

00:40:09.190 --> 00:40:11.605 so therefore they used whole

00:40:11.605 --> 00:40:13.054 blood clotting time.

00:40:13.060 --> 00:40:16.276 So now the abstract itself actually

00:40:16.276 --> 00:40:19.391 presents the two studies to phase

00:40:19.391 --> 00:40:21.581 two will see what controlled

00:40:21.581 --> 00:40:24.357 RCT one for Apixaban and the

00:40:24.357 --> 00:40:27.099 other one for rear axle band,

00:40:27.100 --> 00:40:30.289 where they actually.

00:40:30.290 --> 00:40:33.465 Looked at reversal Cedar parents

00:40:33.465 --> 00:40:36.640 like versus placebo and it’s

00:40:36.640 --> 00:40:39.840
very simple design in both arms.

Both studies.

Essentially they used doac to reach a steady state and then they gave patients Sera parent tag on different doses and contract the whole blood. Including time and again because the other parameters cannot be used. And in point was that WBC T should be below 10%, and so how fast that actually happens. And So what they showed again, that in both cases for the Pixel banner over oxygen that indeed within hours within actually minutes the for in
NOTE Confidence: 0.76944727
00:41:29.615 --> 00:41:32.957 different doses of shared parent tag,
NOTE Confidence: 0.76944727
00:41:32.960 --> 00:41:36.640 the reversal was rather.
NOTE Confidence: 0.76944727
00:41:36.640 --> 00:41:38.071 Especially in this,
NOTE Confidence: 0.76944727
00:41:38.071 --> 00:41:41.410 in higher doses like syntax 60 milligrams,
NOTE Confidence: 0.76944727
00:41:41.410 --> 00:41:45.674 220 milligrams in takes a band and higher
NOTE Confidence: 0.76944727
00:41:45.674 --> 00:41:49.630 doses in rivaroxaban group as well.
NOTE Confidence: 0.76944727
00:41:49.630 --> 00:41:54.265 Then they also looked at how fast in again,
NOTE Confidence: 0.76944727
00:41:54.270 --> 00:41:56.840 how long the reversal remained.
NOTE Confidence: 0.76944727
00:41:56.840 --> 00:41:57.870 And again,
NOTE Confidence: 0.76944727
00:41:57.870 --> 00:42:00.445 in both groups fix again,
NOTE Confidence: 0.76944727
00:42:00.450 --> 00:42:03.540 but were actually in the high
NOTE Confidence: 0.76944727
00:42:03.540 --> 00:42:05.600 dose single parent tag.
NOTE Confidence: 0.76944727
00:42:05.600 --> 00:42:09.720 The highest dose children tag in each group.
NOTE Confidence: 0.76944727
00:42:09.720 --> 00:42:12.225 River traversal was rather fast
NOTE Confidence: 0.76944727
00:42:12.225 --> 00:42:14.730 within within 660 minutes in
NOTE Confidence: 0.76944727

68
apixaban 100% patients have been reversed to the target. Of less than 10% of baseline for a whole bottle of whole blood clotting time and in Russia ban even faster in 30 minutes. So it’s an interesting concept is interesting new molecule which product which is undergoing studies like phase two and probably would be. Can soon enter phase three with a very exciting profile. There’s no prothrombotic signal, no evidence to promote it signaled they actually looked at the D dimer and. Uh, and that was not affected.
There's potential.
The interesting question that could be raised is whether magnesium and calcium in vivo could have any effect on pulling Ramtek out of the setup. Interaction with anticoagulation agents is possible if necessary, and 24-hour reversal can be established without any additional cost. Anticoagulation agents can be stored and reestablished if necessary without really affecting the issue.
and I’m sure George some point will do the cost analysis.

I hope if that comes to that and then with that I’ll move to.

To our final discussion of the work that we sort of presented at ASH.

That in form has been informing us beyond COVID-19,

which is quite interesting discussion.

So what we wanted to.

Look at is a weather items test 13.

