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. Unmet 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 and an antithrombotic therapy? Advances from ash and then our bright fellow George Joshua will finish their presentations, covering other important and relevant classical hematolgy 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.
00:04:02.060 --> 00:04:04.004 in the management of COVID-19 and
NOTE Confidence: 0.8116819
00:04:04.004 --> 00:04:07.001 provide an update on where we stand
NOTE Confidence: 0.8116819
00:04:07.001 --> 00:04:09.269 with this treatment currently.
NOTE Confidence: 0.8116819
00:04:09.270 --> 00:04:10.347 So to begin,
NOTE Confidence: 0.8116819
00:04:10.347 --> 00:04:12.142 doctor Charlotte Bradbury from the
NOTE Confidence: 0.8116819
00:04:12.142 --> 00:04:14.431 University of Bristol in the United
NOTE Confidence: 0.8116819
00:04:14.431 --> 00:04:16.316 Kingdom presented a late breaking
NOTE Confidence: 0.8116819
00:04:16.316 --> 00:04:17.928 abstract on the flight trial,
NOTE Confidence: 0.8116819
00:04:17.930 --> 00:04:19.354 which is a multicenter,
NOTE Confidence: 0.8116819
00:04:19.354 --> 00:04:21.134 randomized trial evaluating the addition
NOTE Confidence: 0.8116819
00:04:21.134 --> 00:04:23.348 of mycophenolate to standard of care.
NOTE Confidence: 0.8116819
00:04:23.350 --> 00:04:24.622 Corticosteroids in the management
NOTE Confidence: 0.8116819
00:04:24.622 --> 00:04:26.212 of patients with newly diagnosed
NOTE Confidence: 0.8116819
00:04:26.212 --> 00:04:27.320 immune thrombocytopenia.
NOTE Confidence: 0.8116819
00:04:27.320 --> 00:04:30.071 This study was developed due to the
NOTE Confidence: 0.8116819
00:04:30.071 --> 00:04:32.073 heterogeneous responses in ITP to
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,

followed by a taper or corticosteroids plus MMF,

which was initially dosed at 500 milligrams twice daily and then escalated to a Max dose of 1 gram daily with a plan to taper and then stop after six months of treatment.

The investigators from this trial hypothesize that MF, combined with steroids, would be more effective than steroids alone, and the primary outcome measured was time from randomization to treatment failure, defined as a platelet count less than 30 and a clinical need
00:05:34.809 --> 00:05:36.645 for second line treatment.

00:05:36.650 --> 00:05:38.150 Secondary outcomes are outlined here and included bleeding events,

00:05:40.030 --> 00:05:40.758 side effects,

00:05:40.758 --> 00:05:42.942 and patient reported outcomes both at baseline and AT246 and 12 months as measured by validated questionnaires.

00:05:49.220 --> 00:05:51.719 120 patients were included in this study,

00:05:51.720 --> 00:05:55.999 patients receiving steroids alone.

