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

 $00{:}00{:}01{.}332 \dashrightarrow 00{:}00{:}03{.}996$ Thank you so much for coming.

NOTE Confidence: 0.97178832

00:00:04.000 $\operatorname{-->}$ 00:00:05.974 It's really a true pleasure today

NOTE Confidence: 0.97178832

 $00{:}00{:}05{.}974 \dashrightarrow 00{:}00{:}08{.}382$ to have with us one of the gents

NOTE Confidence: 0.97178832

 $00:00:08.382 \longrightarrow 00:00:10.500$ of acute myeloid leukemia and

NOTE Confidence: 0.97178832

 $00{:}00{:}10.500 \dashrightarrow 00{:}00{:}12.360$ 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

 $00:00:14.570 \longrightarrow 00:00:17.374$ 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

 $00{:}00{:}19.438 \dashrightarrow 00{:}00{:}22.018$ and the Merriam Faculty Scholar

NOTE Confidence: 0.97178832

 $00{:}00{:}22.093 \dashrightarrow 00{:}00{:}24.215$ in Cancer Research at the Albert

NOTE Confidence: 0.97178832

 $00{:}00{:}24.215 \dashrightarrow 00{:}00{:}25.732$ Einstein College of Medicine.

NOTE Confidence: 0.97178832

 $00:00:25.732 \longrightarrow 00:00:26.728$ After spending many,

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

NOTE Confidence: 0.97178832

 $00:00:28.720 \longrightarrow 00:00:31.260$ where she has really made

NOTE Confidence: 0.97178832

 $00:00:31.260 \longrightarrow 00:00:32.276$ fantastic contributions,

NOTE Confidence: 0.97178832

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

NOTE Confidence: 0.97178832

 $00{:}00{:}33{.}948 \dashrightarrow 00{:}00{:}36{.}033$ that have been approved both

NOTE Confidence: 0.97178832

 $00{:}00{:}36{.}033 \dashrightarrow 00{:}00{:}39{.}040$ in acute myeloid leukemia and

NOTE Confidence: 0.97178832

 $00:00:39.040 \dashrightarrow 00:00:42.320$ plastic denritic myelo neoplasm.

NOTE Confidence: 0.97178832

 $00{:}00{:}42.320 \dashrightarrow 00{:}00{:}45.043$ So she received her Doctor of Medicine

NOTE Confidence: 0.97178832

 $00{:}00{:}45.043 \dashrightarrow 00{:}00{:}47.315$ 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

 $00{:}00{:}50{.}400 \dashrightarrow 00{:}00{:}52{.}850$ 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

 $00:00:54.974 \rightarrow 00:00:57.479$ of Hematology and Blood Transfusion.

NOTE Confidence: 0.97178832

 $00{:}00{:}57.480 \dashrightarrow 00{:}00{:}59.004$ So Doctor Konopliva's research

NOTE Confidence: 0.97178832

 $00{:}00{:}59{.}004 \dashrightarrow 00{:}01{:}00{.}909$ has focused on patients with

NOTE Confidence: 0.97178832

 $00:01:00.909 \rightarrow 00:01:02.255$ 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
- $00:01:05.475 \longrightarrow 00:01:08.274$ as well as high risk MD's.
- NOTE Confidence: 0.97178832
- $00{:}01{:}08.274 \dashrightarrow 00{:}01{:}09.696$ And her research,
- NOTE Confidence: 0.97178832
- 00:01:09.696 --> 00:01:11.118 as I mentioned,
- NOTE Confidence: 0.97178832
- $00:01:11.120 \longrightarrow 00:01:13.466$ 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
- $00:01:14.640 \rightarrow 00:01:17.012$ but also the rapeutic translation,
- NOTE Confidence: 0.97178832
- 00:01:17.012 --> 00:01:18.198 especially venetoclax,
- NOTE Confidence: 0.97178832
- $00:01:18.200 \rightarrow 00:01:20.665$ which really has changed the landscape
- NOTE Confidence: 0.97178832
- $00{:}01{:}20.665 \dashrightarrow 00{:}01{:}25.306$ 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
- $00{:}01{:}28.620 \dashrightarrow 00{:}01{:}30.696$ 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
- $00{:}01{:}32{.}436 \dashrightarrow 00{:}01{:}34{.}236$ 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

 $00{:}01{:}39{.}507 \dashrightarrow 00{:}01{:}42{.}091$ as well as being a very nice and

NOTE Confidence: 0.97178832

 $00:01:42.172 \longrightarrow 00:01:43.920$ very good person to interact with.

NOTE Confidence: 0.97178832

 $00{:}01{:}43{.}920 \dashrightarrow 00{:}01{:}45{.}568$ So I encourage as many of you to

NOTE Confidence: 0.97178832

 $00:01:45.568 \longrightarrow 00:01:47.116$ talk to her if you can today.

NOTE Confidence: 0.97178832

 $00:01:47.120 \longrightarrow 00:01:48.236$ 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

 $00{:}01{:}55{.}905 \dashrightarrow 00{:}01{:}57{.}180$ for this very kind introduction.

NOTE Confidence: 0.591625295

 $00:01:57.180 \longrightarrow 00:01:58.180$ I'm happy to be here.

NOTE Confidence: 0.591625295

 $00{:}01{:}58{.}180 \dashrightarrow 00{:}02{:}00{.}273$ 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

 $00:02:02.140 \longrightarrow 00:02:04.233$ day and meeting a lot of you.

NOTE Confidence: 0.591625295

 $00:02:04.240 \longrightarrow 00:02:06.655$ 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

 $00:02:09.000 \rightarrow 00:02:10.832$ I know this is like a general grand

 $00:02:10.832 \rightarrow 00:02:12.880$ round for both human solid malignancies,

NOTE Confidence: 0.591625295

 $00:02:12.880 \longrightarrow 00:02:15.764$ 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

 $00{:}02{:}17{.}240 \dashrightarrow 00{:}02{:}18{.}680$ for the solid tumors as well.

NOTE Confidence: 0.591625295

 $00{:}02{:}18.680 \dashrightarrow 00{:}02{:}20.386$ And I'll show you some of the kind

NOTE Confidence: 0.591625295

 $00:02:20.386 \dashrightarrow 00:02:22.514$ of ways we think about that as well.

NOTE Confidence: 0.867402208

 $00{:}02{:}25{.}120 \dashrightarrow 00{:}02{:}28{.}104$ So these are my disclosures and as

NOTE Confidence: 0.867402208

 $00:02:28.104 \rightarrow 00:02:30.252$ you all know, the resistance to cell

NOTE Confidence: 0.867402208

 $00{:}02{:}30{.}252 \dashrightarrow 00{:}02{:}33{.}242$ death is one of the hallmarks of cancer

NOTE Confidence: 0.867402208

 $00{:}02{:}33.242 \dashrightarrow 00{:}02{:}35.832$ and it's largely governed by the B22

NOTE Confidence: 0.867402208

 $00:02:35.832 \rightarrow 00:02:38.439$ family proteins which are listed here.

NOTE Confidence: 0.867402208

 $00{:}02{:}38{.}440 \dashrightarrow 00{:}02{:}39{.}337$ It's quite complicated.

NOTE Confidence: 0.867402208

 $00:02:39.337 \dashrightarrow 00:02:41.800$ I'll show you later how the system works,

NOTE Confidence: 0.867402208

 $00{:}02{:}41.800 \dashrightarrow 00{:}02{:}43.640$ but essentially there's over

NOTE Confidence: 0.867402208

 $00:02:43.640 \longrightarrow 00:02:45.940$ expression of different B22 family

 $00{:}02{:}45{.}940 \dashrightarrow 00{:}02{:}48{.}276$ 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

 $00:02:56.199 \rightarrow 00:02:58.223$ and M So one is kind of ubiquitous

NOTE Confidence: 0.867402208

 $00:02:58.292 \dashrightarrow 00:03:00.512$ 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

 $00{:}03{:}06{.}350 \dashrightarrow 00{:}03{:}09{.}006$ dimerization of anti apoptotic with a

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 $00{:}03{:}09{.}006 \dashrightarrow 00{:}03{:}11.492$ propoptotic family members and there are

NOTE Confidence: 0.867402208

 $00{:}03{:}11{.}492 \dashrightarrow 00{:}03{:}13{.}976$ quite a few of those as well So bags.

NOTE Confidence: 0.867402208

 $00:03:13.976 \rightarrow 00:03:16.920$ I will talk to you several times in my talk.

NOTE Confidence: 0.867402208

 $00{:}03{:}16{.}920 \dashrightarrow 00{:}03{:}18{.}915$ So this is what we call execution

NOTE Confidence: 0.867402208

 $00{:}03{:}18{.}915 \dashrightarrow 00{:}03{:}20{.}320$ of cell death protein.

NOTE Confidence: 0.867402208

 $00:03:20.320 \rightarrow 00:03:22.448$ So essentially kills the cells by making

NOTE Confidence: 0.867402208

 $00{:}03{:}22{.}448 \dashrightarrow 00{:}03{:}24{.}341$ pores in the mitochondria membrane

 $00:03:24.341 \rightarrow 00:03:26.636$ and inducing cytochrome C release.

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 $00{:}03{:}26.640 \dashrightarrow 00{:}03{:}28.749$ And then there are a lot of this will be A

NOTE Confidence: 0.867402208

 $00:03:28.749 \dashrightarrow 00:03:30.597$ share only proteins which essentially bind B,

NOTE Confidence: 0.867402208

 $00{:}03{:}30{.}600 \dashrightarrow 00{:}03{:}34{.}320$ so two or others and inhibit their function

NOTE Confidence: 0.867402208

 $00:03:34.320 \rightarrow 00:03:36.200$ because it works through demoralization.

NOTE Confidence: 0.867402208

 $00{:}03{:}36{.}200 \dashrightarrow 00{:}03{:}38{.}432$ You can actually inhibit the function

NOTE Confidence: 0.867402208

 $00{:}03{:}38{.}432 \dashrightarrow 00{:}03{:}42{.}423$ of B so 2 by inhibiting the protein

NOTE Confidence: 0.867402208

 $00:03:42.423 \longrightarrow 00:03:44.218$ protein interactions between for

NOTE Confidence: 0.867402208

 $00{:}03{:}44{.}218 \dashrightarrow 00{:}03{:}46{.}530$ example B so two and some of this

NOTE Confidence: 0.867402208

 $00:03:46.600 \rightarrow 00:03:49.029$ protest proteins and as a result you'll

NOTE Confidence: 0.867402208

 $00:03:49.029 \longrightarrow 00:03:51.297$ have a release of this propagatoric

NOTE Confidence: 0.867402208

 $00{:}03{:}51{.}297 \dashrightarrow 00{:}03{:}53{.}999$ members and killing of the cell deaths.

NOTE Confidence: 0.867402208

 $00{:}03{:}54.000 \dashrightarrow 00{:}03{:}58.057$ So this was pioneered in the first attempt.

NOTE Confidence: 0.867402208

 $00:03:58.057 \rightarrow 00:04:00.925$ This was a paper back in 2005.

NOTE Confidence: 0.867402208

 $00:04:00.925 \rightarrow 00:04:03.845$ At the time the company was called Abbott

 $00:04:03.845 \rightarrow 00:04:06.793$ 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

 $00:04:12.232 \longrightarrow 00:04:14.813$ Sol Rosenberg and others that

NOTE Confidence: 0.867402208

 $00{:}04{:}14.813 \dashrightarrow 00{:}04{:}17.478$ effectively inhibited the BCL two.

NOTE Confidence: 0.867402208

 $00{:}04{:}17{.}480 \dashrightarrow 00{:}04{:}18{.}965$ So the structure here is

NOTE Confidence: 0.867402208

 $00:04:18.965 \dashrightarrow 00:04:20.680$ actually the structure of BCL XL.

NOTE Confidence: 0.867402208

 $00{:}04{:}20.680 \dashrightarrow 00{:}04{:}23.760$ So they used the NMR based technology to

NOTE Confidence: 0.867402208

 $00{:}04{:}23.760 \dashrightarrow 00{:}04{:}26.057$ engineer this molecule and green protein

NOTE Confidence: 0.867402208

 $00{:}04{:}26.057 \dashrightarrow 00{:}04{:}30.439$ here is one of this proteins called back.

NOTE Confidence: 0.867402208

 $00:04:30.440 \dashrightarrow 00:04:32.960$ It's not even here but it's one of the BHA.

NOTE Confidence: 0.867402208

 $00{:}04{:}32{.}960 \dashrightarrow 00{:}04{:}35{.}240$ On your proteins there's some critical

NOTE Confidence: 0.867402208

 $00:04:35.240 \longrightarrow 00:04:37.258$ critical rates reduced how it binds

NOTE Confidence: 0.867402208

 $00{:}04{:}37{.}258 \dashrightarrow 00{:}04{:}39{.}350$ to B cell XL and this is the actual

NOTE Confidence: 0.867402208

 $00:04:39.350 \rightarrow 00:04:41.436$ molecule which you can see it sits

- NOTE Confidence: 0.867402208
- $00:04:41.436 \rightarrow 00:04:44.120$ into that pocket and this mimics the
- NOTE Confidence: 0.867402208
- $00{:}04{:}44{.}120 \dashrightarrow 00{:}04{:}46{.}920$ B back interaction with B cell XL.
- NOTE Confidence: 0.867402208
- $00{:}04{:}46{.}920 \dashrightarrow 00{:}04{:}50{.}280$ In this matter there's another structure,
- NOTE Confidence: 0.867402208
- $00:04:50.280 \rightarrow 00:04:52.680$ this is pretty large molecule about
- NOTE Confidence: 0.867402208
- $00{:}04{:}52{.}680 \dashrightarrow 00{:}04{:}56{.}336$ 960 KD but this was the 1st and I
- NOTE Confidence: 0.867402208
- $00{:}04{:}56{.}336 \dashrightarrow 00{:}04{:}57{.}976$ think the most successful protein
- NOTE Confidence: 0.867402208
- 00:04:57.976 --> 00:04:58.960 protein inhibitor interaction.
- NOTE Confidence: 0.867402208
- $00:04:58.960 \dashrightarrow 00:05:01.744$ I think the only other class that I'm
- NOTE Confidence: 0.867402208
- $00:05:01.744 \longrightarrow 00:05:04.465$ aware of MDM 2P53 inhibitors but they
- NOTE Confidence: 0.867402208
- $00:05:04.465 \rightarrow 00:05:07.400$ still not approved due to toxicities.
- NOTE Confidence: 0.867402208
- $00:05:07.400 \dashrightarrow 00:05:10.040$ Now this molecule was A2 molecule
- NOTE Confidence: 0.867402208
- $00:05:10.040 \longrightarrow 00:05:12.372$ 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
- $00{:}05{:}14.840 \dashrightarrow 00{:}05{:}16.736$ 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

 $00:05:18.000 \dashrightarrow 00:05:20.790$ 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

 $00:05:23.124 \rightarrow 00:05:25.518$ XL is important for plated production.

NOTE Confidence: 0.867402208

 $00:05:25.520 \longrightarrow 00:05:26.915$ 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

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 $00:05:29.391 \longrightarrow 00:05:30.450$ important and there

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 $00:05:30.522 \rightarrow 00:05:33.234$ 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

 $00{:}05{:}35{.}560 \dashrightarrow 00{:}05{:}39{.}875$ And so moving forward in 2013,

NOTE Confidence: 0.839489687777778

 $00{:}05{:}39.875 \dashrightarrow 00{:}05{:}42.360$ the same company now it's called Abbi

NOTE Confidence: 0.839489687777778

 $00:05:42.360 \longrightarrow 00:05:44.505$ engineered the original molecule and

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 $00{:}05{:}44.505 \dashrightarrow 00{:}05{:}47.880$ they got rid of BCL XL interaction.

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 $00:05:47.880 \dashrightarrow 00:05:49.725$ So apparently this aspartate one

NOTE Confidence: 0.839489687777778

 $00{:}05{:}49{.}725 \dashrightarrow 00{:}05{:}52{.}846$ O 3 is a critical residue which is

NOTE Confidence: 0.839489687777778

 $00{:}05{:}52.846 \dashrightarrow 00{:}05{:}55.639$ different between BCL two and BCL XL.

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

 $00:05:57.530 \rightarrow 00:05:59.623$ molecule that had now very specific

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

NOTE Confidence: 0.839489687777778

 $00:06:01.160 \longrightarrow 00:06:03.824$ So it only bound BCL two was about

NOTE Confidence: 0.839489687777778

 $00:06:03.824 \rightarrow 00:06:06.492$ 10 times more important than original

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 $00:06:06.492 \dashrightarrow 00:06:09.999$ nebidoclax and it did not inhibit BCL XL.

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 $00{:}06{:}10.000 \dashrightarrow 00{:}06{:}12.024$ And this is what we now know

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 $00:06:12.024 \longrightarrow 00:06:13.720$ as the neto clocks,

NOTE Confidence: 0.839489687777778

 $00:06:13.720 \longrightarrow 00:06:16.107$ the drug that is approved for several

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 $00{:}06{:}16.107 \dashrightarrow 00{:}06{:}17.960$ types of hematologic malignancies.

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

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

NOTE Confidence: 0.839489687777778

 $00{:}06{:}22.360 \dashrightarrow 00{:}06{:}24.236$ So I said I work on B.

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 $00{:}06{:}24.240 \dashrightarrow 00{:}06{:}25.675$ So too when I came to us,

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 $00{:}06{:}25{.}680 \dashrightarrow 00{:}06{:}27{.}560$ that was my first project at the time.

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 $00{:}06{:}27.560 \dashrightarrow 00{:}06{:}29.400$ We initially used the antisense,

 $00{:}06{:}29{.}400 \dashrightarrow 00{:}06{:}31{.}437$ but antisense didn't make it in clinic.

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

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 $00:06:32.920 \rightarrow 00:06:34.258$ not specific enough.

NOTE Confidence: 0.839489687777778

 $00:06:34.258 \rightarrow 00:06:36.488$ And then when the original

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 $00:06:36.488 \longrightarrow 00:06:38.119$ camp compound came out,

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 $00{:}06{:}38{.}120 \dashrightarrow 00{:}06{:}40{.}320$ we developed the story on

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 $00{:}06{:}40{.}320 \dashrightarrow 00{:}06{:}43{.}252$ AML and BCO 2 with ABT 737,

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 $00:06:43.252 \longrightarrow 00:06:45.075$ which were published in 2006.

NOTE Confidence: 0.839489687777778

 $00{:}06{:}45{.}075 \dashrightarrow 00{:}06{:}47{.}915$ 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

 $00{:}06{:}49{.}180 \dashrightarrow 00{:}06{:}50{.}755$ 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

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 $00:06:53.077 \longrightarrow 00:06:54.998$ all low platelets to start with.

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 $00:06:55.000 \dashrightarrow 00:06:57.224$ So it was kind of impossible at the

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 $00:06:57.224 \dashrightarrow 00:06:59.599$ time to transition into AML trials.

- NOTE Confidence: 0.839489687777778
- $00:06:59.600 \rightarrow 00:07:01.000$ When the newcomer came out,
- NOTE Confidence: 0.839489687777778
- $00{:}07{:}01{.}000 \dashrightarrow 00{:}07{:}03{.}240$ we teamed up with a Tony Litais lab
- NOTE Confidence: 0.839489687777778
- $00{:}07{:}03.240 \dashrightarrow 00{:}07{:}05.325$ at Denif Harbor and we worked for
- NOTE Confidence: 0.839489687777778
- $00:07:05.325 \rightarrow 00:07:07.916$ a year between two of our labs and
- NOTE Confidence: 0.839489687777778
- $00{:}07{:}07{.}916 \dashrightarrow 00{:}07{:}09{.}681$ published a cancer discovery paper
- NOTE Confidence: 0.839489687777778
- $00{:}07{:}09.681 \dashrightarrow 00{:}07{:}12.206$ 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
- $00:07:16.272 \rightarrow 00:07:17.896$ so these are just I'm not going
- NOTE Confidence: 0.839489687777778
- $00:07:17.896 \longrightarrow 00:07:20.078$ to go through the paper or data
- NOTE Confidence: 0.839489687777778
- $00:07:20.078 \longrightarrow 00:07:21.074$ that's all published,
- NOTE Confidence: 0.839489687777778
- $00:07:21.080 \dashrightarrow 00:07:23.520$ but these are just mRNA level for B,
- NOTE Confidence: 0.839489687777778
- $00:07:23.520 \rightarrow 00:07:26.088$ so two amongst different types of
- NOTE Confidence: 0.839489687777778
- $00{:}07{:}26.088 \dashrightarrow 00{:}07{:}28.245$ leukemia and the red line represents
- NOTE Confidence: 0.839489687777778

 $00:07:28.245 \dashrightarrow 00:07:30.648$ to the normal uninvolved bone marrow.