Another imbalance of atoms TS 13 an Fonville burn factor could potentially serve as a marker of uniform doses in patients with COVID-19,

that was our initial goal,
so we last year we right in the beginning of pandemic we sort of have this lack of having number of.

Great researchers working, collaborating with George Washago shoe and Enchong after deadly and math mileage.

And we.

Show that one from building factor, of course.

It’s been shown since then many times is quite elevated in patients with coded 19, many times is quite elevated in patients with critical disease.

We also know from other studies
from studies so far not related to coordinating at all, that Adams TS13 deficiency.

13 is reduced in inflammatory states like cancer stroke and sepsis. Interestingly enough, in animal models, Adams, tutti and efficiency increases. Release of from building factor from from platelets. It increases increases adhesion to white. Neutrophils, white count white cells to the civilian and enhances neutrophil extravasation.

So what we then looked we going back to the to the cohort to our data
and we will look at what kind of relationship exists between Adams test and villain factor antigen activity. We found that indeed. In critical disease in patients, it’s indeed lower. The balance is such that this ratio is lower. We also showed earlier this year that there’s several markers of neutrophil activation that have been associated with ICU status, and we collaborate with this with adjacency Cheyenne David Friend. **** and what we can infer that
we show that at the absolute neutrophil count and image resized to neutrophils have been associated and could discriminate mortality and we used our Dom Kodiaks database. For that so then when we went to Adams just watching from Wilburton ratio, we also showed that that he had actually inversely related to neutrophil and initial to lymphocyte ratio, and Furthermore we when we looked at whether this disbalance also associated with the the neutrophil markers markers of neutrophil activation is GF resistant Lipo Callanan I’ll eight that indeed we found that.
All those markers were associated with worsening. Reducing the rate reduces the ratio for Adams Tester team to fund building factor, which again could indicate the potential prothrombotic process. Furthermore, we also looked at the same exact idea about. L Association with the ratio with Taiwan with. Fabulous inhibitor and again the same situation with where Adams just looking for the ratio is lower. So overall we show that lower so Adam Sistine Info Bill from building.
factor Disbalance exist.

So shaded with inhibitor for lysis, markers of neutrophil activation and there are four its potential email somebody in uniform biotic market foreign botic complication. What’s really interesting now is that what we do now is actually we’re looking specifically at people at patients with COVID-19 and without coordinating but who had actual thrombosis. So now we actually will be able to Tying this with this ratio with thrombosis itself, and of course going beyond COVID-19, all of it applies.
This platform can be scaled up.

This idea can be scaled up to basically any uniform body disorder, and also synthetic malignancies, which we would like to explore as well and with that will yield the floor.

Thank you so much, Alex and For the last part of the talk. I am going to talk about other topics in classical mythology. Good afternoon everybody. My name is George Joshua and one of the senior fellows in the Yale Hematology Oncology Fellowship program. And it is a pleasure to
be talking to you today.
I have no disclosures.
There are four apps we’re going to cover and I will speak through this,
so we finish on time and we’re going to talk about gene editing.
And we’re going to talk about complement system performance,
health outcomes, research.
And a little bit of coping.
And lastly.
First abstract #4 entitled CRISPR CAS 9 gene editing for sickle cell disease and beta thalassemia by doctors.
Frangou and colleagues.
Miss was a plenary talk and
also simultaneously published in human Journal Medicine.
For context to the reason why the study is important.
Football.
Emma.
Valve should have.
What is speed? Your line is.
Is script more than one?
For the intervention,
here is analogous selling 001,
and it is edited.
Speak.
OK, I suppose we disconnected there.
Alright. Alright, so back to the figure as it was saying. So this is crisper cast 9 technology on the X axis. You see months before birth and on the Y axis globin synthesis and percentage fetal hemoglobin goes to adult hemoglobin. BCL 11 is an important transcription factor so. If you take a look at the nucleus and the guide RNA. The target is in the Erythroid Enhancer region and by disrupting that with gene editing we can alter the expression of BCL 11A.
Effectively shutting down.