00:05:58.150 --> 00:05:59.955 52.4% of patients were male

00:05:59.955 --> 00:06:02.070 with a median age of 54,

00:06:02.070 --> 00:06:04.541 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 platelet 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 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 two or 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
consecutive platelet counts that were greater than 50,000 with an increase of more than 20,000 from the patients baseline without requiring any rescue or additional medications. The investigators also performed subgroup analysis to determine the impact of certain prior treatments on this primary endpoint. A long term extension study was also conducted to further assess safety and durability of this medication, and so this specific abstract presented on 38 patients who had received the dose of 400.
milligrams twice daily and the 13
NOTE Confidence: 0.875766
patients who entered the long term
NOTE Confidence: 0.875766
extension study at this same dose.
NOTE Confidence: 0.85495913
So patients in the 400 milligram twice
daily cohort had a median duration of
NOTE Confidence: 0.85495913
ITP of six years and had received a
NOTE Confidence: 0.85495913
median of six prior lines of therapy.
NOTE Confidence: 0.85495913
Their median age was 50, with a little
NOTE Confidence: 0.85495913
more than half of patients being female.
NOTE Confidence: 0.85495913
At the time of data cutoff,
NOTE Confidence: 0.85495913
which was July of 2020, forty 2% of
NOTE Confidence: 0.85495913
patients had achieved the primary endpoint.
NOTE Confidence: 0.85495913
Furthermore, responses were relatively
NOTE Confidence: 0.85495913
similar whether or not these patients
NOTE Confidence: 0.85495913
had responded to prior therapy,
NOTE Confidence: 0.85495913
as outlined here,
including thrombopoietin receptor agonist, rituximab, or fostamatinib, and notably responses were quite rapid, with 53% of patients achieving a platelet count of more than 30 by day 8. And responses were also durable in nature. A real rose alot nib was generally well tolerated in all portions of the trial with approximately half of patients experiencing grade one or two side effects that were transient and mostly GI. In nature, though there were no serious adverse events or treatment related bleeding or
00:10:19.430 --> 00:10:21.535 thrombotic complications during this study.
NOTE Confidence: 0.85495913
00:10:21.540 --> 00:10:22.521 So, in conclusion,
NOTE Confidence: 0.85495913
00:10:22.521 --> 00:10:24.810 reels reels of Bruton AB therapy at
NOTE Confidence: 0.85495913
00:10:24.877 --> 00:10:27.551 a dose of 400 milligrams twice daily
NOTE Confidence: 0.85495913
00:10:27.551 --> 00:10:29.499 achieved significant rapid and long
NOTE Confidence: 0.85495913
00:10:29.499 --> 00:10:31.349 lasting platelet responses in about
NOTE Confidence: 0.85495913
00:10:31.349 --> 00:10:33.495 a slightly under half a percent
NOTE Confidence: 0.85495913
00:10:33.495 --> 00:10:35.220 percentage of this patient population
NOTE Confidence: 0.85495913
00:10:35.220 --> 00:10:37.189 with heavily treated pretreated ITP,
NOTE Confidence: 0.85495913
00:10:37.190 --> 00:10:39.668 and this was observed irrespective of the
NOTE Confidence: 0.85495913
00:10:39.668 --> 00:10:42.290 response to prior lines of treatment rules.
NOTE Confidence: 0.85495913
00:10:42.290 --> 00:10:44.105 Ibrutinib was granted fast track
NOTE Confidence: 0.85495913
00:10:44.105 --> 00:10:46.345 designation by the FDA in October
NOTE Confidence: 0.85495913
00:10:46.345 --> 00:10:48.523 of this past year and further
NOTE Confidence: 0.85495913
00:10:48.523 --> 00:10:50.300 clinical trials with this drug.
NOTE Confidence: 0.85495913
00:10:50.300 --> 00:10:51.820 That drug is current.
Currently ongoing.

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.
00:11:25.000 --> 00:11:27.828 even despite our evidence based use of platelet transfusions prophylactically
NOTE Confidence: 0.8092774
00:11:27.828 --> 00:11:29.040 and while anti fibrinolytic therapy
NOTE Confidence: 0.8092774
00:11:29.100 --> 00:11:33.393 has certainly been used with pain in patients with hematologic malignancy
NOTE Confidence: 0.8092774
00:11:33.393 --> 00:11:35.145 undergoing treatment evidence,
NOTE Confidence: 0.8092774
00:11:35.145 --> 00:11:36.459 evidence of its benefit has really been lacking.
NOTE Confidence: 0.8092774
00:11:36.460 --> 00:11:38.830 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.
NOTE Confidence: 0.8092774
00:11:39.620 --> 00:11:42.780 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
Platelet count had dropped below 30.

Tranexamic acid or placebo was discontinued after 30 days or when platelet counts had recovered to more than 30,000.

The primary endpoint was the proportion of patients with WHO grade two or above bleeding with Grade 2 being moderate bleeding, Grade 3 being severe bleeding requiring transfusion of red blood cells or other intervention and grade for being life threatening or debilitating bleed.

