WEBVTT

NOTE duration:"01:03:09"

NOTE recognizability:0.806

NOTE language:en-us

NOTE Confidence: 0.97178832

00:00:00.000 --> 00:00:01.332 Good morning, everyone.

NOTE Confidence: 0.97178832

00:00:01.332 --> 00:00:03.996 Thank you so much for coming.

NOTE Confidence: 0.97178832

00:00:04.000 --> 00:00:05.974 It's really a true pleasure today

NOTE Confidence: 0.97178832

00:00:05.974 --> 00:00:08.382 to have with us one of the gents

NOTE Confidence: 0.97178832

00:00:08.382 --> 00:00:10.500 of acute myeloid leukemia and

NOTE Confidence: 0.97178832

00:00:10.500 --> 00:00:12.360 myeloid neoplasms in general.

NOTE Confidence: 0.97178832

00:00:12.360 --> 00:00:14.570 So Doctor Marina Konopoliva is

NOTE Confidence: 0.97178832

00:00:14.570 --> 00:00:17.374 a professor in the Department of

NOTE Confidence: 0.97178832

00:00:17.374 --> 00:00:19.438 Oncology and Molecular Pharmacology

NOTE Confidence: 0.97178832

00:00:19.438 --> 00:00:22.018 and the Merriam Faculty Scholar

NOTE Confidence: 0.97178832

00:00:22.093 --> 00:00:24.215 in Cancer Research at the Albert

NOTE Confidence: 0.97178832

00:00:24.215 --> 00:00:25.732 Einstein College of Medicine.

NOTE Confidence: 0.97178832

00:00:25.732 --> 00:00:26.728 After spending many,

NOTE Confidence: 0.97178832

00:00:26.728 --> 00:00:28.720 many years in the Andy Anderson,

NOTE Confidence: 0.97178832

00:00:28.720 --> 00:00:31.260 where she has really made

NOTE Confidence: 0.97178832

00:00:31.260 --> 00:00:32.276 fantastic contributions,

NOTE Confidence: 0.97178832

00:00:32.280 --> 00:00:33.948 including very important drugs

NOTE Confidence: 0.97178832

00:00:33.948 --> 00:00:36.033 that have been approved both

NOTE Confidence: 0.97178832

00:00:36.033 --> 00:00:39.040 in acute myeloid leukemia and

NOTE Confidence: 0.97178832

00:00:39.040 --> 00:00:42.320 plastic denritic myelo neoplasm.

NOTE Confidence: 0.97178832

00:00:42.320 --> 00:00:45.043 So she received her Doctor of Medicine

NOTE Confidence: 0.97178832

00:00:45.043 --> 00:00:47.315 from the First Pavlov Medicine

NOTE Confidence: 0.97178832

00:00:47.315 --> 00:00:50.399 Institute in Saint Pittsburgh in Russia,

NOTE Confidence: 0.97178832

00:00:50.400 --> 00:00:52.850 and then got a PhD in experimental

NOTE Confidence: 0.97178832

00:00:52.850 --> 00:00:54.974 hematology from the Federal Institute

NOTE Confidence: 0.97178832

00:00:54.974 --> 00:00:57.479 of Hematology and Blood Transfusion.

NOTE Confidence: 0.97178832

00:00:57.480 --> 00:00:59.004 So Doctor Konopliva's research

NOTE Confidence: 0.97178832

00:00:59.004 --> 00:01:00.909 has focused on patients with

NOTE Confidence: 0.97178832

00:01:00.909 --> 00:01:02.255 hematologic malignancies both

NOTE Confidence: 0.97178832

00:01:02.255 --> 00:01:04.079 including acute myeloid leukemia,

NOTE Confidence: 0.97178832

00:01:04.080 --> 00:01:05.475 acute lymphoblastic leukemia

NOTE Confidence: 0.97178832

00:01:05.475 --> 00:01:08.274 as well as high risk MD's.

NOTE Confidence: 0.97178832

00:01:08.274 --> 00:01:09.696 And her research,

NOTE Confidence: 0.97178832

00:01:09.696 --> 00:01:11.118 as I mentioned,

NOTE Confidence: 0.97178832

00:01:11.120 --> 00:01:13.466 have led to important not only

NOTE Confidence: 0.97178832

00:01:13.466 --> 00:01:14.639 science and advancing,

NOTE Confidence: 0.97178832

00:01:14.640 --> 00:01:17.012 but also therapeutic translation,

NOTE Confidence: 0.97178832

00:01:17.012 --> 00:01:18.198 especially venetoclax,

NOTE Confidence: 0.97178832

00:01:18.200 --> 00:01:20.665 which really has changed the landscape

NOTE Confidence: 0.97178832

00:01:20.665 --> 00:01:25.306 of how we treat patients with the AM, LCLL,

NOTE Confidence: 0.97178832

00:01:25.306 --> 00:01:28.620 potentially MD's and other conditions.

NOTE Confidence: 0.97178832

00:01:28.620 --> 00:01:30.696 And on a personal level,

NOTE Confidence: 0.97178832

00:01:30.696 --> 00:01:32.436 I think Doctor Konopleva is very known

NOTE Confidence: 0.97178832

00:01:32.436 --> 00:01:34.236 in the field to be a fantastic mentor.

NOTE Confidence: 0.97178832

00:01:34.240 --> 00:01:37.418 She has mentored some of the most

NOTE Confidence: 0.97178832

00:01:37.418 --> 00:01:39.507 productive researchers in the field

NOTE Confidence: 0.97178832

00:01:39.507 --> 00:01:42.091 as well as being a very nice and

NOTE Confidence: 0.97178832

00:01:42.172 --> 00:01:43.920 very good person to interact with.

NOTE Confidence: 0.97178832

00:01:43.920 --> 00:01:45.568 So I encourage as many of you to

NOTE Confidence: 0.97178832

00:01:45.568 --> 00:01:47.116 talk to her if you can today.

NOTE Confidence: 0.97178832

00:01:47.120 --> 00:01:48.236 Thank you so much for coming.

NOTE Confidence: 0.591625295

00:01:55.140 --> 00:01:55.905 Thank you, Amir,

NOTE Confidence: 0.591625295

00:01:55.905 --> 00:01:57.180 for this very kind introduction.

NOTE Confidence: 0.591625295

00:01:57.180 --> 00:01:58.180 I'm happy to be here.

NOTE Confidence: 0.591625295

00:01:58.180 --> 00:02:00.273 This is my first time at Yale

NOTE Confidence: 0.591625295

00:02:00.273 --> 00:02:02.140 and I'm looking forward for the

NOTE Confidence: 0.591625295

00:02:02.140 --> 00:02:04.233 day and meeting a lot of you.

NOTE Confidence: 0.591625295

00:02:04.240 --> 00:02:06.655 And so today I wanted to take

NOTE Confidence: 0.591625295

00:02:06.655 --> 00:02:09.000 you through our story on Biso 2.

NOTE Confidence: 0.591625295

00:02:09.000 --> 00:02:10.832 I know this is like a general grand

NOTE Confidence: 0.591625295

00:02:10.832 --> 00:02:12.880 round for both human solid malignancies,

NOTE Confidence: 0.591625295

00:02:12.880 --> 00:02:15.764 but I think targeting cell death is

NOTE Confidence: 0.591625295

00:02:15.764 --> 00:02:17.240 probably important for including

NOTE Confidence: 0.591625295

00:02:17.240 --> 00:02:18.680 for the solid tumors as well.

NOTE Confidence: 0.591625295

00:02:18.680 --> 00:02:20.386 And I'll show you some of the kind

NOTE Confidence: 0.591625295

00:02:20.386 --> 00:02:22.514 of ways we think about that as well.

NOTE Confidence: 0.867402208

00:02:25.120 --> 00:02:28.104 So these are my disclosures and as

NOTE Confidence: 0.867402208

00:02:28.104 --> 00:02:30.252 you all know, the resistance to cell

NOTE Confidence: 0.867402208

00:02:30.252 --> 00:02:33.242 death is one of the hallmarks of cancer

NOTE Confidence: 0.867402208

00:02:33.242 --> 00:02:35.832 and it's largely governed by the B22

NOTE Confidence: 0.867402208

00:02:35.832 --> 00:02:38.439 family proteins which are listed here.

NOTE Confidence: 0.867402208

00:02:38.440 --> 00:02:39.337 It's quite complicated.

NOTE Confidence: 0.867402208

00:02:39.337 --> 00:02:41.800 I'll show you later how the system works,

NOTE Confidence: 0.867402208

00:02:41.800 --> 00:02:43.640 but essentially there's over

NOTE Confidence: 0.867402208

00:02:43.640 --> 00:02:45.940 expression of different B22 family

NOTE Confidence: 0.867402208

00:02:45.940 --> 00:02:48.276 members depending on the tumor type.

NOTE Confidence: 0.867402208

00:02:48.280 --> 00:02:50.650 For example in myeloid malignancies

NOTE Confidence: 0.867402208

00:02:50.650 --> 00:02:53.750 and we have mainly B so 2IN TALL.

NOTE Confidence: 0.867402208

00:02:53.750 --> 00:02:56.199 We also have B cell XL and B so two

NOTE Confidence: 0.867402208

00:02:56.199 --> 00:02:58.223 and M So one is kind of ubiquitous

NOTE Confidence: 0.867402208

00:02:58.292 --> 00:03:00.512 and I think in SO2 must B cell XL is

NOTE Confidence: 0.867402208

00:03:00.520 --> 00:03:03.760 a primary anti apoptotic molecule.

NOTE Confidence: 0.867402208

00:03:03.760 --> 00:03:06.350 The way the system works is by

NOTE Confidence: 0.867402208

00:03:06.350 --> 00:03:09.006 dimerization of anti apoptotic with a

NOTE Confidence: 0.867402208

00:03:09.006 --> 00:03:11.492 propoptotic family members and there are

NOTE Confidence: 0.867402208

00:03:11.492 --> 00:03:13.976 quite a few of those as well So bags.

NOTE Confidence: 0.867402208

00:03:13.976 --> 00:03:16.920 I will talk to you several times in my talk.

NOTE Confidence: 0.867402208

00:03:16.920 --> 00:03:18.915 So this is what we call execution

NOTE Confidence: 0.867402208

00:03:18.915 --> 00:03:20.320 of cell death protein.

NOTE Confidence: 0.867402208

00:03:20.320 --> 00:03:22.448 So essentially kills the cells by making

NOTE Confidence: 0.867402208

00:03:22.448 --> 00:03:24.341 pores in the mitochondria membrane

NOTE Confidence: 0.867402208

00:03:24.341 --> 00:03:26.636 and inducing cytochrome C release.

NOTE Confidence: 0.867402208

00:03:26.640 --> 00:03:28.749 And then there are a lot of this will be A

NOTE Confidence: 0.867402208

00:03:28.749 --> 00:03:30.597 share only proteins which essentially bind B,

NOTE Confidence: 0.867402208

00:03:30.600 --> 00:03:34.320 so two or others and inhibit their function

NOTE Confidence: 0.867402208

00:03:34.320 --> 00:03:36.200 because it works through demoralization.

NOTE Confidence: 0.867402208

00:03:36.200 --> 00:03:38.432 You can actually inhibit the function

NOTE Confidence: 0.867402208

00:03:38.432 --> 00:03:42.423 of B so 2 by inhibiting the protein

NOTE Confidence: 0.867402208

00:03:42.423 --> 00:03:44.218 protein interactions between for

NOTE Confidence: 0.867402208

00:03:44.218 --> 00:03:46.530 example B so two and some of this

NOTE Confidence: 0.867402208

00:03:46.600 --> 00:03:49.029 protest proteins and as a result you'll

NOTE Confidence: 0.867402208

00:03:49.029 --> 00:03:51.297 have a release of this propagatoric

NOTE Confidence: 0.867402208

00:03:51.297 --> 00:03:53.999 members and killing of the cell deaths.

NOTE Confidence: 0.867402208

00:03:54.000 --> 00:03:58.057 So this was pioneered in the first attempt.

NOTE Confidence: 0.867402208

00:03:58.057 --> 00:04:00.925 This was a paper back in 2005.

NOTE Confidence: 0.867402208

00:04:00.925 --> 00:04:03.845 At the time the company was called Abbott

NOTE Confidence: 0.867402208

00:04:03.845 --> 00:04:06.793 and they designed the first protein

NOTE Confidence: 0.867402208

00:04:06.793 --> 00:04:10.360 protein inhibitor which was called Abt 737.

NOTE Confidence: 0.867402208

00:04:10.360 --> 00:04:11.718 So this was a work from Steven,

NOTE Confidence: 0.867402208

00:04:11.720 --> 00:04:12.232 Fasig,

NOTE Confidence: 0.867402208

00:04:12.232 --> 00:04:14.813 Sol Rosenberg and others that

NOTE Confidence: 0.867402208

00:04:14.813 --> 00:04:17.478 effectively inhibited the BCL two.

NOTE Confidence: 0.867402208

00:04:17.480 --> 00:04:18.965 So the structure here is

NOTE Confidence: 0.867402208

00:04:18.965 --> 00:04:20.680 actually the structure of BCL XL.

NOTE Confidence: 0.867402208

00:04:20.680 --> 00:04:23.760 So they used the NMR based technology to

NOTE Confidence: 0.867402208

00:04:23.760 --> 00:04:26.057 engineer this molecule and green protein

NOTE Confidence: 0.867402208

00:04:26.057 --> 00:04:30.439 here is one of this proteins called back.

NOTE Confidence: 0.867402208

00:04:30.440 --> 00:04:32.960 It's not even here but it's one of the BHA.

NOTE Confidence: 0.867402208

00:04:32.960 --> 00:04:35.240 On your proteins there's some critical

NOTE Confidence: 0.867402208

00:04:35.240 --> 00:04:37.258 critical rates reduced how it binds

NOTE Confidence: 0.867402208

00:04:37.258 --> 00:04:39.350 to B cell XL and this is the actual

NOTE Confidence: 0.867402208

00:04:39.350 --> 00:04:41.436 molecule which you can see it sits

NOTE Confidence: 0.867402208

00:04:41.436 --> 00:04:44.120 into that pocket and this mimics the

NOTE Confidence: 0.867402208

00:04:44.120 --> 00:04:46.920 B back interaction with B cell XL.

NOTE Confidence: 0.867402208

00:04:46.920 --> 00:04:50.280 In this matter there's another structure,

NOTE Confidence: 0.867402208

00:04:50.280 --> 00:04:52.680 this is pretty large molecule about

NOTE Confidence: 0.867402208

00:04:52.680 --> 00:04:56.336 960 KD but this was the 1st and I

NOTE Confidence: 0.867402208

00:04:56.336 --> 00:04:57.976 think the most successful protein

NOTE Confidence: 0.867402208

00:04:57.976 --> 00:04:58.960 protein inhibitor interaction.

NOTE Confidence: 0.867402208

00:04:58.960 --> 00:05:01.744 I think the only other class that I'm

NOTE Confidence: 0.867402208

00:05:01.744 --> 00:05:04.465 aware of MDM 2P53 inhibitors but they

NOTE Confidence: 0.867402208

00:05:04.465 --> 00:05:07.400 still not approved due to toxicities.

NOTE Confidence: 0.867402208

00:05:07.400 --> 00:05:10.040 Now this molecule was A2 molecule

NOTE Confidence: 0.867402208

00:05:10.040 --> 00:05:12.372 and it's analogue called Navidoclax

NOTE Confidence: 0.867402208

00:05:12.372 --> 00:05:14.837 did go into clinical trials,

NOTE Confidence: 0.867402208

00:05:14.840 --> 00:05:16.736 but because it blocked both BCL

NOTE Confidence: 0.867402208

00:05:16.736 --> 00:05:18.000 XL and BCL two,

NOTE Confidence: 0.867402208

00:05:18.000 --> 00:05:20.790 it encountered some toxicities in the

NOTE Confidence: 0.867402208

00:05:20.790 --> 00:05:23.124 form of thrombocytopenia because BCL

NOTE Confidence: 0.867402208

00:05:23.124 --> 00:05:25.518 XL is important for plated production.

NOTE Confidence: 0.867402208

00:05:25.520 --> 00:05:26.915 But I'll get back to you in the end.

NOTE Confidence: 0.867402208

00:05:26.920 --> 00:05:29.391 I think BCL XL targeting is very

NOTE Confidence: 0.867402208

00:05:29.391 --> 00:05:30.450 important and there

NOTE Confidence: 0.839489687777778

00:05:30.522 --> 00:05:33.234 are other ways of safely inhibit BCL XL.

NOTE Confidence: 0.839489687777778

00:05:33.240 --> 00:05:35.556 So Nabilox is still not approved.

NOTE Confidence: 0.839489687777778

00:05:35.560 --> 00:05:39.875 And so moving forward in 2013,

NOTE Confidence: 0.839489687777778

00:05:39.875 --> 00:05:42.360 the same company now it's called Abbi

NOTE Confidence: 0.839489687777778

00:05:42.360 --> 00:05:44.505 engineered the original molecule and

NOTE Confidence: 0.839489687777778

00:05:44.505 --> 00:05:47.880 they got rid of BCL XL interaction.

NOTE Confidence: 0.839489687777778

00:05:47.880 --> 00:05:49.725 So apparently this aspartate one

NOTE Confidence: 0.839489687777778

00:05:49.725 --> 00:05:52.846 O 3 is a critical residue which is

NOTE Confidence: 0.839489687777778

00:05:52.846 --> 00:05:55.639 different between BCL two and BCL XL.

NOTE Confidence: 0.839489687777778

00:05:55.640 --> 00:05:57.530 And so they engineered the new

NOTE Confidence: 0.839489687777778

00:05:57.530 --> 00:05:59.623 molecule that had now very specific

NOTE Confidence: 0.839489687777778

00:05:59.623 --> 00:06:01.159 BCL two only properties.

NOTE Confidence: 0.839489687777778

00:06:01.160 --> 00:06:03.824 So it only bound BCL two was about

NOTE Confidence: 0.839489687777778

00:06:03.824 --> 00:06:06.492 10 times more important than original

NOTE Confidence: 0.839489687777778

00:06:06.492 --> 00:06:09.999 nebidoclax and it did not inhibit BCL XL.

NOTE Confidence: 0.839489687777778

00:06:10.000 --> 00:06:12.024 And this is what we now know

NOTE Confidence: 0.839489687777778

00:06:12.024 --> 00:06:13.720 as the neto clocks,

NOTE Confidence: 0.839489687777778

00:06:13.720 --> 00:06:16.107 the drug that is approved for several

NOTE Confidence: 0.839489687777778

00:06:16.107 --> 00:06:17.960 types of hematologic malignancies.

NOTE Confidence: 0.839489687777778

00:06:17.960 --> 00:06:19.892 And of course it's paid playlists

NOTE Confidence: 0.839489687777778

00:06:19.892 --> 00:06:22.357 because it did not inhibit B cell XL.

NOTE Confidence: 0.839489687777778

00:06:22.360 --> 00:06:24.236 So I said I work on B.

NOTE Confidence: 0.839489687777778

00:06:24.240 --> 00:06:25.675 So too when I came to us,

NOTE Confidence: 0.839489687777778

00:06:25.680 --> 00:06:27.560 that was my first project at the time.

NOTE Confidence: 0.839489687777778

00:06:27.560 --> 00:06:29.400 We initially used the antisense,

NOTE Confidence: 0.839489687777778

00:06:29.400 --> 00:06:31.437 but antisense didn't make it in clinic.

NOTE Confidence: 0.839489687777778

00:06:31.440 --> 00:06:32.920 They were not effective enough,

NOTE Confidence: 0.839489687777778

00:06:32.920 --> 00:06:34.258 not specific enough.

NOTE Confidence: 0.839489687777778

00:06:34.258 --> 00:06:36.488 And then when the original

NOTE Confidence: 0.839489687777778

00:06:36.488 --> 00:06:38.119 camp compound came out,

NOTE Confidence: 0.839489687777778

00:06:38.120 --> 00:06:40.320 we developed the story on

NOTE Confidence: 0.839489687777778

00:06:40.320 --> 00:06:43.252 AML and BCO 2 with ABT 737,

NOTE Confidence: 0.839489687777778

00:06:43.252 --> 00:06:45.075 which were published in 2006.

NOTE Confidence: 0.839489687777778

00:06:45.075 --> 00:06:47.915 And then when the new compound came out,

NOTE Confidence: 0.839489687777778

00:06:47.920 --> 00:06:49.180 because Nevada clocks never

NOTE Confidence: 0.839489687777778

00:06:49.180 --> 00:06:50.755 made it to AML trials,

NOTE Confidence: 0.839489687777778

00:06:50.760 --> 00:06:51.091 again,

NOTE Confidence: 0.839489687777778

00:06:51.091 --> 00:06:53.077 AML patients as you know have

NOTE Confidence: 0.839489687777778

00:06:53.077 --> 00:06:54.998 all low platelets to start with.

NOTE Confidence: 0.839489687777778

00:06:55.000 --> 00:06:57.224 So it was kind of impossible at the

NOTE Confidence: 0.839489687777778

00:06:57.224 --> 00:06:59.599 time to transition into AML trials.

NOTE Confidence: 0.839489687777778

00:06:59.600 --> 00:07:01.000 When the newcomer came out,

NOTE Confidence: 0.839489687777778

00:07:01.000 --> 00:07:03.240 we teamed up with a Tony Litais lab

NOTE Confidence: 0.839489687777778

00:07:03.240 --> 00:07:05.325 at Denif Harbor and we worked for

NOTE Confidence: 0.839489687777778

00:07:05.325 --> 00:07:07.916 a year between two of our labs and

NOTE Confidence: 0.839489687777778

00:07:07.916 --> 00:07:09.681 published a cancer discovery paper

NOTE Confidence: 0.839489687777778

00:07:09.681 --> 00:07:12.206 in 2014 showing that the Nanoclax is

NOTE Confidence: 0.839489687777778

00:07:12.206 --> 00:07:14.178 highly effective in acute myeloid

NOTE Confidence: 0.839489687777778

00:07:14.178 --> 00:07:16.038 leukemia pre clinical studies.

NOTE Confidence: 0.839489687777778

00:07:16.040 --> 00:07:16.272 So,

NOTE Confidence: 0.839489687777778

00:07:16.272 --> 00:07:17.896 so these are just I'm not going

NOTE Confidence: 0.839489687777778

00:07:17.896 --> 00:07:20.078 to go through the paper or data

NOTE Confidence: 0.839489687777778

00:07:20.078 --> 00:07:21.074 that's all published,

NOTE Confidence: 0.839489687777778

00:07:21.080 --> 00:07:23.520 but these are just mRNA level for B,

NOTE Confidence: 0.839489687777778

00:07:23.520 --> 00:07:26.088 so two amongst different types of

NOTE Confidence: 0.839489687777778

00:07:26.088 --> 00:07:28.245 leukemia and the red line represents

NOTE Confidence: 0.839489687777778

00:07:28.245 --> 00:07:30.648 to the normal uninvolved bone marrow.

NOTE Confidence: 0.839489687777778

00:07:30.648 --> 00:07:33.840 This was from a Hyperlux MLL collection.

NOTE Confidence: 0.839489687777778

00:07:33.840 --> 00:07:35.856 So you can see that majority of

NOTE Confidence: 0.839489687777778

00:07:35.856 --> 00:07:38.191 AML this is log scale have upper

NOTE Confidence: 0.839489687777778

00:07:38.191 --> 00:07:39.595 related mRNA for BC2.

NOTE Confidence: 0.839489687777778

00:07:39.600 --> 00:07:41.072 There's some examples here,

NOTE Confidence: 0.839489687777778

00:07:41.072 --> 00:07:42.912 some some some that don't.

NOTE Confidence: 0.839489687777778

00:07:42.920 --> 00:07:45.440 For example this inversion 3 AML do not,

NOTE Confidence: 0.839489687777778

00:07:45.440 --> 00:07:49.160 but majority have high levels of BC two.

NOTE Confidence: 0.839489687777778

00:07:49.160 --> 00:07:51.080 We also show that it's expressed

NOTE Confidence: 0.839489687777778

00:07:51.080 --> 00:07:52.918 on leukemia stem cells and then

NOTE Confidence: 0.839489687777778

00:07:52.918 --> 00:07:54.918 we show that if you target BC two,

NOTE Confidence: 0.839489687777778

00:07:54.920 --> 00:07:57.344 you eliminate AML blasts and AML

NOTE Confidence: 0.839489687777778

00:07:57.344 --> 00:07:59.600 stem cells to some extent.

NOTE Confidence: 0.839489687777778

00:07:59.600 --> 00:08:02.120 And also the compound had efficacy in vivo,

NOTE Confidence: 0.839489687777778

00:08:02.120 --> 00:08:03.308 although by itself it,

NOTE Confidence: 0.839489687777778

00:08:03.308 --> 00:08:05.580 it was not curative and it wasn't

NOTE Confidence: 0.839489687777778

00:08:05.580 --> 00:08:07.280 curative in patients either.