NOTE Confidence: 0.839489687777778

 $00:07:30.648 \dashrightarrow 00:07:33.840$ This was from a Hyperlux MLL collection.

NOTE Confidence: 0.839489687777778

 $00:07:33.840 \longrightarrow 00:07:35.856$ 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

 $00{:}07{:}38.191 \dashrightarrow 00{:}07{:}39.595$ related mRNA for BC2.

NOTE Confidence: 0.839489687777778

 $00:07:39.600 \rightarrow 00:07:41.072$ There's some examples here,

NOTE Confidence: 0.83948968777778

 $00:07:41.072 \longrightarrow 00:07:42.912$ some some some that don't.

NOTE Confidence: 0.839489687777778

 $00:07:42.920 \longrightarrow 00:07:45.440$ For example this inversion 3 AML do not,

NOTE Confidence: 0.839489687777778

 $00:07:45.440 \dashrightarrow 00:07:49.160$ but majority have high levels of BC two.

NOTE Confidence: 0.839489687777778

 $00:07:49.160 \dashrightarrow 00:07:51.080$ We also show that it's expressed

NOTE Confidence: 0.839489687777778

 $00{:}07{:}51{.}080 \dashrightarrow 00{:}07{:}52{.}918$ on leukemia stem cells and then

NOTE Confidence: 0.839489687777778

 $00:07:52.918 \dashrightarrow 00:07:54.918$ we show that if you target BC two,

NOTE Confidence: 0.839489687777778

 $00{:}07{:}54{.}920 \dashrightarrow 00{:}07{:}57{.}344$ you eliminate AML blasts and AML

NOTE Confidence: 0.839489687777778

 $00{:}07{:}57{.}344 \dashrightarrow 00{:}07{:}59{.}600$ stem cells to some extent.

NOTE Confidence: 0.839489687777778

 $00:07:59.600 \rightarrow 00:08:02.120$ And also the compound had efficacy in vivo,

NOTE Confidence: 0.839489687777778

 $00:08:02.120 \longrightarrow 00:08:03.308$ although by itself it,

 $00{:}08{:}03{.}308 \dashrightarrow 00{:}08{:}05{.}580$ it was not curative and it wasn't

NOTE Confidence: 0.839489687777778

 $00:08:05.580 \rightarrow 00:08:07.280$ curative in patients either.

NOTE Confidence: 0.839489687777778

 $00:08:07.280 \longrightarrow 00:08:10.760$ So this work in conjunction with

NOTE Confidence: 0.839489687777778

 $00:08:10.760 \dashrightarrow 00:08:12.680$ the CLL data that Amar mentioned.

NOTE Confidence: 0.839489687777778

 $00{:}08{:}12.680 \dashrightarrow 00{:}08{:}15.158$ So that time the Netflix was already

NOTE Confidence: 0.839489687777778

 $00:08:15.158 \rightarrow 00:08:17.919$ in CLL trials and was very effective.

NOTE Confidence: 0.839489687777778

 $00:08:17.920 \longrightarrow 00:08:20.002$ It caused tumorlysis and actually they

NOTE Confidence: 0.83948968777778

 $00:08:20.002 \dashrightarrow 00:08:22.239$ had some deaths because of tumorlysis.

NOTE Confidence: 0.839489687777778

 $00{:}08{:}22{.}240 \dashrightarrow 00{:}08{:}25{.}072$ So it's CLL is super dependent on B, so true.

NOTE Confidence: 0.839489687777778

 $00:08:25.072 \rightarrow 00:08:26.920$ So it's like the primary B,

NOTE Confidence: 0.839489687777778

 $00:08:26.920 \longrightarrow 00:08:28.360$ so two dependent disease,

NOTE Confidence: 0.891740146666667

 $00:08:28.360 \longrightarrow 00:08:30.520$ but we already knew the dose,

NOTE Confidence: 0.8917401466666667

 $00:08:30.520 \longrightarrow 00:08:33.028$ we knew the safety profile of

NOTE Confidence: 0.8917401466666667

 $00{:}08{:}33{.}028 \dashrightarrow 00{:}08{:}35{.}080$ this molecules was fairly safe

NOTE Confidence: 0.8917401466666667

 $00{:}08{:}35{.}080 \dashrightarrow 00{:}08{:}37{.}124$ besides this tumuliser syndrome.

 $00{:}08{:}37{.}124 \dashrightarrow 00{:}08{:}40{.}733$ So it was sort of sufficient based

NOTE Confidence: 0.8917401466666667

 $00{:}08{:}40.733 \dashrightarrow 00{:}08{:}43.445$ on this work to take venetoclax

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:08:46.320 \longrightarrow 00:08:49.182$ So this study was conducted between

NOTE Confidence: 0.8917401466666667

 $00{:}08{:}49{.}182 \dashrightarrow 00{:}08{:}51{.}610$ different institutions and was published

NOTE Confidence: 0.8917401466666667

 $00:08:51.610 \rightarrow 00:08:54.232$ in cancer discovery back in 2016.

NOTE Confidence: 0.8917401466666667

 $00:08:54.232 \rightarrow 00:08:56.584$ So initially we projected that we're

NOTE Confidence: 0.8917401466666667

 $00{:}08{:}56{.}584 \dashrightarrow 00{:}08{:}59{.}398$ going to treat 50ML patients and we

NOTE Confidence: 0.8917401466666667

 $00{:}08{:}59{.}398 \dashrightarrow 00{:}09{:}02{.}027$ were hoping for response rate around 40

NOTE Confidence: 0.8917401466666667

 $00:09:02.027 \dashrightarrow 00:09:04.600$ to 50% based on our preclinical work.

NOTE Confidence: 0.8917401466666667

 $00:09:04.600 \rightarrow 00:09:06.840$ And I have to say that this did not pan out.

NOTE Confidence: 0.8917401466666667

 $00:09:06.840 \dashrightarrow 00:09:09.344$ So we learned that AML is way too

NOTE Confidence: 0.8917401466666667

 $00:09:09.344 \dashrightarrow 00:09:11.444$ complicated and probably our preclinical

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:09:13.779 \longrightarrow 00:09:16.319$ recapitulate the response in in patients.

NOTE Confidence: 0.8917401466666667

 $00:09:16.320 \rightarrow 00:09:17.564$ So the response rate,

- NOTE Confidence: 0.8917401466666667
- $00{:}09{:}17.564 \dashrightarrow 00{:}09{:}19.430$ objective response rate in the trial
- NOTE Confidence: 0.8917401466666667
- $00:09:19.490 \longrightarrow 00:09:23.240$ was only 19% with the CRCRI rates,
- NOTE Confidence: 0.8917401466666667
- 00:09:23.240 --> 00:09:25.610 but about 50% of patients did
- NOTE Confidence: 0.8917401466666667
- 00:09:25.610 --> 00:09:27.684 have blast reductions as shown
- NOTE Confidence: 0.8917401466666667
- $00:09:27.684 \longrightarrow 00:09:29.759$ here on this waterfall plot.
- NOTE Confidence: 0.8917401466666667
- $00{:}09{:}29{.}760 \dashrightarrow 00{:}09{:}32{.}064$ And then there were some subsets of patients
- NOTE Confidence: 0.8917401466666667
- $00:09:32.064 \longrightarrow 00:09:34.279$ who tend to be more sensitive to that.
- NOTE Confidence: 0.891740146666667
- $00:09:34.280 \longrightarrow 00:09:34.952$ For example,
- NOTE Confidence: 0.8917401466666667
- 00:09:34.952 --> 00:09:37.400 patients who had IDH 1-2 mutations,
- NOTE Confidence: 0.8917401466666667
- $00:09:37.400 \longrightarrow 00:09:40.280$ they generally had response and the
- NOTE Confidence: 0.8917401466666667
- $00:09:40.280 \longrightarrow 00:09:42.912$ response among those was about 32%.
- NOTE Confidence: 0.8917401466666667
- $00:09:42.912 \longrightarrow 00:09:44.800$ So that was encouraging.
- NOTE Confidence: 0.8917401466666667
- $00{:}09{:}44.800 \dashrightarrow 00{:}09{:}45.895$ And in fact,
- NOTE Confidence: 0.8917401466666667
- $00{:}09{:}45.895 \dashrightarrow 00{:}09{:}48.302$ we enriched the study for the IDH
- NOTE Confidence: 0.8917401466666667
- $00{:}09{:}48{.}302 \dashrightarrow 00{:}09{:}49{.}872$ 1-2 mutated patients because at
- NOTE Confidence: 0.8917401466666667

 $00:09:49.872 \rightarrow 00:09:52.159$ the same time the paper came out

NOTE Confidence: 0.8917401466666667

 $00{:}09{:}52.159 \dashrightarrow 00{:}09{:}53.565$ from Stanford showing that this

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:09:55.406 \rightarrow 00:09:57.359$ dependent and that turns to be true.

NOTE Confidence: 0.8917401466666667

 $00:09:57.360 \longrightarrow 00:09:58.932$ Till now this patients respond very

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:10:01.852 \rightarrow 00:10:04.517$ but essentially that was encouraging,

NOTE Confidence: 0.8917401466666667

 $00:10:04.520 \longrightarrow 00:10:06.473$ but it was clearly not enough for

NOTE Confidence: 0.8917401466666667

 $00:10:06.473 \longrightarrow 00:10:08.748$ to get this drug approved as a

NOTE Confidence: 0.8917401466666667

 $00:10:08.748 \rightarrow 00:10:10.800$ single agent in the salvage setting.

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:10:13.072 \rightarrow 00:10:14.636$ that was disappointment because I

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00{:}10{:}17{.}017 \dashrightarrow 00{:}10{:}18{.}785$ I ever had in the lab and still

NOTE Confidence: 0.8917401466666667

 $00:10:18.785 \longrightarrow 00:10:20.559$ it's not you know curing people.

NOTE Confidence: 0.8917401466666667

 $00{:}10{:}20.560 \dashrightarrow 00{:}10{:}22.534$ The duration of responses was also

- NOTE Confidence: 0.8917401466666667
- $00:10:22.534 \rightarrow 00:10:24.637$ pretty sure about three to six months
- NOTE Confidence: 0.8917401466666667
- $00{:}10{:}24.637 \dashrightarrow 00{:}10{:}27.120$ and all patients progressed after that.
- NOTE Confidence: 0.8917401466666667
- $00{:}10{:}27{.}120 \dashrightarrow 00{:}10{:}29{.}490$ So fortunately the story did not
- NOTE Confidence: 0.8917401466666667
- $00:10:29.490 \longrightarrow 00:10:32.080$ stop at this point as you know.
- NOTE Confidence: 0.8917401466666667
- $00:10:32.080 \longrightarrow 00:10:35.314$ 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: 0.8917401466666667
- $00:10:36.320 \longrightarrow 00:10:38.678$ so two alone is not sufficient?
- NOTE Confidence: 0.8917401466666667
- 00:10:38.680 --> 00:10:38.984 Well,
- NOTE Confidence: 0.8917401466666667
- 00:10:38.984 --> 00:10:39.896 first of all,
- NOTE Confidence: 0.8917401466666667
- $00{:}10{:}39.896 \dashrightarrow 00{:}10{:}41.416$ because there's a redundancy and
- NOTE Confidence: 0.8917401466666667
- 00:10:41.416 --> 00:10:43.080 expression of BCL two family proteins.
- NOTE Confidence: 0.8917401466666667
- 00:10:43.080 --> 00:10:45.195 So if you just look at this western blood,
- NOTE Confidence: 0.8917401466666667
- 00:10:45.200 --> 00:10:47.870 this is from Andrew Ways publication
- NOTE Confidence: 0.8917401466666667
- $00{:}10{:}47.870 \dashrightarrow 00{:}10{:}50.475$ and BCL two is almost ubiquitously
- NOTE Confidence: 0.8917401466666667
- $00:10:50.475 \longrightarrow 00:10:52.199$ expressed at high levels.
- NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:10:54.648 \longrightarrow 00:10:55.872$ or low expressed.

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00{:}10{:}58.148 \dashrightarrow 00{:}11{:}01.080$ do have BCL XL And then there's

NOTE Confidence: 0.8917401466666667

 $00{:}11{:}01.080 \dashrightarrow 00{:}11{:}03.744$ MCL one which is mildly specific

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:11:06.304 \rightarrow 00:11:08.634$ it's ubiquitously expressed as well.

NOTE Confidence: 0.8917401466666667

 $00{:}11{:}08.640 \dashrightarrow 00{:}11{:}10.740$ So you can imagine that if

NOTE Confidence: 0.8917401466666667

 $00{:}11{:}10.740 \dashrightarrow 00{:}11{:}12.840$ you target only be so true,

NOTE Confidence: 0.8917401466666667

 $00{:}11{:}12{.}840 \dashrightarrow 00{:}11{:}15{.}576$ you leave some other members untouched

NOTE Confidence: 0.8917401466666667

 $00{:}11{:}15{.}576 \dashrightarrow 00{:}11{:}17{.}817$ and therefore cells probably quickly

NOTE Confidence: 0.8917401466666667

 $00:11:17.817 \rightarrow 00:11:20.632$ adapt to the this effect and they

NOTE Confidence: 0.8917401466666667

 $00{:}11{:}20.632 \dashrightarrow 00{:}11{:}22.872$ rewire and they become resistant.

NOTE Confidence: 0.8917401466666667

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

NOTE Confidence: 0.8917401466666667

 $00:11:24.760 \longrightarrow 00:11:27.280$ So the next thing is that any

NOTE Confidence: 0.8917401466666667

 $00:11:27.280 \rightarrow 00:11:29.156$ type of chemotherapy can actually

 $00:11:29.156 \longrightarrow 00:11:31.754$ in the setting of wild type B53

NOTE Confidence: 0.8917401466666667

 $00:11:31.754 \longrightarrow 00:11:33.924$ can induce expression of this

NOTE Confidence: 0.8917401466666667

 $00:11:33.924 \rightarrow 00:11:35.660$ proprietoric family members that

NOTE Confidence: 0.752763328148148

 $00{:}11{:}35{.}729 \dashrightarrow 00{:}11{:}38{.}165$ 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

 $00{:}11{:}40{.}240 \dashrightarrow 00{:}11{:}43{.}095$ 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

 $00:11:45.720 \longrightarrow 00:11:47.540$ you can have synergy between

NOTE Confidence: 0.752763328148148

 $00{:}11{:}47{.}540 \dashrightarrow 00{:}11{:}49{.}828$ venetoclax and pretty much any type

NOTE Confidence: 0.752763328148148

 $00:11:49.828 \rightarrow 00:11:51.833$ of chemotherapy that would induce

NOTE Confidence: 0.752763328148148

 $00:11:51.833 \rightarrow 00:11:53.600$ this response and then you inhibit B.

NOTE Confidence: 0.752763328148148

 $00{:}11{:}53.600 \dashrightarrow 00{:}11{:}55.610$ So two, so you sensitize the

NOTE Confidence: 0.752763328148148

 $00{:}11{:}55{.}610 \dashrightarrow 00{:}11{:}57{.}792$ cells and then there's bags back

NOTE Confidence: 0.752763328148148

 $00{:}11{:}57.792 \dashrightarrow 00{:}11{:}59.717$ interaction and the cell death.

NOTE Confidence: 0.752763328148148

 $00{:}11{:}59{.}720 \dashrightarrow 00{:}12{:}02{.}168$ So practically speaking this went into

 $00{:}12{:}02{.}168 \dashrightarrow 00{:}12{:}04{.}765$ development in all the AML patients

NOTE Confidence: 0.752763328148148

 $00:12:04.765 \rightarrow 00:12:07.005$ 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

 $00:12:09.629 \rightarrow 00:12:11.212$ we still have and they were doing

NOTE Confidence: 0.752763328148148

 $00:12:11.212 \rightarrow 00:12:12.277$ pretty well with the transplant.

NOTE Confidence: 0.752763328148148

 $00{:}12{:}12{.}280 \dashrightarrow 00{:}12{:}14{.}317$ But for all the patients there was

NOTE Confidence: 0.752763328148148

 $00{:}12{:}14{.}317 \dashrightarrow 00{:}12{:}16{.}198$ really like no standard of care

NOTE Confidence: 0.752763328148148

 $00:12:16.200 \longrightarrow 00:12:18.200$ low dosa turbine or hypermethylene

NOTE Confidence: 0.752763328148148

 $00{:}12{:}18{.}200 \dashrightarrow 00{:}12{:}19{.}800$ agents have been used.

NOTE Confidence: 0.752763328148148

 $00:12:19.800 \longrightarrow 00:12:22.644$ So I have to say that based on the

NOTE Confidence: 0.752763328148148

 $00:12:22.644 \longrightarrow 00:12:24.879$ clinical need more than the signs,

NOTE Confidence: 0.752763328148148

 $00{:}12{:}24.880 \dashrightarrow 00{:}12{:}26.945$ the combination trials were with

NOTE Confidence: 0.752763328148148

 $00:12:26.945 \rightarrow 00:12:29.010$ hypermethylene agents and low dose

NOTE Confidence: 0.752763328148148

 $00{:}12{:}29{.}076 \dashrightarrow 00{:}12{:}31{.}332$ Iturbin and all done fit there

NOTE Confidence: 0.752763328148148

 $00:12:31.332 \rightarrow 00:12:32.836$ for chemotherapy AML patients.

NOTE Confidence: 0.752763328148148

 $00{:}12{:}32{.}840 \dashrightarrow 00{:}12{:}35{.}080$ And this were the results of the

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

NOTE Confidence: 0.752763328148148

 $00:12:37.380 \rightarrow 00:12:39.455$ Vanetta glass was combined either

NOTE Confidence: 0.752763328148148

 $00:12:39.455 \rightarrow 00:12:42.396$ with azacitidine or with a decitabine,

NOTE Confidence: 0.752763328148148

 $00:12:42.400 \rightarrow 00:12:44.365$ 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

 $00{:}12{:}48{.}960 \dashrightarrow 00{:}12{:}51{.}291$ And you can see here that well you know

NOTE Confidence: 0.752763328148148

 $00:12:51.291 \rightarrow 00:12:53.438$ this was a newly diagnosed patients.

NOTE Confidence: 0.752763328148148

 $00{:}12{:}53{.}440 \dashrightarrow 00{:}12{:}55{.}336$ So was very rapidly was transitioned

NOTE Confidence: 0.752763328148148

 $00:12:55.336 \rightarrow 00:12:57.591$ to the newly diagnosed CML which I

NOTE Confidence: 0.752763328148148

 $00{:}12{:}57{.}591 \dashrightarrow 00{:}12{:}59{.}146$ think was another difference with

NOTE Confidence: 0.752763328148148

 $00{:}12{:}59{.}146 \dashrightarrow 00{:}13{:}00{.}979$ the original trial that we used

NOTE Confidence: 0.752763328148148

 $00:13:00.979 \rightarrow 00:13:02.424$ where we used phonetically where

NOTE Confidence: 0.752763328148148

 $00{:}13{:}02{.}424 \dashrightarrow 00{:}13{:}04{.}268$ it was relapsed refractory setting.