Additional secondary and safety
endpoints are outlined on the slide
here and include rate of thrombosis,
vinocclusive 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,
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 and chemotherapy alone. The time to 1st WH 2 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 2 or more bleeding an mean red blood cell
NOTE Confidence: 0.85934526
00:14:12.748 --> 00:14:13.978 transfusion per thrombocytopenia.
NOTE Confidence: 0.85934526
00:14:13.980 --> 00:14:16.530 CdaI were also not impacted by
NOTE Confidence: 0.85934526
00:14:16.530 --> 00:14:18.730 the use of tranexamic acid.
NOTE Confidence: 0.85934526
00:14:18.730 --> 00:14:19.442 There was,
NOTE Confidence: 0.85934526
00:14:19.442 --> 00:14:19.798 however,
NOTE Confidence: 0.85934526
00:14:19.798 --> 00:14:20.864 a statistically significant
NOTE Confidence: 0.85934526
00:14:20.866 --> 00:14:22.664 increase in the overall thrombotic
NOTE Confidence: 0.85934526
00:14:22.664 --> 00:14:24.596 events on the tranexamic acid arm,
NOTE Confidence: 0.85934526
00:14:24.600 --> 00:14:27.176 though this primarily was made up of
NOTE Confidence: 0.85934526
00:14:27.176 --> 00:14:29.638 line occlusions with a trend that was
NOTE Confidence: 0.85934526
00:14:29.638 --> 00:14:31.576 actually fewer in of non catheter
NOTE Confidence: 0.85934526
00:14:31.641 --> 00:14:34.155 thrombotic events in the treatment arm.
NOTE Confidence: 0.85934526
00:14:34.160 --> 00:14:36.379 There was no increase in Vino occlusive,
NOTE Confidence: 0.85934526
00:14:36.380 --> 00:14:36.705 disease,
NOTE Confidence: 0.85934526
00:14:36.705 --> 00:14:38.330 or alcors all cause mortality
NOTE Confidence: 0.85934526
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...
of central line occlusion events, and so the authors emphasize, despite these findings, that the utility of tranexamic acid in other settings with thrombocytopenia cannot be excluded. By this study alone.

So moving on to an abstract presented by Doctor Steven Pipe from the University of Michigan on the long term, durability, safety, and efficacy of fat userin prophylaxis in patients with hemophilia A or B with or without inhibitors as seen on the slide here.
So for twos are in 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.

So in this trial adult male patients
with moderate severe haemophilia

00:16:17.374 --> 00:16:19.924 B who had tolerated for chooser in

00:16:24.260 --> 00:16:24.966 A2 cohort,

00:16:29.120 --> 00:16:31.703 are in at a dose of 50 or 80

00:16:31.703 --> 00:16:33.610 milligrams subcutaneous monthly.

00:16:33.610 --> 00:16:35.102 The primary endpoints were

00:16:36.600 --> 00:16:38.796 and there were key secondary endpoints

00:16:38.796 --> 00:16:40.720 that included a calculated median.

00:16:40.720 --> 00:16:42.800 Analyze the annualized bleed rate
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, with 22 being on the 80 milligram dose. But user and was 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

32
an bleeds severity and from left to right in patients with hemophilia. A patients with no inhibitor hemophilia. A patients with an inhibitor hemophilia. B 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, ran 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 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 Geno type analysis of adolescents with low. One willibrand factor, an heavy menstrual bleeding. She noted that heavy menstrual bleeding occurs in about 1/3 of adolescent women 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 with bleeding or haematologic diseases

00:20:48.692 --> 00:20:50.662 as outlined in the slide here.

00:20:50.662 --> 00:20:52.936 There was also an excess of rare pathogenic variants that were observed in jeans that cause anemia or cause disease with anemia as a major symptom.

00:20:52.940 --> 00:20:55.677 This included variance in Adams TS 13, Fink, CA and G6PD and the other jeans that are listed here.

00:20:55.677 --> 00:20:57.317 major symptoms of major symptom.

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

00:21:02.408 --> 00:21:04.278 This included variance in Adams TS 13, Fink, CA and G6PD and the other jeans that are listed here.

00:21:04.280 --> 00:21:07.017 There was analysis Additionally for common single nucleotide polymorphism’s
or snips that were identified, 3 common snips infirm too, and this past genome wide significance as seen in the figure here on the right firm T2, encodes a cytoskeletal protein that is important in hemostasis, angiogenesis and blood vessel homeostasis, and so.

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, 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...
some additional data.

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 24 and 72 hours after transfusion. Convalescent plasma, and mortality.
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 multi center phase two trial presented by Doctor Al Hashmi compared 178 covid convalescent plasma recipients to 391 matched controls.
00:23:32.520 --> 00:23:34.176 Is a significant reduction in 30
day mortality in the treatment arm.

00:23:34.176 --> 00:23:36.069 In this study,

00:23:36.070 --> 00:23:37.111 though Interestingly they observed that

00:23:37.111 --> 00:23:38.846 the hospital and ICU length of stay

00:23:38.846 --> 00:23:40.766 as well as duration of intubation was

00:23:40.766 --> 00:23:42.582 longer and that was actually longer

00:23:42.582 --> 00:23:44.358 in the convalescent Plasma Group.