NOTE Confidence: 0.839489687777778

00:08:07.280 --> 00:08:10.760 So this work in conjunction with

NOTE Confidence: 0.839489687777778

00:08:10.760 --> 00:08:12.680 the CLL data that Amar mentioned.

NOTE Confidence: 0.839489687777778

00:08:12.680 --> 00:08:15.158 So that time the Netflix was already

NOTE Confidence: 0.839489687777778

00:08:15.158 --> 00:08:17.919 in CLL trials and was very effective.

NOTE Confidence: 0.839489687777778

00:08:17.920 --> 00:08:20.002 It caused tumorlysis and actually they

NOTE Confidence: 0.839489687777778

00:08:20.002 --> 00:08:22.239 had some deaths because of tumorlysis.

NOTE Confidence: 0.839489687777778

00:08:22.240 --> 00:08:25.072 So it's CLL is super dependent on B, so true.

NOTE Confidence: 0.839489687777778

00:08:25.072 --> 00:08:26.920 So it's like the primary B,

NOTE Confidence: 0.839489687777778

00:08:26.920 --> 00:08:28.360 so two dependent disease,

NOTE Confidence: 0.891740146666667

00:08:28.360 --> 00:08:30.520 but we already knew the dose,

NOTE Confidence: 0.891740146666667

00:08:30.520 --> 00:08:33.028 we knew the safety profile of

NOTE Confidence: 0.891740146666667

00:08:33.028 --> 00:08:35.080 this molecules was fairly safe

NOTE Confidence: 0.891740146666667

00:08:35.080 --> 00:08:37.124 besides this tumuliser syndrome.

NOTE Confidence: 0.891740146666667

00:08:37.124 --> 00:08:40.733 So it was sort of sufficient based

NOTE Confidence: 0.891740146666667

00:08:40.733 --> 00:08:43.445 on this work to take venetoclax

NOTE Confidence: 0.891740146666667

00:08:43.445 --> 00:08:46.320 into AML relapse refractory study.

NOTE Confidence: 0.891740146666667

00:08:46.320 --> 00:08:49.182 So this study was conducted between

NOTE Confidence: 0.891740146666667

00:08:49.182 --> 00:08:51.610 different institutions and was published

NOTE Confidence: 0.891740146666667

00:08:51.610 --> 00:08:54.232 in cancer discovery back in 2016.

NOTE Confidence: 0.891740146666667

00:08:54.232 --> 00:08:56.584 So initially we projected that we're

NOTE Confidence: 0.891740146666667

00:08:56.584 --> 00:08:59.398 going to treat 50ML patients and we

NOTE Confidence: 0.891740146666667

00:08:59.398 --> 00:09:02.027 were hoping for response rate around 40

NOTE Confidence: 0.891740146666667

00:09:02.027 --> 00:09:04.600 to 50% based on our preclinical work.

NOTE Confidence: 0.891740146666667

00:09:04.600 --> 00:09:06.840 And I have to say that this did not pan out.

NOTE Confidence: 0.891740146666667

00:09:06.840 --> 00:09:09.344 So we learned that AML is way too

NOTE Confidence: 0.891740146666667

00:09:09.344 --> 00:09:11.444 complicated and probably our preclinical

NOTE Confidence: 0.891740146666667

00:09:11.444 --> 00:09:13.779 models do not really faithfully

NOTE Confidence: 0.891740146666667

00:09:13.779 --> 00:09:16.319 recapitulate the response in in patients.

NOTE Confidence: 0.891740146666667

00:09:16.320 --> 00:09:17.564 So the response rate,

NOTE Confidence: 0.891740146666667

00:09:17.564 --> 00:09:19.430 objective response rate in the trial

NOTE Confidence: 0.891740146666667

00:09:19.490 --> 00:09:23.240 was only 19% with the CRCRI rates,

NOTE Confidence: 0.891740146666667

00:09:23.240 --> 00:09:25.610 but about 50% of patients did

NOTE Confidence: 0.891740146666667

00:09:25.610 --> 00:09:27.684 have blast reductions as shown

NOTE Confidence: 0.891740146666667

00:09:27.684 --> 00:09:29.759 here on this waterfall plot.

NOTE Confidence: 0.891740146666667

00:09:29.760 --> 00:09:32.064 And then there were some subsets of patients

NOTE Confidence: 0.891740146666667

00:09:32.064 --> 00:09:34.279 who tend to be more sensitive to that.

NOTE Confidence: 0.891740146666667

00:09:34.280 --> 00:09:34.952 For example,

NOTE Confidence: 0.891740146666667

00:09:34.952 --> 00:09:37.400 patients who had IDH 1-2 mutations,

NOTE Confidence: 0.891740146666667

00:09:37.400 --> 00:09:40.280 they generally had response and the

NOTE Confidence: 0.891740146666667

00:09:40.280 --> 00:09:42.912 response among those was about 32%.

NOTE Confidence: 0.891740146666667

00:09:42.912 --> 00:09:44.800 So that was encouraging.

NOTE Confidence: 0.891740146666667

00:09:44.800 --> 00:09:45.895 And in fact,

NOTE Confidence: 0.891740146666667

00:09:45.895 --> 00:09:48.302 we enriched the study for the IDH

NOTE Confidence: 0.891740146666667

00:09:48.302 --> 00:09:49.872 1-2 mutated patients because at

NOTE Confidence: 0.891740146666667

00:09:49.872 --> 00:09:52.159 the same time the paper came out

NOTE Confidence: 0.891740146666667

00:09:52.159 --> 00:09:53.565 from Stanford showing that this

NOTE Confidence: 0.891740146666667

00:09:53.565 --> 00:09:55.350 subset of AML is highly be so

NOTE Confidence: 0.891740146666667

00:09:55.406 --> 00:09:57.359 dependent and that turns to be true.

NOTE Confidence: 0.891740146666667

00:09:57.360 --> 00:09:58.932 Till now this patients respond very

NOTE Confidence: 0.891740146666667

00:09:58.932 --> 00:10:01.852 well to nine, 8:00 to 9:00, sorry,

NOTE Confidence: 0.891740146666667

00:10:01.852 --> 00:10:04.517 but essentially that was encouraging,

NOTE Confidence: 0.891740146666667

00:10:04.520 --> 00:10:06.473 but it was clearly not enough for

NOTE Confidence: 0.891740146666667

00:10:06.473 --> 00:10:08.748 to get this drug approved as a

NOTE Confidence: 0.891740146666667

00:10:08.748 --> 00:10:10.800 single agent in the salvage setting.

NOTE Confidence: 0.891740146666667

00:10:10.800 --> 00:10:13.072 And of course for me as a researcher

NOTE Confidence: 0.891740146666667

00:10:13.072 --> 00:10:14.636 that was disappointment because I

NOTE Confidence: 0.891740146666667

00:10:14.636 --> 00:10:16.960 thought this was like the best drug

NOTE Confidence: 0.891740146666667

00:10:17.017 --> 00:10:18.785 I ever had in the lab and still

NOTE Confidence: 0.891740146666667

00:10:18.785 --> 00:10:20.559 it's not you know curing people.

NOTE Confidence: 0.891740146666667

00:10:20.560 --> 00:10:22.534 The duration of responses was also

NOTE Confidence: 0.891740146666667

00:10:22.534 --> 00:10:24.637 pretty sure about three to six months

NOTE Confidence: 0.891740146666667

00:10:24.637 --> 00:10:27.120 and all patients progressed after that.

NOTE Confidence: 0.891740146666667

00:10:27.120 --> 00:10:29.490 So fortunately the story did not

NOTE Confidence: 0.891740146666667

00:10:29.490 --> 00:10:32.080 stop at this point as you know.

NOTE Confidence: 0.891740146666667

00:10:32.080 --> 00:10:35.314 And so why we think that AML

NOTE Confidence: 0.891740146666667

00:10:35.320 --> 00:10:36.320 in AML target and B,

NOTE Confidence: 0.891740146666667

00:10:36.320 --> 00:10:38.678 so two alone is not sufficient?

NOTE Confidence: 0.891740146666667

00:10:38.680 --> 00:10:38.984 Well,

NOTE Confidence: 0.891740146666667

00:10:38.984 --> 00:10:39.896 first of all,

NOTE Confidence: 0.891740146666667

00:10:39.896 --> 00:10:41.416 because there's a redundancy and

NOTE Confidence: 0.891740146666667

00:10:41.416 --> 00:10:43.080 expression of BCL two family proteins.

NOTE Confidence: 0.891740146666667

00:10:43.080 --> 00:10:45.195 So if you just look at this western blood,

NOTE Confidence: 0.891740146666667

00:10:45.200 --> 00:10:47.870 this is from Andrew Ways publication

NOTE Confidence: 0.891740146666667

00:10:47.870 --> 00:10:50.475 and BCL two is almost ubiquitously

NOTE Confidence: 0.891740146666667

00:10:50.475 --> 00:10:52.199 expressed at high levels.

NOTE Confidence: 0.891740146666667

00:10:52.200 --> 00:10:54.648 BCL XL is usually not expressed

NOTE Confidence: 0.891740146666667

00:10:54.648 --> 00:10:55.872 or low expressed.

NOTE Confidence: 0.891740146666667

00:10:55.880 --> 00:10:58.148 But I'll tell you which subsets

NOTE Confidence: 0.891740146666667

00:10:58.148 --> 00:11:01.080 do have BCL XL And then there's

NOTE Confidence: 0.891740146666667

00:11:01.080 --> 00:11:03.744 MCL one which is mildly specific

NOTE Confidence: 0.891740146666667

00:11:03.744 --> 00:11:06.304 sort of BCL two family member,

NOTE Confidence: 0.891740146666667

00:11:06.304 --> 00:11:08.634 it's ubiquitously expressed as well.

NOTE Confidence: 0.891740146666667

00:11:08.640 --> 00:11:10.740 So you can imagine that if

NOTE Confidence: 0.891740146666667

00:11:10.740 --> 00:11:12.840 you target only be so true,

NOTE Confidence: 0.891740146666667

00:11:12.840 --> 00:11:15.576 you leave some other members untouched

NOTE Confidence: 0.891740146666667

00:11:15.576 --> 00:11:17.817 and therefore cells probably quickly

NOTE Confidence: 0.891740146666667

00:11:17.817 --> 00:11:20.632 adapt to the this effect and they

NOTE Confidence: 0.891740146666667

00:11:20.632 --> 00:11:22.872 rewire and they become resistant.

NOTE Confidence: 0.891740146666667

00:11:22.880 --> 00:11:24.756 So how can you get around that?

NOTE Confidence: 0.891740146666667

00:11:24.760 --> 00:11:27.280 So the next thing is that any

NOTE Confidence: 0.891740146666667

00:11:27.280 --> 00:11:29.156 type of chemotherapy can actually

NOTE Confidence: 0.891740146666667

00:11:29.156 --> 00:11:31.754 in the setting of wild type B53

NOTE Confidence: 0.891740146666667

00:11:31.754 --> 00:11:33.924 can induce expression of this

NOTE Confidence: 0.891740146666667

00:11:33.924 --> 00:11:35.660 proprietoric family members that

NOTE Confidence: 0.752763328148148

00:11:35.729 --> 00:11:38.165 I mentioned before what we call BHA

NOTE Confidence: 0.752763328148148

00:11:38.165 --> 00:11:40.240 only proteins and this PH3 only

NOTE Confidence: 0.752763328148148

00:11:40.240 --> 00:11:43.095 proteins can in fact inhibit MCO one.

NOTE Confidence: 0.752763328148148

00:11:43.095 --> 00:11:45.720 So as you can envision,

NOTE Confidence: 0.752763328148148

00:11:45.720 --> 00:11:47.540 you can have synergy between

NOTE Confidence: 0.752763328148148

00:11:47.540 --> 00:11:49.828 venetoclax and pretty much any type

NOTE Confidence: 0.752763328148148

00:11:49.828 --> 00:11:51.833 of chemotherapy that would induce

NOTE Confidence: 0.752763328148148

00:11:51.833 --> 00:11:53.600 this response and then you inhibit B.

NOTE Confidence: 0.752763328148148

00:11:53.600 --> 00:11:55.610 So two, so you sensitize the

NOTE Confidence: 0.752763328148148

00:11:55.610 --> 00:11:57.792 cells and then there's bags back

NOTE Confidence: 0.752763328148148

00:11:57.792 --> 00:11:59.717 interaction and the cell death.

NOTE Confidence: 0.752763328148148

00:11:59.720 --> 00:12:02.168 So practically speaking this went into

NOTE Confidence: 0.752763328148148

00:12:02.168 --> 00:12:04.765 development in all the AML patients

NOTE Confidence: 0.752763328148148

00:12:04.765 --> 00:12:07.005 unfit for chemotherapy because for

NOTE Confidence: 0.752763328148148

00:12:07.005 --> 00:12:09.629 younger patients we had 7 + 3 which

NOTE Confidence: 0.752763328148148

00:12:09.629 --> 00:12:11.212 we still have and they were doing

NOTE Confidence: 0.752763328148148

00:12:11.212 --> 00:12:12.277 pretty well with the transplant.

NOTE Confidence: 0.752763328148148

00:12:12.280 --> 00:12:14.317 But for all the patients there was

NOTE Confidence: 0.752763328148148

00:12:14.317 --> 00:12:16.198 really like no standard of care

NOTE Confidence: 0.752763328148148

00:12:16.200 --> 00:12:18.200 low dosa turbine or hypermethylene

NOTE Confidence: 0.752763328148148

00:12:18.200 --> 00:12:19.800 agents have been used.

NOTE Confidence: 0.752763328148148

00:12:19.800 --> 00:12:22.644 So I have to say that based on the

NOTE Confidence: 0.752763328148148

00:12:22.644 --> 00:12:24.879 clinical need more than the signs,

NOTE Confidence: 0.752763328148148

00:12:24.880 --> 00:12:26.945 the combination trials were with

NOTE Confidence: 0.752763328148148

00:12:26.945 --> 00:12:29.010 hypermethylene agents and low dose

NOTE Confidence: 0.752763328148148

00:12:29.076 --> 00:12:31.332 Iturbin and all done fit there

NOTE Confidence: 0.752763328148148

00:12:31.332 --> 00:12:32.836 for chemotherapy AML patients.

NOTE Confidence: 0.752763328148148

00:12:32.840 --> 00:12:35.080 And this were the results of the

NOTE Confidence: 0.752763328148148

00:12:35.080 --> 00:12:37.380 initial Phase 1B study when the

NOTE Confidence: 0.752763328148148

00:12:37.380 --> 00:12:39.455 Vanetta glass was combined either

NOTE Confidence: 0.752763328148148

00:12:39.455 --> 00:12:42.396 with azacitidine or with a decitabine,

NOTE Confidence: 0.752763328148148

00:12:42.400 --> 00:12:44.365 hypermethylene agents or even with

NOTE Confidence: 0.752763328148148

00:12:44.365 --> 00:12:46.767 low dose Iturbin which by itself

NOTE Confidence: 0.752763328148148

00:12:46.767 --> 00:12:48.957 has very little activity in AML.

NOTE Confidence: 0.752763328148148

00:12:48.960 --> 00:12:51.291 And you can see here that well you know

NOTE Confidence: 0.752763328148148

00:12:51.291 --> 00:12:53.438 this was a newly diagnosed patients.

NOTE Confidence: 0.752763328148148

00:12:53.440 --> 00:12:55.336 So was very rapidly was transitioned

NOTE Confidence: 0.752763328148148

00:12:55.336 --> 00:12:57.591 to the newly diagnosed CML which I

NOTE Confidence: 0.752763328148148

00:12:57.591 --> 00:12:59.146 think was another difference with

NOTE Confidence: 0.752763328148148

00:12:59.146 --> 00:13:00.979 the original trial that we used

NOTE Confidence: 0.752763328148148

00:13:00.979 --> 00:13:02.424 where we used phonetically where

NOTE Confidence: 0.752763328148148

00:13:02.424 --> 00:13:04.268 it was relapsed refractory setting.

NOTE Confidence: 0.752763328148148

00:13:04.268 --> 00:13:07.426 But you can see that you know majority

NOTE Confidence: 0.752763328148148

00:13:07.426 --> 00:13:09.706 of patients in fact responded and

NOTE Confidence: 0.752763328148148

00:13:09.706 --> 00:13:12.039 they did achieve like true CRS.

NOTE Confidence: 0.752763328148148

00:13:12.040 --> 00:13:13.612 There was some of those escalation

NOTE Confidence: 0.752763328148148

00:13:13.612 --> 00:13:14.398 findings as well,

NOTE Confidence: 0.752763328148148

00:13:14.400 --> 00:13:16.465 but eventually 400 milligram ended

NOTE Confidence: 0.752763328148148

00:13:16.465 --> 00:13:19.120 up the right dose for the HMA

NOTE Confidence: 0.752763328148148

00:13:19.120 --> 00:13:20.680 and 600 for the low dose,

NOTE Confidence: 0.752763328148148

00:13:20.680 --> 00:13:22.099 high turbine combination.

NOTE Confidence: 0.752763328148148

00:13:22.099 --> 00:13:23.518 So the responses,

NOTE Confidence: 0.752763328148148

00:13:23.520 --> 00:13:25.482 the responses tend to be durable

NOTE Confidence: 0.752763328148148

00:13:25.482 --> 00:13:27.880 and there was very little toxicity.

NOTE Confidence: 0.752763328148148

00:13:27.880 --> 00:13:29.812 So suddenly the all the patients

NOTE Confidence: 0.752763328148148

00:13:29.812 --> 00:13:31.821 which for which we didn't really

NOTE Confidence: 0.752763328148148

00:13:31.821 --> 00:13:33.789 have QS before in one month

NOTE Confidence: 0.752763328148148

00:13:33.789 --> 00:13:35.839 that we're going into remission,

NOTE Confidence: 0.752763328148148

00:13:35.840 --> 00:13:37.320 the infections and mouse suppression

NOTE Confidence: 0.752763328148148

00:13:37.320 --> 00:13:38.800 was still the main toxicity.

NOTE Confidence: 0.752763328148148

00:13:38.800 --> 00:13:40.767 But other than that we didn't see

NOTE Confidence: 0.752763328148148

00:13:40.767 --> 00:13:42.439 like much effects on the kidney,

NOTE Confidence: 0.752763328148148

00:13:42.440 --> 00:13:44.672 liver or anything which was to me always

NOTE Confidence: 0.752763328148148

00:13:44.672 --> 00:13:46.726 the most surprising thing because B

NOTE Confidence: 0.752763328148148

00:13:46.726 --> 00:13:48.880 so two is so ubiquitously expressed.

NOTE Confidence: 0.752763328148148

00:13:48.880 --> 00:13:50.305 So who could imagine that

NOTE Confidence: 0.752763328148148

00:13:50.305 --> 00:13:52.280 targeting B so two is so safe.

NOTE Confidence: 0.752763328148148

00:13:52.280 --> 00:13:53.995 I think before we go into clinic,

NOTE Confidence: 0.752763328148148

00:13:54.000 --> 00:13:57.318 we can never really predict what happens.

NOTE Confidence: 0.752763328148148

00:13:57.320 --> 00:13:59.895 And then eventually this resulted

NOTE Confidence: 0.752763328148148

00:13:59.895 --> 00:14:03.009 in the randomized phase three study

NOTE Confidence: 0.752763328148148

00:14:03.009 --> 00:14:05.344 called VLA study where VENESA,

NOTE Confidence: 0.752763328148148

00:14:05.344 --> 00:14:08.296 what we call venetocide was randomized

NOTE Confidence: 0.752763328148148

00:14:08.296 --> 00:14:10.918 to azacide and placebo control.

NOTE Confidence: 0.752763328148148

00:14:10.920 --> 00:14:13.258 It was 2 to 1 randomization and

NOTE Confidence: 0.752763328148148

00:14:13.258 --> 00:14:16.386 this was for all the patients with

NOTE Confidence: 0.752763328148148

00:14:16.386 --> 00:14:18.434 AML ineligible for chemotherapy.

NOTE Confidence: 0.752763328148148

00:14:18.440 --> 00:14:21.016 The median age was close to 70

NOTE Confidence: 0.752763328148148

00:14:21.016 --> 00:14:23.060 years old and you can see that

NOTE Confidence: 0.752763328148148

00:14:23.060 --> 00:14:24.235 there's far as response rate,

NOTE Confidence: 0.752763328148148

00:14:24.240 --> 00:14:26.185 majority of the patients achieved

NOTE Confidence: 0.752763328148148

00:14:26.185 --> 00:14:28.130 response it was which was

NOTE Confidence: 0.752763328148148

00:14:28.203 --> 00:14:29.918 in the range of 60 to 70%.

NOTE Confidence: 0.752763328148148

00:14:29.920 --> 00:14:32.164 There was lower in PPG mutated

NOTE Confidence: 0.752763328148148

00:14:32.164 --> 00:14:34.666 AML which we learned later is a

NOTE Confidence: 0.752763328148148

00:14:34.666 --> 00:14:36.396 a prom for this approach.

NOTE Confidence: 0.896374091428571

00:14:36.400 --> 00:14:38.514 But overall there was high response rate,

NOTE Confidence: 0.896374091428571

00:14:38.520 --> 00:14:41.280 but most important there was survival

NOTE Confidence: 0.896374091428571

00:14:41.280 --> 00:14:43.864 advantage compared with ASA with medium

NOTE Confidence: 0.896374091428571

00:14:43.864 --> 00:14:46.468 overall survival of about 14 months and

NOTE Confidence: 0.896374091428571

00:14:46.468 --> 00:14:48.954 compared to nine months with ASA cited in.

NOTE Confidence: 0.896374091428571

00:14:48.960 --> 00:14:52.668 So this LED in 2018 to the accelerated

NOTE Confidence: 0.896374091428571

00:14:52.668 --> 00:14:55.742 approval of the Naglo X and AML and

NOTE Confidence: 0.896374091428571

00:14:55.742 --> 00:14:58.304 subsequently to the full approval in

NOTE Confidence: 0.896374091428571

00:14:58.304 --> 00:15:00.360 combination with the chemotherapy

NOTE Confidence: 0.896374091428571

00:15:00.360 --> 00:15:02.118 low Dosa turbine is also approved.

NOTE Confidence: 0.896374091428571

00:15:02.120 --> 00:15:03.695 But even though they missed

NOTE Confidence: 0.896374091428571

00:15:03.695 --> 00:15:04.640 the primary endpoint,

NOTE Confidence: 0.896374091428571

00:15:04.640 --> 00:15:07.118 but the overall survival was still better.

NOTE Confidence: 0.896374091428571

00:15:07.120 --> 00:15:10.452 But I think it's very rarely used

NOTE Confidence: 0.896374091428571

00:15:10.452 --> 00:15:12.999 in United States and this survival

NOTE Confidence: 0.896374091428571

00:15:12.999 --> 00:15:15.237 is shorter only about nine months.

NOTE Confidence: 0.896374091428571

00:15:15.240 --> 00:15:17.608 So this is like what Amar said is

NOTE Confidence: 0.896374091428571

00:15:17.608 --> 00:15:19.280 considered to be breakthrough.

NOTE Confidence: 0.896374091428571

00:15:19.280 --> 00:15:21.359 But you know if you look at the curves,

NOTE Confidence: 0.896374091428571

00:15:21.360 --> 00:15:23.384 you can say that is this really like

NOTE Confidence: 0.896374091428571

00:15:23.384 --> 00:15:24.798 a breakthrough because majority of

NOTE Confidence: 0.896374091428571

00:15:24.798 --> 00:15:26.514 the patients are still you know,

NOTE Confidence: 0.896374091428571

00:15:26.520 --> 00:15:27.928 dying from their disease.

NOTE Confidence: 0.896374091428571

00:15:27.928 --> 00:15:30.040 Initially it seemed to be like

NOTE Confidence: 0.896374091428571

00:15:30.103 --> 00:15:31.359 plateau here at 30%.

NOTE Confidence: 0.896374091428571

00:15:31.360 --> 00:15:33.632 So now the curve dropped down to about

NOTE Confidence: 0.896374091428571

00:15:33.632 --> 00:15:36.480 20 to 25% with about four years of follow up.

NOTE Confidence: 0.896374091428571

00:15:36.480 --> 00:15:38.176 So it still stands,

NOTE Confidence: 0.896374091428571

00:15:38.176 --> 00:15:41.897 but clearly you know it was not a

NOTE Confidence: 0.896374091428571

00:15:41.897 --> 00:15:44.036 curative approach and that kind of

NOTE Confidence: 0.896374091428571

00:15:44.036 --> 00:15:46.200 prompted our lab and many other groups

NOTE Confidence: 0.896374091428571

00:15:46.200 --> 00:15:48.360 going back to the kind of drawing

NOTE Confidence: 0.896374091428571

00:15:48.360 --> 00:15:50.280 board and trying to understand how

NOTE Confidence: 0.896374091428571

00:15:50.280 --> 00:15:53.069 we can improve on that and what are

NOTE Confidence: 0.896374091428571

00:15:53.069 --> 00:15:54.782 mechanisms of resistance and how

NOTE Confidence: 0.896374091428571

00:15:54.782 --> 00:15:56.636 we can combine with other agents.