NOTE Confidence: 0.752763328148148

 $00:13:04.268 \rightarrow 00:13:07.426$ But you can see that you know majority

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

 $00{:}13{:}12{.}040 \dashrightarrow 00{:}13{:}13{.}612$ There was some of those escalation

NOTE Confidence: 0.752763328148148

 $00:13:13.612 \rightarrow 00:13:14.398$ findings as well,

NOTE Confidence: 0.752763328148148

 $00:13:14.400 \longrightarrow 00:13:16.465$ 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

 $00:13:19.120 \longrightarrow 00:13:20.680$ and 600 for the low dose,

NOTE Confidence: 0.752763328148148

 $00:13:20.680 \longrightarrow 00:13:22.099$ high turbine combination.

NOTE Confidence: 0.752763328148148

 $00:13:22.099 \longrightarrow 00:13:23.518$ So the responses,

NOTE Confidence: 0.752763328148148

 $00:13:23.520 \longrightarrow 00:13:25.482$ the responses tend to be durable

NOTE Confidence: 0.752763328148148

 $00:13:25.482 \dashrightarrow 00:13:27.880$ and there was very little toxicity.

NOTE Confidence: 0.752763328148148

 $00{:}13{:}27.880 \dashrightarrow 00{:}13{:}29.812$ So suddenly the all the patients

NOTE Confidence: 0.752763328148148

 $00:13:29.812 \longrightarrow 00:13:31.821$ 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

 $00:13:33.789 \rightarrow 00:13:35.839$ that we're going into remission,

NOTE Confidence: 0.752763328148148

 $00:13:35.840 \rightarrow 00:13:37.320$ the infections and mouse suppression

- NOTE Confidence: 0.752763328148148
- $00:13:37.320 \longrightarrow 00:13:38.800$ was still the main toxicity.
- NOTE Confidence: 0.752763328148148
- $00{:}13{:}38{.}800 \dashrightarrow 00{:}13{:}40{.}767$ 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
- $00:13:42.440 \rightarrow 00:13:44.672$ liver or anything which was to me always
- NOTE Confidence: 0.752763328148148
- $00:13:44.672 \rightarrow 00:13:46.726$ the most surprising thing because B
- NOTE Confidence: 0.752763328148148
- $00:13:46.726 \rightarrow 00:13:48.880$ so two is so ubiquitously expressed.
- NOTE Confidence: 0.752763328148148
- $00:13:48.880 \longrightarrow 00:13:50.305$ 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
- $00:13:54.000 \rightarrow 00:13:57.318$ we can never really predict what happens.
- NOTE Confidence: 0.752763328148148
- $00:13:57.320 \rightarrow 00:13:59.895$ And then eventually this resulted
- NOTE Confidence: 0.752763328148148
- $00:13:59.895 \rightarrow 00:14:03.009$ in the randomized phase three study
- NOTE Confidence: 0.752763328148148
- $00{:}14{:}03.009 \dashrightarrow 00{:}14{:}05.344$ called VLA study where VENESA,
- NOTE Confidence: 0.752763328148148
- $00{:}14{:}05{.}344 \dashrightarrow 00{:}14{:}08{.}296$ what we call venetocide was randomized
- NOTE Confidence: 0.752763328148148
- $00:14:08.296 \longrightarrow 00:14:10.918$ to azacide and placebo control.
- NOTE Confidence: 0.752763328148148

 $00:14:10.920 \longrightarrow 00:14:13.258$ 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

 $00:14:18.440 \longrightarrow 00:14:21.016$ The median age was close to 70

NOTE Confidence: 0.752763328148148

 $00:14:21.016 \longrightarrow 00:14:23.060$ years old and you can see that

NOTE Confidence: 0.752763328148148

 $00:14:23.060 \longrightarrow 00:14:24.235$ there's far as response rate,

NOTE Confidence: 0.752763328148148

 $00:14:24.240 \rightarrow 00:14:26.185$ majority of the patients achieved

NOTE Confidence: 0.752763328148148

 $00:14:26.185 \longrightarrow 00:14:28.130$ response it was which was

NOTE Confidence: 0.752763328148148

 $00:14:28.203 \longrightarrow 00:14:29.918$ in the range of 60 to 70%.

NOTE Confidence: 0.752763328148148

 $00:14:29.920 \longrightarrow 00:14:32.164$ There was lower in PPG mutated

NOTE Confidence: 0.752763328148148

 $00{:}14{:}32{.}164 \dashrightarrow 00{:}14{:}34{.}666$ AML which we learned later is a

NOTE Confidence: 0.752763328148148

 $00:14:34.666 \longrightarrow 00:14:36.396$ a prom for this approach.

NOTE Confidence: 0.896374091428571

 $00:14:36.400 \rightarrow 00:14:38.514$ But overall there was high response rate,

NOTE Confidence: 0.896374091428571

 $00:14:38.520 \longrightarrow 00:14:41.280$ but most important there was survival

NOTE Confidence: 0.896374091428571

 $00:14:41.280 \rightarrow 00:14:43.864$ advantage compared with ASA with medium

NOTE Confidence: 0.896374091428571

 $00:14:43.864 \rightarrow 00:14:46.468$ overall survival of about 14 months and

- NOTE Confidence: 0.896374091428571
- $00:14:46.468 \rightarrow 00:14:48.954$ compared to nine months with ASA cited in.
- NOTE Confidence: 0.896374091428571
- $00{:}14{:}48{.}960 \dashrightarrow 00{:}14{:}52{.}668$ So this LED in 2018 to the accelerated
- NOTE Confidence: 0.896374091428571
- $00:14:52.668 \rightarrow 00:14:55.742$ approval of the Naglo X and AML and
- NOTE Confidence: 0.896374091428571
- $00:14:55.742 \rightarrow 00:14:58.304$ subsequently to the full approval in
- NOTE Confidence: 0.896374091428571
- $00:14:58.304 \rightarrow 00:15:00.360$ combination with the chemotherapy
- NOTE Confidence: 0.896374091428571
- $00:15:00.360 \dashrightarrow 00:15:02.118$ low Dosa turbine is also approved.
- NOTE Confidence: 0.896374091428571
- $00:15:02.120 \longrightarrow 00:15:03.695$ But even though they missed
- NOTE Confidence: 0.896374091428571
- $00:15:03.695 \rightarrow 00:15:04.640$ the primary endpoint,
- NOTE Confidence: 0.896374091428571
- $00{:}15{:}04.640 \dashrightarrow 00{:}15{:}07.118$ 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
- $00:15:12.999 \rightarrow 00:15:15.237$ is shorter only about nine months.
- NOTE Confidence: 0.896374091428571
- $00{:}15{:}15{.}240 \dashrightarrow 00{:}15{:}17{.}608$ So this is like what Amar said is
- NOTE Confidence: 0.896374091428571
- $00{:}15{:}17.608 \dashrightarrow 00{:}15{:}19.280$ considered to be break through.
- NOTE Confidence: 0.896374091428571
- $00:15:19.280 \rightarrow 00:15:21.359$ But you know if you look at the curves,
- NOTE Confidence: 0.896374091428571

 $00:15:21.360 \rightarrow 00:15:23.384$ you can say that is this really like

NOTE Confidence: 0.896374091428571

 $00:15:23.384 \rightarrow 00:15:24.798$ a breakthrough because majority of

NOTE Confidence: 0.896374091428571

 $00{:}15{:}24.798 \dashrightarrow 00{:}15{:}26.514$ the patients are still you know,

NOTE Confidence: 0.896374091428571

 $00:15:26.520 \longrightarrow 00:15:27.928$ dying from their disease.

NOTE Confidence: 0.896374091428571

 $00:15:27.928 \longrightarrow 00:15:30.040$ Initially it seemed to be like

NOTE Confidence: 0.896374091428571

 $00:15:30.103 \longrightarrow 00:15:31.359$ plateau here at 30%.

NOTE Confidence: 0.896374091428571

 $00{:}15{:}31{.}360 \dashrightarrow 00{:}15{:}33{.}632$ So now the curve dropped down to about

NOTE Confidence: 0.896374091428571

 $00:15:33.632 \rightarrow 00:15:36.480$ 20 to 25% with about four years of follow up.

NOTE Confidence: 0.896374091428571

 $00{:}15{:}36{.}480 \dashrightarrow 00{:}15{:}38{.}176$ So it still stands,

NOTE Confidence: 0.896374091428571

 $00{:}15{:}38{.}176 \dashrightarrow 00{:}15{:}41{.}897$ but clearly you know it was not a

NOTE Confidence: 0.896374091428571

 $00{:}15{:}41.897 \dashrightarrow 00{:}15{:}44.036$ curative approach and that kind of

NOTE Confidence: 0.896374091428571

 $00:15:44.036 \rightarrow 00:15:46.200$ 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

 $00{:}15{:}48{.}360 \dashrightarrow 00{:}15{:}50{.}280$ board and trying to understand how

NOTE Confidence: 0.896374091428571

 $00:15:50.280 \longrightarrow 00:15:53.069$ we can improve on that and what are

NOTE Confidence: 0.896374091428571

 $00{:}15{:}53.069 \dashrightarrow 00{:}15{:}54.782$ mechanisms of resistance and how

- NOTE Confidence: 0.896374091428571
- $00{:}15{:}54{.}782 \dashrightarrow 00{:}15{:}56{.}636$ we can combine with other agents.
- NOTE Confidence: 0.896374091428571
- $00:15:56.640 \longrightarrow 00:15:57.760$ 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
- $00{:}15{:}59{.}776 \dashrightarrow 00{:}16{:}02{.}026$ examples from our lab how we kind of
- NOTE Confidence: 0.896374091428571
- $00:16:02.026 \rightarrow 00:16:04.319$ developed the new agents for the combination.
- NOTE Confidence: 0.896374091428571
- $00:16:04.320 \longrightarrow 00:16:06.000$ Some of them are in trial,
- NOTE Confidence: 0.896374091428571
- $00{:}16{:}06{.}000 \dashrightarrow 00{:}16{:}09{.}360$ some of them are hopefully getting to
- NOTE Confidence: 0.896374091428571
- $00{:}16{:}09{.}360 \dashrightarrow 00{:}16{:}11{.}934$ approval soon and this is sort of a
- NOTE Confidence: 0.896374091428571
- $00{:}16{:}11{.}934 \dashrightarrow 00{:}16{:}14{.}763$ summary how we can think of potential
- NOTE Confidence: 0.896374091428571
- $00{:}16{:}14.763 \dashrightarrow 00{:}16{:}16.999$ 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
- $00{:}16{:}19.736 \dashrightarrow 00{:}16{:}21.360$ fellows and again going back to
- NOTE Confidence: 0.896374091428571
- $00:16:21.360 \rightarrow 00:16:22.942$ 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
- $00{:}16{:}24.760 \dashrightarrow 00{:}16{:}27.161$ you have it pre complex with BHA
- NOTE Confidence: 0.896374091428571

 $00:16:27.161 \longrightarrow 00:16:29.511$ only protein which allows you to

NOTE Confidence: 0.896374091428571

 $00:16:29.511 \longrightarrow 00:16:30.756$ 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

 $00{:}16{:}32.840 \dashrightarrow 00{:}16{:}34.760$ it's called BHA mimetic because

NOTE Confidence: 0.896374091428571

 $00:16:34.760 \longrightarrow 00:16:36.680$ 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

 $00{:}16{:}38.296 \dashrightarrow 00{:}16{:}41.388$ it displaces this BHA only and then this

NOTE Confidence: 0.896374091428571

 $00:16:41.388 \rightarrow 00:16:43.880$ products have to activate backs and back.

NOTE Confidence: 0.896374091428571

 $00{:}16{:}43.880 \dashrightarrow 00{:}16{:}46.120$ So again backs and back are very

NOTE Confidence: 0.896374091428571

 $00{:}16{:}46{.}120 \dashrightarrow 00{:}16{:}47{.}723$ critical because without that there's

NOTE Confidence: 0.896374091428571

 $00{:}16{:}47.723 \dashrightarrow 00{:}16{:}50.720$ no cell death and they have to go

NOTE Confidence: 0.896374091428571

 $00{:}16{:}50.720 \dashrightarrow 00{:}16{:}52.416$ into the mitochondrial membrane

NOTE Confidence: 0.896374091428571

 $00:16:52.416 \rightarrow 00:16:55.157$ and they induce sacrum C release.

NOTE Confidence: 0.896374091428571

 $00:16:55.160 \longrightarrow 00:16:56.720$ So one thing that I already

NOTE Confidence: 0.896374091428571

 $00:16:56.720 \rightarrow 00:16:58.360$ mentioned that there's a redundancy,

NOTE Confidence: 0.896374091428571

 $00:16:58.360 \longrightarrow 00:17:00.376$ so if you have a regulation of

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

 $00{:}17{:}04.516 \dashrightarrow 00{:}17{:}06.412$ Because they can even though you

NOTE Confidence: 0.896374091428571

 $00:17:06.412 \longrightarrow 00:17:07.360$ do have displacement,

NOTE Confidence: 0.896374091428571

 $00{:}17{:}07{.}360 \dashrightarrow 00{:}17{:}09{.}866$ what happens is that this BHA only

NOTE Confidence: 0.896374091428571

 $00{:}17{:}09.866 \dashrightarrow 00{:}17{:}12.423$ protein instead of going to the bags it

NOTE Confidence: 0.896374091428571

 $00:17:12.423 \rightarrow 00:17:15.399$ will go and bind this other protein members.

NOTE Confidence: 0.896374091428571

 $00:17:15.400 \rightarrow 00:17:18.440$ So how can you get this app regulation?

NOTE Confidence: 0.896374091428571

 $00{:}17{:}18{.}440 \dashrightarrow 00{:}17{:}19{.}840$ 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

 $00{:}17{:}20.680 \dashrightarrow 00{:}17{:}22.966$ For example in monostatic AML there's

NOTE Confidence: 0.896374091428571

 $00{:}17{:}22.966 \dashrightarrow 00{:}17{:}25.608$ app regulation of MCL one because of

NOTE Confidence: 0.896374091428571

 $00{:}17{:}25.608 \dashrightarrow 00{:}17{:}27.714$ the lineage dependency on MCL one.

NOTE Confidence: 0.896374091428571

 $00{:}17{:}27{.}720 \dashrightarrow 00{:}17{:}29{.}547$ But then there are a lot of

NOTE Confidence: 0.896374091428571

 $00{:}17{:}29{.}547 \dashrightarrow 00{:}17{:}30{.}330$ mutations and this

 $00:17:30.394 \rightarrow 00:17:32.836$ mutations we call them signalling mutations

NOTE Confidence: 0.789430363125

 $00:17:32.840 \rightarrow 00:17:35.234$ which we now can up regulate both MCO one,

NOTE Confidence: 0.789430363125

 $00{:}17{:}35{.}240 \dashrightarrow 00{:}17{:}38{.}448$ BCL XL and BCL 12A1 and I'll

NOTE Confidence: 0.789430363125

 $00:17:38.448 \rightarrow 00:17:39.960$ show you some examples of those.

NOTE Confidence: 0.789430363125

 $00{:}17{:}39{.}960 \dashrightarrow 00{:}17{:}41{.}670$ 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

 $00:17:43.937 \rightarrow 00:17:45.717$ think of targeting those mutations.

NOTE Confidence: 0.789430363125

 $00:17:45.720 \longrightarrow 00:17:47.850$ So the other major mechanism of

NOTE Confidence: 0.789430363125

 $00{:}17{:}47.850 \dashrightarrow 00{:}17{:}50.356$ resistance is the P53 loss and I

NOTE Confidence: 0.789430363125

 $00:17:50.356 \rightarrow 00:17:52.510$ already mentioned that PhD is critical

NOTE Confidence: 0.789430363125

 $00{:}17{:}52.587 \dashrightarrow 00{:}17{:}54.757$ for BHA only proteins induction.

NOTE Confidence: 0.789430363125

 $00:17:54.760 \longrightarrow 00:17:56.843$ But on top of that P53

NOTE Confidence: 0.789430363125

 $00:17:56.843 \rightarrow 00:17:58.652$ transcriptionally controls Bax,

NOTE Confidence: 0.789430363125

 $00{:}17{:}58.652 \dashrightarrow 00{:}18{:}02.696$ so BAX levels are lower and P

NOTE Confidence: 0.789430363125

 $00{:}18{:}02.696 \dashrightarrow 00{:}18{:}04.906$ and P3 lost AML and there's also

NOTE Confidence: 0.789430363125

 $00{:}18{:}04{.}906 \dashrightarrow 00{:}18{:}06{.}114$ other mechanism of resistance.

- NOTE Confidence: 0.789430363125
- $00{:}18{:}06{.}120 \dashrightarrow 00{:}18{:}08{.}620$ So this remains unmet need
- NOTE Confidence: 0.789430363125
- $00{:}18{:}08{.}620 \dashrightarrow 00{:}18{:}11{.}950$ in the field of AML and MD's.
- NOTE Confidence: 0.789430363125
- $00{:}18{:}11{.}950 \dashrightarrow 00{:}18{:}14{.}680$ And then there are some other mechanisms.
- NOTE Confidence: 0.789430363125
- $00:18:14.680 \longrightarrow 00:18:15.684$ For example,
- NOTE Confidence: 0.789430363125
- $00:18:15.684 \rightarrow 00:18:18.194$ Yanis offenders group has published
- NOTE Confidence: 0.789430363125
- $00{:}18{:}18{.}200 \dashrightarrow 00{:}18{:}20{.}585$ the mitochondria resistance to the
- NOTE Confidence: 0.789430363125
- $00:18:20.585 \longrightarrow 00:18:22.970$ venetoclax through our regulation of
- NOTE Confidence: 0.789430363125
- $00:18:23.041 \longrightarrow 00:18:25.337$ 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
- $00:18:28.325 \rightarrow 00:18:30.800$ selection of the healthy mitochondria.
- NOTE Confidence: 0.789430363125
- $00{:}18{:}30{.}800 \dashrightarrow 00{:}18{:}33{.}836$ And there's some effort as far as
- NOTE Confidence: 0.789430363125
- $00{:}18{:}33{.}836 \dashrightarrow 00{:}18{:}35{.}588$ drug discovery in that field as
- NOTE Confidence: 0.789430363125
- $00{:}18{:}35{.}588 \dashrightarrow 00{:}18{:}37{.}360$ well going back to the patients.
- NOTE Confidence: 0.789430363125
- $00{:}18{:}37{.}360 \dashrightarrow 00{:}18{:}40{.}474$ So what did we see like from this mechanisms?
- NOTE Confidence: 0.789430363125
- $00{:}18{:}40{.}480 \dashrightarrow 00{:}18{:}43{.}488$ What did we see as far as the
- NOTE Confidence: 0.789430363125

 $00:18:43.488 \rightarrow 00:18:44.240$ resistance development?

NOTE Confidence: 0.789430363125

 $00:18:44.240 \longrightarrow 00:18:46.922$ And before that I have to say that we

NOTE Confidence: 0.789430363125

 $00:18:46.922 \rightarrow 00:18:49.915$ also developed in the lab habanero clocks,

NOTE Confidence: 0.789430363125

 $00:18:49.920 \longrightarrow 00:18:50.739$ resistance cell lines.

NOTE Confidence: 0.789430363125

 $00{:}18{:}50{.}739 \dashrightarrow 00{:}18{:}52{.}650$ So we decided to take some of

NOTE Confidence: 0.789430363125

 $00:18:52.706 \rightarrow 00:18:55.205$ unbiased approach and we generated

NOTE Confidence: 0.789430363125

 $00:18:55.205 \longrightarrow 00:18:57.880$ 4 vein resistance cell lines.

NOTE Confidence: 0.789430363125

 $00:18:57.880 \rightarrow 00:18:59.500$ They're available for anyone who

NOTE Confidence: 0.789430363125

 $00:18:59.500 \rightarrow 00:19:01.560$ wants to use them by prolonged

NOTE Confidence: 0.789430363125

 $00:19:01.560 \rightarrow 00:19:04.220$ exposure to the drug in the tissue

NOTE Confidence: 0.789430363125

 $00:19:04.220 \longrightarrow 00:19:05.712$ culture lab and took only about

NOTE Confidence: 0.789430363125

 $00:19:05.712 \longrightarrow 00:19:06.960$ 3 months to generate the cells.