00:23:44.358 --> 00:23:46.264 Another phase,

00:23:46.264 --> 00:23:47.140 two matched case control study looked

00:23:47.140 --> 00:23:49.084 at a smaller number of hospitalized

00:23:49.084 --> 00:23:51.232 COVID-19 patients who received 2 units

00:23:51.232 --> 00:23:53.590 of transfusion and there was a trend

00:23:53.590 --> 00:23:55.916 in this group towards improved survival,

00:23:55.916 --> 00:23:57.742 though this was not

00:23:57.742 --> 00:23:59.110 statistically significant,
It was noted in this study that the donor plasma was quite heterogeneous, with an increase in antibody activity observed in some, but not all, of the patients included in the study, and interesting Lee, those who had undergone anti CD 20 treatment in the last year had a demonstrated an impaired response. In regards to antibody activity and Lastly a multi center Phase 1 trial of 70 patients who had received COVID-19 convalescent plasma found that 30 day overall
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 second that was observed to have a venous thromboembolic event. So the QR code included here on this slide links to a section of the ash website that discuss is our available evidence on COVID-19. As you can see, just from
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
actually potentiates the already increased thrombotic risk.

An end to Ophelia Opathy that we now know occurs with COVID-19 and further investigation into this is warranted.

So taking this all into account as of just actually last week, the FDA has updated their emergency use authorization for COVID-19 convalescent plasma.

Really limiting it to use of high titer plasma for hospitalized patients that are early in their disease course and those who may have impaired humoral immunity.

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
base and our own work.

Thrombosis and COVID-19.

How it actually. Informed us about in conditions beyond COVID-19.

No disclosures on my end.

One of the first highlight the this abstract about machine learning for prediction of cancer.

Social verbalism, especially in the setting of new guidelines that have been just released about cancer regarding cancer.

Associated venous thromboembolism just the other day and as you all
know we there are several clinical prediction rules of which score. Is most validated and had been. Used to stratify the risk in multiple trials, including most recently a PERT and Cassini RCT S42 Deluxe prophylactic regimen versus placebo and recall. It’s pretty simple score to use the questions. We have been raised over the over years is exactly where prophylaxis versus which group to sort if at all.
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.
An original paper by Doctor Corona.

We know that the rate of DTE was about 7% in high risk cohort,

so the authors of this app start from Libor Sloan, Kettering, US Sameta and.

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.

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 in the 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,
NOTE Confidence: 0.750427
although how they get it not clearly was outlined as well,
NOTE Confidence: 0.750427
Incidence of VTE I presume,
NOTE Confidence: 0.78821117
and it’s five risk groups based on the.
NOTE Confidence: 0.78821117
Per their validation metric that was validated, model was performed well.
NOTE Confidence: 0.78821117
and so then they validated this with the model in the said that that is.
NOTE Confidence: 0.78821117
Per their validation metric that was validated, model was performed well.
NOTE Confidence: 0.78821117
With, Interestingly enough,
NOTE Confidence: 0.78821117
when they looked at which
NOTE Confidence: 0.78821117
predictors had been most predictive
NOTE Confidence: 0.78821117
of the venous thromboembolism,
they found that it’s a cancer type came, whether patient received chemotherapy, platelet count. 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 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
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 a 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 with 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. A pain where you can see that several hours after administration of edoxaban. Sorry for typo the. 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

in same sort of data that, with different doses of Sopron tags.

The universal was fairly complete. Below 10% of baseline.

Now the metric that’s being used to determine this is a whole blood clotting time,

and that’s actually important, because apparently I cannot activity of Sharon Cycle rather reversal.

Enter calculation cannot be determined using regular typical methods.

For instance using PT PTT because your parent act would be in the tube,
in the inner tube of blood. It would be pulled competitively inhibited by like say, citrate or ETA that already present in the tube, so therefore they used whole blood clotting time. So now the abstract itself actually presents the two studies to phase two will see what controlled RCT one for Apixaban and the other one for rear axle band, where they actually. Looked at reversal Cedar parents versus placebo and it’s
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
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
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 that whether magnesium and calcium in vivo could have any effect on sort of pulling setup Ramtek out of the. Interaction with the aid with the agents. Anticoagulation agents but it probably in molar concentration such that probably not really likely an interesting concept that an anticoagulation, if necessary can be re stored and re established 24 hour reversal without any. In effect cost, of course 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 to my final discussion of the work that we sort of we 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

many times is quite elevated

in patients with coded 19,

and this specifically much more elevated

in patients with critical disease.