NOTE Confidence: 0.896374091428571

00:15:56.640 --> 00:15:57.760 So in the rest of my talk,

NOTE Confidence: 0.896374091428571

00:15:57.760 --> 00:15:59.776 I will show you like several like

NOTE Confidence: 0.896374091428571

00:15:59.776 --> 00:16:02.026 examples from our lab how we kind of

NOTE Confidence: 0.896374091428571

00:16:02.026 --> 00:16:04.319 developed the new agents for the combination.

NOTE Confidence: 0.896374091428571

00:16:04.320 --> 00:16:06.000 Some of them are in trial,

NOTE Confidence: 0.896374091428571

00:16:06.000 --> 00:16:09.360 some of them are hopefully getting to

NOTE Confidence: 0.896374091428571

00:16:09.360 --> 00:16:11.934 approval soon and this is sort of a

NOTE Confidence: 0.896374091428571

00:16:11.934 --> 00:16:14.763 summary how we can think of potential

NOTE Confidence: 0.896374091428571

00:16:14.763 --> 00:16:16.999 combinations and resistance mechanisms.

NOTE Confidence: 0.896374091428571

00:16:17.000 --> 00:16:19.736 This figure was done by one of our

NOTE Confidence: 0.896374091428571

00:16:19.736 --> 00:16:21.360 fellows and again going back to

NOTE Confidence: 0.896374091428571

00:16:21.360 --> 00:16:22.942 like how the drugs work, right.

NOTE Confidence: 0.896374091428571

00:16:22.942 --> 00:16:24.754 So again you have BSO 2,

NOTE Confidence: 0.896374091428571

00:16:24.760 --> 00:16:27.161 you have it pre complex with BHA

NOTE Confidence: 0.896374091428571

00:16:27.161 --> 00:16:29.511 only protein which allows you to

NOTE Confidence: 0.896374091428571

00:16:29.511 --> 00:16:30.756 block this interaction.

NOTE Confidence: 0.896374091428571

00:16:30.760 --> 00:16:32.836 And this is a drug venetoclax,

NOTE Confidence: 0.896374091428571

00:16:32.840 --> 00:16:34.760 it's called BHA mimetic because

NOTE Confidence: 0.896374091428571

00:16:34.760 --> 00:16:36.680 it mimics PHA only proteins.

NOTE Confidence: 0.896374091428571

00:16:36.680 --> 00:16:38.296 So it binds here,

NOTE Confidence: 0.896374091428571

00:16:38.296 --> 00:16:41.388 it displaces this BHA only and then this

NOTE Confidence: 0.896374091428571

00:16:41.388 --> 00:16:43.880 products have to activate backs and back.

NOTE Confidence: 0.896374091428571

00:16:43.880 --> 00:16:46.120 So again backs and back are very

NOTE Confidence: 0.896374091428571

00:16:46.120 --> 00:16:47.723 critical because without that there's

NOTE Confidence: 0.896374091428571

00:16:47.723 --> 00:16:50.720 no cell death and they have to go

NOTE Confidence: 0.896374091428571

00:16:50.720 --> 00:16:52.416 into the mitochondrial membrane

NOTE Confidence: 0.896374091428571

00:16:52.416 --> 00:16:55.157 and they induce sacrum C release.

NOTE Confidence: 0.896374091428571

00:16:55.160 --> 00:16:56.720 So one thing that I already

NOTE Confidence: 0.896374091428571

00:16:56.720 --> 00:16:58.360 mentioned that there's a redundancy,

NOTE Confidence: 0.896374091428571

00:16:58.360 --> 00:17:00.376 so if you have a regulation of

NOTE Confidence: 0.896374091428571

00:17:00.376 --> 00:17:02.580 this other B SU-2 family members,

NOTE Confidence: 0.896374091428571

00:17:02.580 --> 00:17:04.516 you can get resistance right?

NOTE Confidence: 0.896374091428571

00:17:04.516 --> 00:17:06.412 Because they can even though you

NOTE Confidence: 0.896374091428571

00:17:06.412 --> 00:17:07.360 do have displacement,

NOTE Confidence: 0.896374091428571

00:17:07.360 --> 00:17:09.866 what happens is that this BHA only

NOTE Confidence: 0.896374091428571

00:17:09.866 --> 00:17:12.423 protein instead of going to the bags it

NOTE Confidence: 0.896374091428571

00:17:12.423 --> 00:17:15.399 will go and bind this other protein members.

NOTE Confidence: 0.896374091428571

00:17:15.400 --> 00:17:18.440 So how can you get this app regulation?

NOTE Confidence: 0.896374091428571

00:17:18.440 --> 00:17:19.840 Of course it may have

NOTE Confidence: 0.896374091428571

00:17:19.840 --> 00:17:20.680 been before pre-existing.

NOTE Confidence: 0.896374091428571

00:17:20.680 --> 00:17:22.966 For example in monostatic AML there's

NOTE Confidence: 0.896374091428571

00:17:22.966 --> 00:17:25.608 app regulation of MCL one because of

NOTE Confidence: 0.896374091428571

00:17:25.608 --> 00:17:27.714 the lineage dependency on MCL one.

NOTE Confidence: 0.896374091428571

00:17:27.720 --> 00:17:29.547 But then there are a lot of

NOTE Confidence: 0.896374091428571

00:17:29.547 --> 00:17:30.330 mutations and this

NOTE Confidence: 0.789430363125

00:17:30.394 --> 00:17:32.836 mutations we call them signalling mutations

NOTE Confidence: 0.789430363125

00:17:32.840 --> 00:17:35.234 which we now can up regulate both MCO one,

NOTE Confidence: 0.789430363125

00:17:35.240 --> 00:17:38.448 BCL XL and BCL 12A1 and I'll

NOTE Confidence: 0.789430363125

00:17:38.448 --> 00:17:39.960 show you some examples of those.

NOTE Confidence: 0.789430363125

00:17:39.960 --> 00:17:41.670 So this will lead to resistance

NOTE Confidence: 0.789430363125

00:17:41.670 --> 00:17:43.937 and of course you might want to

NOTE Confidence: 0.789430363125

00:17:43.937 --> 00:17:45.717 think of targeting those mutations.

NOTE Confidence: 0.789430363125

00:17:45.720 --> 00:17:47.850 So the other major mechanism of

NOTE Confidence: 0.789430363125

00:17:47.850 --> 00:17:50.356 resistance is the P53 loss and I

NOTE Confidence: 0.789430363125

00:17:50.356 --> 00:17:52.510 already mentioned that PhD is critical

NOTE Confidence: 0.789430363125

00:17:52.587 --> 00:17:54.757 for BHA only proteins induction.

NOTE Confidence: 0.789430363125

00:17:54.760 --> 00:17:56.843 But on top of that P53

NOTE Confidence: 0.789430363125

00:17:56.843 --> 00:17:58.652 transcriptionally controls Bax,

NOTE Confidence: 0.789430363125

00:17:58.652 --> 00:18:02.696 so BAX levels are lower and P

NOTE Confidence: 0.789430363125

00:18:02.696 --> 00:18:04.906 and P3 lost AML and there's also

NOTE Confidence: 0.789430363125

00:18:04.906 --> 00:18:06.114 other mechanism of resistance.

NOTE Confidence: 0.789430363125

00:18:06.120 --> 00:18:08.620 So this remains unmet need

NOTE Confidence: 0.789430363125

00:18:08.620 --> 00:18:11.950 in the field of AML and MD's.

NOTE Confidence: 0.789430363125

00:18:11.950 --> 00:18:14.680 And then there are some other mechanisms.

NOTE Confidence: 0.789430363125

00:18:14.680 --> 00:18:15.684 For example,

NOTE Confidence: 0.789430363125

00:18:15.684 --> 00:18:18.194 Yanis offenders group has published

NOTE Confidence: 0.789430363125

00:18:18.200 --> 00:18:20.585 the mitochondria resistance to the

NOTE Confidence: 0.789430363125

00:18:20.585 --> 00:18:22.970 venetoclax through our regulation of

NOTE Confidence: 0.789430363125

00:18:23.041 --> 00:18:25.337 some of this crystal proteins such as

NOTE Confidence: 0.789430363125

00:18:25.337 --> 00:18:28.325 Glib B and also mitophagia kind of

NOTE Confidence: 0.789430363125

00:18:28.325 --> 00:18:30.800 selection of the healthy mitochondria.

NOTE Confidence: 0.789430363125

00:18:30.800 --> 00:18:33.836 And there's some effort as far as

NOTE Confidence: 0.789430363125

00:18:33.836 --> 00:18:35.588 drug discovery in that field as

NOTE Confidence: 0.789430363125

00:18:35.588 --> 00:18:37.360 well going back to the patients.

NOTE Confidence: 0.789430363125

00:18:37.360 --> 00:18:40.474 So what did we see like from this mechanisms?

NOTE Confidence: 0.789430363125

00:18:40.480 --> 00:18:43.488 What did we see as far as the

NOTE Confidence: 0.789430363125

00:18:43.488 --> 00:18:44.240 resistance development?

NOTE Confidence: 0.789430363125

00:18:44.240 --> 00:18:46.922 And before that I have to say that we

NOTE Confidence: 0.789430363125

00:18:46.922 --> 00:18:49.915 also developed in the lab habanero clocks,

NOTE Confidence: 0.789430363125

00:18:49.920 --> 00:18:50.739 resistance cell lines.

NOTE Confidence: 0.789430363125

00:18:50.739 --> 00:18:52.650 So we decided to take some of

NOTE Confidence: 0.789430363125

00:18:52.706 --> 00:18:55.205 unbiased approach and we generated

NOTE Confidence: 0.789430363125

00:18:55.205 --> 00:18:57.880 4 vein resistance cell lines.

NOTE Confidence: 0.789430363125

00:18:57.880 --> 00:18:59.500 They're available for anyone who

NOTE Confidence: 0.789430363125

00:18:59.500 --> 00:19:01.560 wants to use them by prolonged

NOTE Confidence: 0.789430363125

00:19:01.560 --> 00:19:04.220 exposure to the drug in the tissue

NOTE Confidence: 0.789430363125

00:19:04.220 --> 00:19:05.712 culture lab and took only about

NOTE Confidence: 0.789430363125

00:19:05.712 --> 00:19:06.960 3 months to generate the cells.

NOTE Confidence: 0.789430363125

00:19:06.960 --> 00:19:09.004 So about the same time as our

NOTE Confidence: 0.789430363125

00:19:09.004 --> 00:19:09.880 patients to progress.

NOTE Confidence: 0.789430363125

00:19:09.880 --> 00:19:12.824 And then we did all kind of metabolomic

NOTE Confidence: 0.789430363125

00:19:12.824 --> 00:19:16.600 genomic proteomic profiling and

NOTE Confidence: 0.789430363125

00:19:16.600 --> 00:19:17.884 epigenetic profiling as well.

NOTE Confidence: 0.789430363125

00:19:17.884 --> 00:19:20.402 So one pathway that came out kind of

NOTE Confidence: 0.789430363125

00:19:20.402 --> 00:19:22.718 screaming at us, which was not a new pathway,

NOTE Confidence: 0.789430363125

00:19:22.720 --> 00:19:24.820 but it was something that we already

NOTE Confidence: 0.789430363125

00:19:24.820 --> 00:19:25.720 knew from before.

NOTE Confidence: 0.789430363125

00:19:25.720 --> 00:19:27.400 It was MEP kinase pathways.

NOTE Confidence: 0.789430363125

00:19:27.400 --> 00:19:30.320 So it was upregulated on the RNA level.

NOTE Confidence: 0.789430363125

00:19:30.320 --> 00:19:32.192 And then we confirmed that in

NOTE Confidence: 0.789430363125

00:19:32.192 --> 00:19:34.040 the by immuno blotting analysis,

NOTE Confidence: 0.789430363125

00:19:34.040 --> 00:19:36.294 you can see application of some of

NOTE Confidence: 0.789430363125

00:19:36.294 --> 00:19:38.360 this MEP kinase pathway proteins

NOTE Confidence: 0.789430363125

00:19:38.360 --> 00:19:41.391 and as a result MEP kinase can

NOTE Confidence: 0.789430363125

00:19:41.391 --> 00:19:43.600 stabilize MCL one proteins.

NOTE Confidence: 0.789430363125

00:19:43.600 --> 00:19:45.196 So it's not transcriptional but on

NOTE Confidence: 0.789430363125

00:19:45.196 --> 00:19:47.433 the level of the protein and we did

NOTE Confidence: 0.789430363125

00:19:47.433 --> 00:19:49.540 see that in all the three cell lines

NOTE Confidence: 0.789430363125

00:19:49.540 --> 00:19:51.514 M so one levels were up regulated

NOTE Confidence: 0.789430363125

00:19:51.514 --> 00:19:53.904 as you would expect And then if you

NOTE Confidence: 0.789430363125

00:19:53.904 --> 00:19:55.864 use the either M so one inhibitors

NOTE Confidence: 0.789430363125

00:19:55.864 --> 00:19:58.656 or knockout of M so one you get

NOTE Confidence: 0.789430363125

00:19:58.656 --> 00:20:00.175 tremendous synergy with venetoclax

NOTE Confidence: 0.789430363125

00:20:00.175 --> 00:20:02.751 and the cells are are dying off.

NOTE Confidence: 0.789430363125

00:20:02.760 --> 00:20:04.312 So I'm not going to talk about M

NOTE Confidence: 0.789430363125

00:20:04.312 --> 00:20:05.873 so one inhibitors but suffice to

NOTE Confidence: 0.789430363125

00:20:05.873 --> 00:20:07.547 say that they are not approved

NOTE Confidence: 0.789430363125

00:20:07.602 --> 00:20:08.598 because of toxicity.

NOTE Confidence: 0.789430363125

00:20:08.600 --> 00:20:11.273 So again like thinking why B so two so

NOTE Confidence: 0.789430363125

00:20:11.273 --> 00:20:14.200 safe and M so one is not safe so M so one.

NOTE Confidence: 0.789430363125

00:20:14.200 --> 00:20:16.597 Tends to be very important for the heart

NOTE Confidence: 0.789430363125

00:20:16.597 --> 00:20:19.376 muscles and so patients treated on the

NOTE Confidence: 0.789430363125

00:20:19.376 --> 00:20:21.560 clinical trials with MC1 inhibitors,

NOTE Confidence: 0.789430363125

00:20:21.560 --> 00:20:24.344 they have what we call Troponin leak and

NOTE Confidence: 0.789430363125

00:20:24.344 --> 00:20:26.478 potentially you know cardiac toxicity.

NOTE Confidence: 0.789430363125

00:20:26.480 --> 00:20:28.634 So that Hanford the whole like

NOTE Confidence: 0.789430363125

00:20:28.634 --> 00:20:30.070 development of MC1 inhibitors

NOTE Confidence: 0.810300709

00:20:30.130 --> 00:20:32.500 and it's not clear whether they

NOTE Confidence: 0.810300709

00:20:32.500 --> 00:20:34.080 actually have therapeutic windows.

NOTE Confidence: 0.810300709

00:20:34.080 --> 00:20:37.746 So, but in the lab, these are the

NOTE Confidence: 0.810300709

00:20:37.746 --> 00:20:39.594 great sensitizers to Vanadacolexa.

NOTE Confidence: 0.810300709

00:20:39.600 --> 00:20:41.696 So then we went back to patients and

NOTE Confidence: 0.810300709

00:20:41.696 --> 00:20:43.924 we know that in patients Ras mutations

NOTE Confidence: 0.810300709

00:20:43.924 --> 00:20:46.399 are fairly common in AML on their own.

NOTE Confidence: 0.810300709

00:20:46.400 --> 00:20:48.320 They don't have prognostic significance,

NOTE Confidence: 0.810300709

00:20:48.320 --> 00:20:50.666 but they can arise at the

NOTE Confidence: 0.810300709

00:20:50.666 --> 00:20:51.839 time of progression.

NOTE Confidence: 0.810300709

00:20:51.840 --> 00:20:54.312 And so when we looked at the patients

NOTE Confidence: 0.810300709

00:20:54.312 --> 00:20:56.053 treated on the HMA venetoclax

NOTE Confidence: 0.810300709

00:20:56.053 --> 00:20:58.159 trials at the time of relapse,

NOTE Confidence: 0.810300709

00:20:58.160 --> 00:21:01.360 they had like expansion of this Ras, K,

NOTE Confidence: 0.810300709

00:21:01.360 --> 00:21:04.968 Ras and Ras clones also PTPN 11 clones,

NOTE Confidence: 0.810300709

00:21:04.968 --> 00:21:07.350 which is not shown here fairly

NOTE Confidence: 0.810300709

00:21:07.350 --> 00:21:09.240 quickly within like 6 months or so.

NOTE Confidence: 0.810300709

00:21:09.240 --> 00:21:12.999 This has single cell DNA sequencing data.

NOTE Confidence: 0.810300709

00:21:13.000 --> 00:21:15.128 We also looked at the sort of

NOTE Confidence: 0.810300709

00:21:15.128 --> 00:21:16.040 patients by immunoblotting.

NOTE Confidence: 0.810300709

00:21:16.040 --> 00:21:17.804 So we did show up regulation of

NOTE Confidence: 0.810300709

00:21:17.804 --> 00:21:19.537 MCL one and the approgation of

NOTE Confidence: 0.810300709

00:21:19.537 --> 00:21:21.367 MAP kinase pathway and this is

NOTE Confidence: 0.810300709

00:21:21.367 --> 00:21:23.200 on the histochemistry level.

NOTE Confidence: 0.810300709

00:21:23.200 --> 00:21:25.517 At the time progression MCL one was

NOTE Confidence: 0.810300709

00:21:25.517 --> 00:21:28.240 up and BCL two was down regulated.

NOTE Confidence: 0.810300709

00:21:28.240 --> 00:21:29.848 The problem of course that in

NOTE Confidence: 0.810300709

00:21:29.848 --> 00:21:31.839 AML we don't have Ras inhibitors.

NOTE Confidence: 0.810300709

00:21:31.840 --> 00:21:33.807 We are really hoping that we can

NOTE Confidence: 0.810300709

00:21:33.807 --> 00:21:35.760 get them from the solid tumors.

NOTE Confidence: 0.810300709

00:21:35.760 --> 00:21:37.332 But the companies have been so

NOTE Confidence: 0.810300709

00:21:37.332 --> 00:21:39.244 focused on the lung cancer and they

NOTE Confidence: 0.810300709

00:21:39.244 --> 00:21:41.120 have been reluctant to go into AML.

NOTE Confidence: 0.810300709

00:21:41.120 --> 00:21:43.598 So we are still trying to convince

NOTE Confidence: 0.810300709

00:21:43.598 --> 00:21:46.218 them that Pan Ras inhibitor would be

NOTE Confidence: 0.810300709

00:21:46.218 --> 00:21:48.990 a great thing to have an AML and we

NOTE Confidence: 0.810300709

00:21:48.990 --> 00:21:51.504 actually have data with the in the lab

NOTE Confidence: 0.810300709

00:21:51.504 --> 00:21:53.720 that the combination is really striking,

NOTE Confidence: 0.810300709

00:21:53.720 --> 00:21:55.016 the papers submitted.

NOTE Confidence: 0.810300709

00:21:55.016 --> 00:21:58.040 But right now we don't have anything.

NOTE Confidence: 0.810300709

00:21:58.040 --> 00:22:00.320 So we also did the engineer this in the lab.

NOTE Confidence: 0.810300709

00:22:00.320 --> 00:22:04.104 So we put the NRAS G12D into AML

NOTE Confidence: 0.810300709

00:22:04.104 --> 00:22:06.792 cell line which was dox inducible.

NOTE Confidence: 0.810300709

00:22:06.800 --> 00:22:08.552 We showed that the cells become

NOTE Confidence: 0.810300709

00:22:08.552 --> 00:22:09.720 resistant to another clocks.

NOTE Confidence: 0.810300709

00:22:09.720 --> 00:22:12.144 But again the MCL one inhibitors

NOTE Confidence: 0.810300709

00:22:12.144 --> 00:22:13.760 work alone on combination.

NOTE Confidence: 0.810300709

00:22:13.760 --> 00:22:15.531 We did the mouse study with MCL

NOTE Confidence: 0.810300709

00:22:15.531 --> 00:22:17.173 1 inhibitors and there was a

NOTE Confidence: 0.810300709

00:22:17.173 --> 00:22:18.553 reduction of the tumor growth,

NOTE Confidence: 0.810300709

00:22:18.560 --> 00:22:19.855 but we don't have MCL 1 inhibitors

NOTE Confidence: 0.810300709

00:22:19.855 --> 00:22:21.238 and we don't have resin inhibits.

NOTE Confidence: 0.810300709

00:22:21.240 --> 00:22:24.273 So we are like at a loss right now,

NOTE Confidence: 0.810300709

00:22:24.280 --> 00:22:26.600 but we're working on that.

NOTE Confidence: 0.810300709

00:22:26.600 --> 00:22:28.454 So this MEP kinase upregulation I

NOTE Confidence: 0.810300709

00:22:28.454 --> 00:22:31.074 think is one of the major kind of

NOTE Confidence: 0.810300709

00:22:31.074 --> 00:22:33.678 resistance when you use HMA Van.

NOTE Confidence: 0.810300709

00:22:33.680 --> 00:22:35.560 It's not an issue when you use chemotherapy,

NOTE Confidence: 0.810300709

00:22:35.560 --> 00:22:35.948 van,

NOTE Confidence: 0.810300709

00:22:35.948 --> 00:22:37.888 because Rascalone is very sensitive

NOTE Confidence: 0.810300709

00:22:37.888 --> 00:22:39.440 to the regular chemotherapy,

NOTE Confidence: 0.810300709

00:22:39.440 --> 00:22:42.476 which is kind of a relief.

NOTE Confidence: 0.810300709

00:22:42.480 --> 00:22:44.440 And this data we have sort of confirmed

NOTE Confidence: 0.810300709

00:22:44.440 --> 00:22:46.039 that this was a large analysis.

NOTE Confidence: 0.810300709

00:22:46.040 --> 00:22:48.774 I think the paper is under review from Viali,

NOTE Confidence: 0.810300709

00:22:48.774 --> 00:22:51.216 a study looking at different genomic

NOTE Confidence: 0.810300709

00:22:51.216 --> 00:22:54.457 subsets of patients who are and time to

NOTE Confidence: 0.810300709

00:22:54.457 --> 00:22:56.720 progressional this is rather survival.

NOTE Confidence: 0.810300709

00:22:56.720 --> 00:22:58.922 This was presented at by Hartman

NOTE Confidence: 0.810300709

00:22:58.922 --> 00:23:00.760 donor at the last ASH.

NOTE Confidence: 0.810300709

00:23:00.760 --> 00:23:03.126 And so they basically show that the

NOTE Confidence: 0.810300709

00:23:03.126 --> 00:23:04.972 classical kind of ELN classifications

NOTE Confidence: 0.810300709

00:23:04.972 --> 00:23:07.270 do not predict very well the

NOTE Confidence: 0.810300709

00:23:07.270 --> 00:23:09.438 response or duration of response.

NOTE Confidence: 0.810300709

00:23:09.440 --> 00:23:11.516 But when they did looked at

NOTE Confidence: 0.810300709

00:23:11.516 --> 00:23:12.554 different genomic subsets,

NOTE Confidence: 0.810300709

00:23:12.560 --> 00:23:15.955 again P50 mutated AML did very poorly.

NOTE Confidence: 0.810300709

00:23:15.960 --> 00:23:18.600 So survival was only about 5 months here,

NOTE Confidence: 0.810300709

00:23:18.600 --> 00:23:21.078 same as you get with HMA.

NOTE Confidence: 0.810300709

00:23:21.080 --> 00:23:22.592 But this intermediate cohort,

NOTE Confidence: 0.810300709

00:23:22.592 --> 00:23:24.860 it actually included patients with Ras

NOTE Confidence: 0.853982455454546

00:23:24.923 --> 00:23:27.195 mutations. So Ras mutation was confirmed

NOTE Confidence: 0.853982455454546

00:23:27.195 --> 00:23:29.681 to be like resistance factor for the HMA

NOTE Confidence: 0.853982455454546

00:23:29.681 --> 00:23:32.070 band and also another mutation signaling

NOTE Confidence: 0.853982455454546

00:23:32.070 --> 00:23:35.560 mutation F FLIX free FLIX free ITD mutation.