The production of globin and increasing fetal hemoglobin.

So you will see the results here in the first 2 patients presented by Doctor Strangle and colleagues on the left you have a patient with data. After CTX user, one infusion on the Y axis, one infusion on the Y axis, hemoglobin in grams per deciliter and on the and on the right panel you have patients sickle cell disease. Pay attention to the areas in the blue as they expand that’s fetal.
hemoglobin and you see that in the case of beta Thal the last transfusion was at one month.
Prior Post 2 CTX 01 infusion and in the case of sickle cell disease the last transfusion was at 19 days. Status Post ETF 001 infusion the adverse events are listed here and all of them were treated.
Abstract number 445 is entitled very inherited defects of the complement system and poor performance. This was presented by Doctor Bendapudi and colleagues out of the Harvard system. The context here is that PF is on the extreme thrombotic end of the GIC spectrum,
and elucidating PF quite gladly may pave the way for a better understanding of DIC including. Are you asking in this subset? Peach boss Richmond Cody, their competitor. This with this from the NHL VR. And you will see violin plots on the left and the right on the left is the compliment. You can set the enrichment in PFS compared to an slips patients and on the right quality. At the doctor. Global in the slides looking at all the unique variants that the
Researchers have found so far to date, but let me summarize it here.

26 out of have one or more rare putatively delete, delete serious mutations.

Sorry for the audio difficulties. I think George you might wanna like hide your camera. Maybe that will help the audio connection. It might be a connectivity issue. Um, I wouldn’t having connectivity issues at all and all prior talks.

Can you see this summer right now? Or no, we can. We see you, but it keeps freezing, yet it keeps freezing. Not quite. Sorry bout that.
00:53:46.600 --> 00:53:49.410 Um? Let me try this again.

00:53:54.520 --> 00:53:55.700 Can you see this here?

00:54:00.798 --> 00:54:03.380 Yeah, we can see, but probably better if you hide your camera so that it flows nicely.

00:54:06.730 --> 00:54:08.627 Sorry, I’m not sure what you mean by hide the camera ’cause all I’m seeing is the screen on the screen.

00:54:08.627 --> 00:54:10.688 by hide the camera 'cause all I'm seeing is the screen on the screen.

00:54:10.688 --> 00:54:12.950 Let’s see here OK.

00:54:12.950 --> 00:54:14.670 Alright, just let me know if we get disconnected again. You can go ahead. I think we’re good now.

00:54:14.670 --> 00:54:16.047 Let’s see here OK.

00:54:18.500 --> 00:54:21.076 Alright, just let me know if we get disconnected again. You can go ahead. I think we’re good now.

00:54:21.080 --> 00:54:23.330 disconnected again. You can go ahead. I think we’re good now.

00:54:23.330 --> 00:54:24.618 think we’re good now.

00:54:24.618 --> 00:54:26.280 OK, sounds good. Thank you.

00:54:26.280 --> 00:54:27.955 So with regards to the bendapudi at all study, they found that six of the 8 CR

00:54:29.130 --> 00:54:31.130 they found that six of the 8 CR
3 variants were loss of function and these are anti-inflammatory, while three of seven CR variants are gaining function and these are pro-inflammatory. So overall supporting very inflammatory milieu in these patients. Abstract 47 cost effectiveness of capitalism had been acquired. Thrombotic thrombocytopenia purpura was presented by Joshua and colleagues. The context for this study is that complexes map is the first FDA approved medication. In TTP. It’s endorsed in ITP guidelines, recently approved in the context of
confidential patient access schemes

for use in the National Health Service,

both discomfort in England has

a high list price of 270,000

US dollars per TCP episode.

Here is a cartoon schematic on

the bottom you see the summary

of the two of the phase two in

the Phase three clinical trials.