We also know from other studies

We
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 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 cohort to our data
and we will look at what kind of relationship exists between Adams test and from villain factor antigen activity. We found that indeed. In critical disease in patients with critical disease, 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,
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. 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.
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, an 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
00:49:02.472 --> 00:49:04.340 be talking to you today.
NOTE Confidence: 0.89763653
00:49:04.340 --> 00:49:05.730 I have no disclosures.
NOTE Confidence: 0.89763653
00:49:05.730 --> 00:49:08.035 There are four apps we’re going to
NOTE Confidence: 0.89763653
00:49:08.035 --> 00:49:10.599 cover and I will speak through this,
NOTE Confidence: 0.89763653
00:49:10.600 --> 00:49:12.777 so we finish on time and we’re
NOTE Confidence: 0.89763653
00:49:12.777 --> 00:49:15.129 going to talk about gene editing.
NOTE Confidence: 0.89763653
00:49:15.130 --> 00:49:17.212 And we’re going to talk about
NOTE Confidence: 0.89763653
00:49:17.212 --> 00:49:18.253 complement system performance,
NOTE Confidence: 0.89763653
00:49:18.260 --> 00:49:19.541 health outcomes, research.
NOTE Confidence: 0.89763653
00:49:19.541 --> 00:49:22.103 And a little bit of coping.
NOTE Confidence: 0.89763653
00:49:22.110 --> 00:49:23.720 So to start off.
NOTE Confidence: 0.89763653
00:49:23.720 --> 00:49:25.514 First abstract #4 entitled CRISPR CAS
NOTE Confidence: 0.89763653
00:49:25.514 --> 00:49:27.804 gene editing for sickle cell disease
NOTE Confidence: 0.89763653
00:49:27.804 --> 00:49:29.539 and beta thalassemia by doctors.
NOTE Confidence: 0.89763653
00:49:29.540 --> 00:49:30.344 Frangou and colleagues.
NOTE Confidence: 0.89763653
00:49:30.344 --> 00:49:31.952 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.
Bo team. Both.
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. This is crisper cast 9 technology on the X axis. You see months before birth and after 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 on the X axis you have months.

After CTX user, one infusion on the Y axis, hemoglobin in grams per deciliter 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 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?

00:53:58.080 --> 00:54:00.798 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.

00:54:10.688 --> 00:54:12.950 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

00:54:27.955 --> 00:54:29.129 bendapudi at all study,

00:54:29.130 --> 00:54:31.130 they found that six of the 8 CR

NOTE Confidence: 0.8047364

NOTE Confidence: 0.85032344

NOTE Confidence: 0.85032344

NOTE Confidence: 0.85032344

NOTE Confidence: 0.8047364
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.

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 of 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 icier for capitalism, 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 an 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 elii 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 in hospital death. The competing risk of discharge. I’m showing only a portion of the Yale guidelines for thromboprophylaxis
for hospitalizations.

COVID-19 on the top right, and you see that there was a D dimer cut off that was utilized.

This is the overall study design in overall cohort of some 2800 patients. 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. Aspirin versus NASCAR, notably on patients who were not 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.
NOTE Confidence: 0.7826892

Thank you.
NOTE Confidence: 0.78495073

To be a payment, go ahead.
NOTE Confidence: 0.78495073

At the Harford, I figured we could.
NOTE Confidence: 0.78495073

We could like pick,
NOTE Confidence: 0.78495073

introduce some of the questions
NOTE Confidence: 0.78495073

that are added in there.
NOTE Confidence: 0.78495073

Sabrina. Can you also talk a
NOTE Confidence: 0.78495073

bit about tranexamic acid in he
NOTE Confidence: 0.78495073

malignancy’s and thrombocytopenia?
NOTE Confidence: 0.78495073

You know there is positive data for its use.
NOTE Confidence: 0.78495073

It’s been completely lifesaving in trauma.
NOTE Confidence: 0.78495073

In postpartum hemorrhage,
NOTE Confidence: 0.78495073

particularly in Third World
NOTE Confidence: 0.78495073

countries and under resourced areas,
NOTE Confidence: 0.78495073

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 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
01:01:01.100 --> 01:01:10.500 less anyone in the audience

01:01:10.500 --> 01:01:12.051 has a question, you could raise

01:01:12.051 --> 01:01:13.600 your hand and will unmute you.