NOTE Confidence: 0.853982455454546

00:23:35.560 --> 00:23:38.080 So this data are being sort of refined that

NOTE Confidence: 0.853982455454546

00:23:38.080 --> 00:23:40.798 I told you a little about the Ras story.

NOTE Confidence: 0.853982455454546

00:23:40.800 --> 00:23:43.040 Now Flix 3 is another very common mutation,

NOTE Confidence: 0.853982455454546

00:23:43.040 --> 00:23:46.080 about 30% of patients have Flix 3 mutation.

NOTE Confidence: 0.853982455454546

00:23:46.080 --> 00:23:47.520 Unfortunately we have drugs for

NOTE Confidence: 0.853982455454546

00:23:47.520 --> 00:23:48.960 those that are being approved.

NOTE Confidence: 0.853982455454546

00:23:48.960 --> 00:23:51.520 So of course like we jumped into that

NOTE Confidence: 0.853982455454546

00:23:51.520 --> 00:23:53.944 very early on and in fact we saw that

NOTE Confidence: 0.853982455454546

00:23:53.944 --> 00:23:56.074 even in the original phase one study

NOTE Confidence: 0.853982455454546

00:23:56.074 --> 00:23:58.090 where which showed up regulation of

NOTE Confidence: 0.853982455454546

00:23:58.090 --> 00:24:00.114 this or selection of the clones with

NOTE Confidence: 0.853982455454546

00:24:00.114 --> 00:24:02.875 the Flix 3 IT do or as mutations and

NOTE Confidence: 0.853982455454546

00:24:02.875 --> 00:24:05.172 people who relapse or wear primary

NOTE Confidence: 0.853982455454546

00:24:05.172 --> 00:24:07.455 fracture and very similar this like

NOTE Confidence: 0.853982455454546

00:24:07.455 --> 00:24:10.783 selection of the Flix 3 ITT clone with a

NOTE Confidence: 0.853982455454546

00:24:10.783 --> 00:24:13.069 therapy using the single cell tapestry

NOTE Confidence: 0.853982455454546

00:24:13.146 --> 00:24:15.695 sequencing and the sort of why Flix 3

NOTE Confidence: 0.853982455454546

00:24:15.695 --> 00:24:18.076 ITT the story is very similar to Ras.

NOTE Confidence: 0.853982455454546

00:24:18.080 --> 00:24:19.956 So here you have you know the

NOTE Confidence: 0.853982455454546

00:24:19.956 --> 00:24:21.920 same Ras map kindness pathway.

NOTE Confidence: 0.853982455454546

00:24:21.920 --> 00:24:24.728 You also have a prolation of some other

NOTE Confidence: 0.853982455454546

00:24:24.728 --> 00:24:27.376 ones that five PS3 kines AKT but eventually

NOTE Confidence: 0.853982455454546

00:24:27.376 --> 00:24:29.680 it all comes down to this MCL one.

NOTE Confidence: 0.853982455454546

00:24:29.680 --> 00:24:32.476 So MCL one phosphorylation is regulated

NOTE Confidence: 0.853982455454546

00:24:32.476 --> 00:24:36.142 by both MAP kinase and also there's a

NOTE Confidence: 0.853982455454546

00:24:36.142 --> 00:24:37.810 stead pathway dependent phosphorylation.

NOTE Confidence: 0.853982455454546

00:24:37.810 --> 00:24:40.645 So when MCL one is phosphorylated it's

NOTE Confidence: 0.853982455454546

00:24:40.645 --> 00:24:42.605 stable so the levels are increased

NOTE Confidence: 0.853982455454546

00:24:42.605 --> 00:24:44.573 and the product cannot be degraded

NOTE Confidence: 0.853982455454546

00:24:44.573 --> 00:24:46.638 otherwise it's short lived protein.

NOTE Confidence: 0.853982455454546

00:24:46.640 --> 00:24:48.060 So essentially there's also some

NOTE Confidence: 0.853982455454546

00:24:48.060 --> 00:24:49.196 B cell XL component,

NOTE Confidence: 0.853982455454546

00:24:49.200 --> 00:24:50.916 but I think it's a minor,

NOTE Confidence: 0.853982455454546

00:24:50.920 --> 00:24:52.404 but the nice thing is all downstream

NOTE Confidence: 0.853982455454546

00:24:52.404 --> 00:24:53.280 or Flix 3 ITD.

NOTE Confidence: 0.853982455454546

00:24:53.280 --> 00:24:55.464 So it's OK if we're here Flix 3

NOTE Confidence: 0.853982455454546

00:24:55.464 --> 00:24:56.880 what happens with MCL one.

NOTE Confidence: 0.853982455454546

00:24:56.880 --> 00:24:59.392 So we used Quizactinib for that matter and

NOTE Confidence: 0.853982455454546

00:24:59.392 --> 00:25:02.138 we showed nice inhibition of the Flix 3 MCL.

NOTE Confidence: 0.853982455454546

00:25:02.138 --> 00:25:04.224 One did go down by wasn't that

NOTE Confidence: 0.853982455454546

00:25:04.224 --> 00:25:05.999 huge up down regulation.

NOTE Confidence: 0.853982455454546

00:25:06.000 --> 00:25:08.464 But we also show that the protein

NOTE Confidence: 0.853982455454546

00:25:08.464 --> 00:25:10.477 called BEM was induced and BEM

NOTE Confidence: 0.853982455454546

00:25:10.477 --> 00:25:13.305 can is a prop of Tory BC on a

NOTE Confidence: 0.853982455454546

00:25:13.305 --> 00:25:15.393 protein that can inhibit MCL one.

NOTE Confidence: 0.853982455454546

00:25:15.400 --> 00:25:17.596 So the combination of these two

NOTE Confidence: 0.853982455454546

00:25:17.600 --> 00:25:20.920 makes cells sensitive to venetoclax.

NOTE Confidence: 0.853982455454546

00:25:20.920 --> 00:25:22.858 And this is BHA profiling essay

NOTE Confidence: 0.853982455454546

00:25:22.858 --> 00:25:25.362 which I have time to explain in

NOTE Confidence: 0.853982455454546

00:25:25.362 --> 00:25:27.272 detail by essentially you throw

NOTE Confidence: 0.853982455454546

00:25:27.272 --> 00:25:29.851 the peptides on the cells and see

NOTE Confidence: 0.853982455454546

00:25:29.851 --> 00:25:31.596 which dependence that they have.

NOTE Confidence: 0.853982455454546

00:25:31.600 --> 00:25:33.264 But the point here is that if you

NOTE Confidence: 0.853982455454546

00:25:33.264 --> 00:25:34.797 treat cells with Flix 3 inhibitors,

NOTE Confidence: 0.853982455454546

00:25:34.800 --> 00:25:36.515 you have huge up regulation of B.

NOTE Confidence: 0.853982455454546

00:25:36.520 --> 00:25:39.028 So two dependency to the peptide

NOTE Confidence: 0.853982455454546

00:25:39.028 --> 00:25:42.239 or to the actual venetoclax drugs.

NOTE Confidence: 0.853982455454546

00:25:42.240 --> 00:25:43.920 So you have synergy in vitro.

NOTE Confidence: 0.853982455454546

00:25:43.920 --> 00:25:45.024 And in this model,

NOTE Confidence: 0.853982455454546

00:25:45.024 --> 00:25:47.040 which there was like a subcutaneous model,

NOTE Confidence: 0.853982455454546

00:25:47.040 --> 00:25:48.678 not a great model for AML,

NOTE Confidence: 0.853982455454546

00:25:48.680 --> 00:25:51.039 but we subsequently publish also PDX models,

NOTE Confidence: 0.853982455454546

00:25:51.040 --> 00:25:52.790 we show like essential cures

NOTE Confidence: 0.853982455454546

00:25:52.790 --> 00:25:55.120 of the mice for that matter,

NOTE Confidence: 0.853982455454546

00:25:55.120 --> 00:25:56.320 when we use the Quizad,

NOTE Confidence: 0.853982455454546

00:25:56.320 --> 00:25:59.800 snip and Venetoclax combination.

NOTE Confidence: 0.853982455454546

00:25:59.800 --> 00:26:01.795 So this did go into clinical development.

NOTE Confidence: 0.853982455454546

00:26:01.800 --> 00:26:04.968 And for the trials another flixster

NOTE Confidence: 0.853982455454546

00:26:04.968 --> 00:26:06.552 inhibitor second generation

NOTE Confidence: 0.853982455454546

00:26:06.552 --> 00:26:08.920 guilt treatment was selected.

NOTE Confidence: 0.853982455454546

00:26:08.920 --> 00:26:11.902 And this paper is now published in

NOTE Confidence: 0.853982455454546

00:26:11.902 --> 00:26:14.775 JCO by MD Anderson Group and many

NOTE Confidence: 0.853982455454546

00:26:14.775 --> 00:26:16.790 other collaborators where there was

NOTE Confidence: 0.853982455454546

00:26:16.864 --> 00:26:19.139 combination of venetoclax and guilt

NOTE Confidence: 0.853982455454546

00:26:19.139 --> 00:26:21.414 retina for relapse refractory Flex

NOTE Confidence: 0.620285854347826

00:26:21.488 --> 00:26:22.400 3 mutated AML.

NOTE Confidence: 0.620285854347826

00:26:22.400 --> 00:26:25.244 And there was quite significant response

NOTE Confidence: 0.620285854347826

00:26:25.244 --> 00:26:28.344 rate in all patients or in those

NOTE Confidence: 0.620285854347826

00:26:28.344 --> 00:26:30.955 who failed prior Flex 3 Tki's alone.

NOTE Confidence: 0.620285854347826

00:26:30.960 --> 00:26:33.158 And if they went for the transplant,

NOTE Confidence: 0.620285854347826

00:26:33.160 --> 00:26:36.919 they actually the survival looks fairly good.

NOTE Confidence: 0.620285854347826

00:26:36.920 --> 00:26:39.098 The data by Kathy Smith showed

NOTE Confidence: 0.620285854347826

00:26:39.098 --> 00:26:40.880 that the Flixtree clones were

NOTE Confidence: 0.620285854347826

00:26:40.880 --> 00:26:42.076 extinguished after this combination.

NOTE Confidence: 0.620285854347826

00:26:42.076 --> 00:26:44.439 I have to say that she did show

NOTE Confidence: 0.620285854347826

00:26:44.439 --> 00:26:45.729 that Ras clones were coming

NOTE Confidence: 0.620285854347826

00:26:45.729 --> 00:26:47.319 up in patients who progressed.

NOTE Confidence: 0.620285854347826

00:26:47.320 --> 00:26:49.462 So Ras is still a resistance

NOTE Confidence: 0.620285854347826

00:26:49.462 --> 00:26:51.520 mechanism even in that setting.

NOTE Confidence: 0.620285854347826

00:26:51.520 --> 00:26:53.897 But again,

NOTE Confidence: 0.620285854347826

00:26:53.897 --> 00:26:56.879 this was quite impressive sort of

NOTE Confidence: 0.620285854347826

00:26:56.880 --> 00:27:00.480 advance in the field of Flixtree mutated AML.

NOTE Confidence: 0.620285854347826

00:27:00.480 --> 00:27:02.608 Now of course we all know that treating

NOTE Confidence: 0.620285854347826

00:27:02.608 --> 00:27:04.760 patients is best at the time of diagnosis.

NOTE Confidence: 0.620285854347826

00:27:04.760 --> 00:27:07.238 So for all the patients we

NOTE Confidence: 0.620285854347826

00:27:07.238 --> 00:27:08.477 cannot use chemotherapy.

NOTE Confidence: 0.620285854347826

00:27:08.480 --> 00:27:10.044 So Ambiencin's group has

NOTE Confidence: 0.620285854347826

00:27:10.044 --> 00:27:11.999 pioneered what we call triplet.

NOTE Confidence: 0.620285854347826

00:27:12.000 --> 00:27:13.885 So triplet is essentially Azovan

NOTE Confidence: 0.620285854347826

00:27:13.885 --> 00:27:16.222 which is a backbone and then you

NOTE Confidence: 0.620285854347826

00:27:16.222 --> 00:27:18.140 add the third drug in this case

NOTE Confidence: 0.620285854347826

00:27:18.203 --> 00:27:19.998 is guilt written and this paper

NOTE Confidence: 0.620285854347826

00:27:19.998 --> 00:27:22.255 is also now accepted in JC or now

NOTE Confidence: 0.620285854347826

00:27:22.255 --> 00:27:23.915 this is single sounded trial.

NOTE Confidence: 0.620285854347826

00:27:23.920 --> 00:27:26.272 There's a lot of discussion on Twitter

NOTE Confidence: 0.620285854347826

00:27:26.272 --> 00:27:28.600 whether it's like you know true or not,

NOTE Confidence: 0.620285854347826

00:27:28.600 --> 00:27:31.274 but at least you know data from

NOTE Confidence: 0.620285854347826

00:27:31.274 --> 00:27:33.719 Indiannis and look very impressive.

NOTE Confidence: 0.620285854347826

00:27:33.720 --> 00:27:35.800 Now when you see 100% response rate,

NOTE Confidence: 0.620285854347826

00:27:35.800 --> 00:27:37.400 you always kind of pause,

NOTE Confidence: 0.620285854347826

00:27:37.400 --> 00:27:40.284 but that's what they reported and 30

NOTE Confidence: 0.620285854347826

00:27:40.284 --> 00:27:43.004 newly diagnosed patients with AML and

NOTE Confidence: 0.620285854347826

00:27:43.004 --> 00:27:46.236 they estimated survival at two years was 70%.

NOTE Confidence: 0.620285854347826

00:27:46.240 --> 00:27:47.914 So this is like way better

NOTE Confidence: 0.620285854347826

00:27:47.914 --> 00:27:49.560 than what we had before,

NOTE Confidence: 0.620285854347826

00:27:49.560 --> 00:27:51.709 but they had to like reduce a

NOTE Confidence: 0.620285854347826

00:27:51.709 --> 00:27:53.798 lot of duration of the drugs and

NOTE Confidence: 0.620285854347826

00:27:53.800 --> 00:27:55.816 work out the schedule because the

NOTE Confidence: 0.620285854347826

00:27:55.816 --> 00:27:57.160 combination is mild suppressive.

NOTE Confidence: 0.620285854347826

00:27:57.160 --> 00:27:59.470 So the major like heme toxicity of

NOTE Confidence: 0.620285854347826

00:27:59.470 --> 00:28:01.280 venetoclax is mild suppression.

NOTE Confidence: 0.620285854347826

00:28:01.280 --> 00:28:03.232 So Neutropenias because Mallo

NOTE Confidence: 0.620285854347826

00:28:03.232 --> 00:28:05.672 itself express B so too.

NOTE Confidence: 0.620285854347826

00:28:05.680 --> 00:28:07.640 And so when you use the vanadium

NOTE Confidence: 0.620285854347826

00:28:07.640 --> 00:28:08.480 clocks in combinations,

NOTE Confidence: 0.620285854347826

00:28:08.480 --> 00:28:10.755 you have to cut back and that's

NOTE Confidence: 0.620285854347826

00:28:10.760 --> 00:28:12.428 continued discussions with FDA

NOTE Confidence: 0.620285854347826

00:28:12.428 --> 00:28:14.930 because the approved scale is 28

NOTE Confidence: 0.620285854347826

00:28:14.997 --> 00:28:16.517 days of vanadium clock.

NOTE Confidence: 0.620285854347826

00:28:16.520 --> 00:28:18.410 So there's a randomized study right

NOTE Confidence: 0.620285854347826

00:28:18.410 --> 00:28:19.920 now ongoing which hopefully will

NOTE Confidence: 0.620285854347826

00:28:19.920 --> 00:28:22.292 kind of solidify this question run

NOTE Confidence: 0.620285854347826

00:28:22.292 --> 00:28:25.400 by a Stellas and AbbVie where the

NOTE Confidence: 0.620285854347826

00:28:25.400 --> 00:28:27.320 same combination is being used in

NOTE Confidence: 0.620285854347826

00:28:27.320 --> 00:28:29.200 the frontline all the AML settings.

NOTE Confidence: 0.620285854347826

00:28:29.200 --> 00:28:31.720 So we'll see how that goes,

NOTE Confidence: 0.620285854347826

00:28:31.720 --> 00:28:34.480 but again what do we do about Ras.

NOTE Confidence: 0.620285854347826

00:28:34.480 --> 00:28:38.440 So this is like very early preclinical work.

NOTE Confidence: 0.620285854347826

00:28:38.440 --> 00:28:40.906 We're working with Everest Gavasitis at

NOTE Confidence: 0.620285854347826

00:28:40.906 --> 00:28:43.760 Einstein and he developed the RAF inhibitor.

NOTE Confidence: 0.620285854347826

00:28:43.760 --> 00:28:47.411 So kind of downstream of Ras that inhibit

NOTE Confidence: 0.620285854347826

00:28:47.411 --> 00:28:49.913 is allosteric RAF inhibitor that he

NOTE Confidence: 0.620285854347826

00:28:49.913 --> 00:28:52.915 is about to publish in solid tumors.

NOTE Confidence: 0.620285854347826

00:28:52.920 --> 00:28:55.120 But we show that P in cell lines

NOTE Confidence: 0.620285854347826

00:28:55.120 --> 00:28:58.237 with K or N Ras mutation is highly

NOTE Confidence: 0.620285854347826

00:28:58.237 --> 00:28:59.901 effective drug using inhibition

NOTE Confidence: 0.620285854347826

00:28:59.973 --> 00:29:02.142 of the pathway and there's some

NOTE Confidence: 0.620285854347826

00:29:02.142 --> 00:29:03.718 additive effects with venetoclax.

NOTE Confidence: 0.620285854347826

00:29:03.720 --> 00:29:05.920 So we kind of continue working on that.

NOTE Confidence: 0.620285854347826

00:29:05.920 --> 00:29:07.680 So hopefully we'll get either

NOTE Confidence: 0.620285854347826

00:29:07.680 --> 00:29:09.440 Ras inhibitors or RAF inhibitors.

NOTE Confidence: 0.620285854347826

00:29:09.440 --> 00:29:11.678 We did test the MECH inhibitors.

NOTE Confidence: 0.620285854347826

00:29:11.680 --> 00:29:13.880 I didn't show you that we published that.

NOTE Confidence: 0.620285854347826

00:29:13.880 --> 00:29:15.238 We went all the way into clinic,

NOTE Confidence: 0.620285854347826

00:29:15.240 --> 00:29:17.760 but MECH inhibitors caused a lot of

NOTE Confidence: 0.620285854347826

00:29:17.760 --> 00:29:20.718 GI talks and so the trial was unsuccessful.

NOTE Confidence: 0.620285854347826

00:29:20.720 --> 00:29:23.555 So it was stopped for lack of

NOTE Confidence: 0.620285854347826

00:29:23.555 --> 00:29:24.770 efficacy and high

NOTE Confidence: 0.902856236363636

00:29:24.863 --> 00:29:27.712 toxicity. So we can't really use the Mac

NOTE Confidence: 0.902856236363636

00:29:27.712 --> 00:29:29.559 inhibits unfortunately in this combination.

NOTE Confidence: 0.902856236363636

00:29:29.560 --> 00:29:34.280 So work to be continued on this topic.

NOTE Confidence: 0.902856236363636

00:29:34.280 --> 00:29:35.813 So there are a lot of other

NOTE Confidence: 0.902856236363636

00:29:35.813 --> 00:29:36.750 combinations with banana glass

NOTE Confidence: 0.902856236363636

00:29:36.750 --> 00:29:38.160 that have been sort of published.

NOTE Confidence: 0.902856236363636

00:29:38.160 --> 00:29:41.380 This is just some nice summary that

NOTE Confidence: 0.902856236363636

00:29:41.380 --> 00:29:44.348 was presented at last EHA and the

NOTE Confidence: 0.902856236363636

00:29:44.348 --> 00:29:46.318 the combination with IDH inhibitors

NOTE Confidence: 0.902856236363636

00:29:46.318 --> 00:29:49.173 that are now in clinical trials and

NOTE Confidence: 0.902856236363636

00:29:49.173 --> 00:29:51.837 both in AML and MDSI have to say

NOTE Confidence: 0.902856236363636

00:29:51.840 --> 00:29:53.580 there's many inhibited combination

NOTE Confidence: 0.902856236363636

00:29:53.580 --> 00:29:55.320 which looks super exciting.

NOTE Confidence: 0.902856236363636

00:29:55.320 --> 00:29:57.840 Of course, I'm still 1 went to to trials,

NOTE Confidence: 0.902856236363636

00:29:57.840 --> 00:29:59.244 but it's struggling.

NOTE Confidence: 0.902856236363636

00:29:59.244 --> 00:30:01.584 There was McGraw mop combination

NOTE Confidence: 0.902856236363636

00:30:01.584 --> 00:30:03.360 which we pioneered,

NOTE Confidence: 0.902856236363636

00:30:03.360 --> 00:30:04.830 but right now McGraw mop is

NOTE Confidence: 0.902856236363636

00:30:04.830 --> 00:30:06.280 all the trials have stopped.

NOTE Confidence: 0.902856236363636

00:30:06.280 --> 00:30:08.611 So I'm not going to talk to you about

NOTE Confidence: 0.902856236363636

00:30:08.611 --> 00:30:11.069 that today and but I want to show some

NOTE Confidence: 0.902856236363636

00:30:11.069 --> 00:30:13.173 data with the immune approaches in

NOTE Confidence: 0.902856236363636

00:30:13.173 --> 00:30:15.435 this case is antibody drug conugate.

NOTE Confidence: 0.902856236363636

00:30:15.440 --> 00:30:17.456 So kind of a little bit different

NOTE Confidence: 0.902856236363636

00:30:17.456 --> 00:30:18.320 story with venetoclax.

NOTE Confidence: 0.902856236363636

00:30:18.320 --> 00:30:20.680 So, so we used the,

NOTE Confidence: 0.902856236363636

00:30:20.680 --> 00:30:23.767 we looked at CD 123 because CD 123 is

NOTE Confidence: 0.902856236363636

00:30:23.767 --> 00:30:27.278 a subunit of all three receptor alpha

NOTE Confidence: 0.902856236363636

00:30:27.280 --> 00:30:29.680 and it's ubiquitously expressed in AML.

NOTE Confidence: 0.902856236363636

00:30:29.680 --> 00:30:32.248 Also this other level of my

NOTE Confidence: 0.902856236363636

00:30:32.248 --> 00:30:35.080 BPDCN and in some ALR as well,

NOTE Confidence: 0.902856236363636

00:30:35.080 --> 00:30:37.552 it's expressed in stem cells based

NOTE Confidence: 0.902856236363636

00:30:37.552 --> 00:30:39.818 on Craig Jordan's work and it's

NOTE Confidence: 0.902856236363636

00:30:39.818 --> 00:30:41.981 sort of the only antigen right now

NOTE Confidence: 0.902856236363636

00:30:41.981 --> 00:30:44.336 that we kind of trying to target as

NOTE Confidence: 0.902856236363636

00:30:44.336 --> 00:30:46.292 far as immune therapy and EMLMDS.

NOTE Confidence: 0.902856236363636

00:30:46.292 --> 00:30:48.284 There are other efforts but none

NOTE Confidence: 0.902856236363636

00:30:48.284 --> 00:30:50.600 of them have been successful yet.

NOTE Confidence: 0.902856236363636

00:30:50.600 --> 00:30:53.354 So we've been working with this

NOTE Confidence: 0.902856236363636

00:30:53.354 --> 00:30:55.190 company Immunogen that developed

NOTE Confidence: 0.902856236363636

00:30:55.265 --> 00:30:56.986 the antibody drug Conugate.

NOTE Confidence: 0.902856236363636

00:30:56.986 --> 00:31:00.533 So they have the antibody gain C123

NOTE Confidence: 0.902856236363636

00:31:00.533 --> 00:31:03.731 that's through the linker is bound

NOTE Confidence: 0.902856236363636

00:31:03.731 --> 00:31:06.240 to the alculator that produces

NOTE Confidence: 0.902856236363636

00:31:06.240 --> 00:31:08.640 the single strand DNA damage.

NOTE Confidence: 0.902856236363636

00:31:08.640 --> 00:31:11.600 So obviously it's internalized and

NOTE Confidence: 0.902856236363636

00:31:11.600 --> 00:31:14.092 and you know kills the cells for

NOTE Confidence: 0.902856236363636

00:31:14.092 --> 00:31:16.573 the DNA damage kind of chemotherapy

NOTE Confidence: 0.902856236363636

00:31:16.573 --> 00:31:18.798 but in a targeted fashion.