You have a patient with the disease state,

the hospitalization for TCP,

who then receive treatment with

their capitalism admin standard

of care labeled as a or placebo

standard care labeled as B and
they can either progress to death or they can go into remission. Once in remission they can again relapse. The total cost for each arm are in front of you, 324 thousand. For the campuses in my bar, 84,000 for the standard of care arm. The five year time Horizon incremental cost effectiveness ratio here was $1.5 million for the use of capitalism have in addition to the standard of care with a 95% confidence interval of 1.3 to $1.7 million. Of note, this is the sensitivity analysis and I'll just highlight one specific area here.
Researchers looked at parameters that affect the climate for capitalism, AB and the one that affected the most by far is capitalism that costs itself. Finally, abstract 529 entitled intermediate dose anticoagulation and aspirin COVID-19 and Propensity Score match analysis by not this mindless and colleagues. The context here is the current active for preliminary unadjudicated data which shows 2 main things. One that therapeutic versus prophylactic dose anticoagulation in severely ill, i.e.
Critically ill patients was halted utility in December and then January pre specified security boundary was achieved in moderately ill non critically ill patients on therapeutic versus prophylactic dose anticoagulation. So it is in this background that optimization colleagues published their study in the American Journal of Hematology. This is an observation ULL study looking at about 2800 patients with the primary outcome being time with the competing risk of discharge. I’m showing only a portion of the Yale guidelines for thromboprophylaxis.
00:56:56.109 --> 00:56:57.189 for hospitalizations.

00:56:57.190 --> 00:56:58.660 COVID-19 on the top right, and you see that there was a D dimer cut off that was utilized.

00:57:01.228 --> 00:57:03.728 This is the overall study design in overall cohort of some 2800 patients.

00:57:05.879 --> 00:57:11.380 Researchers identified risk factors for in hospital death and then created two nested cohorts on the left anticoagulation court that were Ben City scored matched for those risk factors and on the right.

00:57:09.328 --> 00:57:13.457 created two nested cohorts on the left anticoagulation court that left anticoagulation court that

00:57:11.435 --> 00:57:13.457 left anticoagulation court that

00:57:07.960 --> 00:57:13.457 created two nested cohorts on the left anticoagulation court that

00:57:13.457 --> 00:57:14.805 left anticoagulation court that

00:57:09.328 --> 00:57:13.457 created two nested cohorts on the left anticoagulation court that

00:57:14.858 --> 00:57:16.568 were Ben City scored matched for

00:57:16.568 --> 00:57:18.685 those risk factors and on the right.

00:57:18.685 --> 00:57:19.660 Aspirin versus NASCAR,

00:57:19.660 --> 00:57:21.610 notably on patients who were not

00:57:21.610 --> 00:57:22.910 on home antiplatelet therapy.
And finally the results of the multiple analysis following the propensity score matching. You will see the hazard ratio for death for the use of intermediate dose anticoagulation as compared to prophylactic is .5 two and again for in hospital. Aspirin compared to and no aspirin again .5 two.

So take homes gene editing in Dallas, EMEA and sickle cell disease can alter the disease scorers. Target gene discoveries facility genomic studies of breakfast acquisition by bending colleagues,
capitalism, app costs, and ATP is quite expensive. And finally we randomized trial data on intermediate dose anticoagulation and antiplatelet therapy. Thank you. Look forward to taking your questions. Yeah, thank you so much George, and apologies about the technical difficulties. For the next 10 minutes, doctor Bone and hopefully will moderate questions for those of you have to leave. As mentioned, this will be recorded.
and should be available for subsequent full option.

Doctor Bone and Alfred.

Great, thank you everybody.

So maybe I can start with a question that came in through the chat room so you Sabrina. How robust or how good do you feel about the mycophenolate? In addition to corticosteroids that it might begin to alter practice at this point. Yeah, I I have pause. I don’t think it’s practice changing at this point. You know, I think it’s interesting.
that there were some decrease in quality of life in the mpharm.

I think it’s important to kind of recognize that clinical response and kind of patient experience may not always correlate.

You know, the this steroid alone arm more than 50%? About 56% of patients actually at the end of follow up.