01:01:15.760 --> 01:01:17.520 But still waiting for

01:01:17.520 --> 01:01:21.040 I I had a question for Alex.

01:01:21.040 --> 01:01:24.120 So Alex, the data on Adams 13

01:01:24.120 --> 01:01:26.760 and BWF levels. Do you think

01:01:26.760 --> 01:01:29.400 that could be the basis for

01:01:29.400 --> 01:01:31.600 identifying high risk patients who

01:01:31.600 --> 01:01:34.922 then might be part of a randomized

01:01:34.922 --> 01:01:39.014 control trial of anticoagulation or not?

01:01:39.020 --> 01:01:41.660 In in COVID-19 and perhaps other

01:01:41.660 --> 01:01:43.860 people who are severely infected.

01:01:45.670 --> 01:01:47.462 Yes, but thank you.

01:01:47.462 --> 01:01:49.259 Thanks for question. Indeed.
01:01:49.259 --> 01:01:51.504 I actually have great hopes
NOTE Confidence: 0.77955836
01:01:51.504 --> 01:01:53.300 until data shows otherwise,
NOTE Confidence: 0.77955836
01:01:53.300 --> 01:01:56.191 but I have great hopes that this
NOTE Confidence: 0.77955836
01:01:56.191 --> 01:01:58.490 imbalance Adams just routine for
NOTE Confidence: 0.77955836
01:01:58.490 --> 01:02:00.940 Willebrand factor in balance is,
NOTE Confidence: 0.77955836
01:02:00.940 --> 01:02:04.076 you know for the lack of a better
NOTE Confidence: 0.77955836
01:02:04.076 --> 01:02:07.669 word may be fundamental to Infosys it.
NOTE Confidence: 0.77955836
01:02:07.670 --> 01:02:11.254 Whether it is a marker or A cause,
NOTE Confidence: 0.77955836
01:02:11.260 --> 01:02:15.124 that’s I think it remains to be.
NOTE Confidence: 0.77955836
01:02:15.130 --> 01:02:17.470 Is to be seen.
NOTE Confidence: 0.77955836
01:02:17.470 --> 01:02:21.565 But from from Pathophysiologic
NOTE Confidence: 0.77955836
01:02:21.570 --> 01:02:25.371 understanding of how Infosys happens,
NOTE Confidence: 0.77955836
01:02:25.371 --> 01:02:28.095 I think this two markers would be
NOTE Confidence: 0.77955836
01:02:28.095 --> 01:02:31.077 potentially could have that that
NOTE Confidence: 0.77955836
01:02:31.080 --> 01:02:31.550 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 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.

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’s that stuff.