NOTE Confidence: 0.789430363125

 $00{:}19{:}06{.}960 \dashrightarrow 00{:}19{:}09{.}004$ So about the same time as our

NOTE Confidence: 0.789430363125

 $00:19:09.004 \rightarrow 00:19:09.880$ patients to progress.

NOTE Confidence: 0.789430363125

 $00{:}19{:}09{.}880 \dashrightarrow 00{:}19{:}12{.}824$ And then we did all kind of metabolomic

NOTE Confidence: 0.789430363125

 $00:19:12.824 \rightarrow 00:19:16.600$ genomic proteomic profiling and

- NOTE Confidence: 0.789430363125
- $00:19:16.600 \rightarrow 00:19:17.884$ 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
- $00:19:20.402 \rightarrow 00:19:22.718$ screaming at us, which was not a new pathway,
- NOTE Confidence: 0.789430363125
- $00:19:22.720 \rightarrow 00:19:24.820$ but it was something that we already
- NOTE Confidence: 0.789430363125
- $00{:}19{:}24.820 \dashrightarrow 00{:}19{:}25.720$ knew from before.
- NOTE Confidence: 0.789430363125
- $00:19:25.720 \longrightarrow 00:19:27.400$ It was MEP kinase pathways.
- NOTE Confidence: 0.789430363125
- $00:19:27.400 \longrightarrow 00:19:30.320$ So it was upregulated on the RNA level.
- NOTE Confidence: 0.789430363125
- $00:19:30.320 \longrightarrow 00:19:32.192$ And then we confirmed that in
- NOTE Confidence: 0.789430363125
- $00:19:32.192 \longrightarrow 00:19:34.040$ the by immuno blotting analysis,
- NOTE Confidence: 0.789430363125
- $00:19:34.040 \longrightarrow 00:19:36.294$ 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
- $00{:}19{:}38{.}360 \dashrightarrow 00{:}19{:}41{.}391$ and as a result MEP kinase can
- NOTE Confidence: 0.789430363125
- $00:19:41.391 \rightarrow 00:19:43.600$ 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
- $00:19:45.196 \longrightarrow 00:19:47.433$ the level of the protein and we did
- NOTE Confidence: 0.789430363125

 $00{:}19{:}47{.}433 \dashrightarrow 00{:}19{:}49{.}540$ 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

 $00:19:51.514 \rightarrow 00:19:53.904$ as you would expect And then if you NOTE Confidence: 0.789430363125

 $00:19:53.904 \rightarrow 00:19:55.864$ use the either M so one inhibitors

NOTE Confidence: 0.789430363125

00:19:55.864 --> 00:19:58.656 or knock
out 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

 $00{:}20{:}04{.}312 \dashrightarrow 00{:}20{:}05{.}873$ so one inhibitors but suffice to

NOTE Confidence: 0.789430363125

 $00{:}20{:}05{.}873 \dashrightarrow 00{:}20{:}07{.}547$ say that they are not approved

NOTE Confidence: 0.789430363125

 $00:20:07.602 \longrightarrow 00:20:08.598$ 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

 $00{:}20{:}11.273 \dashrightarrow 00{:}20{:}14.200$ safe and M so one is not safe so M so one.

NOTE Confidence: 0.789430363125

 $00{:}20{:}14.200 \dashrightarrow 00{:}20{:}16.597$ Tends to be very important for the heart

NOTE Confidence: 0.789430363125

 $00{:}20{:}16.597 \dashrightarrow 00{:}20{:}19.376$ 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
- $00:20:21.560 \rightarrow 00:20:24.344$ 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
- $00:20:26.480 \longrightarrow 00:20:28.634$ 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
- $00{:}20{:}30{.}130 \dashrightarrow 00{:}20{:}32{.}500$ and it's not clear whether they
- NOTE Confidence: 0.810300709
- $00:20:32.500 \rightarrow 00:20:34.080$ actually have the rapeutic windows.
- NOTE Confidence: 0.810300709
- $00:20:34.080 \longrightarrow 00:20:37.746$ So, but in the lab, these are the
- NOTE Confidence: 0.810300709
- $00{:}20{:}37.746 \dashrightarrow 00{:}20{:}39.594$ great sensitizers to Vanada colexa.
- NOTE Confidence: 0.810300709
- $00{:}20{:}39{.}600 \dashrightarrow 00{:}20{:}41{.}696$ 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
- $00:20:43.924 \rightarrow 00:20:46.399$ are fairly common in AML on their own.
- NOTE Confidence: 0.810300709
- $00:20:46.400 \longrightarrow 00:20:48.320$ They don't have prognostic significance,
- NOTE Confidence: 0.810300709
- $00:20:48.320 \longrightarrow 00:20:50.666$ but they can arise at the
- NOTE Confidence: 0.810300709
- $00{:}20{:}50.666 \dashrightarrow 00{:}20{:}51.839$ time of progression.
- NOTE Confidence: 0.810300709
- $00{:}20{:}51{.}840 \dashrightarrow 00{:}20{:}54{.}312$ And so when we looked at the patients
- NOTE Confidence: 0.810300709

- $00{:}20{:}54.312 \dashrightarrow 00{:}20{:}56.053$ treated on the HMA venetoclax
- NOTE Confidence: 0.810300709
- $00{:}20{:}56.053 \dashrightarrow 00{:}20{:}58.159$ trials at the time of relapse,
- NOTE Confidence: 0.810300709
- $00:20:58.160 \dashrightarrow 00:21:01.360$ they had like expansion of this Ras, K,
- NOTE Confidence: 0.810300709
- $00{:}21{:}01{.}360 \dashrightarrow 00{:}21{:}04{.}968$ Ras and Ras clones also PTPN 11 clones,
- NOTE Confidence: 0.810300709
- $00:21:04.968 \rightarrow 00:21:07.350$ which is not shown here fairly
- NOTE Confidence: 0.810300709
- $00:21:07.350 \longrightarrow 00:21:09.240$ quickly within like 6 months or so.
- NOTE Confidence: 0.810300709
- $00{:}21{:}09{.}240 \dashrightarrow 00{:}21{:}12{.}999$ This has single cell DNA sequencing data.
- NOTE Confidence: 0.810300709
- $00{:}21{:}13.000 \dashrightarrow 00{:}21{:}15.128$ We also looked at the sort of
- NOTE Confidence: 0.810300709
- $00{:}21{:}15{.}128 \dashrightarrow 00{:}21{:}16{.}040$ patients by immunoblotting.
- NOTE Confidence: 0.810300709
- $00:21:16.040 \longrightarrow 00:21:17.804$ So we did show up regulation of
- NOTE Confidence: 0.810300709
- $00:21:17.804 \longrightarrow 00:21:19.537$ MCL one and the appropation of
- NOTE Confidence: 0.810300709
- 00:21:19.537 -> 00:21:21.367 MAP kinase pathway and this is
- NOTE Confidence: 0.810300709
- $00:21:21.367 \longrightarrow 00:21:23.200$ on the histochemistry level.
- NOTE Confidence: 0.810300709
- $00{:}21{:}23{.}200 \dashrightarrow 00{:}21{:}25{.}517$ At the time progression MCL one was
- NOTE Confidence: 0.810300709
- $00{:}21{:}25{.}517 \dashrightarrow 00{:}21{:}28{.}240$ up and BCL two was down regulated.
- NOTE Confidence: 0.810300709
- $00:21:28.240 \longrightarrow 00:21:29.848$ The problem of course that in

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

NOTE Confidence: 0.810300709

 $00{:}21{:}31{.}840 \dashrightarrow 00{:}21{:}33{.}807$ We are really hoping that we can

NOTE Confidence: 0.810300709

 $00:21:33.807 \longrightarrow 00:21:35.760$ get them from the solid tumors.

NOTE Confidence: 0.810300709

 $00:21:35.760 \longrightarrow 00:21:37.332$ But the companies have been so

NOTE Confidence: 0.810300709

 $00{:}21{:}37{.}332 \dashrightarrow 00{:}21{:}39{.}244$ focused on the lung cancer and they

NOTE Confidence: 0.810300709

 $00{:}21{:}39{.}244 \dashrightarrow 00{:}21{:}41{.}120$ have been reluctant to go into AML.

NOTE Confidence: 0.810300709

 $00{:}21{:}41{.}120 \dashrightarrow 00{:}21{:}43{.}598$ So we are still trying to convince

NOTE Confidence: 0.810300709

 $00{:}21{:}43{.}598 \dashrightarrow 00{:}21{:}46{.}218$ 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

 $00{:}21{:}48{.}990 \dashrightarrow 00{:}21{:}51{.}504$ actually have data with the in the lab NOTE Confidence: 0.810300709

 $00:21:51.504 \rightarrow 00:21:53.720$ that the combination is really striking,

NOTE Confidence: 0.810300709

 $00{:}21{:}53.720 \dashrightarrow 00{:}21{:}55.016$ the papers submitted.

NOTE Confidence: 0.810300709

 $00{:}21{:}55.016 \dashrightarrow 00{:}21{:}58.040$ But right now we don't have anything.

NOTE Confidence: 0.810300709

 $00{:}21{:}58{.}040 \dashrightarrow 00{:}22{:}00{.}320$ So we also did the engineer this in the lab.

NOTE Confidence: 0.810300709

 $00{:}22{:}00{.}320 \dashrightarrow 00{:}22{:}04{.}104$ So we put the NRAS G12D into AML

 $00:22:04.104 \longrightarrow 00:22:06.792$ cell line which was dox inducible.

NOTE Confidence: 0.810300709

 $00{:}22{:}06{.}800 \dashrightarrow 00{:}22{:}08{.}552$ 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

 $00:22:09.720 \rightarrow 00:22:12.144$ But again the MCL one inhibitors

NOTE Confidence: 0.810300709

 $00:22:12.144 \longrightarrow 00:22:13.760$ work alone on combination.

NOTE Confidence: 0.810300709

 $00{:}22{:}13.760 \dashrightarrow 00{:}22{:}15.531$ We did the mouse study with MCL

NOTE Confidence: 0.810300709

 $00{:}22{:}15{.}531 \dashrightarrow 00{:}22{:}17{.}173$ 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

 $00{:}22{:}19.855 \dashrightarrow 00{:}22{:}21.238$ and we don't have resin inhibits.

NOTE Confidence: 0.810300709

 $00:22:21.240 \longrightarrow 00:22:24.273$ So we are like at a loss right now,

NOTE Confidence: 0.810300709

 $00:22:24.280 \longrightarrow 00:22:26.600$ but we're working on that.

NOTE Confidence: 0.810300709

 $00{:}22{:}26.600 \dashrightarrow 00{:}22{:}28.454$ So this MEP kinase upregulation I

NOTE Confidence: 0.810300709

 $00:22:28.454 \rightarrow 00:22:31.074$ think is one of the major kind of

NOTE Confidence: 0.810300709

 $00{:}22{:}31.074 \dashrightarrow 00{:}22{:}33.678$ resistance when you use HMA Van.

NOTE Confidence: 0.810300709

 $00:22:33.680 \rightarrow 00:22:35.560$ It's not an issue when you use chemotherapy,

- NOTE Confidence: 0.810300709
- $00:22:35.560 \longrightarrow 00:22:35.948$ van,
- NOTE Confidence: 0.810300709
- $00:22:35.948 \rightarrow 00:22:37.888$ because Rascalone is very sensitive
- NOTE Confidence: 0.810300709
- $00:22:37.888 \longrightarrow 00:22:39.440$ to the regular chemotherapy,
- NOTE Confidence: 0.810300709
- $00:22:39.440 \longrightarrow 00:22:42.476$ which is kind of a relief.
- NOTE Confidence: 0.810300709
- $00{:}22{:}42{.}480 \dashrightarrow 00{:}22{:}44{.}440$ And this data we have sort of confirmed
- NOTE Confidence: 0.810300709
- $00{:}22{:}44{.}440 \dashrightarrow 00{:}22{:}46{.}039$ 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
- $00{:}22{:}48.774 \dashrightarrow 00{:}22{:}51.216$ a study looking at different genomic
- NOTE Confidence: 0.810300709
- $00:22:51.216 \longrightarrow 00:22:54.457$ subsets of patients who are and time to
- NOTE Confidence: 0.810300709
- $00:22:54.457 \rightarrow 00:22:56.720$ progressional this is rather survival.
- NOTE Confidence: 0.810300709
- $00{:}22{:}56{.}720 \dashrightarrow 00{:}22{:}58{.}922$ This was presented at by Hartman
- NOTE Confidence: 0.810300709
- $00{:}22{:}58{.}922 \dashrightarrow 00{:}23{:}00{.}760$ donor at the last ASH.
- NOTE Confidence: 0.810300709
- $00{:}23{:}00{.}760 \dashrightarrow 00{:}23{:}03{.}126$ And so they basically show that the
- NOTE Confidence: 0.810300709
- $00{:}23{:}03{.}126 \dashrightarrow 00{:}23{:}04{.}972$ classical kind of ELN classifications
- NOTE Confidence: 0.810300709
- $00:23:04.972 \longrightarrow 00:23:07.270$ do not predict very well the
- NOTE Confidence: 0.810300709

 $00:23:07.270 \rightarrow 00:23:09.438$ response or duration of response.

NOTE Confidence: 0.810300709

 $00:23:09.440 \longrightarrow 00:23:11.516$ 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

 $00:23:15.960 \rightarrow 00:23:18.600$ So survival was only about 5 months here,

NOTE Confidence: 0.810300709

 $00:23:18.600 \longrightarrow 00:23:21.078$ 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

 $00:23:22.592 \rightarrow 00:23:24.860$ 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

 $00{:}23{:}27.195 \dashrightarrow 00{:}23{:}29.681$ to be like resistance factor for the HMA

NOTE Confidence: 0.853982455454546

 $00{:}23{:}29{.}681 \dashrightarrow 00{:}23{:}32{.}070$ 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

 $00:23:35.560 \rightarrow 00:23:38.080$ 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

 $00{:}23{:}43.040 \dashrightarrow 00{:}23{:}46.080$ about 30% of patients have Flix 3 mutation.

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

NOTE Confidence: 0.853982455454546

 $00:23:47.520 \longrightarrow 00:23:48.960$ those that are being approved.

NOTE Confidence: 0.853982455454546

 $00{:}23{:}48{.}960 \dashrightarrow 00{:}23{:}51{.}520$ So of course like we jumped into that

NOTE Confidence: 0.853982455454546

 $00{:}23{:}51{.}520 \dashrightarrow 00{:}23{:}53{.}944$ very early on and in fact we saw that

NOTE Confidence: 0.853982455454546

 $00{:}23{:}53{.}944 \dashrightarrow 00{:}23{:}56{.}074$ even in the original phase one study

NOTE Confidence: 0.853982455454546

 $00:23:56.074 \rightarrow 00:23:58.090$ where which showed up regulation of

NOTE Confidence: 0.853982455454546

 $00{:}23{:}58{.}090 \dashrightarrow 00{:}24{:}00{.}114$ this or selection of the clones with

NOTE Confidence: 0.853982455454546

 $00{:}24{:}00{.}114 \dashrightarrow 00{:}24{:}02{.}875$ the Flix 3 IT do or as mutations and

NOTE Confidence: 0.853982455454546

 $00{:}24{:}02{.}875 \dashrightarrow 00{:}24{:}05{.}172$ people who relapse or wear primary

NOTE Confidence: 0.853982455454546

 $00:24:05.172 \rightarrow 00:24:07.455$ fracture and very similar this like

NOTE Confidence: 0.853982455454546

 $00{:}24{:}07{.}455 \dashrightarrow 00{:}24{:}10{.}783$ selection of the Flix 3 ITT clone with a

NOTE Confidence: 0.853982455454546

 $00{:}24{:}10.783 \dashrightarrow 00{:}24{:}13.069$ therapy using the single cell tapes try

NOTE Confidence: 0.853982455454546

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

NOTE Confidence: 0.853982455454546

 $00{:}24{:}15.695 \dashrightarrow 00{:}24{:}18.076$ ITT the story is very similar to Ras.

NOTE Confidence: 0.853982455454546

 $00:24:18.080 \longrightarrow 00:24:19.956$ So here you have you know the

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

NOTE Confidence: 0.853982455454546

 $00{:}24{:}21{.}920 \dashrightarrow 00{:}24{:}24{.}728$ 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

 $00:24:27.376 \longrightarrow 00:24:29.680$ it all comes down to this MCL one.

NOTE Confidence: 0.853982455454546

 $00{:}24{:}29.680 \dashrightarrow 00{:}24{:}32.476$ 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

 $00:24:36.142 \rightarrow 00:24:37.810$ stead pathway dependent phosphorylation.

NOTE Confidence: 0.853982455454546

 $00:24:37.810 \longrightarrow 00:24:40.645$ So when MCL one is phosphorylated it's

NOTE Confidence: 0.853982455454546

 $00{:}24{:}40.645 \dashrightarrow 00{:}24{:}42.605$ stable so the levels are increased

NOTE Confidence: 0.853982455454546

 $00:24:42.605 \rightarrow 00:24:44.573$ and the product cannot be degraded

NOTE Confidence: 0.853982455454546

 $00{:}24{:}44{.}573 \dashrightarrow 00{:}24{:}46{.}638$ otherwise it's short lived protein.

NOTE Confidence: 0.853982455454546

 $00{:}24{:}46.640 \dashrightarrow 00{:}24{:}48.060$ 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

 $00{:}24{:}50{.}920 \dashrightarrow 00{:}24{:}52{.}404$ but the nice thing is all downstream

NOTE Confidence: 0.853982455454546

 $00{:}24{:}52{.}404 \dashrightarrow 00{:}24{:}53{.}280$ or Flix 3 ITD.

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

NOTE Confidence: 0.853982455454546

 $00:24:55.464 \rightarrow 00:24:56.880$ what happens with MCL one.

NOTE Confidence: 0.853982455454546

 $00{:}24{:}56{.}880 \dashrightarrow 00{:}24{:}59{.}392$ So we used Quizactinib for that matter and

NOTE Confidence: 0.853982455454546

 $00{:}24{:}59{.}392 \dashrightarrow 00{:}25{:}02{.}138$ we showed nice inhibition of the Flix 3 MCL.

NOTE Confidence: 0.853982455454546

 $00:25:02.138 \longrightarrow 00:25:04.224$ One did go down by wasn't that

NOTE Confidence: 0.853982455454546

 $00:25:04.224 \rightarrow 00:25:05.999$ huge up down regulation.

NOTE Confidence: 0.853982455454546

 $00{:}25{:}06{.}000 \dashrightarrow 00{:}25{:}08{.}464$ But we also show that the protein

NOTE Confidence: 0.853982455454546

 $00{:}25{:}08{.}464 \dashrightarrow 00{:}25{:}10{.}477$ called BEM was induced and BEM

NOTE Confidence: 0.853982455454546

 $00:25:10.477 \longrightarrow 00:25:13.305$ can is a prop of Tory BC on a

NOTE Confidence: 0.853982455454546

 $00{:}25{:}13{.}305 \dashrightarrow 00{:}25{:}15{.}393$ protein that can inhibit MCL one.

NOTE Confidence: 0.853982455454546

 $00{:}25{:}15{.}400 \dashrightarrow 00{:}25{:}17{.}596$ So the combination of these two

NOTE Confidence: 0.853982455454546

 $00{:}25{:}17.600 \dashrightarrow 00{:}25{:}20.920$ makes cells sensitive to veneto clax.

NOTE Confidence: 0.853982455454546

 $00{:}25{:}20{.}920 \dashrightarrow 00{:}25{:}22{.}858$ And this is BHA profiling essay

NOTE Confidence: 0.853982455454546

 $00{:}25{:}22{.}858 \dashrightarrow 00{:}25{:}25{.}362$ which I have time to explain in

NOTE Confidence: 0.853982455454546

 $00:25:25.362 \rightarrow 00:25:27.272$ detail by essentially you throw

 $00:25:27.272 \rightarrow 00:25:29.851$ the peptides on the cells and see

NOTE Confidence: 0.853982455454546

 $00:25:29.851 \rightarrow 00:25:31.596$ which dependence that they have.