Which was about two years, had not required second line treatment, so they did well as in addition and better than prior studies.

So you know, I think it’s interesting, but I think we need more data.
before we move it to the first line.

Thank you.

To be a payment, go ahead.

At the Harford, I figured we could.

We could like pick,

introduce some of the questions

that are are added in there.

Sabrina. Can you also talk a

bit about tranexamic acid in he

malignancy’s and thrombocytopenia?

You know there is positive data for its use.

It’s been completely lifesaving in trauma.

In postpartum hemorrhage,

particularly in Third World

countries and under resourced areas,

do any comments on why you think it didn’t
work in the setting of hematologic, malignancy, and thrombocytopenia?

Yeah things, but I think that’s a great question and a question that came up for the presenters. The authors as well. You know, I think what they spoke to, which makes sense to me, is kind of the complexity of microvascular and India theal damage. That happens as a rolls result of chemotherapy, ’cause all of these patients were getting treatment. You know, we know that while prophylactic platelet transfusions has helped
in terms of bleeding incidents, there are still a good proportion of patients that do have bleeding. So you know, I think there may just be more complex pathophysiology in terms of why these patients believe that is beyond low platelets and impaired fibrinolysis. But I agree that I think there are definitely rules and you know, I think even within this population, there may be a role for this in patients who are bleeding or who need procedures or other kind of subgroups.

Great Bob, do you want to just sort of tag team back and forth? Uh, sure, in
less anyone in the audience has a question, you could raise your hand and will unmute you. But still waiting for that. I had a question for Alex. So Alex, the data on Adams 13 and BWF levels. Do you think that could be the basis for identifying high risk patients who then might be part of a randomized control trial of anticoagulation or not? In in COVID-19 and perhaps other people who are severely infected. Yes, but thank you. Thanks for question. Indeed.
I actually have great hopes until data shows otherwise,
but I have great hopes that this imbalance Adams just routine for Willebrand factor in balance is, you know for the lack of a better word may be fundamental to Infosys it. Whether it is a marker or cause, that’s I think it remains to be. Is to be seen. But from Pathophysiologic understanding of how Infosys happens, I think this two markers would be potentially could have that that could have that role. Thank you.
Another question for you Alex again, great session, great summaries. All of you guys you know for predicting cancer, associated thrombosis. You kind of mentioned this that you know the Corona score has been around awhile. There been other scores. There’s been positive data to support the use of prophylactic integration for years and years and years, but an even most recently with doacs and yet no major consensus group has come down to support that practice. So so do you feel that this machine
01:02:59.954 --> 01:03:01.169 learning algorithm will change
NOTE Confidence: 0.8076803
01:03:01.170 --> 01:03:02.680 clinical practice in that regard?
NOTE Confidence: 0.8076803
01:03:02.680 --> 01:03:05.176 Or do you still feel that we need?
NOTE Confidence: 0.8076803
01:03:05.180 --> 01:03:08.042 Better tools to predict who will
NOTE Confidence: 0.8076803
01:03:08.042 --> 01:03:09.950 actually get cancer thrombosis.
NOTE Confidence: 0.8076803
01:03:09.950 --> 01:03:12.918 So I’m a big believer in machine
NOTE Confidence: 0.8076803
01:03:12.918 --> 01:03:15.175 learning just because it make it
NOTE Confidence: 0.8076803
01:03:15.175 --> 01:03:17.740 can crunch a lot of data in that.
NOTE Confidence: 0.8076803
01:03:17.740 --> 01:03:18.607 From that perspective,
NOTE Confidence: 0.8076803
01:03:18.607 --> 01:03:20.630 I think as a data generator and
NOTE Confidence: 0.8076803
01:03:20.688 --> 01:03:22.940 hypothesis generator generating technique,
NOTE Confidence: 0.8076803
01:03:22.940 --> 01:03:25.280 I think it’s very important tool
NOTE Confidence: 0.8076803
01:03:25.280 --> 01:03:27.958 in we should not shy from it
NOTE Confidence: 0.8076803
01:03:27.958 --> 01:03:30.359 and utilized as much as we can.
NOTE Confidence: 0.8076803
01:03:30.360 --> 01:03:32.520 The question becomes sort of whether
NOTE Confidence: 0.8076803
01:03:32.520 --> 01:03:34.776 it’s become sort of garbage in
garbage out kind of situation.