At the same time we have utilized complement in vision therapy when necessary in patients,
NOTE Confidence: 0.8234763
01:04:57.480 --> 01:04:59.420 For example, with catastrophic APS.
NOTE Confidence: 0.8234763
01:04:59.420 --> 01:05:00.968 The difficulty, of course,
NOTE Confidence: 0.8234763
01:05:00.968 --> 01:05:03.290 because when there’s a common infection,
NOTE Confidence: 0.8234763
01:05:03.290 --> 01:05:05.408 so I think that becomes a
NOTE Confidence: 0.8234763
01:05:05.408 --> 01:05:07.540 discussion of risks and benefits,
NOTE Confidence: 0.8234763
01:05:07.540 --> 01:05:09.220 including with our infectious
NOTE Confidence: 0.8234763
01:05:09.220 --> 01:05:10.060 disease specialists.
NOTE Confidence: 0.8234763
01:05:10.060 --> 01:05:10.837 Beyond of course,
NOTE Confidence: 0.8234763
01:05:10.837 --> 01:05:12.132 the vaccination and the use
NOTE Confidence: 0.8234763
01:05:12.132 --> 01:05:13.299 of amoxicillin or penicillin,
NOTE Confidence: 0.8234763
01:05:13.300 --> 01:05:15.190 or something like that to be able
NOTE Confidence: 0.8234763
01:05:15.190 --> 01:05:17.860 to cover the next serial organisms.
NOTE Confidence: 0.8234763
01:05:17.860 --> 01:05:20.280 Thank you.
NOTE Confidence: 0.83295316
01:05:20.280 --> 01:05:22.248 Question for Sabrina the convalescent plasma.
NOTE Confidence: 0.83295316
01:05:22.250 --> 01:05:24.266 The most recent recovery is a
NOTE Confidence: 0.83295316
recovery truck from the UK.
01:05:25.870 --> 01:05:27.182 Was a negative study,
NOTE Confidence: 0.83295316
01:05:27.182 --> 01:05:28.822 but there’s many positive ones,
NOTE Confidence: 0.83295316
01:05:28.830 --> 01:05:30.480 including our own data that
NOTE Confidence: 0.83295316
01:05:30.480 --> 01:05:31.470 you brilliantly presented.
NOTE Confidence: 0.83295316
01:05:31.470 --> 01:05:33.438 Can you reconcile all of this
NOTE Confidence: 0.83295316
01:05:33.438 --> 01:05:35.740 for us and how we should think
NOTE Confidence: 0.83295316
01:05:35.740 --> 01:05:37.060 about using convalescent plasma
NOTE Confidence: 0.83295316
01:05:37.060 --> 01:05:38.050 and COVID-19 patients?
NOTE Confidence: 0.83295316
01:05:38.050 --> 01:05:39.030 Yeah, it thank
NOTE Confidence: 0.83295316
01:05:39.030 --> 01:05:40.346 you all for that.
NOTE Confidence: 0.83295316
01:05:40.346 --> 01:05:42.320 I think it’s been challenging ’cause,
NOTE Confidence: 0.83295316
01:05:42.320 --> 01:05:44.665 as you mentioned that the data has
NOTE Confidence: 0.83295316
01:05:44.665 --> 01:05:46.599 been quite mixed and you know,
NOTE Confidence: 0.83295316
01:05:46.600 --> 01:05:48.826 I think just recently we’re getting
NOTE Confidence: 0.83295316
01:05:48.826 --> 01:05:50.310 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 a 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. Sabrina question about it for two zaran if I could. 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 a as along with 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. 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,
01:08:28.863 --> 01:08:30.267 allergic effects or immunological
NOTE Confidence: 0.79507476
01:08:30.267 --> 01:08:32.730 effects and and the reason being that
NOTE Confidence: 0.79507476
01:08:32.730 --> 01:08:35.830 you know there there is another set of.
NOTE Confidence: 0.79507476
01:08:35.830 --> 01:08:36.095 Essentially,
NOTE Confidence: 0.79507476
01:08:36.095 --> 01:08:37.152 gene editing treatments that
NOTE Confidence: 0.79507476
01:08:37.152 --> 01:08:38.724 we can use in these disorders,
NOTE Confidence: 0.79507476
01:08:38.730 --> 01:08:40.055 which is stem cell transplant.
NOTE Confidence: 0.79507476
01:08:40.055 --> 01:08:41.834 So it just makes you wonder that
NOTE Confidence: 0.79507476
01:08:41.834 --> 01:08:43.310 if there are these unknown effects
NOTE Confidence: 0.79507476
01:08:43.354 --> 01:08:44.538 with these newer therapies,
NOTE Confidence: 0.79507476
01:08:44.540 --> 01:08:44.810 then
NOTE Confidence: 0.80985254
01:08:44.810 --> 01:08:46.388 why not just go for stem
NOTE Confidence: 0.80985254
01:08:46.390 --> 01:08:48.388 cell transplant instead?
NOTE Confidence: 0.80985254
01:08:48.390 --> 01:08:49.620 Yeah, thank you.
NOTE Confidence: 0.80985254
01:08:49.620 --> 01:08:51.670 Yeah that’s a great question.
NOTE Confidence: 0.80985254
01:08:51.670 --> 01:08:53.495 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 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
we can start talking about this right.

And then beyond that long term too, ‘cause it’s not just a year or two that people will live right.

Hopefully in that good state so.

So I have a question. Maybe for George about the anticoagulant. I’m sorry. Not George Alex about the anticoagulant inhibitor. Where are we in 2021 in terms of first line therapy for reversal, let’s say, induce? 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 next I next one is for the internal hemorrhage
which is randomized trial.
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 anti of reversal agents is an infancy. Yeah, I agree. I think we’re 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.