NOTE Confidence: 0.902856236363636

00:31:18.800 --> 00:31:22.027 So it had the good single agent

NOTE Confidence: 0.902856236363636

00:31:22.027 --> 00:31:24.638 activity and BPDC and then EMO

NOTE Confidence: 0.902856236363636

00:31:24.640 --> 00:31:26.710 the company has filed approval for

NOTE Confidence: 0.902856236363636

00:31:26.710 --> 00:31:28.919 BPDC and patients a second line.

NOTE Confidence: 0.902856236363636

00:31:28.920 --> 00:31:31.026 So hopefully we get this drug

NOTE Confidence: 0.902856236363636

00:31:31.026 --> 00:31:32.079 approved pretty soon.

NOTE Confidence: 0.902856236363636

00:31:32.080 --> 00:31:34.040 And so we of course asked the question,

NOTE Confidence: 0.902856236363636

00:31:34.040 --> 00:31:35.528 can we combine the two because

NOTE Confidence: 0.902856236363636

00:31:35.528 --> 00:31:37.435 this is like you know the immune

NOTE Confidence: 0.902856236363636

00:31:37.435 --> 00:31:39.157 therapy that seems to be working.

NOTE Confidence: 0.902856236363636

00:31:39.160 --> 00:31:40.360 So we've done quite a bit

NOTE Confidence: 0.902856236363636

00:31:40.360 --> 00:31:40.960 of preclinical work.

NOTE Confidence: 0.902856236363636

00:31:40.960 --> 00:31:42.400 It's not published yet,

NOTE Confidence: 0.902856236363636

00:31:42.400 --> 00:31:45.239 but we show that the compound is fairly

NOTE Confidence: 0.902856236363636

00:31:45.240 --> 00:31:47.478 specific. So these are AML cells.

NOTE Confidence: 0.902856236363636

00:31:47.480 --> 00:31:49.760 This in red is CD123 expression.

NOTE Confidence: 0.902856236363636

00:31:49.760 --> 00:31:50.448 So again,

NOTE Confidence: 0.902856236363636

00:31:50.448 --> 00:31:52.856 majority of cells do express it and

NOTE Confidence: 0.902856236363636

00:31:52.856 --> 00:31:54.960 they're being killed by this drug,

NOTE Confidence: 0.902856236363636

00:31:54.960 --> 00:31:57.599 but then the cells that don't express

NOTE Confidence: 0.902856236363636

00:31:57.600 --> 00:32:00.000 there's no killing and KG one is resistant.

NOTE Confidence: 0.902856236363636

00:32:00.000 --> 00:32:01.640 We're not quite sure why,

NOTE Confidence: 0.902856236363636

00:32:01.640 --> 00:32:04.160 but it seems to be specific.

NOTE Confidence: 0.902856236363636

00:32:04.160 --> 00:32:06.068 And then we ran the combinations

NOTE Confidence: 0.902856236363636

00:32:06.068 --> 00:32:07.717 both with another clogs and

NOTE Confidence: 0.902856236363636

00:32:07.717 --> 00:32:09.307 azacitidine and the triplet because

NOTE Confidence: 0.902856236363636

00:32:09.307 --> 00:32:11.633 now we're in the triplet era, right?

NOTE Confidence: 0.902856236363636

00:32:11.633 --> 00:32:13.198 And you can see here.

NOTE Confidence: 0.902856236363636

00:32:13.200 --> 00:32:14.676 So these are different cell lines.

NOTE Confidence: 0.902856236363636

00:32:14.680 --> 00:32:16.759 I have to say that ITD cells

NOTE Confidence: 0.902856236363636

00:32:16.759 --> 00:32:18.151 have high expression of C123,

NOTE Confidence: 0.902856236363636

00:32:18.151 --> 00:32:20.017 which is why we selected those

NOTE Confidence: 0.902856236363636

00:32:20.017 --> 00:32:21.400 for the combination trials.

NOTE Confidence: 0.902856236363636

00:32:21.400 --> 00:32:23.000 But especially with the triplet,

NOTE Confidence: 0.902856236363636

00:32:23.000 --> 00:32:27.158 there's quite a bit of synergy.

NOTE Confidence: 0.902856236363636

00:32:27.160 --> 00:32:29.800 What about PPG mutant AML,

NOTE Confidence: 0.695363446666667

00:32:29.800 --> 00:32:31.438 So these are wild type cells,

NOTE Confidence: 0.695363446666667

00:32:31.440 --> 00:32:35.344 so they're sensitive and they mutant or loss,

NOTE Confidence: 0.695363446666667

00:32:35.344 --> 00:32:37.712 PPG loss, we see less activity.

NOTE Confidence: 0.695363446666667

00:32:37.712 --> 00:32:39.880 There's still some induction of cell does,

NOTE Confidence: 0.695363446666667

00:32:39.880 --> 00:32:41.880 but it's actually quite resistant

NOTE Confidence: 0.695363446666667

00:32:41.880 --> 00:32:43.880 to both of the compounds.

NOTE Confidence: 0.695363446666667

00:32:43.880 --> 00:32:46.240 We're not quite sure how that is affected.

NOTE Confidence: 0.695363446666667

00:32:46.240 --> 00:32:47.842 So for some reason the cells

NOTE Confidence: 0.695363446666667

00:32:47.842 --> 00:32:49.319 had very high expression of MSL.

NOTE Confidence: 0.695363446666667

00:32:49.320 --> 00:32:51.749 One, we're still working on to understand

NOTE Confidence: 0.695363446666667

00:32:51.749 --> 00:32:54.079 that because we did see induction of

NOTE Confidence: 0.695363446666667

00:32:54.079 --> 00:32:56.258 DNA damage in both knock down cells

NOTE Confidence: 0.695363446666667

00:32:56.258 --> 00:32:58.546 and the wild cap cells and there's a

NOTE Confidence: 0.695363446666667

00:32:58.546 --> 00:33:02.140 part cleavage but it's less killing and

NOTE Confidence: 0.695363446666667

00:33:02.140 --> 00:33:03.960 that is also reflected in the trial.

NOTE Confidence: 0.695363446666667

00:33:03.960 --> 00:33:06.210 The PhD media patients didn't

NOTE Confidence: 0.695363446666667

00:33:06.210 --> 00:33:08.904 do as well as you can imagine.

NOTE Confidence: 0.695363446666667

00:33:08.904 --> 00:33:10.920 The drug abolishes the S phase.

NOTE Confidence: 0.695363446666667

00:33:10.920 --> 00:33:14.696 So this is like IMGN alone and the

NOTE Confidence: 0.695363446666667

00:33:14.696 --> 00:33:16.360 different concentrations and then

NOTE Confidence: 0.695363446666667

00:33:16.360 --> 00:33:18.845 when you combine with the Vanasa you

NOTE Confidence: 0.695363446666667

00:33:18.845 --> 00:33:21.120 essentially you kill off the S phase

NOTE Confidence: 0.695363446666667

00:33:21.120 --> 00:33:23.756 cells so you don't have anything left.

NOTE Confidence: 0.695363446666667

00:33:23.760 --> 00:33:26.425 You do get activation of gamma H3X

NOTE Confidence: 0.695363446666667

00:33:26.425 --> 00:33:29.120 as adna damage and Cliff cast space.

NOTE Confidence: 0.695363446666667

00:33:29.120 --> 00:33:31.040 So then we try to understand the mechanism,

NOTE Confidence: 0.695363446666667

00:33:31.040 --> 00:33:33.500 how that works.

NOTE Confidence: 0.695363446666667

00:33:33.500 --> 00:33:36.280 And so one thing is we know that

NOTE Confidence: 0.695363446666667

00:33:36.280 --> 00:33:37.120 again I'm Gen.

NOTE Confidence: 0.695363446666667

00:33:37.120 --> 00:33:40.039 inducing the single cell DNA strand breaks.

NOTE Confidence: 0.695363446666667

00:33:40.040 --> 00:33:43.012 So we showed the phosphor P53UP

NOTE Confidence: 0.695363446666667

00:33:43.012 --> 00:33:45.272 regulation which was the same

NOTE Confidence: 0.695363446666667

00:33:45.272 --> 00:33:47.080 with or without venetoclax.

NOTE Confidence: 0.695363446666667

00:33:47.080 --> 00:33:49.800 But then we saw that the drug inducing

NOTE Confidence: 0.695363446666667

00:33:49.800 --> 00:33:52.998 the DNA repair pathway phosphor check one

NOTE Confidence: 0.695363446666667

00:33:53.000 --> 00:33:55.680 and it seemed to be less with venetoclax.

NOTE Confidence: 0.695363446666667

00:33:55.680 --> 00:33:56.640 So we are,

NOTE Confidence: 0.695363446666667

00:33:56.640 --> 00:33:58.240 it's kind of off story,

NOTE Confidence: 0.695363446666667

00:33:58.240 --> 00:34:00.095 but we are trying to understand if

NOTE Confidence: 0.695363446666667

00:34:00.095 --> 00:34:01.791 BCL 2 inhibition can actually be

NOTE Confidence: 0.695363446666667

00:34:01.791 --> 00:34:03.758 involved in the control of DNA damage,

NOTE Confidence: 0.695363446666667

00:34:03.760 --> 00:34:06.292 which is hard to understand because

NOTE Confidence: 0.695363446666667

00:34:06.292 --> 00:34:08.440 it's cytosolic and this is DNA.

NOTE Confidence: 0.695363446666667

00:34:08.440 --> 00:34:10.555 But we are kind of working through the story,

NOTE Confidence: 0.695363446666667

00:34:10.560 --> 00:34:12.420 still trying to figure out all

NOTE Confidence: 0.695363446666667

00:34:12.420 --> 00:34:14.520 the parts of the DNA pathway.

NOTE Confidence: 0.695363446666667

00:34:14.520 --> 00:34:16.278 But it has some like clinical,

NOTE Confidence: 0.695363446666667

00:34:16.280 --> 00:34:18.460 preclinical implications because if you

NOTE Confidence: 0.695363446666667

00:34:18.460 --> 00:34:21.840 use IMGN first followed by the nether class,

NOTE Confidence: 0.695363446666667

00:34:21.840 --> 00:34:23.560 you have very striking synergy.

NOTE Confidence: 0.695363446666667

00:34:23.560 --> 00:34:25.800 This BLISS index is 18.

NOTE Confidence: 0.695363446666667

00:34:25.800 --> 00:34:28.488 If you do the reverse then

NOTE Confidence: 0.695363446666667

00:34:28.488 --> 00:34:30.280 first followed by IMGN,

NOTE Confidence: 0.695363446666667

00:34:30.280 --> 00:34:32.320 there's very little synergy now in

NOTE Confidence: 0.695363446666667

00:34:32.320 --> 00:34:34.600 the clinic it's given concomitantly.

NOTE Confidence: 0.695363446666667

00:34:34.600 --> 00:34:37.684 So I think it's fine but and nobody's

NOTE Confidence: 0.695363446666667

00:34:37.684 --> 00:34:39.794 interested in understanding the kinetics.

NOTE Confidence: 0.695363446666667

00:34:39.800 --> 00:34:41.900 But I think the biologically this

NOTE Confidence: 0.695363446666667

00:34:41.900 --> 00:34:43.300 is interesting phenomenon and

NOTE Confidence: 0.695363446666667

00:34:43.361 --> 00:34:45.263 perhaps something to do with DNA

NOTE Confidence: 0.695363446666667

00:34:45.263 --> 00:34:47.200 damage repair that we're working on.

NOTE Confidence: 0.695363446666667

00:34:47.200 --> 00:34:49.916 We also showed that the IMGN primes

NOTE Confidence: 0.695363446666667

00:34:49.916 --> 00:34:52.279 towards be so to inhibition.

NOTE Confidence: 0.695363446666667

00:34:52.280 --> 00:34:53.927 So I didn't I have a lot of like

NOTE Confidence: 0.695363446666667

00:34:53.927 --> 00:34:55.559 mouse data which I didn't show you,

NOTE Confidence: 0.695363446666667

00:34:55.560 --> 00:34:58.440 but the clinical trial has been

NOTE Confidence: 0.695363446666667

00:34:58.440 --> 00:35:01.352 reported at ASH and the paper is

NOTE Confidence: 0.695363446666667

00:35:01.352 --> 00:35:03.192 also now accepted in JCO.

NOTE Confidence: 0.695363446666667

00:35:03.200 --> 00:35:05.240 So this is a triplet.

NOTE Confidence: 0.695363446666667

00:35:05.240 --> 00:35:07.760 So again the drug is now called

NOTE Confidence: 0.695363446666667

00:35:07.760 --> 00:35:08.882 Pivacomab P VAC.

NOTE Confidence: 0.695363446666667

00:35:08.882 --> 00:35:11.696 We abbreviate that it was used with

NOTE Confidence: 0.695363446666667

00:35:11.696 --> 00:35:14.200 Azovan in newly diagnosed AML.

NOTE Confidence: 0.695363446666667

00:35:14.200 --> 00:35:15.475 All the patients,

NOTE Confidence: 0.695363446666667

00:35:15.475 --> 00:35:17.600 you know majority were unfit,

NOTE Confidence: 0.695363446666667

00:35:17.600 --> 00:35:21.320 but there were some fit patients as well.

NOTE Confidence: 0.695363446666667

00:35:21.320 --> 00:35:23.120 So it was fairly safe.

NOTE Confidence: 0.695363446666667

00:35:23.120 --> 00:35:26.319 So again the drug has some toxicities,

NOTE Confidence: 0.695363446666667

00:35:26.320 --> 00:35:29.757 but generally speaking it was well tolerated.

NOTE Confidence: 0.695363446666667

00:35:29.760 --> 00:35:31.993 And then the response rates where I

NOTE Confidence: 0.695363446666667

00:35:31.993 --> 00:35:34.039 would say similar to the ACE event,

NOTE Confidence: 0.931259272

00:35:34.040 --> 00:35:35.640 but what was impressive

NOTE Confidence: 0.931259272

00:35:35.640 --> 00:35:37.510 was MRD negativity rate.

NOTE Confidence: 0.931259272

00:35:37.510 --> 00:35:41.688 So the depths of response was you get about

NOTE Confidence: 0.931259272

00:35:41.688 --> 00:35:45.272 40% with ACE event it was about 76% of 79.

NOTE Confidence: 0.931259272

00:35:45.272 --> 00:35:47.680 So almost doubling the depths of response.

NOTE Confidence: 0.931259272

00:35:47.680 --> 00:35:49.528 Now we don't know yet if that

NOTE Confidence: 0.931259272

00:35:49.528 --> 00:35:50.320 translates into survival,

NOTE Confidence: 0.931259272

00:35:50.320 --> 00:35:53.158 which will be a critical question.

NOTE Confidence: 0.931259272

00:35:53.160 --> 00:35:55.280 So now Immunogen is bought by ABB vie.

NOTE Confidence: 0.931259272

00:35:55.280 --> 00:35:57.387 So we're hoping that this will continue

NOTE Confidence: 0.931259272

00:35:57.387 --> 00:35:59.242 and to randomized phase three study

NOTE Confidence: 0.931259272

00:35:59.242 --> 00:36:01.485 and maybe we'll have that triplet in

NOTE Confidence: 0.931259272

00:36:01.485 --> 00:36:04.155 a few years fully characterized that.

NOTE Confidence: 0.931259272

00:36:04.160 --> 00:36:06.770 But if you look at this like 3 subsets

NOTE Confidence: 0.931259272

00:36:06.770 --> 00:36:09.196 that I showed you before, so again,

NOTE Confidence: 0.931259272

00:36:09.196 --> 00:36:11.344 the good kind of prognostic patient

NOTE Confidence: 0.931259272

00:36:11.344 --> 00:36:13.239 that respond well to to azavan,

NOTE Confidence: 0.931259272

00:36:13.240 --> 00:36:15.320 they did really well.

NOTE Confidence: 0.931259272

00:36:15.320 --> 00:36:18.440 This response rates in PVC mutant,

NOTE Confidence: 0.931259272

00:36:18.440 --> 00:36:21.198 there was about 20% full CR rate,

NOTE Confidence: 0.931259272

00:36:21.200 --> 00:36:23.480 but 50% overall response rate.

NOTE Confidence: 0.931259272

00:36:23.480 --> 00:36:25.000 So maybe there's kind of,

NOTE Confidence: 0.931259272

00:36:25.000 --> 00:36:27.640 you know some signal again with PVC mutation,

NOTE Confidence: 0.931259272

00:36:27.640 --> 00:36:29.040 we are kind of really at loss.

NOTE Confidence: 0.931259272

00:36:29.040 --> 00:36:30.552 So that you know,

NOTE Confidence: 0.931259272

00:36:30.552 --> 00:36:32.820 but again this will be developed

NOTE Confidence: 0.931259272

00:36:32.897 --> 00:36:35.648 hopefully further and we'll see a few

NOTE Confidence: 0.931259272

00:36:35.648 --> 00:36:38.928 years from now where that lens now P 53.

NOTE Confidence: 0.931259272

00:36:38.928 --> 00:36:41.635 So I already told you several times that this

NOTE Confidence: 0.931259272

00:36:41.635 --> 00:36:44.559 is like a major unmet need in AML and MD's.

NOTE Confidence: 0.931259272

00:36:44.560 --> 00:36:46.888 All the drugs that we had in phase

NOTE Confidence: 0.931259272

00:36:46.888 --> 00:36:49.160 three have failed for the most part.

NOTE Confidence: 0.931259272

00:36:49.160 --> 00:36:52.079 And even from the very initial studies,

NOTE Confidence: 0.931259272

00:36:52.080 --> 00:36:54.648 we've showed that this was a major resistance

NOTE Confidence: 0.931259272

00:36:54.648 --> 00:36:57.280 factor to venetoclax as well unfortunately.

NOTE Confidence: 0.931259272

00:36:57.280 --> 00:36:59.100 So patients who again relapsed

NOTE Confidence: 0.931259272

00:36:59.100 --> 00:37:00.920 or who were primary fracture,

NOTE Confidence: 0.931259272

00:37:00.920 --> 00:37:06.620 they had high rates of 17 P loss or P50C

NOTE Confidence: 0.931259272

00:37:06.620 --> 00:37:11.120 mutation or both and why that is the case.

NOTE Confidence: 0.931259272

00:37:11.120 --> 00:37:13.136 So first of all if you do like

NOTE Confidence: 0.931259272

00:37:13.136 --> 00:37:14.600 single cell DNA sequencing,

NOTE Confidence: 0.931259272

00:37:14.600 --> 00:37:16.970 this is from Andrew Way's paper

NOTE Confidence: 0.931259272

00:37:16.970 --> 00:37:19.108 you showed you know all this

NOTE Confidence: 0.931259272

00:37:19.108 --> 00:37:20.793 clones are being selected for.

NOTE Confidence: 0.931259272

00:37:20.800 --> 00:37:23.232 So it's almost like a pressure to select

NOTE Confidence: 0.931259272

00:37:23.232 --> 00:37:25.454 this clones for that because they do

NOTE Confidence: 0.931259272

00:37:25.454 --> 00:37:27.360 not get killed by venetoclax cell.

NOTE Confidence: 0.931259272

00:37:27.360 --> 00:37:29.664 And what he showed in this paper is

NOTE Confidence: 0.931259272

00:37:29.664 --> 00:37:32.640 that while in parental cells venetoclax

NOTE Confidence: 0.931259272

00:37:32.640 --> 00:37:35.880 induces backs activation by this essay,

NOTE Confidence: 0.931259272

00:37:35.880 --> 00:37:39.160 there's much less in the PVC knockouts also.

NOTE Confidence: 0.931259272

00:37:39.160 --> 00:37:43.080 And you can sensitize it by MC1 inhibition.

NOTE Confidence: 0.931259272

00:37:43.080 --> 00:37:43.720 But again,

NOTE Confidence: 0.931259272

00:37:43.720 --> 00:37:46.280 we don't have MC1 inhibitors in the clinic.

NOTE Confidence: 0.931259272

00:37:46.280 --> 00:37:47.638 So what do we do about that?

NOTE Confidence: 0.931259272

00:37:47.640 --> 00:37:48.760 We we don't really know.

NOTE Confidence: 0.931259272

00:37:48.760 --> 00:37:51.168 But I want to show you some clinical

NOTE Confidence: 0.931259272

00:37:51.168 --> 00:37:53.362 data from our Einstein program that

NOTE Confidence: 0.931259272

00:37:53.362 --> 00:37:55.642 was developed before I got there

NOTE Confidence: 0.931259272

00:37:55.710 --> 00:37:57.478 using a different approach.

NOTE Confidence: 0.931259272

00:37:57.480 --> 00:38:00.848 So the approach that they decided to go

NOTE Confidence: 0.931259272

00:38:00.848 --> 00:38:03.917 forward was really developed by Jogan.

NOTE Confidence: 0.931259272

00:38:03.920 --> 00:38:05.120 I cannot promise the last name,

NOTE Confidence: 0.931259272

00:38:05.120 --> 00:38:07.720 but that at Cleveland Clinic.

NOTE Confidence: 0.931259272

00:38:07.720 --> 00:38:08.440 So he is I think,

NOTE Confidence: 0.931259272

00:38:08.440 --> 00:38:10.340 the most knowledgeable person

NOTE Confidence: 0.931259272

00:38:10.340 --> 00:38:12.240 in HMAI feel that.

NOTE Confidence: 0.931259272

00:38:12.240 --> 00:38:13.500 So essentially he published

NOTE Confidence: 0.931259272

00:38:13.500 --> 00:38:15.055 the first study in MD's,

NOTE Confidence: 0.931259272

00:38:15.055 --> 00:38:17.120 as I'm sure Amara knows very well.

NOTE Confidence: 0.931259272

00:38:17.120 --> 00:38:19.682 And he compared the traditional dosing of

NOTE Confidence: 0.931259272

00:38:19.682 --> 00:38:22.520 decybin with what he calls metronomic dosing,

NOTE Confidence: 0.931259272

00:38:22.520 --> 00:38:25.480 which is once a week like 1/5 of the dose.

NOTE Confidence: 0.931259272

00:38:25.480 --> 00:38:28.119 So really like tiny doses of decybin.

NOTE Confidence: 0.931259272

00:38:28.120 --> 00:38:30.568 But he showed that this is

NOTE Confidence: 0.931259272

00:38:30.568 --> 00:38:32.472 enough to deplete DN MT3DMT1.

NOTE Confidence: 0.931259272

00:38:32.472 --> 00:38:35.160 So you don't really need to induce this,

NOTE Confidence: 0.836275078888889

00:38:35.160 --> 00:38:37.416 you know, constant cytotoxic

NOTE Confidence: 0.836275078888889

00:38:37.416 --> 00:38:40.236 DNA damaging response of HMAS.

NOTE Confidence: 0.836275078888889

00:38:40.240 --> 00:38:42.228 And then he showed in preclinical work

NOTE Confidence: 0.836275078888889

00:38:42.228 --> 00:38:44.085 that it can induce differentiation

NOTE Confidence: 0.836275078888889

00:38:44.085 --> 00:38:46.404 of P53 novel loss clones.

NOTE Confidence: 0.836275078888889

00:38:46.404 --> 00:38:49.170 Now the resistance to the decided

NOTE Confidence: 0.836275078888889

00:38:49.259 --> 00:38:51.914 men is mediated by approvalation

NOTE Confidence: 0.836275078888889

00:38:51.914 --> 00:38:54.038 of pyramid and synthesis.

NOTE Confidence: 0.836275078888889

00:38:54.040 --> 00:38:56.565 Again, this is all his work and

NOTE Confidence: 0.836275078888889

00:38:56.565 --> 00:38:58.990 he had some preclinical data

NOTE Confidence: 0.836275078888889

00:38:58.990 --> 00:39:01.640 that Veneto clerks can in fact

NOTE Confidence: 0.836275078888889

00:39:01.640 --> 00:39:03.728 reduce the pyramid incentives.

NOTE Confidence: 0.836275078888889

00:39:03.728 --> 00:39:07.440 So there may be potential synergy there.

NOTE Confidence: 0.836275078888889

00:39:07.440 --> 00:39:10.110 So based on this sort of

NOTE Confidence: 0.836275078888889

00:39:10.110 --> 00:39:11.000 preclinical rationale,

NOTE Confidence: 0.836275078888889

00:39:11.000 --> 00:39:13.600 the team at Einstein have

NOTE Confidence: 0.836275078888889

00:39:13.600 --> 00:39:15.680 developed this metronomic dosing

NOTE Confidence: 0.836275078888889

00:39:15.680 --> 00:39:17.528 of Decidabin and Veneto clerks.

NOTE Confidence: 0.836275078888889

00:39:17.528 --> 00:39:20.001 So now you have a newly diagnosed

NOTE Confidence: 0.836275078888889

00:39:20.001 --> 00:39:22.252 patient with Amalo MTS who comes

NOTE Confidence: 0.836275078888889

00:39:22.252 --> 00:39:24.394 to clinic and gets once a week

NOTE Confidence: 0.836275078888889

00:39:24.400 --> 00:39:26.120 injection of the SIBIN subcutaneously

NOTE Confidence: 0.836275078888889

00:39:26.120 --> 00:39:28.240 and one dose of another class.