NOTE Confidence: 0.853982455454546

 $00:25:31.600 \rightarrow 00:25:33.264$ 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

 $00{:}25{:}36{.}520 \dashrightarrow 00{:}25{:}39{.}028$ So two dependency to the peptide

NOTE Confidence: 0.853982455454546

 $00{:}25{:}39{.}028 \dashrightarrow 00{:}25{:}42{.}239$ 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

 $00:25:43.920 \longrightarrow 00:25:45.024$ And in this model,

NOTE Confidence: 0.853982455454546

 $00:25:45.024 \rightarrow 00:25:47.040$ which there was like a subcutaneous model,

NOTE Confidence: 0.853982455454546

 $00:25:47.040 \longrightarrow 00:25:48.678$ 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

 $00{:}25{:}51.040 \dashrightarrow 00{:}25{:}52.790$ we show like essential cures

NOTE Confidence: 0.853982455454546

 $00:25:52.790 \rightarrow 00:25:55.120$ of the mice for that matter,

NOTE Confidence: 0.853982455454546

 $00:25:55.120 \rightarrow 00:25:56.320$ when we use the Quizad,

NOTE Confidence: 0.853982455454546

 $00:25:56.320 \rightarrow 00:25:59.800$ snip and Venetoclax combination.

 $00:25:59.800 \rightarrow 00:26:01.795$ So this did go into clinical development.

NOTE Confidence: 0.853982455454546

 $00{:}26{:}01{.}800 \dashrightarrow 00{:}26{:}04{.}968$ And for the trials another flix ster

NOTE Confidence: 0.853982455454546

 $00:26:04.968 \longrightarrow 00:26:06.552$ inhibitor second generation

NOTE Confidence: 0.853982455454546

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

NOTE Confidence: 0.853982455454546

 $00:26:08.920 \rightarrow 00:26:11.902$ 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

 $00{:}26{:}14.775 \dashrightarrow 00{:}26{:}16.790$ other collaborators where there was

NOTE Confidence: 0.853982455454546

 $00{:}26{:}16.864 \dashrightarrow 00{:}26{:}19.139$ combination of venetoclax and guilt

NOTE Confidence: 0.853982455454546

 $00:26:19.139 \rightarrow 00:26:21.414$ retina for relapse refractory Flex

NOTE Confidence: 0.620285854347826

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

NOTE Confidence: 0.620285854347826

 $00:26:22.400 \rightarrow 00:26:25.244$ And there was quite significant response

NOTE Confidence: 0.620285854347826

 $00{:}26{:}25{.}244 \dashrightarrow 00{:}26{:}28{.}344$ rate in all patients or in those

NOTE Confidence: 0.620285854347826

 $00{:}26{:}28{.}344 \dashrightarrow 00{:}26{:}30{.}955$ who failed prior Flex 3 Tki's alone.

NOTE Confidence: 0.620285854347826

 $00{:}26{:}30{.}960 \dashrightarrow 00{:}26{:}33{.}158$ And if they went for the transplant,

NOTE Confidence: 0.620285854347826

 $00:26:33.160 \rightarrow 00:26:36.919$ they actually the survival looks fairly good.

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

NOTE Confidence: 0.620285854347826

 $00:26:39.098 \longrightarrow 00:26:40.880$ that the Flixtree clones were

NOTE Confidence: 0.620285854347826

 $00:26:40.880 \rightarrow 00:26:42.076$ extinguished after this combination.

NOTE Confidence: 0.620285854347826

 $00:26:42.076 \longrightarrow 00:26:44.439$ I have to say that she did show

NOTE Confidence: 0.620285854347826

 $00{:}26{:}44{.}439 \dashrightarrow 00{:}26{:}45{.}729$ that Ras clones were coming

NOTE Confidence: 0.620285854347826

 $00{:}26{:}45.729 \dashrightarrow 00{:}26{:}47.319$ 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

 $00:26:49.462 \longrightarrow 00:26:51.520$ mechanism even in that setting.

NOTE Confidence: 0.620285854347826

 $00:26:51.520 \longrightarrow 00:26:53.897$ But again,

NOTE Confidence: 0.620285854347826

 $00{:}26{:}53.897 \dashrightarrow 00{:}26{:}56.879$ this was quite impressive sort of

NOTE Confidence: 0.620285854347826

 $00{:}26{:}56{.}880 \dashrightarrow 00{:}27{:}00{.}480$ advance in the field of Flixtree mutated AML.

NOTE Confidence: 0.620285854347826

 $00:27:00.480 \rightarrow 00:27:02.608$ Now of course we all know that treating

NOTE Confidence: 0.620285854347826

 $00:27:02.608 \rightarrow 00:27:04.760$ patients is best at the time of diagnosis.

NOTE Confidence: 0.620285854347826

 $00:27:04.760 \longrightarrow 00:27:07.238$ So for all the patients we

NOTE Confidence: 0.620285854347826

 $00:27:07.238 \longrightarrow 00:27:08.477$ cannot use chemotherapy.

NOTE Confidence: 0.620285854347826

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

- NOTE Confidence: 0.620285854347826
- $00:27:10.044 \rightarrow 00:27:11.999$ pioneered what we call triplet.
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}12.000 \dashrightarrow 00{:}27{:}13.885$ So triplet is essentially Azovan
- NOTE Confidence: 0.620285854347826
- $00:27:13.885 \longrightarrow 00:27:16.222$ which is a backbone and then you
- NOTE Confidence: 0.620285854347826
- $00:27:16.222 \longrightarrow 00:27:18.140$ add the third drug in this case
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}18{.}203 \dashrightarrow 00{:}27{:}19{.}998$ is guilt written and this paper
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}19{.}998 \dashrightarrow 00{:}27{:}22{.}255$ is also now accepted in JC or now
- NOTE Confidence: 0.620285854347826
- $00:27:22.255 \rightarrow 00:27:23.915$ this is single sounded trial.
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}23{.}920 \dashrightarrow 00{:}27{:}26{.}272$ There's a lot of discussion on Twitter
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}26.272 \dashrightarrow 00{:}27{:}28.600$ 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
- $00:27:31.274 \rightarrow 00:27:33.719$ Indiannis and look very impressive.
- NOTE Confidence: 0.620285854347826
- $00:27:33.720 \longrightarrow 00:27:35.800$ Now when you see 100% response rate,
- NOTE Confidence: 0.620285854347826
- $00:27:35.800 \rightarrow 00:27:37.400$ you always kind of pause,
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}37{.}400 \dashrightarrow 00{:}27{:}40{.}284$ but that's what they reported and 30
- NOTE Confidence: 0.620285854347826
- $00{:}27{:}40{.}284 \dashrightarrow 00{:}27{:}43{.}004$ newly diagnosed patients with AML and
- NOTE Confidence: 0.620285854347826

 $00:27:43.004 \rightarrow 00:27:46.236$ they estimated survival at two years was 70%.

NOTE Confidence: 0.620285854347826

 $00:27:46.240 \longrightarrow 00:27:47.914$ So this is like way better

NOTE Confidence: 0.620285854347826

 $00:27:47.914 \longrightarrow 00:27:49.560$ than what we had before,

NOTE Confidence: 0.620285854347826

 $00:27:49.560 \longrightarrow 00:27:51.709$ but they had to like reduce a

NOTE Confidence: 0.620285854347826

 $00{:}27{:}51.709 \dashrightarrow 00{:}27{:}53.798$ 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

 $00:27:55.816 \rightarrow 00:27:57.160$ combination is mild suppressive.

NOTE Confidence: 0.620285854347826

 $00:27:57.160 \longrightarrow 00:27:59.470$ So the major like heme toxicity of

NOTE Confidence: 0.620285854347826

 $00{:}27{:}59{.}470 \dashrightarrow 00{:}28{:}01{.}280$ venetoclax is mild suppression.

NOTE Confidence: 0.620285854347826

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

NOTE Confidence: 0.620285854347826

 $00:28:03.232 \longrightarrow 00:28:05.672$ itself express B so too.

NOTE Confidence: 0.620285854347826

 $00:28:05.680 \longrightarrow 00:28:07.640$ 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

 $00:28:08.480 \longrightarrow 00:28:10.755$ you have to cut back and that's

NOTE Confidence: 0.620285854347826

 $00{:}28{:}10.760 \dashrightarrow 00{:}28{:}12.428$ continued discussions with FDA

NOTE Confidence: 0.620285854347826

 $00:28:12.428 \longrightarrow 00:28:14.930$ because the approved scale is 28

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

 $00:28:19.920 \rightarrow 00:28:22.292$ kind of solidify this question run

NOTE Confidence: 0.620285854347826

 $00{:}28{:}22{.}292 \dashrightarrow 00{:}28{:}25{.}400$ by a Stellas and AbbVie where the

NOTE Confidence: 0.620285854347826

 $00{:}28{:}25{.}400 \dashrightarrow 00{:}28{:}27{.}320$ same combination is being used in

NOTE Confidence: 0.620285854347826

 $00{:}28{:}27{.}320 \dashrightarrow 00{:}28{:}29{.}200$ the frontline all the AML settings.

NOTE Confidence: 0.620285854347826

 $00:28:29.200 \rightarrow 00:28:31.720$ So we'll see how that goes,

NOTE Confidence: 0.620285854347826

 $00:28:31.720 \longrightarrow 00:28:34.480$ but again what do we do about Ras.

NOTE Confidence: 0.620285854347826

 $00:28:34.480 \rightarrow 00:28:38.440$ So this is like very early preclinical work.

NOTE Confidence: 0.620285854347826

 $00:28:38.440 \longrightarrow 00:28:40.906$ We're working with Everest Gavasitis at

NOTE Confidence: 0.620285854347826

 $00{:}28{:}40.906 \dashrightarrow 00{:}28{:}43.760$ Einstein and he developed the RAF inhibitor.

NOTE Confidence: 0.620285854347826

 $00{:}28{:}43.760 \dashrightarrow 00{:}28{:}47.411$ So kind of downstream of Ras that inhibit

NOTE Confidence: 0.620285854347826

 $00{:}28{:}47{.}411 \dashrightarrow 00{:}28{:}49{.}913$ is allosteric RAF inhibitor that he

NOTE Confidence: 0.620285854347826

 $00{:}28{:}49{.}913 \dashrightarrow 00{:}28{:}52{.}915$ is about to publish in solid tumors.

 $00:28:52.920 \longrightarrow 00:28:55.120$ But we show that P in cell lines

NOTE Confidence: 0.620285854347826

 $00{:}28{:}55{.}120 \dashrightarrow 00{:}28{:}58{.}237$ with K or N Ras mutation is highly

NOTE Confidence: 0.620285854347826

 $00:28:58.237 \longrightarrow 00:28:59.901$ 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

 $00{:}29{:}02{.}142 \dashrightarrow 00{:}29{:}03{.}718$ additive effects with venetoclax.

NOTE Confidence: 0.620285854347826

 $00{:}29{:}03.720 \dashrightarrow 00{:}29{:}05.920$ So we kind of continue working on that.

NOTE Confidence: 0.620285854347826

 $00:29:05.920 \longrightarrow 00:29:07.680$ So hopefully we'll get either

NOTE Confidence: 0.620285854347826

 $00{:}29{:}07{.}680 \dashrightarrow 00{:}29{:}09{.}440$ Ras inhibitors or RAF inhibitors.

NOTE Confidence: 0.620285854347826

 $00:29:09.440 \longrightarrow 00:29:11.678$ We did test the MECH inhibitors.

NOTE Confidence: 0.620285854347826

 $00{:}29{:}11.680 \dashrightarrow 00{:}29{:}13.880$ I didn't show you that we published that.

NOTE Confidence: 0.620285854347826

 $00{:}29{:}13.880 \dashrightarrow 00{:}29{:}15.238$ We went all the way into clinic,

NOTE Confidence: 0.620285854347826

 $00{:}29{:}15{.}240 \dashrightarrow 00{:}29{:}17{.}760$ but MECH inhibitors caused a lot of

NOTE Confidence: 0.620285854347826

 $00{:}29{:}17.760 \dashrightarrow 00{:}29{:}20.718$ 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

 $00{:}29{:}23.555 \dashrightarrow 00{:}29{:}24.770$ efficacy and high

NOTE Confidence: 0.902856236363636

 $00{:}29{:}24.863 \dashrightarrow 00{:}29{:}27.712$ toxicity. So we can't really use the Mac

- NOTE Confidence: 0.902856236363636
- $00:29:27.712 \rightarrow 00:29:29.559$ inhibits unfortunately in this combination.
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}29{.}560 \dashrightarrow 00{:}29{:}34{.}280$ So work to be continued on this topic.
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}34{.}280 \dashrightarrow 00{:}29{:}35{.}813$ So there are a lot of other
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}35{.}813 \dashrightarrow 00{:}29{:}36{.}750$ combinations with banana glass
- NOTE Confidence: 0.902856236363636
- $00:29:36.750 \longrightarrow 00:29:38.160$ that have been sort of published.
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}38{.}160 \dashrightarrow 00{:}29{:}41{.}380$ This is just some nice summary that
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}41{.}380 \dashrightarrow 00{:}29{:}44{.}348$ was presented at last EHA and the
- NOTE Confidence: 0.902856236363636
- $00:29:44.348 \longrightarrow 00:29:46.318$ the combination with IDH inhibitors
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}46{.}318 \dashrightarrow 00{:}29{:}49{.}173$ 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
- $00:29:51.840 \rightarrow 00:29:53.580$ there's many inhibited combination
- NOTE Confidence: 0.902856236363636
- $00{:}29{:}53.580 \dashrightarrow 00{:}29{:}55.320$ 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
- $00:29:57.840 \rightarrow 00:29:59.244$ but it's struggling.
- NOTE Confidence: 0.902856236363636
- $00:29:59.244 \rightarrow 00:30:01.584$ There was McGraw mop combination
- NOTE Confidence: 0.902856236363636

 $00:30:01.584 \rightarrow 00:30:03.360$ 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

 $00:30:04.830 \longrightarrow 00:30:06.280$ 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

 $00{:}30{:}08.611 \dashrightarrow 00{:}30{:}11.069$ that today and but I want to show some

NOTE Confidence: 0.902856236363636

 $00{:}30{:}11.069 \dashrightarrow 00{:}30{:}13.173$ data with the immune approaches in

NOTE Confidence: 0.902856236363636

 $00:30:13.173 \rightarrow 00:30:15.435$ this case is antibody drug conugate.

NOTE Confidence: 0.902856236363636

 $00{:}30{:}15{.}440 \dashrightarrow 00{:}30{:}17{.}456$ So kind of a little bit different

NOTE Confidence: 0.902856236363636

 $00:30:17.456 \longrightarrow 00:30:18.320$ story with venetoclax.

NOTE Confidence: 0.902856236363636

 $00:30:18.320 \longrightarrow 00:30:20.680$ So, so we used the,

NOTE Confidence: 0.902856236363636

 $00{:}30{:}20{.}680 \dashrightarrow 00{:}30{:}23{.}767$ we looked at CD 123 because CD 123 is

NOTE Confidence: 0.902856236363636

 $00{:}30{:}23.767 \dashrightarrow 00{:}30{:}27.278$ a subunit of all three receptor alpha

NOTE Confidence: 0.902856236363636

 $00:30:27.280 \rightarrow 00:30:29.680$ and it's ubiquitously expressed in AML.

NOTE Confidence: 0.902856236363636

 $00:30:29.680 \rightarrow 00:30:32.248$ 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

 $00:30:35.080 \rightarrow 00:30:37.552$ 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
- $00:30:39.818 \rightarrow 00:30:41.981$ sort of the only antigen right now
- NOTE Confidence: 0.902856236363636
- $00:30:41.981 \rightarrow 00:30:44.336$ that we kind of trying to target as
- NOTE Confidence: 0.902856236363636
- $00:30:44.336 \rightarrow 00:30:46.292$ far as immune therapy and EMLMDS.
- NOTE Confidence: 0.902856236363636
- $00{:}30{:}46.292 \dashrightarrow 00{:}30{:}48.284$ There are other efforts but none
- NOTE Confidence: 0.902856236363636
- $00:30:48.284 \rightarrow 00:30:50.600$ 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
- $00{:}30{:}53{.}354 \dashrightarrow 00{:}30{:}55{.}190$ company Immunogen that developed
- NOTE Confidence: 0.902856236363636
- 00:30:55.265 --> 00:30:56.986 the antibody drug Conugate.
- NOTE Confidence: 0.902856236363636
- $00:30:56.986 \longrightarrow 00:31:00.533$ 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
- $00:31:03.731 \longrightarrow 00:31:06.240$ to the alculator that produces
- NOTE Confidence: 0.902856236363636
- $00:31:06.240 \dashrightarrow 00:31:08.640$ 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
- $00:31:11.600 \rightarrow 00:31:14.092$ 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

 $00{:}31{:}16{.}573 \dashrightarrow 00{:}31{:}18{.}798$ but in a targeted fashion.

NOTE Confidence: 0.902856236363636

 $00:31:18.800 \longrightarrow 00:31:22.027$ So it had the good single agent

NOTE Confidence: 0.902856236363636

 $00{:}31{:}22.027 \dashrightarrow 00{:}31{:}24.638$ activity and BPDC and then EMO

NOTE Confidence: 0.902856236363636

 $00:31:24.640 \dashrightarrow 00:31:26.710$ the company has filed approval for

NOTE Confidence: 0.902856236363636

 $00{:}31{:}26.710 \dashrightarrow 00{:}31{:}28.919$ BPDC and patients a second line.

NOTE Confidence: 0.902856236363636

 $00:31:28.920 \longrightarrow 00:31:31.026$ So hopefully we get this drug

NOTE Confidence: 0.902856236363636

 $00:31:31.026 \longrightarrow 00:31:32.079$ approved pretty soon.

NOTE Confidence: 0.902856236363636

 $00:31:32.080 \rightarrow 00:31:34.040$ And so we of course asked the question,

NOTE Confidence: 0.902856236363636

 $00{:}31{:}34.040 \dashrightarrow 00{:}31{:}35.528$ can we combine the two because

NOTE Confidence: 0.902856236363636

 $00{:}31{:}35{.}528 \dashrightarrow 00{:}31{:}37{.}435$ this is like you know the immune

NOTE Confidence: 0.902856236363636

 $00:31:37.435 \longrightarrow 00:31:39.157$ therapy that seems to be working.

NOTE Confidence: 0.902856236363636

 $00:31:39.160 \longrightarrow 00:31:40.360$ So we've done quite a bit

NOTE Confidence: 0.902856236363636

 $00:31:40.360 \longrightarrow 00:31:40.960$ of preclinical work.

NOTE Confidence: 0.902856236363636

 $00:31:40.960 \longrightarrow 00:31:42.400$ It's not published yet,

NOTE Confidence: 0.902856236363636

 $00:31:42.400 \rightarrow 00:31:45.239$ but we show that the compound is fairly

- NOTE Confidence: 0.902856236363636
- $00:31:45.240 \rightarrow 00:31:47.478$ 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
- $00:31:50.448 \rightarrow 00:31:52.856$ majority of cells do express it and
- NOTE Confidence: 0.902856236363636
- $00:31:52.856 \rightarrow 00:31:54.960$ they're being killed by this drug,
- NOTE Confidence: 0.902856236363636
- $00{:}31{:}54{.}960 \dashrightarrow 00{:}31{:}57{.}599$ but then the cells that don't express
- NOTE Confidence: 0.902856236363636
- $00:31:57.600 \rightarrow 00:32:00.000$ 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
- $00:32:01.640 \longrightarrow 00:32:04.160$ but it seems to be specific.
- NOTE Confidence: 0.902856236363636
- $00:32:04.160 \dashrightarrow 00:32:06.068$ And then we ran the combinations
- NOTE Confidence: 0.902856236363636
- $00:32:06.068 \longrightarrow 00:32:07.717$ both with another clogs and
- NOTE Confidence: 0.902856236363636
- $00:32:07.717 \dashrightarrow 00:32:09.307$ azacitidine and the triplet because
- NOTE Confidence: 0.902856236363636
- $00:32:09.307 \rightarrow 00:32:11.633$ now we're in the triplet era, right?
- NOTE Confidence: 0.902856236363636
- $00{:}32{:}11{.}633 \dashrightarrow 00{:}32{:}13{.}198$ And you can see here.
- NOTE Confidence: 0.902856236363636
- $00:32:13.200 \longrightarrow 00:32:14.676$ So these are different cell lines.
- NOTE Confidence: 0.902856236363636

 $00:32:14.680 \longrightarrow 00:32:16.759$ 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

 $00:32:18.151 \longrightarrow 00:32:20.017$ which is why we selected those

NOTE Confidence: 0.902856236363636

 $00:32:20.017 \longrightarrow 00:32:21.400$ for the combination trials.