If we feed something that biased to this. So the machine learning algorithms we’re going to get something totally useless, so we have to be very careful about what we really feed these algorithms and how we use these algorithms. And I think we need to collaborate with a lot of artificial intelligence, machine learning people to to get the best out of it. But yes, I agree, that’s actually could be absolutely indispensable tool.
So George question for you if I may. Do you think that the data for complement abnormalities in purpura fulminans has, or will have any therapeutic implications? Thank you Bob, really fascinating question. Really hard question too, especially because we worry about performance often in the infectious setting. One of the first patients that this study was based off of was a patient with Capnocytophaga bacteremia, who ended up having purple foam and ends. So I think that that’s that stuff. At the same time we have utilized complement in vision therapy when necessary in patients,
for example, with catastrophic APS.

The difficulty, of course, because when there’s a common infection, so I think that becomes a discussion of risks and benefits, including with our infectious disease specialists.

Beyond of course, the vaccination and the use of amoxicillin or penicillin, of amoxicillin or penicillin, or something like that to be able to cover the next serial organisms.

Thank you.

Question for Sabrina the convalescent plasma. The most recent recovery is a
recovery truck from the UK.

Was a negative study,

but there’s many positive ones,

including our own data that

you brilliantly presented.

Can you reconcile all of this

for us and how we should think

about using convalescent plasma

and COVID-19 patients?

Yeah, it thank

you all for that.

I think it’s been challenging ’cause,

as you mentioned that the data has

been quite mixed and you know,

just recently we’re getting

additional information from from
larger and more randomized trials.
The early trials that were randomized had stopped early for a number of reasons, one being that there were patients that actually were SERO positive at the time they got convalescent plasma, and then there were issues with recruitment in other studies. I think we're going to have to really kind of look through the details of what antibody titer was an neutralizing function in the convalescent plasma with each randomized trial as well as timing and timing of receiving the plasma.
and the severity of the disease, because I think there has been signal for patients who get high titer plasma earlier in disease, that there is benefit there, you know, and I don’t know that there the details of the recovery trial have been released yet in terms of. The timing of convalescent plasma and how heterogeneous the convalescent donor plasma was at that time. Great, thank you. So you mentioned that there
were some adverse events, notably thrombosis, presumably due to the sustained reduction in anti thrombin levels. Do you know if those individuals were treated with antithrombin concentrates as well as anticoagulation? That's a great question but I didn’t find any evidence that or any data on whether or not they were treated, so I don’t know the answer to that. I do know when dosing was paused,
you know they looked at the group and found that patients who had an antithrombin level that was less than 20% and had the higher risk highest risk of thrombosis. And those patients that were greater than 20% actually had no thrombotic events, and so that’s why the the trials have preceded with the redosing, which is initially going to start at every other month and then kind of increased back to where they had been previously with the goal of monitoring antithrombin levels closely so that they stay kind of between 15 and 35% is what it’s report is,
but I don’t know about the concentrates. OK, great thank you, that’s interesting, thank you.

Question for George. So you know, in the abstract that you presented on using CRISPR CAS to target BCL 11 A. I was literally just Googling what else detail 11/8 does. And you know there are interesting reports about it being involved in metal pieces in B cell, lymph, Genesis and so forth. And so I’m just wondering if the investigators talked about potential, you know, humans.
allergic effects or immunological

effects and the reason being that

you know there is another set of.

Essentially, gene editing treatments that

we can use in these disorders,

which is stem cell transplant.