NOTE Confidence: 0.836275078888889

00:39:28.240 --> 00:39:30.060 So I'll say I had hard time

NOTE Confidence: 0.836275078888889

00:39:30.060 --> 00:39:31.559 believing that when I got there,

NOTE Confidence: 0.836275078888889

00:39:31.560 --> 00:39:34.256 but I think now I'm so converted and

NOTE Confidence: 0.836275078888889

00:39:34.256 --> 00:39:36.971 that we are continuing the development

NOTE Confidence: 0.836275078888889

00:39:36.971 --> 00:39:39.911 of this in the prospective trial.

NOTE Confidence: 0.836275078888889

00:39:39.920 --> 00:39:41.600 So again this is like a schedule,

NOTE Confidence: 0.836275078888889

00:39:41.600 --> 00:39:43.560 this is like traditional what you do,

NOTE Confidence: 0.836275078888889

00:39:43.560 --> 00:39:45.499 you give another class for 28 days

NOTE Confidence: 0.836275078888889

00:39:45.499 --> 00:39:47.747 and you give the SIBIN for five days

NOTE Confidence: 0.836275078888889

00:39:47.747 --> 00:39:49.941 or ASAP for seven days and then you

NOTE Confidence: 0.836275078888889

00:39:49.941 --> 00:39:52.510 repeat the cycle and he is like once a week.

NOTE Confidence: 0.836275078888889

00:39:52.510 --> 00:39:55.014 So the idea is really to get away from

NOTE Confidence: 0.836275078888889

00:39:55.014 --> 00:39:57.066 the DNA damaging response because we

NOTE Confidence: 0.836275078888889

00:39:57.066 --> 00:39:59.408 know that Pfc mutated cells are only

NOTE Confidence: 0.836275078888889

00:39:59.408 --> 00:40:01.848 being selected by any DNA damaging drugs,

NOTE Confidence: 0.836275078888889

00:40:01.848 --> 00:40:04.473 they don't care and get into

NOTE Confidence: 0.836275078888889

00:40:04.473 --> 00:40:06.277 this hyper misleading effect.

NOTE Confidence: 0.836275078888889

00:40:06.280 --> 00:40:08.359 How that works, we don't know right?

NOTE Confidence: 0.836275078888889

00:40:08.360 --> 00:40:10.448 How many agents mechanism of actions

NOTE Confidence: 0.836275078888889

00:40:10.448 --> 00:40:12.600 is still not fully understood,

NOTE Confidence: 0.836275078888889

00:40:12.600 --> 00:40:15.390 but the idea was can we like really use

NOTE Confidence: 0.836275078888889

00:40:15.390 --> 00:40:18.597 that approach and at least have some benefit?

NOTE Confidence: 0.836275078888889

00:40:18.600 --> 00:40:19.960 So they published this paper,

NOTE Confidence: 0.836275078888889

00:40:19.960 --> 00:40:21.910 this was retrospective study using

NOTE Confidence: 0.836275078888889

00:40:21.910 --> 00:40:24.399 this regimen and now as I said,

NOTE Confidence: 0.836275078888889

00:40:24.400 --> 00:40:25.720 we are in the prospective study.

NOTE Confidence: 0.836275078888889

00:40:25.720 --> 00:40:26.296 I'm sorry,

NOTE Confidence: 0.836275078888889

00:40:26.296 --> 00:40:28.312 it's a it's a bit difficult slide

NOTE Confidence: 0.836275078888889

00:40:28.320 --> 00:40:30.770 but the point is that there was

NOTE Confidence: 0.836275078888889

00:40:30.770 --> 00:40:33.200 no really like mouse suppression

NOTE Confidence: 0.836275078888889

00:40:33.200 --> 00:40:35.594 but the response rate was quite

NOTE Confidence: 0.836275078888889

00:40:35.594 --> 00:40:38.502 significant and CR rate was 57% which

NOTE Confidence: 0.836275078888889

00:40:38.502 --> 00:40:42.079 was fairly similar to the VLA study.

NOTE Confidence: 0.836275078888889

00:40:42.080 --> 00:40:44.096 And then when we looked at the small

NOTE Confidence: 0.836275078888889

00:40:44.096 --> 00:40:45.794 numbers again this is all like very

NOTE Confidence: 0.836275078888889

00:40:45.794 --> 00:40:47.440 early on of PVC mutated patients,

NOTE Confidence: 0.836275078888889

00:40:47.440 --> 00:40:48.958 the survival was about 10 months

NOTE Confidence: 0.836275078888889

00:40:48.958 --> 00:40:50.979 and a lot of patients actually

NOTE Confidence: 0.836275078888889

00:40:50.979 --> 00:40:52.398 achieved full remission,

NOTE Confidence: 0.836275078888889

00:40:52.400 --> 00:40:53.750 became transfusion independent

NOTE Confidence: 0.836275078888889

00:40:53.750 --> 00:40:56.000 and they did very well.

NOTE Confidence: 0.836275078888889

00:40:56.000 --> 00:40:58.560 They relapsed like a clock at 10-11 months.

NOTE Confidence: 0.836275078888889

00:40:58.560 --> 00:41:00.300 So it's not curative approach but

NOTE Confidence: 0.836275078888889

00:41:00.300 --> 00:41:02.697 at least you know we can extend the

NOTE Confidence: 0.836275078888889

00:41:02.697 --> 00:41:04.467 survival again and reality is five

NOTE Confidence: 0.836275078888889

00:41:04.530 --> 00:41:06.370 months survival. Many other studies.

NOTE Confidence: 0.836275078888889

00:41:06.370 --> 00:41:07.920 Now this is 10 months.

NOTE Confidence: 0.836275078888889

00:41:07.920 --> 00:41:10.080 Again, small number non randomized studies,

NOTE Confidence: 0.836275078888889

00:41:10.080 --> 00:41:12.160 so with all the Kevas,

NOTE Confidence: 0.836275078888889

00:41:12.160 --> 00:41:13.585 but we're quite excited about

NOTE Confidence: 0.836275078888889

00:41:13.585 --> 00:41:15.496 that and we are thinking of what

NOTE Confidence: 0.836275078888889

00:41:15.496 --> 00:41:17.224 can we add to that to really like

NOTE Confidence: 0.836275078888889

00:41:17.282 --> 00:41:18.758 capitalize on this approach,

NOTE Confidence: 0.836275078888889

00:41:18.760 --> 00:41:22.840 you know using this metronomic dosing.

NOTE Confidence: 0.836275078888889

00:41:22.840 --> 00:41:25.280 So one thing is like in the lab we are

NOTE Confidence: 0.836275078888889

00:41:25.348 --> 00:41:27.916 trying to use some of the BAX activated.

NOTE Confidence: 0.836275078888889

00:41:27.920 --> 00:41:29.614 So I told you several times the

NOTE Confidence: 0.836275078888889

00:41:29.614 --> 00:41:31.191 BAX is really like critical and

NOTE Confidence: 0.836275078888889

00:41:31.191 --> 00:41:33.039 the BAX is not working with PP,

NOTE Confidence: 0.729887153571429

00:41:33.040 --> 00:41:36.876 she's lost. So we have a collaboration

NOTE Confidence: 0.729887153571429

00:41:36.876 --> 00:41:40.135 with again Everest and also Jerry

NOTE Confidence: 0.729887153571429

00:41:40.135 --> 00:41:42.912 Chipok would develop the direct

NOTE Confidence: 0.729887153571429

00:41:42.912 --> 00:41:45.752 Bax activators or Bax modulators.

NOTE Confidence: 0.729887153571429

00:41:45.760 --> 00:41:47.320 So we are thinking maybe

NOTE Confidence: 0.729887153571429

00:41:47.320 --> 00:41:48.880 if we use those compounds,

NOTE Confidence: 0.729887153571429

00:41:48.880 --> 00:41:50.815 there's a preclinical stage we

NOTE Confidence: 0.729887153571429

00:41:50.815 --> 00:41:53.160 can overcome the PVC mutant loss,

NOTE Confidence: 0.729887153571429

00:41:53.160 --> 00:41:56.400 but this remains to be seen.

NOTE Confidence: 0.729887153571429

00:41:56.400 --> 00:41:57.560 OK. So switching gears,

NOTE Confidence: 0.729887153571429

00:41:57.560 --> 00:42:00.006 so this was PVC new dated AML and

NOTE Confidence: 0.729887153571429

00:42:00.006 --> 00:42:01.920 now going back to the chemotherapy.

NOTE Confidence: 0.729887153571429

00:42:01.920 --> 00:42:03.516 So as I showed you before,

NOTE Confidence: 0.729887153571429

00:42:03.520 --> 00:42:05.638 there's like very good rationale to

NOTE Confidence: 0.729887153571429

00:42:05.638 --> 00:42:07.444 combine the Netherlands with the

NOTE Confidence: 0.729887153571429

00:42:07.444 --> 00:42:09.205 chemotherapy and AML and there are

NOTE Confidence: 0.729887153571429

00:42:09.205 --> 00:42:10.990 a lot of trials which have been

NOTE Confidence: 0.729887153571429

00:42:11.052 --> 00:42:13.336 already reported and now we're getting

NOTE Confidence: 0.729887153571429

00:42:13.336 --> 00:42:15.400 the response rate of about 90%.

NOTE Confidence: 0.729887153571429

00:42:15.400 --> 00:42:19.000 So this is like like was unheard of before,

NOTE Confidence: 0.729887153571429

00:42:19.000 --> 00:42:21.232 but when you add the Netherlands

NOTE Confidence: 0.729887153571429

00:42:21.232 --> 00:42:23.272 to chemotherapy you really get

NOTE Confidence: 0.729887153571429

00:42:23.272 --> 00:42:24.240 tremendous synergy.

NOTE Confidence: 0.729887153571429

00:42:24.240 --> 00:42:26.445 So in our centre we have this

NOTE Confidence: 0.729887153571429

00:42:26.445 --> 00:42:28.422 also IST that is run by Doctor

NOTE Confidence: 0.729887153571429

00:42:28.422 --> 00:42:30.281 Manzaris where we use the standard

NOTE Confidence: 0.729887153571429

00:42:30.281 --> 00:42:32.357 Sam plus sheep plus another class,

NOTE Confidence: 0.729887153571429

00:42:32.360 --> 00:42:34.520 different durations and so forth.

NOTE Confidence: 0.729887153571429

00:42:34.520 --> 00:42:35.840 The trial is still ongoing,

NOTE Confidence: 0.729887153571429

00:42:35.840 --> 00:42:38.080 but again the response rate are about

NOTE Confidence: 0.729887153571429

00:42:38.080 --> 00:42:40.476 90% is still like short follow up.

NOTE Confidence: 0.729887153571429

00:42:40.480 --> 00:42:42.958 So we don't really know like survival,

NOTE Confidence: 0.729887153571429

00:42:42.960 --> 00:42:45.060 but we are quite excited about this

NOTE Confidence: 0.729887153571429

00:42:45.060 --> 00:42:46.688 approach except PVC MUDA patients,

NOTE Confidence: 0.729887153571429

00:42:46.688 --> 00:42:49.040 they relapse and they don't do well.

NOTE Confidence: 0.729887153571429

00:42:49.040 --> 00:42:51.266 So we stopped using this for even

NOTE Confidence: 0.729887153571429

00:42:51.266 --> 00:42:53.720 younger PVC MUDA patients because all

NOTE Confidence: 0.729887153571429

00:42:53.720 --> 00:42:55.720 patients, 5 patients were treated with,

NOTE Confidence: 0.729887153571429

00:42:55.720 --> 00:42:57.832 they're all relapsed and they died

NOTE Confidence: 0.729887153571429

00:42:57.832 --> 00:43:00.086 from despite the fact that some

NOTE Confidence: 0.729887153571429

00:43:00.086 --> 00:43:01.638 of them achieved remission.

NOTE Confidence: 0.729887153571429

00:43:01.640 --> 00:43:04.160 So again, PVC remains an issue.

NOTE Confidence: 0.729887153571429

00:43:04.160 --> 00:43:06.617 So we're looking at the stem cell

NOTE Confidence: 0.729887153571429

00:43:06.617 --> 00:43:08.424 extinction with the therapy and

NOTE Confidence: 0.729887153571429

00:43:08.424 --> 00:43:10.797 doing a lot of research with that.

NOTE Confidence: 0.729887153571429

00:43:10.800 --> 00:43:12.915 And in the last 10 minutes of my talk,

NOTE Confidence: 0.729887153571429

00:43:12.920 --> 00:43:14.480 I'll go back to BCL XL,

NOTE Confidence: 0.729887153571429

00:43:14.480 --> 00:43:17.492 which may be of interest more

NOTE Confidence: 0.729887153571429

00:43:17.492 --> 00:43:19.356 broader kind of auditorium.

NOTE Confidence: 0.729887153571429

00:43:19.356 --> 00:43:22.560 So BCL XL is a cousin of BCL two

NOTE Confidence: 0.729887153571429

00:43:22.645 --> 00:43:25.480 and it's less expressed in the AML,

NOTE Confidence: 0.729887153571429

00:43:25.480 --> 00:43:27.796 but it's expressed in solar tumors,

NOTE Confidence: 0.729887153571429

00:43:27.800 --> 00:43:30.446 it is expressed in the TELL subsets.

NOTE Confidence: 0.729887153571429

00:43:30.446 --> 00:43:32.567 So this was work from Tony Lataev

NOTE Confidence: 0.729887153571429

00:43:32.567 --> 00:43:33.877 now a few years ago,

NOTE Confidence: 0.729887153571429

00:43:33.880 --> 00:43:36.680 a number of years ago that showed

NOTE Confidence: 0.729887153571429

00:43:36.680 --> 00:43:38.720 that the typical TELL actually

NOTE Confidence: 0.729887153571429

00:43:38.720 --> 00:43:41.885 depends on BCL XL and if you use this

NOTE Confidence: 0.729887153571429

00:43:41.885 --> 00:43:43.600 Navitoclax drug that didn't make it,

NOTE Confidence: 0.729887153571429

00:43:43.600 --> 00:43:46.276 you actually get very good responses.

NOTE Confidence: 0.729887153571429

00:43:46.280 --> 00:43:47.516 There's a subset that is B,

NOTE Confidence: 0.729887153571429

00:43:47.520 --> 00:43:48.432 so two dependent,

NOTE Confidence: 0.729887153571429

00:43:48.432 --> 00:43:50.960 but I'm not going to go into that.

NOTE Confidence: 0.729887153571429

00:43:50.960 --> 00:43:51.279 Now.

NOTE Confidence: 0.729887153571429

00:43:51.279 --> 00:43:53.193 I already told you that the

NOTE Confidence: 0.729887153571429

00:43:53.193 --> 00:43:56.045 liability of B cell X inhibitors is

NOTE Confidence: 0.729887153571429

00:43:56.045 --> 00:43:57.410 thrombocytopenia because platelets

NOTE Confidence: 0.729887153571429

00:43:57.410 --> 00:44:00.279 depend on B cell XL for survival.

NOTE Confidence: 0.729887153571429

00:44:00.280 --> 00:44:03.480 So you get on target toxicity and of

NOTE Confidence: 0.729887153571429

00:44:03.480 --> 00:44:06.120 course it's challenging to those.

NOTE Confidence: 0.729887153571429

00:44:06.120 --> 00:44:08.456 So and you know this is just a

NOTE Confidence: 0.729887153571429

00:44:08.456 --> 00:44:10.079 couture published review recently.

NOTE Confidence: 0.729887153571429

00:44:10.080 --> 00:44:11.574 So Nevito clocks right the drug

NOTE Confidence: 0.729887153571429

00:44:11.574 --> 00:44:13.080 that is still not approved,

NOTE Confidence: 0.729887153571429

00:44:13.080 --> 00:44:15.866 it was just as the venetoclax so

NOTE Confidence: 0.729887153571429

00:44:15.866 --> 00:44:18.184 inhibits the complexes inducing bags

NOTE Confidence: 0.729887153571429

00:44:18.184 --> 00:44:20.794 back but it causes thrombocytopenia

NOTE Confidence: 0.729887153571429

00:44:20.794 --> 00:44:22.360 killing the platelets.

NOTE Confidence: 0.729887153571429

00:44:22.360 --> 00:44:25.181 So the way around that at least

NOTE Confidence: 0.729887153571429

00:44:25.181 --> 00:44:28.217 that's ongoing work is to use the

NOTE Confidence: 0.729887153571429

00:44:28.217 --> 00:44:29.957 degraders for BCLXL degraders.

NOTE Confidence: 0.729887153571429

00:44:29.960 --> 00:44:31.360 So,

NOTE Confidence: 0.729887153571429

00:44:31.360 --> 00:44:33.652 so we have been collaborating with

NOTE Confidence: 0.729887153571429

00:44:33.652 --> 00:44:35.945 the team from Dalhoung Zhou who

NOTE Confidence: 0.729887153571429

00:44:35.945 --> 00:44:37.685 was before University of Florida

NOTE Confidence: 0.729887153571429

00:44:37.685 --> 00:44:38.729 and now he

NOTE Confidence: 0.8156123268

00:44:38.804 --> 00:44:40.479 moved to the San Antonio.

NOTE Confidence: 0.8156123268

00:44:40.480 --> 00:44:44.410 So he developed this Protac BCL

NOTE Confidence: 0.8156123268

00:44:44.410 --> 00:44:46.575 XL degrader where the legend

NOTE Confidence: 0.8156123268

00:44:46.575 --> 00:44:47.715 is essentially native o'clock.

NOTE Confidence: 0.8156123268

00:44:47.720 --> 00:44:51.560 So same drug, but then there's a linker

NOTE Confidence: 0.8156123268

00:44:51.560 --> 00:44:54.233 that links it to the VHL E3 ligase.

NOTE Confidence: 0.8156123268

00:44:54.233 --> 00:44:55.990 So you can ask why that is

NOTE Confidence: 0.8156123268

00:44:56.053 --> 00:44:57.617 better than inhibitor, right?

NOTE Confidence: 0.8156123268

00:44:57.617 --> 00:44:58.919 First of all, it's huge molecules.

NOTE Confidence: 0.8156123268

00:44:58.920 --> 00:45:01.290 So it's has a pharmacological

NOTE Confidence: 0.8156123268

00:45:01.290 --> 00:45:02.238 properties issues.

NOTE Confidence: 0.8156123268

00:45:02.240 --> 00:45:04.680 But The thing is that this E3 ligase

NOTE Confidence: 0.8156123268

00:45:04.680 --> 00:45:06.998 is not expressed in platelets.

NOTE Confidence: 0.8156123268

00:45:07.000 --> 00:45:08.720 So you're not getting degradation

NOTE Confidence: 0.8156123268

00:45:08.720 --> 00:45:11.200 of B cell XL and platelets.

NOTE Confidence: 0.8156123268

00:45:11.200 --> 00:45:13.084 And therefore you can see here

NOTE Confidence: 0.8156123268

00:45:13.084 --> 00:45:15.253 there's no B cell cell degradation

NOTE Confidence: 0.8156123268

00:45:15.253 --> 00:45:17.358 in platelets with this drug.

NOTE Confidence: 0.8156123268

00:45:17.360 --> 00:45:19.720 But it's like a TLO tumor cell line,

NOTE Confidence: 0.8156123268

00:45:19.720 --> 00:45:21.160 it's very nice degradation.

NOTE Confidence: 0.8156123268

00:45:21.160 --> 00:45:23.879 So this is just the schematics of that.

NOTE Confidence: 0.8156123268

00:45:23.880 --> 00:45:26.280 And again as a result,

NOTE Confidence: 0.8156123268

00:45:26.280 --> 00:45:28.614 you can kill the tumor cells

NOTE Confidence: 0.8156123268

00:45:28.614 --> 00:45:31.080 but you don't kill platelets.

NOTE Confidence: 0.8156123268

00:45:31.080 --> 00:45:33.664 So this drug right now is in clinical

NOTE Confidence: 0.8156123268

00:45:33.664 --> 00:45:36.731 trial in solar tumors and it's actually

NOTE Confidence: 0.8156123268

00:45:36.731 --> 00:45:39.756 completed the phase one portion of it.

NOTE Confidence: 0.8156123268

00:45:39.760 --> 00:45:42.280 They did see some drop in platelets,

NOTE Confidence: 0.8156123268

00:45:42.280 --> 00:45:44.268 but there was much less than whenever

NOTE Confidence: 0.8156123268

00:45:44.268 --> 00:45:46.383 the clocks I think because the drug

NOTE Confidence: 0.8156123268

00:45:46.383 --> 00:45:48.544 still binds to some extent and still

NOTE Confidence: 0.8156123268

00:45:48.544 --> 00:45:50.912 inhibits a little bit of BCL XL function,

NOTE Confidence: 0.8156123268

00:45:50.920 --> 00:45:52.900 but it was reversible and

NOTE Confidence: 0.8156123268

00:45:52.900 --> 00:45:54.880 no other toxicity was seen.

NOTE Confidence: 0.8156123268

00:45:54.880 --> 00:45:57.208 We published that it's quite effective

NOTE Confidence: 0.8156123268

00:45:57.208 --> 00:46:00.380 and the TL models and recently we

NOTE Confidence: 0.8156123268

00:46:00.380 --> 00:46:03.760 also moved towards the dual BCL 2XL

NOTE Confidence: 0.8156123268

00:46:03.760 --> 00:46:06.480 product which is not yet in the clinic

NOTE Confidence: 0.8156123268

00:46:06.480 --> 00:46:09.518 and we published this work in AML

NOTE Confidence: 0.8156123268

00:46:09.520 --> 00:46:11.235 and we showed that this dual product,

NOTE Confidence: 0.8156123268

00:46:11.240 --> 00:46:12.652 we call it 753-B,

NOTE Confidence: 0.8156123268

00:46:12.652 --> 00:46:15.260 it was actually quite effective in all

NOTE Confidence: 0.8156123268

00:46:15.260 --> 00:46:17.365 primary AML samples including those

NOTE Confidence: 0.8156123268

00:46:17.365 --> 00:46:19.999 that were resistant to venado clock.

NOTE Confidence: 0.8156123268

00:46:20.000 --> 00:46:22.653 So there's you know there's

NOTE Confidence: 0.8156123268

00:46:22.653 --> 00:46:24.830 degradation of BCL XL as you would

NOTE Confidence: 0.8156123268

00:46:24.893 --> 00:46:26.938 expect basically didn't see much

NOTE Confidence: 0.8156123268

00:46:26.938 --> 00:46:28.924 degradation of BCL 2IN primary cells

NOTE Confidence: 0.8156123268

00:46:28.924 --> 00:46:31.120 but it was seen the cell lines.

NOTE Confidence: 0.8156123268

00:46:31.120 --> 00:46:34.270 So we think that's potential for using

NOTE Confidence: 0.8156123268

00:46:34.270 --> 00:46:38.080 dual BCL 2XL inhibitors in AML as well.

NOTE Confidence: 0.8156123268

00:46:38.080 --> 00:46:40.232 And the other aspect of it that is

NOTE Confidence: 0.8156123268

00:46:40.232 --> 00:46:42.455 very kind of popular and the solid

NOTE Confidence: 0.8156123268

00:46:42.455 --> 00:46:44.890 tumor literature is that the role of

NOTE Confidence: 0.8156123268

00:46:44.890 --> 00:46:47.320 B cell excel in senescence cells.

NOTE Confidence: 0.8156123268

00:46:47.320 --> 00:46:49.000 So what we know the senescence cells,

NOTE Confidence: 0.8156123268

00:46:49.000 --> 00:46:51.345 the cells that survive chemotherapy

NOTE Confidence: 0.8156123268

00:46:51.345 --> 00:46:55.016 and but they can kind of revert back

NOTE Confidence: 0.8156123268

00:46:55.016 --> 00:46:57.420 and become chemo resistant and the

NOTE Confidence: 0.8156123268

00:46:57.420 --> 00:46:59.790 metastatic cells in the setting of

NOTE Confidence: 0.8156123268

00:46:59.859 --> 00:47:02.715 breast cancer or lung cancer and so forth,

NOTE Confidence: 0.8156123268

00:47:02.720 --> 00:47:05.840 It's much less known in senescence in EMO.

NOTE Confidence: 0.8156123268

00:47:05.840 --> 00:47:08.344 But there was a paper by Ari Melnick's

NOTE Confidence: 0.8156123268

00:47:08.344 --> 00:47:10.521 group that showed that chemotherapy

NOTE Confidence: 0.8156123268

00:47:10.521 --> 00:47:12.996 can actually induce senescence cells.