NOTE Confidence: 0.902856236363636

 $00:32:21.400 \rightarrow 00:32:23.000$ But especially with the triplet,

NOTE Confidence: 0.902856236363636

 $00{:}32{:}23.000 \dashrightarrow 00{:}32{:}27.158$ 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: 0.6953634466666667

 $00:32:29.800 \rightarrow 00:32:31.438$ So these are wild type cells,

NOTE Confidence: 0.6953634466666667

 $00:32:31.440 \rightarrow 00:32:35.344$ so they're sensitive and they mutant or loss,

NOTE Confidence: 0.6953634466666667

 $00:32:35.344 \rightarrow 00:32:37.712$ PPG loss, we see less activity.

NOTE Confidence: 0.6953634466666667

 $00{:}32{:}37{.}712 \dashrightarrow 00{:}32{:}39{.}880$ There's still some induction of cell does,

NOTE Confidence: 0.6953634466666667

 $00{:}32{:}39{.}880 \dashrightarrow 00{:}32{:}41{.}880$ but it's actually quite resistant

NOTE Confidence: 0.6953634466666667

 $00:32:41.880 \longrightarrow 00:32:43.880$ to both of the compounds.

NOTE Confidence: 0.6953634466666667

 $00:32:43.880 \rightarrow 00:32:46.240$ We're not quite sure how that is affected.

NOTE Confidence: 0.6953634466666667

 $00:32:46.240 \longrightarrow 00:32:47.842$ So for some reason the cells

NOTE Confidence: 0.6953634466666667

 $00:32:47.842 \rightarrow 00:32:49.319$ had very high expression of MSL.

- NOTE Confidence: 0.6953634466666667
- $00:32:49.320 \rightarrow 00:32:51.749$ One, we're still working on to understand
- NOTE Confidence: 0.6953634466666667
- $00{:}32{:}51{.}749 \dashrightarrow 00{:}32{:}54{.}079$ that because we did see induction of
- NOTE Confidence: 0.6953634466666667
- $00:32:54.079 \rightarrow 00:32:56.258$ DNA damage in both knock down cells
- NOTE Confidence: 0.6953634466666667
- $00{:}32{:}56{.}258 \dashrightarrow 00{:}32{:}58{.}546$ and the wild cap cells and there's a
- NOTE Confidence: 0.6953634466666667
- $00:32:58.546 \rightarrow 00:33:02.140$ part cleavage but it's less killing and
- NOTE Confidence: 0.6953634466666667
- $00:33:02.140 \dashrightarrow 00:33:03.960$ that is also reflected in the trial.
- NOTE Confidence: 0.6953634466666667
- 00:33:03.960 --> 00:33:06.210 The PhD media patients didn't
- NOTE Confidence: 0.6953634466666667
- 00:33:06.210 --> 00:33:08.904 do as well as you can imagine.
- NOTE Confidence: 0.6953634466666667
- $00{:}33{:}08{.}904 \dashrightarrow 00{:}33{:}10{.}920$ The drug abolishes the S phase.
- NOTE Confidence: 0.6953634466666667
- $00:33:10.920 \dashrightarrow 00:33:14.696$ So this is like IMGN alone and the
- NOTE Confidence: 0.6953634466666667
- $00:33:14.696 \rightarrow 00:33:16.360$ different concentrations and then
- NOTE Confidence: 0.6953634466666667
- 00:33:16.360 --> 00:33:18.845 when you combine with the Vanasa you
- NOTE Confidence: 0.6953634466666667
- $00:33:18.845 \dashrightarrow 00:33:21.120$ essentially you kill off the S phase
- NOTE Confidence: 0.6953634466666667
- $00:33:21.120 \longrightarrow 00:33:23.756$ cells so you don't have anything left.
- NOTE Confidence: 0.6953634466666667
- $00{:}33{:}23{.}760 \dashrightarrow 00{:}33{:}26{.}425$ You do get activation of gamma H3X
- NOTE Confidence: 0.6953634466666667

 $00:33:26.425 \dashrightarrow 00:33:29.120$ as adna damage and Cliff cast space.

NOTE Confidence: 0.6953634466666667

 $00:33:29.120 \rightarrow 00:33:31.040$ So then we try to understand the mechanism,

NOTE Confidence: 0.6953634466666667

 $00:33:31.040 \longrightarrow 00:33:33.500$ how that works.

NOTE Confidence: 0.6953634466666667

 $00:33:33.500 \longrightarrow 00:33:36.280$ And so one thing is we know that

NOTE Confidence: 0.6953634466666667

00:33:36.280 --> 00:33:37.120 again I'm Gen.

NOTE Confidence: 0.6953634466666667

 $00:33:37.120 \rightarrow 00:33:40.039$ inducing the single cell DNA strand breaks.

NOTE Confidence: 0.6953634466666667

00:33:40.040 -> 00:33:43.012 So we showed the phosphor P53UP

NOTE Confidence: 0.6953634466666667

 $00:33:43.012 \rightarrow 00:33:45.272$ regulation which was the same

NOTE Confidence: 0.6953634466666667

 $00{:}33{:}45{.}272 \dashrightarrow 00{:}33{:}47{.}080$ with or without venetoclax.

NOTE Confidence: 0.6953634466666667

 $00:33:47.080 \rightarrow 00:33:49.800$ But then we saw that the drug inducing

NOTE Confidence: 0.6953634466666667

 $00:33:49.800 \rightarrow 00:33:52.998$ the DNA repair pathway phosphor check one

NOTE Confidence: 0.6953634466666667

 $00:33:53.000 \dashrightarrow 00:33:55.680$ and it seemed to be less with venetoclax.

NOTE Confidence: 0.6953634466666667

 $00:33:55.680 \longrightarrow 00:33:56.640$ So we are,

NOTE Confidence: 0.6953634466666667

 $00:33:56.640 \rightarrow 00:33:58.240$ it's kind of off story,

NOTE Confidence: 0.6953634466666667

 $00{:}33{:}58{.}240 \dashrightarrow 00{:}34{:}00{.}095$ but we are trying to understand if

NOTE Confidence: 0.6953634466666667

00:34:00.095 - 00:34:01.791 BCL 2 inhibition can actually be

- NOTE Confidence: 0.6953634466666667
- $00:34:01.791 \rightarrow 00:34:03.758$ involved in the control of DNA damage,
- NOTE Confidence: 0.6953634466666667
- $00{:}34{:}03.760 \dashrightarrow 00{:}34{:}06.292$ which is hard to understand because
- NOTE Confidence: 0.6953634466666667
- $00:34:06.292 \rightarrow 00:34:08.440$ it's cytosolic and this is DNA.
- NOTE Confidence: 0.6953634466666667
- $00:34:08.440 \rightarrow 00:34:10.555$ But we are kind of working through the story,
- NOTE Confidence: 0.6953634466666667
- $00:34:10.560 \rightarrow 00:34:12.420$ still trying to figure out all
- NOTE Confidence: 0.6953634466666667
- $00:34:12.420 \longrightarrow 00:34:14.520$ the parts of the DNA pathway.
- NOTE Confidence: 0.6953634466666667
- $00:34:14.520 \longrightarrow 00:34:16.278$ But it has some like clinical,
- NOTE Confidence: 0.6953634466666667
- $00:34:16.280 \longrightarrow 00:34:18.460$ preclinical implications because if you
- NOTE Confidence: 0.6953634466666667
- $00:34:18.460 \longrightarrow 00:34:21.840$ use IMGN first followed by the nether class,
- NOTE Confidence: 0.6953634466666667
- 00:34:21.840 --> 00:34:23.560 you have very striking synergy.
- NOTE Confidence: 0.6953634466666667
- $00:34:23.560 \longrightarrow 00:34:25.800$ This BLISS index is 18.
- NOTE Confidence: 0.6953634466666667
- $00:34:25.800 \longrightarrow 00:34:28.488$ If you do the reverse then
- NOTE Confidence: 0.6953634466666667
- $00:34:28.488 \longrightarrow 00:34:30.280$ first followed by IMGN,
- NOTE Confidence: 0.6953634466666667
- $00{:}34{:}30{.}280 \dashrightarrow 00{:}34{:}32{.}320$ there's very little synergy now in
- NOTE Confidence: 0.6953634466666667
- $00:34:32.320 \rightarrow 00:34:34.600$ the clinic it's given concomitantly.
- NOTE Confidence: 0.6953634466666667

00:34:34.600 --> 00:34:37.684 So I think it's fine but and nobody's

NOTE Confidence: 0.6953634466666667

 $00:34:37.684 \rightarrow 00:34:39.794$ interested in understanding the kinetics.

NOTE Confidence: 0.6953634466666667

00:34:39.800 --> 00:34:41.900 But I think the biologically this

NOTE Confidence: 0.6953634466666667

00:34:41.900 - > 00:34:43.300 is interesting phenomenon and

NOTE Confidence: 0.6953634466666667

 $00{:}34{:}43{.}361 \dashrightarrow 00{:}34{:}45{.}263$ perhaps something to do with DNA

NOTE Confidence: 0.6953634466666667

 $00:34:45.263 \dashrightarrow 00:34:47.200$ damage repair that we're working on.

NOTE Confidence: 0.6953634466666667

 $00{:}34{:}47{.}200 \dashrightarrow 00{:}34{:}49{.}916$ We also showed that the IMGN primes

NOTE Confidence: 0.6953634466666667

 $00:34:49.916 \longrightarrow 00:34:52.279$ towards be so to inhibition.

NOTE Confidence: 0.6953634466666667

00:34:52.280 --> 00:34:53.927 So I didn't I have a lot of like

NOTE Confidence: 0.6953634466666667

00:34:53.927 - 00:34:55.559 mouse data which I didn't show you,

NOTE Confidence: 0.6953634466666667

 $00{:}34{:}55{.}560 \dashrightarrow 00{:}34{:}58{.}440$ but the clinical trial has been

NOTE Confidence: 0.6953634466666667

 $00:34:58.440 \rightarrow 00:35:01.352$ reported at ASH and the paper is

NOTE Confidence: 0.6953634466666667

 $00:35:01.352 \rightarrow 00:35:03.192$ also now accepted in JCO.

NOTE Confidence: 0.6953634466666667

 $00:35:03.200 \rightarrow 00:35:05.240$ So this is a triplet.

NOTE Confidence: 0.6953634466666667

 $00:35:05.240 \longrightarrow 00:35:07.760$ So again the drug is now called

NOTE Confidence: 0.6953634466666667

00:35:07.760 --> 00:35:08.882 Pivacomab P VAC.

- NOTE Confidence: 0.6953634466666667
- $00{:}35{:}08{.}882 \dashrightarrow 00{:}35{:}11{.}696$ We abbreviate that it was used with
- NOTE Confidence: 0.6953634466666667
- 00:35:11.696 --> 00:35:14.200 Azovan in newly diagnosed AML.
- NOTE Confidence: 0.6953634466666667
- $00:35:14.200 \rightarrow 00:35:15.475$ All the patients,
- NOTE Confidence: 0.6953634466666667
- 00:35:15.475 00:35:17.600 you know majority were unfit,
- NOTE Confidence: 0.6953634466666667
- $00:35:17.600 \rightarrow 00:35:21.320$ but there were some fit patients as well.
- NOTE Confidence: 0.6953634466666667
- $00:35:21.320 \longrightarrow 00:35:23.120$ So it was fairly safe.
- NOTE Confidence: 0.6953634466666667
- $00:35:23.120 \rightarrow 00:35:26.319$ So again the drug has some toxicities,
- NOTE Confidence: 0.6953634466666667
- $00:35:26.320 \rightarrow 00:35:29.757$ but generally speaking it was well tolerated.
- NOTE Confidence: 0.6953634466666667
- $00{:}35{:}29{.}760 \dashrightarrow 00{:}35{:}31{.}993$ And then the response rates where I
- NOTE Confidence: 0.6953634466666667
- 00:35:31.993 --> 00:35:34.039 would say similar to the ACE event,
- NOTE Confidence: 0.931259272
- $00:35:34.040 \longrightarrow 00:35:35.640$ but what was impressive
- NOTE Confidence: 0.931259272
- $00{:}35{:}35{.}640 \dashrightarrow 00{:}35{:}37{.}510$ was MRD negativity rate.
- NOTE Confidence: 0.931259272
- $00{:}35{:}37{.}510 \dashrightarrow 00{:}35{:}41{.}688$ 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
- $00:35:45.272 \rightarrow 00:35:47.680$ So almost doubling the depths of response.
- NOTE Confidence: 0.931259272

 $00:35:47.680 \longrightarrow 00:35:49.528$ 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

 $00:35:50.320 \dashrightarrow 00:35:53.158$ which will be a critical question.

NOTE Confidence: 0.931259272

 $00:35:53.160 \rightarrow 00:35:55.280$ So now Immunogen is bought by ABB vie.

NOTE Confidence: 0.931259272

 $00:35:55.280 \rightarrow 00:35:57.387$ So we're hoping that this will continue

NOTE Confidence: 0.931259272

 $00:35:57.387 \dashrightarrow 00:35:59.242$ and to randomized phase three study NOTE Confidence: 0.931259272

 $00{:}35{:}59{.}242 \dashrightarrow 00{:}36{:}01{.}485$ and maybe we'll have that triplet in

NOTE Confidence: 0.931259272

 $00:36:01.485 \longrightarrow 00:36:04.155$ a few years fully characterized that.

NOTE Confidence: 0.931259272

 $00{:}36{:}04{.}160 \dashrightarrow 00{:}36{:}06{.}770$ But if you look at this like 3 subsets NOTE Confidence: 0.931259272

 $00:36:06.770 \rightarrow 00:36:09.196$ 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

 $00:36:11.344 \rightarrow 00:36:13.239$ that respond well to to azavan,

NOTE Confidence: 0.931259272

 $00:36:13.240 \longrightarrow 00:36:15.320$ 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

 $00:36:18.440 \longrightarrow 00:36:21.198$ there was about 20% full CR rate,

NOTE Confidence: 0.931259272

 $00:36:21.200 \longrightarrow 00:36:23.480$ but 50% overall response rate.

- NOTE Confidence: 0.931259272
- $00:36:23.480 \longrightarrow 00:36:25.000$ 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
- $00:36:27.640 \longrightarrow 00:36:29.040$ we are kind of really at loss.
- NOTE Confidence: 0.931259272
- $00:36:29.040 \longrightarrow 00:36:30.552$ So that you know,
- NOTE Confidence: 0.931259272
- $00:36:30.552 \dashrightarrow 00:36:32.820$ but again this will be developed
- NOTE Confidence: 0.931259272
- $00:36:32.897 \longrightarrow 00:36:35.648$ hopefully further and we'll see a few
- NOTE Confidence: 0.931259272
- $00:36:35.648 \dashrightarrow 00:36:38.928$ years from now where that lens now P 53.
- NOTE Confidence: 0.931259272
- $00:36:38.928 \rightarrow 00:36:41.635$ So I already told you several times that this
- NOTE Confidence: 0.931259272
- $00{:}36{:}41.635 \dashrightarrow 00{:}36{:}44.559$ is like a major unmet need in AML and MD's.
- NOTE Confidence: 0.931259272
- $00:36:44.560 \longrightarrow 00:36:46.888$ All the drugs that we had in phase
- NOTE Confidence: 0.931259272
- $00:36:46.888 \rightarrow 00:36:49.160$ three have failed for the most part.
- NOTE Confidence: 0.931259272
- $00{:}36{:}49{.}160 \dashrightarrow 00{:}36{:}52{.}079$ And even from the very initial studies,
- NOTE Confidence: 0.931259272
- $00:36:52.080 \rightarrow 00:36:54.648$ we've showed that this was a major resistance
- NOTE Confidence: 0.931259272
- $00{:}36{:}54{.}648 \dashrightarrow 00{:}36{:}57{.}280$ 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

 $00{:}37{:}00{.}920 \dashrightarrow 00{:}37{:}06{.}620$ they had high rates of 17 P loss or P50C

NOTE Confidence: 0.931259272

 $00:37:06.620 \rightarrow 00:37:11.120$ 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

 $00:37:16.970 \longrightarrow 00:37:19.108$ you showed you know all this

NOTE Confidence: 0.931259272

 $00:37:19.108 \longrightarrow 00:37:20.793$ clones are being selected for.

NOTE Confidence: 0.931259272

 $00{:}37{:}20.800 \dashrightarrow 00{:}37{:}23.232$ So it's almost like a pressure to select

NOTE Confidence: 0.931259272

 $00{:}37{:}23{.}232 \dashrightarrow 00{:}37{:}25{.}454$ this clones for that because they do

NOTE Confidence: 0.931259272

 $00:37:25.454 \dashrightarrow 00:37:27.360$ not get killed by venetoclax cell.

NOTE Confidence: 0.931259272

 $00:37:27.360 \longrightarrow 00:37:29.664$ And what he showed in this paper is

NOTE Confidence: 0.931259272

 $00{:}37{:}29{.}664 \dashrightarrow 00{:}37{:}32{.}640$ that while in parental cells veneto clax

NOTE Confidence: 0.931259272

 $00:37:32.640 \rightarrow 00:37:35.880$ induces backs activation by this essay,

NOTE Confidence: 0.931259272

 $00:37:35.880 \dashrightarrow 00:37:39.160$ there's much less in the PVC knockouts also.