So it just makes you wonder that

if there are these unknown effects

with these newer therapies,

then

So not just go for stem

why not just go for stem

cell transplant instead?

Yeah, thank you.

Yeah that's a great question.

Of course, stem cell transplant
also has adverse effects.

An events just like gene editing does in the initial study,

so they’ve completed follow up in at least two patients and they have another I think 6 to 9 patients in each of the 111 and STD 121.

There is nothing that I saw. Talking about specifically human,

logical and immunological effects, notable things were infectious from both of the first 2 pages,

but The thing is, those other patients still need at least another year of follow up before
01:09:25.368 --> 01:09:27.398 we can start talking about this right.
NOTE Confidence: 0.80985254
01:09:27.400 --> 01:09:29.630 And then beyond that long term too,
NOTE Confidence: 0.80985254
01:09:29.630 --> 01:09:31.744 'cause it’s not just a year or
NOTE Confidence: 0.80985254
01:09:31.744 --> 01:09:33.760 two that people will live right.
NOTE Confidence: 0.80985254
01:09:33.760 --> 01:09:37.069 Hopefully in that good state so.
NOTE Confidence: 0.80985254
01:09:37.070 --> 01:09:38.390 Yeah, I I don’t know more.
NOTE Confidence: 0.8540588
01:09:42.670 --> 01:09:44.740 So I have a question.
NOTE Confidence: 0.8540588
01:09:44.740 --> 01:09:46.803 Maybe for George about the
NOTE Confidence: 0.8540588
01:09:46.803 --> 01:09:48.454 the anticoagulant. I’m sorry.
NOTE Confidence: 0.8540588
01:09:48.454 --> 01:09:50.514 Not George Alex about the
NOTE Confidence: 0.8540588
NOTE Confidence: 0.8661554
01:09:52.290 --> 01:09:54.001 Where, where are we
NOTE Confidence: 0.8661554
01:09:54.001 --> 01:09:56.590 in 2021 in terms of first
NOTE Confidence: 0.8661554
01:09:56.590 --> 01:09:58.310 line therapy for reversal,
NOTE Confidence: 0.8661554
01:09:58.310 --> 01:10:00.425 bleeding for, let’s say, induce?
NOTE Confidence: 0.8661554
01:10:00.425 --> 01:10:01.968 Buy a doac you think?
Well, so we do have access to both. And extra an assistant either season map I believe. I personally have not used them, but I know several people have used them. And, um. I believe it’s costly and what’s interesting is that the decision, as far as I know, decision is made still on the timing of the last those event equivalent. Furthermore, the both trial trial so far both for. Typical Tran and Doac and the factor of 10 anticoagulants inhibitors. Both those trials for the rest of the
reversal agents were without control arms, so with efficacy is not really well established still, so I think there's one trial right now is going on next I next one is for the internal hemorrhage reversal of anticoagulation. People patient with intracranial hemorrhage, which is randomized trial. I think that's going to be informative. But I I think it's data is not super. Super strong about how to reverse and whether to wait. Just kind of, you know, hours since the last administration. So secret parent tag,
as far as I understand it’s a small market which is very easy to fairly easy to make,

which probably will reduce the cost and it’s rapid and you don’t need to necessarily think about when was the last.

Dose I think that I would think that might be an advantage of using it.

Um?

But I think the world of antic of reversal agents is an infancy.

Yeah,

I agree.

I think we’re waiting for some head to

waiting for some head to
Head trials with some of these drugs in the prothrombin complex concentrates as well. Thank you.

Well, thank you so much everybody. Thank you Doctor Pine, Victor, Joshua and Doctor Browning, and the excellent moderation by Doctor Lee and Doctor Bonner.

We probably could go another hour with all of these great questions. Please remember you can reach out to all of the speakers and the moderators by email for any questions and there will be a recording of this session for your convenience will be posted next week.

Thank you so much.
Please remember next week.

Next Friday is the last session which will be focused on cell therapy and bone marrow.

A transplantation and that will conclude our post. Ash highlights.

Thank you so much.