NOTE Confidence: 0.8156123268

00:47:13.000 --> 00:47:15.304 So this is like essay you use for

NOTE Confidence: 0.8156123268

00:47:15.304 --> 00:47:18.386 the C-12 FDG where you can show that

NOTE Confidence: 0.8156123268

00:47:18.386 --> 00:47:21.090 within the viable cells a fraction

NOTE Confidence: 0.8156123268

00:47:21.090 --> 00:47:23.755 of them are actually senescence and

NOTE Confidence: 0.8156123268

00:47:23.755 --> 00:47:25.130 the senescence cells they depend

NOTE Confidence: 0.8156123268

00:47:25.130 --> 00:47:26.999 on BCL X cell for survival.

NOTE Confidence: 0.8156123268

00:47:27.000 --> 00:47:29.360 So when we sorted out the senescence cells,

NOTE Confidence: 0.8156123268

00:47:29.360 --> 00:47:31.488 we showed that BCL XL was up regulated

NOTE Confidence: 0.8156123268

00:47:31.488 --> 00:47:33.219 which was which was consistent

NOTE Confidence: 0.8156123268

00:47:33.219 --> 00:47:34.356 with the literature.

NOTE Confidence: 0.8156123268

00:47:34.360 --> 00:47:36.216 And then when we looked at the markers

NOTE Confidence: 0.8156123268

00:47:36.216 --> 00:47:37.764 of senescence, this is cell line.

NOTE Confidence: 0.8156123268

00:47:37.764 --> 00:47:39.390 So chemo is inducing all the

NOTE Confidence: 0.8156123268

00:47:39.450 --> 00:47:40.720 senescence phenotypes.

NOTE Confidence: 0.8156123268

00:47:40.720 --> 00:47:42.722 But when we use this BCL XL

NOTE Confidence: 0.8156123268

00:47:42.722 --> 00:47:43.580 degrade that we

NOTE Confidence: 0.804974427894737

00:47:43.653 --> 00:47:45.013 can reverse that and

NOTE Confidence: 0.804974427894737

00:47:45.013 --> 00:47:46.713 they showed here as well.

NOTE Confidence: 0.804974427894737

00:47:46.720 --> 00:47:49.219 So we think that there's a potential

NOTE Confidence: 0.804974427894737

00:47:49.219 --> 00:47:52.214 efficacy of BCL XL inhibition and this

NOTE Confidence: 0.804974427894737

00:47:52.214 --> 00:47:54.298 dormant senescence cells plus with

NOTE Confidence: 0.804974427894737

00:47:54.298 --> 00:47:56.741 it's really hard to like identify them

NOTE Confidence: 0.804974427894737

00:47:56.741 --> 00:47:59.167 and patients like you know the the

NOTE Confidence: 0.804974427894737

00:47:59.167 --> 00:48:01.719 essays are not very well established.

NOTE Confidence: 0.804974427894737

00:48:01.720 --> 00:48:03.872 But I think there's a lot of interest

NOTE Confidence: 0.804974427894737

00:48:03.872 --> 00:48:05.432 using BCXL inhibitors as synolytic

NOTE Confidence: 0.804974427894737

00:48:05.432 --> 00:48:07.672 in a variety of different sort of

NOTE Confidence: 0.804974427894737

00:48:07.730 --> 00:48:09.638 conditions including sorry tumors,

NOTE Confidence: 0.804974427894737

00:48:09.640 --> 00:48:11.376 leukemias and so forth.

NOTE Confidence: 0.804974427894737

00:48:11.376 --> 00:48:12.678 And the finally,

NOTE Confidence: 0.804974427894737

00:48:12.680 --> 00:48:14.983 like I told you that there's some

NOTE Confidence: 0.804974427894737

00:48:14.983 --> 00:48:17.180 AML subsets that are BCL Excel

NOTE Confidence: 0.804974427894737

00:48:17.180 --> 00:48:18.640 dependent and this is one of them.

NOTE Confidence: 0.804974427894737

00:48:18.640 --> 00:48:20.656 So this is like totally horrible

NOTE Confidence: 0.804974427894737

00:48:20.656 --> 00:48:22.000 entity called acute Erythroid,

NOTE Confidence: 0.804974427894737

00:48:22.000 --> 00:48:22.796 Erythroid leukemia.

NOTE Confidence: 0.804974427894737

00:48:22.796 --> 00:48:25.582 And now Doctor Xu here has done

NOTE Confidence: 0.804974427894737

00:48:25.582 --> 00:48:27.557 a lot of work on that,

NOTE Confidence: 0.804974427894737

00:48:27.560 --> 00:48:30.440 but it's in the old classification

NOTE Confidence: 0.804974427894737

00:48:30.440 --> 00:48:34.208 is the MLM 6 and it has all of this

NOTE Confidence: 0.804974427894737

00:48:34.208 --> 00:48:36.190 Erythroid markers and it has very

NOTE Confidence: 0.804974427894737

00:48:36.190 --> 00:48:38.142 high rates of PPC mutation, right.

NOTE Confidence: 0.804974427894737

00:48:38.142 --> 00:48:40.238 So I already told you that the NOW

NOTE Confidence: 0.804974427894737

00:48:40.238 --> 00:48:42.400 class does not work for PPC mutant AML.

NOTE Confidence: 0.804974427894737

00:48:42.400 --> 00:48:44.044 And sure enough in all clinical

NOTE Confidence: 0.804974427894737

00:48:44.044 --> 00:48:45.831 trials patients who were AEL patients

NOTE Confidence: 0.804974427894737

00:48:45.831 --> 00:48:47.436 who were treated with Venetoclax,

NOTE Confidence: 0.804974427894737

00:48:47.440 --> 00:48:49.092 they progressed very quickly.

NOTE Confidence: 0.804974427894737

00:48:49.092 --> 00:48:51.157 So that's not a solution,

NOTE Confidence: 0.804974427894737

00:48:51.160 --> 00:48:53.586 but there was a,

NOTE Confidence: 0.804974427894737

00:48:53.586 --> 00:48:55.158 we collaborated with the work with

NOTE Confidence: 0.804974427894737

00:48:55.158 --> 00:48:57.085 a group at University of Helsinki

NOTE Confidence: 0.804974427894737

00:48:57.085 --> 00:48:59.025 and they they published this very

NOTE Confidence: 0.804974427894737

00:48:59.025 --> 00:49:00.675 nice paper last year and blood.

NOTE Confidence: 0.804974427894737

00:49:00.680 --> 00:49:03.184 So they looked at the dependency

NOTE Confidence: 0.804974427894737

00:49:03.184 --> 00:49:06.208 and AEL using the Crispus screens

NOTE Confidence: 0.804974427894737

00:49:06.208 --> 00:49:08.596 or drug screens and one of the

NOTE Confidence: 0.804974427894737

00:49:08.596 --> 00:49:10.120 top one was actually B cell XL.

NOTE Confidence: 0.804974427894737

00:49:10.120 --> 00:49:12.794 This is a gene called B cell

NOTE Confidence: 0.804974427894737

00:49:12.794 --> 00:49:14.839 12/1 that controls B cell XL.

NOTE Confidence: 0.804974427894737

00:49:14.840 --> 00:49:16.728 And you can see that it also was

NOTE Confidence: 0.804974427894737

00:49:16.728 --> 00:49:18.980 true for the drug screen as well.

NOTE Confidence: 0.804974427894737

00:49:18.980 --> 00:49:21.714 They show this and they confirm that

NOTE Confidence: 0.804974427894737

00:49:21.714 --> 00:49:24.585 and the cell lines and if you use a

NOTE Confidence: 0.804974427894737

00:49:24.585 --> 00:49:26.440 different like gene expression data sets,

NOTE Confidence: 0.804974427894737

00:49:26.440 --> 00:49:28.358 so again this is old M6 also

NOTE Confidence: 0.804974427894737

00:49:28.358 --> 00:49:30.559 M7 which is megacaric leukemia,

NOTE Confidence: 0.804974427894737

00:49:30.560 --> 00:49:32.800 they have high expression here,

NOTE Confidence: 0.804974427894737

00:49:32.800 --> 00:49:34.320 very high expression and this

NOTE Confidence: 0.804974427894737

00:49:34.320 --> 00:49:36.200 is Saint Jude Court as well.

NOTE Confidence: 0.804974427894737

00:49:36.200 --> 00:49:38.230 So they have a high expression of

NOTE Confidence: 0.804974427894737

00:49:38.230 --> 00:49:40.799 BCL XL on a transcriptional level.

NOTE Confidence: 0.804974427894737

00:49:40.800 --> 00:49:42.540 So The thing is because the

NOTE Confidence: 0.804974427894737

00:49:42.540 --> 00:49:44.107 erythroid cells have you know

NOTE Confidence: 0.804974427894737

00:49:44.107 --> 00:49:45.491 naturally utilizing this protein

NOTE Confidence: 0.804974427894737

00:49:45.491 --> 00:49:47.840 for survival and this is preserved,

NOTE Confidence: 0.804974427894737

00:49:47.840 --> 00:49:49.500 they also showed some efficacy

NOTE Confidence: 0.804974427894737

00:49:49.500 --> 00:49:51.160 in the in vivo models.

NOTE Confidence: 0.804974427894737

00:49:51.160 --> 00:49:53.316 So we are interested in using the

NOTE Confidence: 0.804974427894737

00:49:53.316 --> 00:49:55.052 product for this indication and

NOTE Confidence: 0.804974427894737

00:49:55.052 --> 00:49:57.302 within mechanistically it makes a lot

NOTE Confidence: 0.804974427894737

00:49:57.302 --> 00:49:59.997 of sense because again in Aristo it

NOTE Confidence: 0.804974427894737

00:49:59.997 --> 00:50:01.872 says the main transcription factor

NOTE Confidence: 0.804974427894737

00:50:01.880 --> 00:50:04.205 that drives kind of development

NOTE Confidence: 0.804974427894737

00:50:04.205 --> 00:50:06.692 is gutter one and we show that

NOTE Confidence: 0.804974427894737

00:50:06.692 --> 00:50:08.330 there is a very direct correlation

NOTE Confidence: 0.804974427894737

00:50:08.385 --> 00:50:10.760 between B SO2L1 and gutter one.

NOTE Confidence: 0.804974427894737

00:50:10.760 --> 00:50:13.357 This is activity from the gene expression

NOTE Confidence: 0.804974427894737

00:50:13.357 --> 00:50:15.800 analysis and both different data sets.

NOTE Confidence: 0.804974427894737

00:50:15.800 --> 00:50:18.117 This was collaboration with Saint Jude team,

NOTE Confidence: 0.804974427894737

00:50:18.120 --> 00:50:19.835 so there's no correlation with BCO 2.

NOTE Confidence: 0.804974427894737

00:50:19.840 --> 00:50:23.176 So really in Ali think there's

NOTE Confidence: 0.804974427894737

00:50:23.176 --> 00:50:24.844 transcriptional up regulation

NOTE Confidence: 0.804974427894737

00:50:24.844 --> 00:50:27.317 and dependency on BCL XL.

NOTE Confidence: 0.804974427894737

00:50:27.320 --> 00:50:29.840 Based on some of the prior work published,

NOTE Confidence: 0.804974427894737

00:50:29.840 --> 00:50:31.996 we know that this got the one

NOTE Confidence: 0.804974427894737

00:50:31.996 --> 00:50:34.045 directly binds the BCO 2L1 locals.

NOTE Confidence: 0.804974427894737

00:50:34.045 --> 00:50:36.670 And we have now also data in

NOTE Confidence: 0.804974427894737

00:50:36.759 --> 00:50:39.269 AL in collaboration with again

NOTE Confidence: 0.804974427894737

00:50:39.269 --> 00:50:41.277 Ilaria from Saint Jude

NOTE Confidence: 0.755040734

00:50:41.280 --> 00:50:43.720 and they're using this degrader.

NOTE Confidence: 0.755040734

00:50:43.720 --> 00:50:45.834 So this is original BCL XL degrader.

NOTE Confidence: 0.755040734

00:50:45.840 --> 00:50:48.000 This is like a next generation.

NOTE Confidence: 0.755040734

00:50:48.000 --> 00:50:50.648 We showed us the cell lines that are

NOTE Confidence: 0.755040734

00:50:50.648 --> 00:50:52.307 completely resistant to the netoclocks

NOTE Confidence: 0.755040734

00:50:52.307 --> 00:50:54.640 here and green they can be nicely

NOTE Confidence: 0.755040734

00:50:54.640 --> 00:50:57.520 killed by this B cell cell degrader.

NOTE Confidence: 0.755040734

00:50:57.520 --> 00:50:59.963 We also tested this in fuel primary

NOTE Confidence: 0.755040734

00:50:59.963 --> 00:51:02.902 samples that you know failed all kind

NOTE Confidence: 0.755040734

00:51:02.902 --> 00:51:05.096 of regiments including macrolimab and

NOTE Confidence: 0.755040734

00:51:05.096 --> 00:51:07.728 the we show the B cell degradation

NOTE Confidence: 0.755040734

00:51:07.728 --> 00:51:10.078 here and very nice response.

NOTE Confidence: 0.755040734

00:51:10.080 --> 00:51:12.360 So again, this is preclinical work.

NOTE Confidence: 0.755040734

00:51:12.360 --> 00:51:15.204 We're trying to get the drug if we get

NOTE Confidence: 0.755040734

00:51:15.204 --> 00:51:17.798 funding for the trials is still ongoing,

NOTE Confidence: 0.755040734

00:51:17.800 --> 00:51:20.680 but we feel that this is a hopeful

NOTE Confidence: 0.755040734

00:51:20.680 --> 00:51:23.861 and in fact I learned that every

NOTE Confidence: 0.755040734

00:51:23.861 --> 00:51:26.514 just approved the nabito clocks

NOTE Confidence: 0.755040734

00:51:26.514 --> 00:51:30.340 for the subset of AL between MSK

NOTE Confidence: 0.755040734

00:51:30.340 --> 00:51:32.560 and the MD Anderson Cancer Center.

NOTE Confidence: 0.755040734

00:51:32.560 --> 00:51:34.464 So there will be a small pilot

NOTE Confidence: 0.755040734

00:51:34.464 --> 00:51:36.211 trial at least testing the proof

NOTE Confidence: 0.755040734

00:51:36.211 --> 00:51:38.646 of principle that B cell XL is a

NOTE Confidence: 0.755040734

00:51:38.646 --> 00:51:40.356 driver in this horrible disease.

NOTE Confidence: 0.755040734

00:51:40.360 --> 00:51:42.960 We also see very similar phenotypes in MPN,

NOTE Confidence: 0.755040734

00:51:42.960 --> 00:51:44.892 but I didn't have time to

NOTE Confidence: 0.755040734

00:51:44.892 --> 00:51:46.640 show this data as well.

NOTE Confidence: 0.755040734

00:51:46.640 --> 00:51:47.964 So I'll end here.

NOTE Confidence: 0.755040734

00:51:47.964 --> 00:51:49.950 And I would like to postulate

NOTE Confidence: 0.755040734

00:51:50.027 --> 00:51:51.717 that AML is generally B,

NOTE Confidence: 0.755040734

00:51:51.720 --> 00:51:53.220 so two dependent disease,

NOTE Confidence: 0.755040734

00:51:53.220 --> 00:51:55.778 but then there's some subsets that are

NOTE Confidence: 0.755040734

00:51:55.778 --> 00:51:57.920 depend on B cell XL or M cell one.

NOTE Confidence: 0.755040734

00:51:57.920 --> 00:52:00.176 And of course we love the drug because

NOTE Confidence: 0.755040734

00:52:00.176 --> 00:52:02.278 it kind of lowers the threshold.

NOTE Confidence: 0.755040734

00:52:02.280 --> 00:52:05.296 So you can see the synergy with pretty

NOTE Confidence: 0.755040734

00:52:05.296 --> 00:52:07.871 much anything you use and then you can

NOTE Confidence: 0.755040734

00:52:07.871 --> 00:52:10.995 kind of go back to lab and figure out why.

NOTE Confidence: 0.755040734

00:52:11.000 --> 00:52:13.200 But but this was really like you know

NOTE Confidence: 0.755040734

00:52:13.200 --> 00:52:15.808 born in the clinical trials where I

NOTE Confidence: 0.755040734

00:52:15.808 --> 00:52:17.798 showed you synergy with chemotherapy,

NOTE Confidence: 0.755040734

00:52:17.800 --> 00:52:19.804 with the hypermethylene agents,

NOTE Confidence: 0.755040734

00:52:19.804 --> 00:52:22.309 with thyristine kinase inhibitors and

NOTE Confidence: 0.755040734

00:52:22.309 --> 00:52:25.434 you know the the fuel has really like

NOTE Confidence: 0.755040734

00:52:25.434 --> 00:52:28.037 exploded using this drug as a sensitizer.

NOTE Confidence: 0.755040734

00:52:28.040 --> 00:52:30.600 Some of the you know trials that I

NOTE Confidence: 0.755040734

00:52:30.600 --> 00:52:32.513 mentioned are ongoing and immune

NOTE Confidence: 0.755040734

00:52:32.513 --> 00:52:34.913 therapies I mentioned to you before

NOTE Confidence: 0.755040734

00:52:34.920 --> 00:52:38.210 now resistance is obviously as a major

NOTE Confidence: 0.755040734

00:52:38.210 --> 00:52:40.672 issue and it's largely driven we think

NOTE Confidence: 0.755040734

00:52:40.672 --> 00:52:43.519 by PC laws or signaling mutations.

NOTE Confidence: 0.755040734

00:52:43.520 --> 00:52:45.585 And you know I showed you what

NOTE Confidence: 0.755040734

00:52:45.585 --> 00:52:47.440 we're trying to do about that.

NOTE Confidence: 0.755040734

00:52:47.440 --> 00:52:50.184 But then the subsets that are B cell

NOTE Confidence: 0.755040734

00:52:50.184 --> 00:52:52.212 excel dependent and we are quite

NOTE Confidence: 0.755040734

00:52:52.212 --> 00:52:54.609 excited about using this B cell excel

NOTE Confidence: 0.755040734

00:52:54.609 --> 00:52:57.159 inhibitors or products in this setting.

NOTE Confidence: 0.755040734

00:52:57.160 --> 00:52:58.220 So I'll end here.

NOTE Confidence: 0.755040734

00:52:58.220 --> 00:52:59.280 So I have many,

NOTE Confidence: 0.755040734

00:52:59.280 --> 00:53:02.235 many Co workers collaborators from

NOTE Confidence: 0.755040734

00:53:02.235 --> 00:53:06.520 both my MD Anderson lab that has now

NOTE Confidence: 0.755040734

00:53:06.520 --> 00:53:08.280 only partially moved to Einstein.

NOTE Confidence: 0.755040734

00:53:08.280 --> 00:53:10.886 So I have a new lab at Einstein and

NOTE Confidence: 0.755040734

00:53:10.886 --> 00:53:13.116 my clinical collaborators at MD

NOTE Confidence: 0.755040734

00:53:13.116 --> 00:53:15.241 Anderson especially Courtney who led

NOTE Confidence: 0.755040734

00:53:15.241 --> 00:53:17.441 AMLVLA trial now who has done a lot

NOTE Confidence: 0.755040734

00:53:17.441 --> 00:53:19.623 of triplet combinations and many

NOTE Confidence: 0.755040734

00:53:19.623 --> 00:53:21.918 other investigators of course Dr.

NOTE Confidence: 0.755040734

00:53:21.920 --> 00:53:24.110 Contagion who has been really like

NOTE Confidence: 0.755040734

00:53:24.110 --> 00:53:26.785 pushing ABVI to go forward with this

NOTE Confidence: 0.755040734

00:53:26.785 --> 00:53:29.438 HMA event trial despite the fact that

NOTE Confidence: 0.755040734

00:53:29.515 --> 00:53:31.999 single agent was not as efficacious.

NOTE Confidence: 0.755040734

00:53:32.000 --> 00:53:34.640 And a lot of collaborators from

NOTE Confidence: 0.755040734

00:53:34.640 --> 00:53:35.520 Montefiore Einstein,

NOTE Confidence: 0.755040734

00:53:35.520 --> 00:53:37.200 we're developing this new programs

NOTE Confidence: 0.755040734

00:53:37.200 --> 00:53:39.704 that I showed to you and many

NOTE Confidence: 0.755040734

00:53:39.704 --> 00:53:41.352 collaborations with the companies

NOTE Confidence: 0.755040734

00:53:41.352 --> 00:53:43.000 but also academic collaborators.

NOTE Confidence: 0.755040734

00:53:43.000 --> 00:53:44.596 So I would like to acknowledge

NOTE Confidence: 0.755040734

00:53:44.596 --> 00:53:45.394 Tony Li Tai

NOTE Confidence: 0.956922252

00:53:45.400 --> 00:53:46.640 who has been really like,

NOTE Confidence: 0.956922252

00:53:46.640 --> 00:53:48.765 you know, developed this first

NOTE Confidence: 0.956922252

00:53:48.765 --> 00:53:51.630 approach with me in the lab.

NOTE Confidence: 0.956922252

00:53:51.630 --> 00:53:54.225 And you know, we think that because of

NOTE Confidence: 0.956922252

00:53:54.225 --> 00:53:56.933 that work and algos really went into AML

NOTE Confidence: 0.956922252

00:53:56.933 --> 00:53:59.077 and we have collaboration with Andrew

NOTE Confidence: 0.956922252

00:53:59.077 --> 00:54:01.376 Way at Melbourne and with the Saint

NOTE Confidence: 0.956922252

00:54:01.376 --> 00:54:04.000 Jude team and Dao Hangzhou for the product.

NOTE Confidence: 0.956922252

00:54:04.000 --> 00:54:04.960 So I'll end here.

NOTE Confidence: 0.956922252

00:54:04.960 --> 00:54:06.380 Sorry, it's like 5 minutes before

NOTE Confidence: 0.956922252

00:54:06.380 --> 00:54:07.560 the end of the hour,

NOTE Confidence: 0.956922252

00:54:07.560 --> 00:54:09.597 but I am happy to take questions.

NOTE Confidence: 0.956922252

00:54:09.600 --> 00:54:10.200 Thank you. Maybe I

NOTE Confidence: 0.260146545

00:54:18.670 --> 00:54:19.150 can start.

NOTE Confidence: 0.70466787

00:54:22.110 --> 00:54:23.310 You have questions in Zoom

NOTE Confidence: 0.707469232222222

00:54:26.480 --> 00:54:27.746 a fantastic talk.

NOTE Confidence: 0.707469232222222

00:54:27.746 --> 00:54:29.856 Very few people actually bridge

NOTE Confidence: 0.707469232222222

00:54:29.856 --> 00:54:32.188 the the clinic and the lab like

NOTE Confidence: 0.707469232222222

00:54:32.188 --> 00:54:34.040 you do clinical trials and lab,

NOTE Confidence: 0.707469232222222

00:54:34.040 --> 00:54:34.931 which is amazing.

NOTE Confidence: 0.707469232222222

00:54:34.931 --> 00:54:36.713 So I know this is not

NOTE Confidence: 0.707469232222222

00:54:36.713 --> 00:54:37.919 primarily your research,

NOTE Confidence: 0.707469232222222

00:54:37.920 --> 00:54:40.279 but why would you think the metronomic

NOTE Confidence: 0.707469232222222

00:54:40.280 --> 00:54:44.012 use of HMA with venetoclax would

NOTE Confidence: 0.707469232222222

00:54:44.012 --> 00:54:47.050 actually work for TP50 TP 53

NOTE Confidence: 0.707469232222222

00:54:47.050 --> 00:54:49.000 while regular dosing would not?

NOTE Confidence: 0.851652816666666

00:54:49.840 --> 00:54:52.258 I think the regular dosing induces

NOTE Confidence: 0.851652816666666

00:54:52.258 --> 00:54:54.276 DNA damage and essentially leads

NOTE Confidence: 0.851652816666666

00:54:54.276 --> 00:54:56.899 to the selection of P53 lost cells,

NOTE Confidence: 0.851652816666666

00:54:56.899 --> 00:54:59.930 so you kind of lose your hypermethylene

NOTE Confidence: 0.851652816666666

00:55:00.012 --> 00:55:01.961 advantage, whatever that is.

NOTE Confidence: 0.851652816666666

00:55:01.961 --> 00:55:04.670 Again, I don't know how the hypermetalline

NOTE Confidence: 0.851652816666666

00:55:04.742 --> 00:55:06.680 agents work in PhD muted EMLO,

NOTE Confidence: 0.851652816666666

00:55:06.680 --> 00:55:09.102 but I think what happens with the

NOTE Confidence: 0.851652816666666

00:55:09.102 --> 00:55:10.625 regular dosing, there's DNA damage,

NOTE Confidence: 0.851652816666666

00:55:10.625 --> 00:55:12.000 which was shown by Steele,

NOTE Confidence: 0.851652816666666

00:55:12.000 --> 00:55:13.644 Gore and others before.