NOTE Confidence: 0.931259272

 $00:37:39.160 \rightarrow 00:37:43.080$ 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
- $00:37:43.720 \longrightarrow 00:37:46.280$ we don't have MC1 inhibitors in the clinic.
- NOTE Confidence: 0.931259272
- $00:37:46.280 \longrightarrow 00:37:47.638$ So what do we do about that?
- NOTE Confidence: 0.931259272
- $00{:}37{:}47.640 \dashrightarrow 00{:}37{:}48.760$ We we don't really know.
- NOTE Confidence: 0.931259272
- $00{:}37{:}48.760 \dashrightarrow 00{:}37{:}51.168$ But I want to show you some clinical
- NOTE Confidence: 0.931259272
- $00{:}37{:}51{.}168 \dashrightarrow 00{:}37{:}53{.}362$ data from our Einstein program that
- NOTE Confidence: 0.931259272
- $00{:}37{:}53{.}362 \dashrightarrow 00{:}37{:}55{.}642$ 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
- $00:37:57.480 \dashrightarrow 00:38:00.848$ So the approach that they decided to go
- NOTE Confidence: 0.931259272
- $00:38:00.848 \rightarrow 00:38:03.917$ 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
- $00{:}38{:}05{.}120 \dashrightarrow 00{:}38{:}07{.}720$ but that at Cleveland Clinic.
- NOTE Confidence: 0.931259272
- $00:38:07.720 \longrightarrow 00:38:08.440$ So he is I think,
- NOTE Confidence: 0.931259272
- $00{:}38{:}08{.}440 \dashrightarrow 00{:}38{:}10{.}340$ the most knowledgeable person
- NOTE Confidence: 0.931259272
- $00{:}38{:}10{.}340 \dashrightarrow 00{:}38{:}12{.}240$ in HMAI feel that.
- NOTE Confidence: 0.931259272

- $00:38:12.240 \longrightarrow 00:38:13.500$ So essentially he published
- NOTE Confidence: 0.931259272
- $00{:}38{:}13.500 \dashrightarrow 00{:}38{:}15.055$ 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
- $00:38:17.120 \longrightarrow 00:38:19.682$ 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
- $00:38:22.520 \longrightarrow 00:38:25.480$ which is once a week like 1/5 of the dose.
- NOTE Confidence: 0.931259272
- $00:38:25.480 \dashrightarrow 00:38:28.119$ So really like tiny doses of decybin.
- NOTE Confidence: 0.931259272
- $00:38:28.120 \longrightarrow 00:38:30.568$ But he showed that this is
- NOTE Confidence: 0.931259272
- $00:38:30.568 \rightarrow 00:38:32.472$ enough to deplete DN MT3DMT1.
- NOTE Confidence: 0.931259272
- $00:38:32.472 \rightarrow 00:38:35.160$ 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
- $00{:}38{:}40{.}240 \dashrightarrow 00{:}38{:}42{.}228$ And then he showed in preclinical work
- NOTE Confidence: 0.836275078888889
- $00{:}38{:}42.228 \dashrightarrow 00{:}38{:}44.085$ that it can induce differentiation
- NOTE Confidence: 0.836275078888889
- $00:38:44.085 \longrightarrow 00:38:46.404$ of P53 novel loss clones.
- NOTE Confidence: 0.836275078888889
- $00:38:46.404 \longrightarrow 00:38:49.170$ Now the resistance to the decided

- NOTE Confidence: 0.836275078888889
- $00:38:49.259 \rightarrow 00:38:51.914$ men is mediated by approvalation
- NOTE Confidence: 0.836275078888889
- $00:38:51.914 \rightarrow 00:38:54.038$ of pyramid and synthesis.
- NOTE Confidence: 0.836275078888889
- $00:38:54.040 \longrightarrow 00:38:56.565$ 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
- $00{:}38{:}58{.}990 \dashrightarrow 00{:}39{:}01{.}640$ that Veneto clerks can in fact
- NOTE Confidence: 0.836275078888889
- $00:39:01.640 \rightarrow 00:39:03.728$ reduce the pyramid incentives.
- NOTE Confidence: 0.836275078888889
- $00:39:03.728 \rightarrow 00:39:07.440$ So there may be potential synergy there.
- NOTE Confidence: 0.836275078888889
- $00:39:07.440 \longrightarrow 00:39:10.110$ 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
- $00:39:13.600 \rightarrow 00:39:15.680$ developed this metronomic dosing
- NOTE Confidence: 0.836275078888889
- $00{:}39{:}15{.}680 \dashrightarrow 00{:}39{:}17{.}528$ 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
- $00{:}39{:}20.001 \dashrightarrow 00{:}39{:}22.252$ patient with Amalo MTS who comes
- NOTE Confidence: 0.836275078888889
- $00:39:22.252 \longrightarrow 00:39:24.394$ to clinic and gets once a week
- NOTE Confidence: 0.836275078888889

 $00:39:24.400 \rightarrow 00:39:26.120$ injection of the SIBIN subcutaneously

NOTE Confidence: 0.836275078888889

 $00:39:26.120 \longrightarrow 00:39:28.240$ and one dose of another class.

NOTE Confidence: 0.836275078888889

 $00:39:28.240 \longrightarrow 00:39:30.060$ So I'll say I had hard time

NOTE Confidence: 0.836275078888889

 $00:39:30.060 \rightarrow 00:39:31.559$ believing that when I got there,

NOTE Confidence: 0.836275078888889

 $00{:}39{:}31{.}560 \dashrightarrow 00{:}39{:}34{.}256$ but I think now I'm so converted and

NOTE Confidence: 0.836275078888889

 $00{:}39{:}34{.}256 \dashrightarrow 00{:}39{:}36{.}971$ that we are continuing the development

NOTE Confidence: 0.836275078888889

 $00:39:36.971 \dashrightarrow 00:39:39.911$ of this in the prospective trial.

NOTE Confidence: 0.836275078888889

 $00:39:39.920 \rightarrow 00:39:41.600$ 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

 $00:39:43.560 \longrightarrow 00:39:45.499$ you give another class for 28 days

NOTE Confidence: 0.836275078888889

 $00:39:45.499 \rightarrow 00:39:47.747$ and you give the SIBIN for five days

NOTE Confidence: 0.836275078888889

 $00{:}39{:}47{.}747 \dashrightarrow 00{:}39{:}49{.}941$ or ASAP for seven days and then you

NOTE Confidence: 0.836275078888889

 $00:39:49.941 \rightarrow 00:39:52.510$ repeat the cycle and he is like once a week.

NOTE Confidence: 0.836275078888889

 $00{:}39{:}52{.}510 \dashrightarrow 00{:}39{:}55{.}014$ So the idea is really to get away from

NOTE Confidence: 0.836275078888889

 $00:39:55.014 \rightarrow 00:39:57.066$ the DNA damaging response because we

NOTE Confidence: 0.836275078888889

 $00:39:57.066 \rightarrow 00:39:59.408$ know that Pfc mutated cells are only

 $00:39:59.408 \rightarrow 00:40:01.848$ being selected by any DNA damaging drugs,

NOTE Confidence: 0.836275078888889

 $00:40:01.848 \longrightarrow 00:40:04.473$ they don't care and get into

NOTE Confidence: 0.836275078888889

 $00:40:04.473 \longrightarrow 00:40:06.277$ this hyper misleading effect.

NOTE Confidence: 0.836275078888889

 $00:40:06.280 \rightarrow 00:40:08.359$ 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

 $00:40:15.390 \rightarrow 00:40:18.597$ that approach and at least have some benefit?

NOTE Confidence: 0.836275078888889

 $00:40:18.600 \longrightarrow 00:40:19.960$ So they published this paper,

NOTE Confidence: 0.836275078888889

 $00:40:19.960 \rightarrow 00:40:21.910$ 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

 $00:40:24.400 \longrightarrow 00:40:25.720$ 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

 $00{:}40{:}26.296 \dashrightarrow 00{:}40{:}28.312$ it's a it's a bit difficult slide

NOTE Confidence: 0.836275078888889

 $00{:}40{:}28{.}320 \dashrightarrow 00{:}40{:}30{.}770$ but the point is that there was

00:40:30.770 --> 00:40:33.200 no really like mouse suppression

NOTE Confidence: 0.836275078888889

 $00{:}40{:}33.200 \dashrightarrow 00{:}40{:}35.594$ 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

 $00:40:38.502 \rightarrow 00:40:42.079$ was fairly similar to the VLA study.

NOTE Confidence: 0.836275078888889

 $00{:}40{:}42.080 \dashrightarrow 00{:}40{:}44.096$ And then when we looked at the small

NOTE Confidence: 0.836275078888889

 $00:40:44.096 \rightarrow 00:40:45.794$ 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

 $00:40:47.440 \longrightarrow 00:40:48.958$ 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

 $00{:}40{:}52{.}400 \dashrightarrow 00{:}40{:}53{.}750$ became transfusion independent

NOTE Confidence: 0.836275078888889

 $00:40:53.750 \longrightarrow 00:40:56.000$ and they did very well.

NOTE Confidence: 0.836275078888889

 $00:40:56.000 \rightarrow 00:40:58.560$ They relapsed like a clock at 10-11 months.

NOTE Confidence: 0.836275078888889

 $00{:}40{:}58{.}560 \dashrightarrow 00{:}41{:}00{.}300$ So it's not curative approach but

NOTE Confidence: 0.836275078888889

 $00:41:00.300 \rightarrow 00:41:02.697$ at least you know we can extend the

NOTE Confidence: 0.836275078888889

 $00:41:02.697 \rightarrow 00:41:04.467$ survival again and reality is five
$00:41:04.530 \rightarrow 00:41:06.370$ months survival. Many other studies.

NOTE Confidence: 0.836275078888889

 $00:41:06.370 \longrightarrow 00:41:07.920$ 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

 $00:41:10.080 \longrightarrow 00:41:12.160$ so with all the Kevas,

NOTE Confidence: 0.836275078888889

 $00:41:12.160 \longrightarrow 00:41:13.585$ but we're quite excited about

NOTE Confidence: 0.836275078888889

 $00{:}41{:}13.585 \dashrightarrow 00{:}41{:}15.496$ that and we are thinking of what

NOTE Confidence: 0.836275078888889

 $00:41:15.496 \longrightarrow 00:41:17.224$ 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

 $00{:}41{:}18.760 \dashrightarrow 00{:}41{:}22.840$ you know using this metronomic dosing.

NOTE Confidence: 0.836275078888889

 $00:41:22.840 \rightarrow 00:41:25.280$ So one thing is like in the lab we are

NOTE Confidence: 0.836275078888889

 $00:41:25.348 \rightarrow 00:41:27.916$ trying to use some of the BAX activated.

NOTE Confidence: 0.836275078888889

 $00:41:27.920 \longrightarrow 00:41:29.614$ So I told you several times the

NOTE Confidence: 0.836275078888889

 $00{:}41{:}29.614 \dashrightarrow 00{:}41{:}31.191$ BAX is really like critical and

NOTE Confidence: 0.836275078888889

 $00{:}41{:}31{.}191 \dashrightarrow 00{:}41{:}33{.}039$ the BAX is not working with PP,

NOTE Confidence: 0.729887153571429

 $00{:}41{:}33.040 \dashrightarrow 00{:}41{:}36.876$ she's lost. So we have a collaboration

 $00:41:36.876 \rightarrow 00:41:40.135$ with again Everest and also Jerry

NOTE Confidence: 0.729887153571429

 $00{:}41{:}40{.}135 \dashrightarrow 00{:}41{:}42{.}912$ Chipok would develop the direct

NOTE Confidence: 0.729887153571429

 $00{:}41{:}42.912 \dashrightarrow 00{:}41{:}45.752$ Bax activators or Bax modulators.

NOTE Confidence: 0.729887153571429

 $00:41:45.760 \longrightarrow 00:41:47.320$ So we are thinking maybe

NOTE Confidence: 0.729887153571429

 $00:41:47.320 \longrightarrow 00:41:48.880$ if we use those compounds,

NOTE Confidence: 0.729887153571429

 $00{:}41{:}48.880 \dashrightarrow 00{:}41{:}50.815$ 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

 $00:41:53.160 \longrightarrow 00:41:56.400$ 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

 $00{:}41{:}57{.}560 \dashrightarrow 00{:}42{:}00{.}006$ so this was PVC new dated AML and

NOTE Confidence: 0.729887153571429

 $00{:}42{:}00{.}006 \dashrightarrow 00{:}42{:}01{.}920$ now going back to the chemotherapy.

NOTE Confidence: 0.729887153571429

 $00:42:01.920 \longrightarrow 00:42:03.516$ So as I showed you before,

NOTE Confidence: 0.729887153571429

 $00:42:03.520 \longrightarrow 00:42:05.638$ there's like very good rationale to

NOTE Confidence: 0.729887153571429

 $00{:}42{:}05{.}638 \dashrightarrow 00{:}42{:}07{.}444$ combine the Netherlands with the

NOTE Confidence: 0.729887153571429

 $00{:}42{:}07{.}444 \dashrightarrow 00{:}42{:}09{.}205$ chemotherapy and AML and there are

NOTE Confidence: 0.729887153571429

 $00:42:09.205 \longrightarrow 00:42:10.990$ a lot of trials which have been

 $00:42:11.052 \rightarrow 00:42:13.336$ already reported and now we're getting

NOTE Confidence: 0.729887153571429

 $00:42:13.336 \longrightarrow 00:42:15.400$ the response rate of about 90%.

NOTE Confidence: 0.729887153571429

 $00:42:15.400 \rightarrow 00:42:19.000$ So this is like like was unheard of before,

NOTE Confidence: 0.729887153571429

 $00:42:19.000 \rightarrow 00:42:21.232$ but when you add the Netherlands

NOTE Confidence: 0.729887153571429

 $00:42:21.232 \rightarrow 00:42:23.272$ to chemotherapy you really get

NOTE Confidence: 0.729887153571429

 $00:42:23.272 \longrightarrow 00:42:24.240$ tremendous synergy.

NOTE Confidence: 0.729887153571429

 $00:42:24.240 \longrightarrow 00:42:26.445$ So in our centre we have this

NOTE Confidence: 0.729887153571429

 $00:42:26.445 \longrightarrow 00:42:28.422$ also IST that is run by Doctor

NOTE Confidence: 0.729887153571429

 $00{:}42{:}28.422 \dashrightarrow 00{:}42{:}30.281$ Manzaris where we use the standard

NOTE Confidence: 0.729887153571429

 $00:42:30.281 \rightarrow 00:42:32.357$ Sam plus sheep plus another class,

NOTE Confidence: 0.729887153571429

 $00{:}42{:}32{.}360 \dashrightarrow 00{:}42{:}34{.}520$ different durations and so forth.

NOTE Confidence: 0.729887153571429

 $00:42:34.520 \longrightarrow 00:42:35.840$ The trial is still ongoing,

NOTE Confidence: 0.729887153571429

 $00{:}42{:}35{.}840 \dashrightarrow 00{:}42{:}38{.}080$ 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

 $00:42:40.480 \rightarrow 00:42:42.958$ So we don't really know like survival,

 $00:42:42.960 \rightarrow 00:42:45.060$ 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

 $00:42:46.688 \longrightarrow 00:42:49.040$ they relapse and they don't do well.

NOTE Confidence: 0.729887153571429

 $00:42:49.040 \rightarrow 00:42:51.266$ So we stopped using this for even

NOTE Confidence: 0.729887153571429

 $00{:}42{:}51{.}266 \dashrightarrow 00{:}42{:}53{.}720$ younger PVC MUDA patients because all

NOTE Confidence: 0.729887153571429

 $00:42:53.720 \rightarrow 00:42:55.720$ patients, 5 patients were treated with,

NOTE Confidence: 0.729887153571429

 $00:42:55.720 \longrightarrow 00:42:57.832$ they're all relapsed and they died

NOTE Confidence: 0.729887153571429

 $00:42:57.832 \longrightarrow 00:43:00.086$ from despite the fact that some

NOTE Confidence: 0.729887153571429

 $00:43:00.086 \longrightarrow 00:43:01.638$ 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

 $00{:}43{:}04{.}160 \dashrightarrow 00{:}43{:}06{.}617$ So we're looking at the stem cell

NOTE Confidence: 0.729887153571429

 $00{:}43{:}06{.}617 \dashrightarrow 00{:}43{:}08{.}424$ extinction with the therapy and

NOTE Confidence: 0.729887153571429

 $00{:}43{:}08{.}424 \dashrightarrow 00{:}43{:}10{.}797$ 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

 $00:43:12.920 \longrightarrow 00:43:14.480$ I'll go back to BCL XL,

NOTE Confidence: 0.729887153571429

 $00:43:14.480 \longrightarrow 00:43:17.492$ which may be of interest more

- NOTE Confidence: 0.729887153571429
- $00:43:17.492 \longrightarrow 00:43:19.356$ 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
- $00:43:25.480 \longrightarrow 00:43:27.796$ but it's expressed in solar tumors,
- NOTE Confidence: 0.729887153571429
- $00{:}43{:}27.800 \dashrightarrow 00{:}43{:}30.446$ it is expressed in the TELL subsets.
- NOTE Confidence: 0.729887153571429
- $00{:}43{:}30{.}446 \dashrightarrow 00{:}43{:}32{.}567$ 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
- $00{:}43{:}33{.}880 \dashrightarrow 00{:}43{:}36{.}680$ a number of years ago that showed
- NOTE Confidence: 0.729887153571429
- $00{:}43{:}36{.}680 \dashrightarrow 00{:}43{:}38{.}720$ that the typical TELL actually
- NOTE Confidence: 0.729887153571429
- $00{:}43{:}38.720 \dashrightarrow 00{:}43{:}41.885$ 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
- $00:43:43.600 \rightarrow 00:43:46.276$ you actually get very good responses.
- NOTE Confidence: 0.729887153571429
- $00:43:46.280 \rightarrow 00:43:47.516$ There's a subset that is B,
- NOTE Confidence: 0.729887153571429
- $00{:}43{:}47{.}520 \dashrightarrow 00{:}43{:}48{.}432$ so two dependent,
- NOTE Confidence: 0.729887153571429
- $00{:}43{:}48{.}432 \dashrightarrow 00{:}43{:}50{.}960$ but I'm not going to go into that.
- NOTE Confidence: 0.729887153571429

 $00:43:50.960 \longrightarrow 00:43:51.279$ Now.

NOTE Confidence: 0.729887153571429

 $00:43:51.279 \longrightarrow 00:43:53.193$ I already told you that the

NOTE Confidence: 0.729887153571429

 $00{:}43{:}53{.}193 \dashrightarrow 00{:}43{:}56{.}045$ liability of B cell X inhibitors is

NOTE Confidence: 0.729887153571429

 $00:43:56.045 \rightarrow 00:43:57.410$ thrombocytopenia because platelets

NOTE Confidence: 0.729887153571429

 $00{:}43{:}57{.}410 \dashrightarrow 00{:}44{:}00{.}279$ depend on B cell XL for survival.

NOTE Confidence: 0.729887153571429

 $00:44:00.280 \longrightarrow 00:44:03.480$ So you get on target toxicity and of NOTE Confidence: 0.729887153571429

 $00:44:03.480 \longrightarrow 00:44:06.120$ course it's challenging to those.

NOTE Confidence: 0.729887153571429

 $00:44:06.120 \longrightarrow 00:44:08.456$ So and you know this is just a

NOTE Confidence: 0.729887153571429

 $00:44:08.456 \rightarrow 00:44:10.079$ couture published review recently.

NOTE Confidence: 0.729887153571429

 $00:44:10.080 \longrightarrow 00:44:11.574$ So Nevito clocks right the drug

NOTE Confidence: 0.729887153571429

 $00:44:11.574 \longrightarrow 00:44:13.080$ that is still not approved,

NOTE Confidence: 0.729887153571429

 $00{:}44{:}13.080 \dashrightarrow 00{:}44{:}15.866$ it was just as the venetoclax so

NOTE Confidence: 0.729887153571429

 $00{:}44{:}15.866 \dashrightarrow 00{:}44{:}18.184$ inhibits the complexes inducing bags

NOTE Confidence: 0.729887153571429

 $00:44:18.184 \longrightarrow 00:44:20.794$ back but it causes thrombocytopenia

NOTE Confidence: 0.729887153571429

 $00{:}44{:}20.794 \dashrightarrow 00{:}44{:}22.360$ killing the platelets.

NOTE Confidence: 0.729887153571429

 $00:44:22.360 \longrightarrow 00:44:25.181$ So the way around that at least

- NOTE Confidence: 0.729887153571429
- $00:44:25.181 \rightarrow 00:44:28.217$ 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
- $00{:}44{:}31{.}360 \dashrightarrow 00{:}44{:}33.652$ so we have been collaborating with
- NOTE Confidence: 0.729887153571429
- $00{:}44{:}33.652 \dashrightarrow 00{:}44{:}35.945$ the team from Dalhoung Zhou who
- NOTE Confidence: 0.729887153571429
- $00{:}44{:}35{.}945 \dashrightarrow 00{:}44{:}37{.}685$ was before University of Florida
- NOTE Confidence: 0.729887153571429
- $00{:}44{:}37.685 \dashrightarrow 00{:}44{:}38.729$ and now he
- NOTE Confidence: 0.8156123268
- $00:44:38.804 \longrightarrow 00:44:40.479$ moved to the San Antonio.
- NOTE Confidence: 0.8156123268
- $00{:}44{:}40{.}480 \dashrightarrow 00{:}44{:}44{.}410$ So he developed this Protac BCL
- NOTE Confidence: 0.8156123268
- $00:44:44.410 \longrightarrow 00:44:46.575$ XL degrader where the legend
- NOTE Confidence: 0.8156123268
- $00:44:46.575 \rightarrow 00:44:47.715$ is essentially native o'clock.
- NOTE Confidence: 0.8156123268
- $00:44:47.720 \longrightarrow 00:44:51.560$ 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
- $00:44:56.053 \rightarrow 00:44:57.617$ 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

 $00{:}44{:}58{.}920 \dashrightarrow 00{:}45{:}01{.}290$ So it's has a pharmacological

NOTE Confidence: 0.8156123268

 $00:45:01.290 \longrightarrow 00:45:02.238$ properties issues.