NOTE Confidence: 0.851652816666666

00:55:13.644 --> 00:55:14.877 And the cells,

NOTE Confidence: 0.851652816666666

00:55:14.880 --> 00:55:17.040 they're just like being selected for.

NOTE Confidence: 0.851652816666666

00:55:17.040 --> 00:55:18.916 So all you get is selection of

NOTE Confidence: 0.851652816666666

00:55:18.916 --> 00:55:20.799 cells that are like PHC mutated.

NOTE Confidence: 0.851652816666666

00:55:20.800 --> 00:55:23.476 They're resistant to DNA damaging drugs.

NOTE Confidence: 0.851652816666666

00:55:23.480 --> 00:55:26.196 And so there's very limited like advantage.

NOTE Confidence: 0.851652816666666

00:55:26.200 --> 00:55:28.125 Well, with metronomic dosing you

NOTE Confidence: 0.851652816666666

00:55:28.125 --> 00:55:30.050 really like rely on hypometallic

NOTE Confidence: 0.851652816666666

00:55:30.117 --> 00:55:31.719 effects of the drug and then

NOTE Confidence: 0.851652816666666

00:55:31.719 --> 00:55:33.560 you know you you get benefit.

NOTE Confidence: 0.851652816666666

00:55:33.560 --> 00:55:35.515 But again you know it's

NOTE Confidence: 0.851652816666666

00:55:35.515 --> 00:55:37.079 a hand waving argument,

NOTE Confidence: 0.851652816666666

00:55:37.080 --> 00:55:39.747 but we are encouraged to see that

NOTE Confidence: 0.851652816666666

00:55:39.747 --> 00:55:41.656 in the prospective trial with

NOTE Confidence: 0.851652816666666

00:55:41.656 --> 00:55:43.620 the you know about 10 patients

NOTE Confidence: 0.851652816666666

00:55:43.620 --> 00:55:45.240 treated that the data stand.

NOTE Confidence: 0.851652816666666

00:55:45.240 --> 00:55:47.368 So this you know again they're going

NOTE Confidence: 0.851652816666666

00:55:47.368 --> 00:55:49.756 to remission about like 5060% and as of

NOTE Confidence: 0.851652816666666

00:55:49.756 --> 00:55:52.080 right now survival is about 11 months.

NOTE Confidence: 0.851652816666666

00:55:52.080 --> 00:55:53.718 But again like short follow up,

NOTE Confidence: 0.851652816666666

00:55:53.720 --> 00:55:56.360 you know it's a small number of patients.

NOTE Confidence: 0.851652816666666

00:55:56.360 --> 00:55:57.560 So I'm like you know,

NOTE Confidence: 0.851652816666666

00:55:57.560 --> 00:55:58.856 I've been hesitant presenting

NOTE Confidence: 0.851652816666666

00:55:58.856 --> 00:56:00.476 this data till I actually,

NOTE Confidence: 0.851652816666666

00:56:00.480 --> 00:56:02.718 you know, saw the survival data,

NOTE Confidence: 0.851652816666666

00:56:02.720 --> 00:56:04.582 but we're hoping that you know this

NOTE Confidence: 0.851652816666666

00:56:04.582 --> 00:56:06.560 will stand, but again it's not curative.

NOTE Confidence: 0.851652816666666

00:56:06.560 --> 00:56:08.040 So we definitely need something

NOTE Confidence: 0.851652816666666

00:56:08.040 --> 00:56:09.520 else to add to that.

NOTE Confidence: 0.851652816666666

00:56:09.520 --> 00:56:09.880 Thank you,

NOTE Confidence: 0.862851972857143

00:56:16.600 --> 00:56:18.790 very nice talk. I was curious

NOTE Confidence: 0.862851972857143

00:56:18.790 --> 00:56:21.808 about what's being done towards

NOTE Confidence: 0.862851972857143

00:56:21.808 --> 00:56:25.118 tissue specific MCL ONE inhibitors.

NOTE Confidence: 0.862851972857143

00:56:25.120 --> 00:56:27.598 So in order to avoid the cardiotoxicity,

NOTE Confidence: 0.862851972857143

00:56:27.600 --> 00:56:29.000 you talk beautifully about BCL

NOTE Confidence: 0.728932983333333

00:56:29.000 --> 00:56:32.153 XL for example. Unfortunately,

NOTE Confidence: 0.728932983333333

00:56:32.153 --> 00:56:35.318 nothing that I'm aware of.

NOTE Confidence: 0.728932983333333

00:56:35.320 --> 00:56:37.702 I heard that there's some approaching

NOTE Confidence: 0.728932983333333

00:56:37.702 --> 00:56:39.600 making approaches making the ADC.

NOTE Confidence: 0.867555357692308

00:56:41.880 --> 00:56:44.064 I haven't had yet chance to

NOTE Confidence: 0.867555357692308

00:56:44.064 --> 00:56:46.439 get any of those to my lab.

NOTE Confidence: 0.867555357692308

00:56:46.440 --> 00:56:48.918 So people are thinking about that.

NOTE Confidence: 0.867555357692308

00:56:48.920 --> 00:56:50.600 I think it's probably ongoing,

NOTE Confidence: 0.867555357692308

00:56:50.600 --> 00:56:52.106 but I'm not aware yet that

NOTE Confidence: 0.867555357692308

00:56:52.106 --> 00:56:53.440 there's any like you know,

NOTE Confidence: 0.867555357692308

00:56:53.440 --> 00:56:55.156 compound that is close to clinic,

NOTE Confidence: 0.867555357692308

00:56:55.160 --> 00:56:57.920 but I think that would be the way to go.

NOTE Confidence: 0.867555357692308

00:56:57.920 --> 00:57:01.637 Now the VHL is expressing the heart.

NOTE Confidence: 0.867555357692308

00:57:01.640 --> 00:57:03.032 So you know,

NOTE Confidence: 0.867555357692308

00:57:03.032 --> 00:57:05.784 there's also effort by Stephen Fazek,

NOTE Confidence: 0.867555357692308

00:57:05.784 --> 00:57:09.088 who is now at the Vanderbilt to look

NOTE Confidence: 0.867555357692308

00:57:09.088 --> 00:57:11.076 at all 600 ubiquitin ligase and try

NOTE Confidence: 0.867555357692308

00:57:11.076 --> 00:57:13.517 to understand the tissue specificity.

NOTE Confidence: 0.867555357692308

00:57:13.520 --> 00:57:14.680 Obviously, if I'm so one,

NOTE Confidence: 0.867555357692308

00:57:14.680 --> 00:57:16.516 we have to avoid the heart.

NOTE Confidence: 0.867555357692308

00:57:16.520 --> 00:57:18.152 I think that effort is still

NOTE Confidence: 0.867555357692308

00:57:18.152 --> 00:57:20.079 ongoing as far as the products,

NOTE Confidence: 0.867555357692308

00:57:20.080 --> 00:57:24.770 but I think perhaps using the antibodrap

NOTE Confidence: 0.867555357692308

00:57:24.770 --> 00:57:27.480 conugate maybe is the way to go.

NOTE Confidence: 0.867555357692308

00:57:27.480 --> 00:57:30.536 You know there was the B7 HCB cell Excel

NOTE Confidence: 0.867555357692308

00:57:30.536 --> 00:57:33.560 conjugate that went into solid tumor trials.

NOTE Confidence: 0.867555357692308

00:57:33.560 --> 00:57:34.680 It somehow didn't make it,

NOTE Confidence: 0.867555357692308

00:57:34.680 --> 00:57:36.170 but kind of similar approach

NOTE Confidence: 0.867555357692308

00:57:36.170 --> 00:57:37.960 perhaps can be used in Amo,

NOTE Confidence: 0.867555357692308

00:57:37.960 --> 00:57:39.760 but nothing close to clinic yet.

NOTE Confidence: 0.867555357692308

00:57:40.640 --> 00:57:40.960 Thank you.

NOTE Confidence: 0.4894056025

00:57:44.120 --> 00:57:47.520 Thank you for that. Thank you.

NOTE Confidence: 0.4894056025

00:57:47.520 --> 00:57:49.092 Looking at the evolution on the

NOTE Confidence: 0.4894056025

00:57:49.092 --> 00:57:51.128 clinical slides that we show on track

NOTE Confidence: 0.4894056025

00:57:51.128 --> 00:57:53.120 right single agent one of the plaques,

NOTE Confidence: 0.4894056025

00:57:53.120 --> 00:57:55.640 we are very modest activity in AML

NOTE Confidence: 0.4894056025

00:57:55.640 --> 00:57:57.845 That phase three study that you show

NOTE Confidence: 0.4894056025

00:57:57.845 --> 00:57:59.720 with Curtney in the first three months

NOTE Confidence: 0.4894056025

00:57:59.720 --> 00:58:02.840 ASA one curves don't separate after

NOTE Confidence: 0.4894056025

00:58:02.840 --> 00:58:05.620 that the curves start to separate but

NOTE Confidence: 0.4894056025

00:58:05.620 --> 00:58:09.400 everybody needs a CR after one cycle.

NOTE Confidence: 0.4894056025

00:58:09.400 --> 00:58:11.120 I think what are we doing there

NOTE Confidence: 0.808251238

00:58:11.760 --> 00:58:14.364 I think the probably the people don't

NOTE Confidence: 0.808251238

00:58:14.364 --> 00:58:16.732 die with ASA after first month either.

NOTE Confidence: 0.808251238

00:58:16.732 --> 00:58:19.281 So they still you know this well with

NOTE Confidence: 0.808251238

00:58:19.281 --> 00:58:21.395 ASA side is about nine months right.

NOTE Confidence: 0.808251238

00:58:21.400 --> 00:58:23.850 So they even though they don't get

NOTE Confidence: 0.808251238

00:58:23.850 --> 00:58:25.520 intermission, they are still, you know,

NOTE Confidence: 0.808251238

00:58:25.520 --> 00:58:27.860 alive and they continue on study

NOTE Confidence: 0.808251238

00:58:27.860 --> 00:58:30.679 and so they curve separate later.

NOTE Confidence: 0.808251238

00:58:30.680 --> 00:58:32.996 That's my guess. But you're right.

NOTE Confidence: 0.808251238

00:58:33.000 --> 00:58:35.107 You know, remissions happen after one to

NOTE Confidence: 0.808251238

00:58:35.107 --> 00:58:37.451 two months with the vanilla clocks and

NOTE Confidence: 0.808251238

00:58:37.451 --> 00:58:39.917 there are no remission with azacitidine.

NOTE Confidence: 0.808251238

00:58:39.920 --> 00:58:42.545 But it's because I guess they're still

NOTE Confidence: 0.808251238

00:58:42.545 --> 00:58:45.412 kind of able to maintain people alive with

NOTE Confidence: 0.808251238

00:58:45.412 --> 00:58:47.116 all our supportive care and everything.

NOTE Confidence: 0.808251238

00:58:47.120 --> 00:58:49.520 They they are still there.

NOTE Confidence: 0.808251238

00:58:49.520 --> 00:58:51.038 That's my understanding

NOTE Confidence: 0.623632461

00:58:51.800 --> 00:58:53.496 because you know if you go back into

NOTE Confidence: 0.623632461

00:58:53.496 --> 00:58:54.946 that paper that you're a part of the

NOTE Confidence: 0.623632461

00:58:54.946 --> 00:58:56.656 Curtis paper that frankly presented

NOTE Confidence: 0.623632461

00:58:56.656 --> 00:58:58.960 at the older NPM on positive.

NOTE Confidence: 0.623632461

00:58:58.960 --> 00:59:00.647 I have a feeling when Nick presents

NOTE Confidence: 0.623632461

00:59:00.647 --> 00:59:02.240 the data after that combination,

NOTE Confidence: 0.623632461

00:59:02.240 --> 00:59:04.844 they're highly choosing NPM on positive

NOTE Confidence: 0.623632461

00:59:04.844 --> 00:59:06.771 patients that is chemosensitive

NOTE Confidence: 0.623632461

00:59:06.771 --> 00:59:08.759 or mild suppression sensitive.

NOTE Confidence: 0.623632461

00:59:08.760 --> 00:59:10.664 And then they're tagging it up with

NOTE Confidence: 0.623632461

00:59:10.664 --> 00:59:12.515 the fixed data because they're seeing

NOTE Confidence: 0.623632461

00:59:12.515 --> 00:59:14.585 a flat like that kurtish paper

NOTE Confidence: 0.623632461

00:59:14.585 --> 00:59:16.072 you have the first three months,

NOTE Confidence: 0.623632461

00:59:16.072 --> 00:59:17.600 it's a flat drop, drop,

NOTE Confidence: 0.623632461

00:59:17.600 --> 00:59:20.948 drop and we know what addition of three

NOTE Confidence: 0.623632461

00:59:20.948 --> 00:59:22.556 class of frequently liberals done too.

NOTE Confidence: 0.623632461

00:59:22.560 --> 00:59:22.800 And

NOTE Confidence: 0.471341158

00:59:24.880 --> 00:59:28.240 the point being is AML being all legal

NOTE Confidence: 0.471341158

00:59:28.240 --> 00:59:30.734 flow now, how much emphasis can we

NOTE Confidence: 0.471341158

00:59:30.734 --> 00:59:33.303 give just the BCL component in looking

NOTE Confidence: 0.471341158

00:59:33.303 --> 00:59:35.413 into resistance because the minor

NOTE Confidence: 0.471341158

00:59:35.413 --> 00:59:37.279 suppression component takes care of it

NOTE Confidence: 0.471341158

00:59:37.279 --> 00:59:39.192 for three to six months, very good.

NOTE Confidence: 0.471341158

00:59:39.192 --> 00:59:40.984 We don't have anything to that extent

NOTE Confidence: 0.471341158

00:59:40.984 --> 00:59:44.200 compared to cytotoxic in the past.

NOTE Confidence: 0.471341158

00:59:44.200 --> 00:59:46.132 Garcia within a recently in the post

NOTE Confidence: 0.471341158

00:59:46.132 --> 00:59:48.119 transplant period in the other one has

NOTE Confidence: 0.471341158

00:59:48.119 --> 00:59:49.775 maintenance even there the curves first

NOTE Confidence: 0.471341158

00:59:49.830 --> 00:59:51.475 three to six months and then drop,

NOTE Confidence: 0.471341158

00:59:51.480 --> 00:59:53.292 drop, drop, you don't have a

NOTE Confidence: 0.471341158

00:59:53.292 --> 00:59:54.920 leukemia there at that stage.

NOTE Confidence: 0.471341158

00:59:54.920 --> 00:59:57.240 So now when I'm going to fight stem cells,

NOTE Confidence: 0.471341158

00:59:57.240 --> 00:59:59.080 what do you think the resistance is in

NOTE Confidence: 0.471341158

00:59:59.080 --> 01:00:00.390 that context when you're using either

NOTE Confidence: 0.471341158

01:00:00.390 --> 01:00:01.920 one in the post transplant context?

NOTE Confidence: 0.854454804545455

01:00:02.560 --> 01:00:04.436 Oh I I don't think I'm able

NOTE Confidence: 0.854454804545455

01:00:04.436 --> 01:00:06.480 to answer that question. So

NOTE Confidence: 0.825061614

01:00:08.520 --> 01:00:11.760 I'm not sure what the you know.

NOTE Confidence: 0.825061614

01:00:11.760 --> 01:00:13.632 I don't think that this is just mouse

NOTE Confidence: 0.825061614

01:00:13.632 --> 01:00:14.720 suppression causing people to die,

NOTE Confidence: 0.825061614

01:00:14.720 --> 01:00:17.800 but there's really like relapses going on,

NOTE Confidence: 0.825061614

01:00:17.800 --> 01:00:19.893 right? And I assume that this is

NOTE Confidence: 0.825061614

01:00:19.893 --> 01:00:22.220 still escape of some of the clones

NOTE Confidence: 0.825061614

01:00:22.220 --> 01:00:23.920 that are not being eliminated.

NOTE Confidence: 0.825061614

01:00:23.920 --> 01:00:26.720 But I don't know the data that well.

NOTE Confidence: 0.825061614

01:00:26.720 --> 01:00:28.407 But yeah, the point is well taken

NOTE Confidence: 0.825061614

01:00:28.407 --> 01:00:31.800 that you know the triplet, the data.

NOTE Confidence: 0.825061614

01:00:31.800 --> 01:00:33.000 As far as like you know,

NOTE Confidence: 0.825061614

01:00:33.000 --> 01:00:34.180 there's a lot of discussion

NOTE Confidence: 0.825061614

01:00:34.180 --> 01:00:35.823 if you have MP1 free, St.

NOTE Confidence: 0.825061614

01:00:35.823 --> 01:00:38.138 Commutative clone can be eliminated

NOTE Confidence: 0.825061614

01:00:38.138 --> 01:00:40.360 with Venetoclax alone or not.

NOTE Confidence: 0.825061614

01:00:40.360 --> 01:00:41.758 The data are not very clear,

NOTE Confidence: 0.825061614

01:00:41.760 --> 01:00:43.734 but at least from VLA data

NOTE Confidence: 0.825061614

01:00:43.734 --> 01:00:45.480 we know that Flixtree mutated

NOTE Confidence: 0.825061614

01:00:45.480 --> 01:00:48.000 patients even if they had MPN one.

NOTE Confidence: 0.825061614

01:00:48.000 --> 01:00:49.032 This is not published,

NOTE Confidence: 0.825061614

01:00:49.032 --> 01:00:51.598 but I looked at that in the rest context.

NOTE Confidence: 0.825061614

01:00:51.600 --> 01:00:53.946 The survival is still shorter than

NOTE Confidence: 0.825061614

01:00:53.946 --> 01:00:56.398 for those who have only MPN 1.

NOTE Confidence: 0.825061614

01:00:56.400 --> 01:00:57.935 So there's still that contribution

NOTE Confidence: 0.825061614

01:00:57.935 --> 01:00:59.866 of the Flixtree clone to the

NOTE Confidence: 0.825061614

01:00:59.866 --> 01:01:01.238 like relapse earlier Relapse,

NOTE Confidence: 0.825061614

01:01:01.240 --> 01:01:03.396 despite the fact that you target the,

NOTE Confidence: 0.825061614

01:01:03.400 --> 01:01:05.320 you know, presumably stem cell MPN,

NOTE Confidence: 0.825061614

01:01:05.320 --> 01:01:06.684 one clone with Venetoclax.

NOTE Confidence: 0.825061614

01:01:06.684 --> 01:01:09.256 But I don't know really how like

NOTE Confidence: 0.825061614

01:01:09.256 --> 01:01:11.076 Clonal Dynamics happened there,

NOTE Confidence: 0.825061614

01:01:11.080 --> 01:01:13.408 but I do think that triplet adds in

NOTE Confidence: 0.825061614

01:01:13.408 --> 01:01:15.727 that sense that it will target the

NOTE Confidence: 0.825061614

01:01:15.727 --> 01:01:18.132 fixture clone within even MP one.

NOTE Confidence: 0.825061614

01:01:18.132 --> 01:01:19.320 But again, you know,

NOTE Confidence: 0.825061614

01:01:19.320 --> 01:01:20.280 I don't have data to that.

NOTE Confidence: 0.752345258

01:01:22.040 --> 01:01:24.400 So maybe one last question,

NOTE Confidence: 0.752345258

01:01:24.400 --> 01:01:26.794 given your extensive work with drug

NOTE Confidence: 0.752345258

01:01:26.794 --> 01:01:29.448 development in AML and you alluded to

NOTE Confidence: 0.752345258

01:01:29.448 --> 01:01:32.104 the Twitter wars on some of these data.

NOTE Confidence: 0.752345258

01:01:32.104 --> 01:01:34.168 I think one big question that

NOTE Confidence: 0.752345258

01:01:34.168 --> 01:01:36.854 keeps coming up is if if an agent

NOTE Confidence: 0.752345258

01:01:36.854 --> 01:01:38.439 has no single agent activity,

NOTE Confidence: 0.752345258

01:01:38.440 --> 01:01:41.160 does it can it have realistically a chance

NOTE Confidence: 0.752345258

01:01:41.160 --> 01:01:43.839 of being synergistic in a combination?

NOTE Confidence: 0.752345258

01:01:43.840 --> 01:01:45.275 Some people pointed to Vinito

NOTE Confidence: 0.752345258

01:01:45.275 --> 01:01:47.040 Clacks as the rule that this,

NOTE Confidence: 0.752345258

01:01:47.040 --> 01:01:48.396 but actually Vinito clacks as you

NOTE Confidence: 0.752345258

01:01:48.396 --> 01:01:49.959 said does have single agent activity.

NOTE Confidence: 0.752345258

01:01:49.960 --> 01:01:50.782 It's not much,

NOTE Confidence: 0.752345258

01:01:50.782 --> 01:01:52.426 but it does have activity and

NOTE Confidence: 0.752345258

01:01:52.426 --> 01:01:54.328 some people took a Victory lab

NOTE Confidence: 0.752345258

01:01:54.328 --> 01:01:55.893 with Magrolimab because it has

NOTE Confidence: 0.752345258

01:01:55.958 --> 01:01:57.861 zero single agent activity and all

NOTE Confidence: 0.752345258

01:01:57.861 --> 01:01:58.966 the fuss about the combinations

NOTE Confidence: 0.752345258

01:01:58.966 --> 01:02:00.320 and then the face reasoning.

NOTE Confidence: 0.752345258

01:02:00.320 --> 01:02:03.680 So so is your sense that if you

NOTE Confidence: 0.752345258

01:02:03.680 --> 01:02:05.280 have no single agent activity,

NOTE Confidence: 0.752345258

01:02:05.280 --> 01:02:07.040 can you really be synergistic

NOTE Confidence: 0.752345258

01:02:07.040 --> 01:02:08.800 in combination as a general?

NOTE Confidence: 0.7396741875

01:02:09.360 --> 01:02:12.880 Yeah, I think it was like general question.

NOTE Confidence: 0.7396741875

01:02:12.880 --> 01:02:15.092 I would probably be very worried about

NOTE Confidence: 0.7396741875

01:02:15.092 --> 01:02:17.340 going to phase three with a drug

NOTE Confidence: 0.7396741875

01:02:17.340 --> 01:02:19.200 that has no single agent activity.

NOTE Confidence: 0.7396741875

01:02:19.200 --> 01:02:21.351 As you said the NOW class did have activity

NOTE Confidence: 0.7396741875

01:02:21.351 --> 01:02:23.558 you know reduced blast in 50% of patients

NOTE Confidence: 0.7396741875

01:02:23.558 --> 01:02:26.566 and the the data also in the front line

NOTE Confidence: 0.7396741875

01:02:26.566 --> 01:02:29.240 setting where they did the bone marrow,

NOTE Confidence: 0.7396741875

01:02:29.240 --> 01:02:31.436 they did seven days venetoclax pretreatment

NOTE Confidence: 0.7396741875

01:02:31.436 --> 01:02:33.821 just single agent and they did bone

NOTE Confidence: 0.7396741875

01:02:33.821 --> 01:02:35.830 marrow that was done in Australia and

NOTE Confidence: 0.7396741875

01:02:35.891 --> 01:02:38.173 they also showed reduction or even like

NOTE Confidence: 0.7396741875

01:02:38.173 --> 01:02:40.012 remission in about 50% of patients.

NOTE Confidence: 0.7396741875

01:02:40.012 --> 01:02:42.000 So it does have single agent activity

NOTE Confidence: 0.7396741875

01:02:42.058 --> 01:02:43.928 but also like different mechanistically

NOTE Confidence: 0.7396741875

01:02:43.928 --> 01:02:46.046 because it's like a sensitizer, right.

NOTE Confidence: 0.7396741875

01:02:46.046 --> 01:02:47.276 So you can, you know,

NOTE Confidence: 0.7396741875

01:02:47.280 --> 01:02:48.888 think that even if you didn't

NOTE Confidence: 0.7396741875

01:02:48.888 --> 01:02:50.335 have that single agent activity

NOTE Confidence: 0.7396741875

01:02:50.335 --> 01:02:52.237 in combination you might have had.

NOTE Confidence: 0.7396741875

01:02:52.240 --> 01:02:54.376 But I personally like I'm very

NOTE Confidence: 0.7396741875

01:02:54.376 --> 01:02:56.300 worried that you know, I I'm,

NOTE Confidence: 0.7396741875

01:02:56.300 --> 01:02:58.748 I'm not sure I would develop the drug that

NOTE Confidence: 0.7396741875

01:02:58.748 --> 01:03:01.094 has absolutely no single aging activity

NOTE Confidence: 0.7396741875

01:03:01.094 --> 01:03:04.080 and combinations, you know, going forward.

NOTE Confidence: 0.7396741875

01:03:04.080 --> 01:03:05.000 I might be wrong.

NOTE Confidence: 0.94450996

01:03:06.200 --> 01:03:06.960 Thank you so much.

NOTE Confidence: 0.94904423

01:03:07.560 --> 01:03:09.000 Thank you everybody.