NOTE Confidence: 0.8156123268

 $00{:}45{:}02{.}240 \dashrightarrow 00{:}45{:}04{.}680$ But The thing is that this E3 ligase

NOTE Confidence: 0.8156123268

 $00{:}45{:}04.680 \dashrightarrow 00{:}45{:}06.998$ is not expressed in platelets.

NOTE Confidence: 0.8156123268

 $00{:}45{:}07.000 \dashrightarrow 00{:}45{:}08.720$ So you're not getting degradation

NOTE Confidence: 0.8156123268

 $00{:}45{:}08.720 \dashrightarrow 00{:}45{:}11.200$ of B cell XL and platelets.

NOTE Confidence: 0.8156123268

 $00:45:11.200 \longrightarrow 00:45:13.084$ And therefore you can see here

NOTE Confidence: 0.8156123268

 $00{:}45{:}13.084 \dashrightarrow 00{:}45{:}15.253$ there's no B cell cell degradation

NOTE Confidence: 0.8156123268

 $00{:}45{:}15{.}253 \dashrightarrow 00{:}45{:}17{.}358$ in platelets with this drug.

NOTE Confidence: 0.8156123268

 $00{:}45{:}17.360 \dashrightarrow 00{:}45{:}19.720$ But it's like a TLO tumor cell line,

NOTE Confidence: 0.8156123268

 $00:45:19.720 \longrightarrow 00:45:21.160$ it's very nice degradation.

NOTE Confidence: 0.8156123268

 $00:45:21.160 \longrightarrow 00:45:23.879$ So this is just the schematics of that.

NOTE Confidence: 0.8156123268

 $00:45:23.880 \longrightarrow 00:45:26.280$ And again as a result,

NOTE Confidence: 0.8156123268

 $00:45:26.280 \longrightarrow 00:45:28.614$ you can kill the tumor cells

NOTE Confidence: 0.8156123268

 $00:45:28.614 \rightarrow 00:45:31.080$ but you don't kill platelets.

 $00:45:31.080 \rightarrow 00:45:33.664$ So this drug right now is in clinical

NOTE Confidence: 0.8156123268

 $00:45:33.664 \rightarrow 00:45:36.731$ trial in solar tumors and it's actually

NOTE Confidence: 0.8156123268

 $00:45:36.731 \rightarrow 00:45:39.756$ completed the phase one portion of it.

NOTE Confidence: 0.8156123268

 $00:45:39.760 \rightarrow 00:45:42.280$ 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

 $00{:}45{:}44{.}268 \dashrightarrow 00{:}45{:}46{.}383$ the clocks I think because the drug

NOTE Confidence: 0.8156123268

 $00{:}45{:}46{.}383 \dashrightarrow 00{:}45{:}48{.}544$ still binds to some extent and still

NOTE Confidence: 0.8156123268

 $00:45:48.544 \rightarrow 00:45:50.912$ inhibits a little bit of BCL XL function,

NOTE Confidence: 0.8156123268

 $00{:}45{:}50{.}920 \dashrightarrow 00{:}45{:}52{.}900$ but it was reversible and

NOTE Confidence: 0.8156123268

 $00:45:52.900 \longrightarrow 00:45:54.880$ no other toxicity was seen.

NOTE Confidence: 0.8156123268

 $00{:}45{:}54{.}880 \dashrightarrow 00{:}45{:}57{.}208$ 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

 $00{:}46{:}00{.}380 \dashrightarrow 00{:}46{:}03{.}760$ also moved towards the dual BCL 2XL

NOTE Confidence: 0.8156123268

 $00{:}46{:}03.760 \dashrightarrow 00{:}46{:}06.480$ product which is not yet in the clinic

NOTE Confidence: 0.8156123268

 $00{:}46{:}06{.}480 \dashrightarrow 00{:}46{:}09{.}518$ and we published this work in AML

 $00:46:09.520 \longrightarrow 00:46:11.235$ 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

 $00:46:12.652 \rightarrow 00:46:15.260$ it was actually quite effective in all

NOTE Confidence: 0.8156123268

 $00:46:15.260 \rightarrow 00:46:17.365$ primary AML samples including those

NOTE Confidence: 0.8156123268

 $00{:}46{:}17.365 \dashrightarrow 00{:}46{:}19.999$ that were resistant to venado clock.

NOTE Confidence: 0.8156123268

 $00:46:20.000 \longrightarrow 00:46:22.653$ So there's you know there's

NOTE Confidence: 0.8156123268

 $00{:}46{:}22.653 \dashrightarrow 00{:}46{:}24.830$ degradation of BCL XL as you would

NOTE Confidence: 0.8156123268

 $00:46:24.893 \rightarrow 00:46:26.938$ 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

 $00:46:28.924 \longrightarrow 00:46:31.120$ but it was seen the cell lines.

NOTE Confidence: 0.8156123268

 $00:46:31.120 \longrightarrow 00:46:34.270$ 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

 $00{:}46{:}38{.}080 \dashrightarrow 00{:}46{:}40{.}232$ And the other aspect of it that is

NOTE Confidence: 0.8156123268

 $00:46:40.232 \longrightarrow 00:46:42.455$ very kind of popular and the solid

NOTE Confidence: 0.8156123268

 $00:46:42.455 \longrightarrow 00:46:44.890$ tumor literature is that the role of

NOTE Confidence: 0.8156123268

 $00{:}46{:}44.890 \dashrightarrow 00{:}46{:}47.320$ B cell excel in senescence cells.

 $00:46:47.320 \longrightarrow 00:46:49.000$ So what we know the senescence cells,

NOTE Confidence: 0.8156123268

 $00:46:49.000 \rightarrow 00:46:51.345$ the cells that survive chemotherapy

NOTE Confidence: 0.8156123268

 $00:46:51.345 \longrightarrow 00:46:55.016$ and but they can kind of revert back

NOTE Confidence: 0.8156123268

 $00{:}46{:}55{.}016 \dashrightarrow 00{:}46{:}57{.}420$ and become chemo resistant and the

NOTE Confidence: 0.8156123268

 $00:46:57.420 \longrightarrow 00:46:59.790$ metastatic cells in the setting of

NOTE Confidence: 0.8156123268

 $00{:}46{:}59{.}859 \dashrightarrow 00{:}47{:}02{.}715$ breast cancer or lung cancer and so forth,

NOTE Confidence: 0.8156123268

 $00:47:02.720 \rightarrow 00:47:05.840$ It's much less known in senescence in EMO.

NOTE Confidence: 0.8156123268

 $00{:}47{:}05{.}840 \dashrightarrow 00{:}47{:}08{.}344$ But there was a paper by Ari Melnick's

NOTE Confidence: 0.8156123268

 $00{:}47{:}08{.}344 \dashrightarrow 00{:}47{:}10{.}521$ group that showed that chemotherapy

NOTE Confidence: 0.8156123268

 $00{:}47{:}10.521 \dashrightarrow 00{:}47{:}12.996$ 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

 $00{:}47{:}18.386 \dashrightarrow 00{:}47{:}21.090$ within the viable cells a fraction

NOTE Confidence: 0.8156123268

 $00{:}47{:}21.090 \dashrightarrow 00{:}47{:}23.755$ of them are actually senescence and

NOTE Confidence: 0.8156123268

 $00{:}47{:}23.755 \dashrightarrow 00{:}47{:}25.130$ the senescence cells they depend

 $00:47:25.130 \longrightarrow 00:47:26.999$ on BCL X cell for survival.

NOTE Confidence: 0.8156123268

 $00{:}47{:}27.000 \dashrightarrow 00{:}47{:}29.360$ So when we sorted out the senescence cells,

NOTE Confidence: 0.8156123268

 $00{:}47{:}29{.}360 \dashrightarrow 00{:}47{:}31{.}488$ we showed that BCL XL was up regulated

NOTE Confidence: 0.8156123268

 $00{:}47{:}31{.}488 \dashrightarrow 00{:}47{:}33{.}219$ which was which was consistent

NOTE Confidence: 0.8156123268

 $00{:}47{:}33{.}219 \dashrightarrow 00{:}47{:}34{.}356$ with the literature.

NOTE Confidence: 0.8156123268

 $00{:}47{:}34{.}360 \dashrightarrow 00{:}47{:}36{.}216$ And then when we looked at the markers

NOTE Confidence: 0.8156123268

 $00:47:36.216 \longrightarrow 00:47:37.764$ of senescence, this is cell line.

NOTE Confidence: 0.8156123268

 $00:47:37.764 \longrightarrow 00:47:39.390$ So chemo is inducing all the

NOTE Confidence: 0.8156123268

 $00:47:39.450 \longrightarrow 00:47:40.720$ senescence phenotypes.

NOTE Confidence: 0.8156123268

 $00{:}47{:}40.720 \dashrightarrow 00{:}47{:}42.722$ But when we use this BCL XL

NOTE Confidence: 0.8156123268

 $00{:}47{:}42.722 \dashrightarrow 00{:}47{:}43.580$ degrade that we

NOTE Confidence: 0.804974427894737

00:47:43.653 --> 00:47:45.013 can reverse that and

NOTE Confidence: 0.804974427894737

 $00:47:45.013 \rightarrow 00:47:46.713$ they showed here as well.

NOTE Confidence: 0.804974427894737

 $00:47:46.720 \longrightarrow 00:47:49.219$ So we think that there's a potential

NOTE Confidence: 0.804974427894737

 $00{:}47{:}49{.}219 \dashrightarrow 00{:}47{:}52{.}214$ efficacy of BCL XL inhibition and this

NOTE Confidence: 0.804974427894737

 $00:47:52.214 \rightarrow 00:47:54.298$ dormant senescence cells plus with

 $00{:}47{:}54{.}298 \dashrightarrow 00{:}47{:}56{.}741$ it's really hard to like identify them

NOTE Confidence: 0.804974427894737

 $00{:}47{:}56{.}741 \dashrightarrow 00{:}47{:}59{.}167$ and patients like you know the the

NOTE Confidence: 0.804974427894737

 $00{:}47{:}59{.}167 \dashrightarrow 00{:}48{:}01{.}719$ essays are not very well established.

NOTE Confidence: 0.804974427894737

 $00{:}48{:}01{.}720 \dashrightarrow 00{:}48{:}03{.}872$ But I think there's a lot of interest

NOTE Confidence: 0.804974427894737

 $00{:}48{:}03.872 \dashrightarrow 00{:}48{:}05.432$ using BCXL inhibitors as synolytic

NOTE Confidence: 0.804974427894737

 $00:48:05.432 \longrightarrow 00:48:07.672$ 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

 $00{:}48{:}09{.}640 \dashrightarrow 00{:}48{:}11{.}376$ leukemias and so forth.

NOTE Confidence: 0.804974427894737

 $00:48:11.376 \longrightarrow 00:48:12.678$ And the finally,

NOTE Confidence: 0.804974427894737

 $00{:}48{:}12.680 \dashrightarrow 00{:}48{:}14.983$ like I told you that there's some

NOTE Confidence: 0.804974427894737

 $00{:}48{:}14.983 \dashrightarrow 00{:}48{:}17.180$ AML subsets that are BCL Excel

NOTE Confidence: 0.804974427894737

 $00{:}48{:}17.180 \dashrightarrow 00{:}48{:}18.640$ dependent and this is one of them.

NOTE Confidence: 0.804974427894737

 $00:48:18.640 \longrightarrow 00:48:20.656$ 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

 $00:48:22.000 \rightarrow 00:48:22.796$ Erythroid leukemia.

 $00:48:22.796 \longrightarrow 00:48:25.582$ And now Doctor Xu here has done

NOTE Confidence: 0.804974427894737

 $00{:}48{:}25{.}582 \dashrightarrow 00{:}48{:}27{.}557$ a lot of work on that,

NOTE Confidence: 0.804974427894737

 $00{:}48{:}27{.}560 \dashrightarrow 00{:}48{:}30{.}440$ but it's in the old classification

NOTE Confidence: 0.804974427894737

 $00{:}48{:}30{.}440 \dashrightarrow 00{:}48{:}34{.}208$ is the MLM 6 and it has all of this

NOTE Confidence: 0.804974427894737

 $00{:}48{:}34{.}208 \dashrightarrow 00{:}48{:}36{.}190$ 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

 $00{:}48{:}38{.}142 \dashrightarrow 00{:}48{:}40{.}238$ So I already told you that the NOW

NOTE Confidence: 0.804974427894737

 $00{:}48{:}40{.}238 \dashrightarrow 00{:}48{:}42{.}400$ class does not work for PPC mutant AML.

NOTE Confidence: 0.804974427894737

 $00:48:42.400 \longrightarrow 00:48:44.044$ And sure enough in all clinical

NOTE Confidence: 0.804974427894737

 $00{:}48{:}44.044 \dashrightarrow 00{:}48{:}45.831$ trials patients who were AEL patients

NOTE Confidence: 0.804974427894737

 $00{:}48{:}45{.}831 \dashrightarrow 00{:}48{:}47{.}436$ who were treated with Venetoclax,

NOTE Confidence: 0.804974427894737

 $00:48:47.440 \longrightarrow 00:48:49.092$ they progressed very quickly.

NOTE Confidence: 0.804974427894737

 $00:48:49.092 \longrightarrow 00:48:51.157$ So that's not a solution,

NOTE Confidence: 0.804974427894737

 $00:48:51.160 \longrightarrow 00:48:53.586$ but there was a,

NOTE Confidence: 0.804974427894737

 $00{:}48{:}53{.}586 \dashrightarrow 00{:}48{:}55{.}158$ we collaborated with the work with

NOTE Confidence: 0.804974427894737

 $00{:}48{:}55{.}158 \dashrightarrow 00{:}48{:}57{.}085$ a group at University of Helsinki

- NOTE Confidence: 0.804974427894737
- $00:48:57.085 \rightarrow 00:48:59.025$ and they they published this very
- NOTE Confidence: 0.804974427894737
- $00:48:59.025 \rightarrow 00:49:00.675$ nice paper last year and blood.
- NOTE Confidence: 0.804974427894737
- $00:49:00.680 \longrightarrow 00:49:03.184$ So they looked at the dependency
- NOTE Confidence: 0.804974427894737
- $00:49:03.184 \rightarrow 00:49:06.208$ and AEL using the Crispus screens
- NOTE Confidence: 0.804974427894737
- $00{:}49{:}06{.}208 \dashrightarrow 00{:}49{:}08{.}596$ 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
- $00:49:10.120 \longrightarrow 00:49:12.794$ This is a gene called B cell
- NOTE Confidence: 0.804974427894737
- $00:49:12.794 \longrightarrow 00:49:14.839 \ 12/1$ that controls B cell XL.
- NOTE Confidence: 0.804974427894737
- $00{:}49{:}14.840 \dashrightarrow 00{:}49{:}16.728$ And you can see that it also was
- NOTE Confidence: 0.804974427894737
- $00:49:16.728 \rightarrow 00:49:18.980$ true for the drug screen as well.
- NOTE Confidence: 0.804974427894737
- $00:49:18.980 \longrightarrow 00:49:21.714$ They show this and they confirm that
- NOTE Confidence: 0.804974427894737
- $00{:}49{:}21{.}714 \dashrightarrow 00{:}49{:}24{.}585$ and the cell lines and if you use a
- NOTE Confidence: 0.804974427894737
- $00{:}49{:}24.585 \dashrightarrow 00{:}49{:}26.440$ different like gene expression data sets,
- NOTE Confidence: 0.804974427894737
- $00{:}49{:}26{.}440 \dashrightarrow 00{:}49{:}28{.}358$ so again this is old M6 also
- NOTE Confidence: 0.804974427894737
- $00:49:28.358 \rightarrow 00:49:30.559$ M7 which is megacaric leukemia,
- NOTE Confidence: 0.804974427894737

 $00:49:30.560 \longrightarrow 00:49:32.800$ they have high expression here,

NOTE Confidence: 0.804974427894737

 $00{:}49{:}32{.}800 \dashrightarrow 00{:}49{:}34{.}320$ 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

 $00:49:36.200 \rightarrow 00:49:38.230$ So they have a high expression of

NOTE Confidence: 0.804974427894737

 $00{:}49{:}38{.}230 \dashrightarrow 00{:}49{:}40{.}799$ BCL XL on a transcriptional level.

NOTE Confidence: 0.804974427894737

 $00{:}49{:}40.800 \dashrightarrow 00{:}49{:}42.540$ So The thing is because the

NOTE Confidence: 0.804974427894737

 $00:49:42.540 \longrightarrow 00:49:44.107$ 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

 $00:49:45.491 \rightarrow 00:49:47.840$ for survival and this is preserved,

NOTE Confidence: 0.804974427894737

 $00{:}49{:}47.840 \dashrightarrow 00{:}49{:}49.500$ they also showed some efficacy

NOTE Confidence: 0.804974427894737

 $00{:}49{:}49{.}500 \dashrightarrow 00{:}49{:}51{.}160$ in the in vivo models.

NOTE Confidence: 0.804974427894737

 $00:49:51.160 \longrightarrow 00:49:53.316$ So we are interested in using the

NOTE Confidence: 0.804974427894737

 $00:49:53.316 \longrightarrow 00:49:55.052$ product for this indication and

NOTE Confidence: 0.804974427894737

 $00{:}49{:}55{.}052 \dashrightarrow 00{:}49{:}57{.}302$ within mechanistically it makes a lot

NOTE Confidence: 0.804974427894737

 $00{:}49{:}57{.}302 \dashrightarrow 00{:}49{:}59{.}997$ of sense because again in Aristo it

NOTE Confidence: 0.804974427894737

 $00{:}49{:}59{.}997 \dashrightarrow 00{:}50{:}01{.}872$ says the main transcription factor

 $00{:}50{:}01.880 \dashrightarrow 00{:}50{:}04.205$ that drives kind of development

NOTE Confidence: 0.804974427894737

 $00:50:04.205 \longrightarrow 00:50:06.692$ is gutter one and we show that

NOTE Confidence: 0.804974427894737

 $00{:}50{:}06.692 \dashrightarrow 00{:}50{:}08.330$ there is a very direct correlation

NOTE Confidence: 0.804974427894737

 $00:50:08.385 \rightarrow 00:50:10.760$ between B SO2L1 and gutter one.

NOTE Confidence: 0.804974427894737

 $00:50:10.760 \rightarrow 00:50:13.357$ This is activity from the gene expression

NOTE Confidence: 0.804974427894737

 $00{:}50{:}13.357 \dashrightarrow 00{:}50{:}15.800$ 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

 $00:50:18.120 \longrightarrow 00:50:19.835$ so there's no correlation with BCO 2.

NOTE Confidence: 0.804974427894737

 $00:50:19.840 \longrightarrow 00:50:23.176$ So really in Ali think there's

NOTE Confidence: 0.804974427894737

 $00:50:23.176 \longrightarrow 00:50:24.844$ transcriptional up regulation

NOTE Confidence: 0.804974427894737

00:50:24.844 --> 00:50:27.317 and dependency on BCL XL.

NOTE Confidence: 0.804974427894737

 $00:50:27.320 \longrightarrow 00:50:29.840$ Based on some of the prior work published,

NOTE Confidence: 0.804974427894737

 $00{:}50{:}29{.}840 \dashrightarrow 00{:}50{:}31{.}996$ we know that this got the one

NOTE Confidence: 0.804974427894737

 $00{:}50{:}31.996 \dashrightarrow 00{:}50{:}34.045$ directly binds the BCO 2L1 locals.

NOTE Confidence: 0.804974427894737

 $00{:}50{:}34.045 \dashrightarrow 00{:}50{:}36.670$ And we have now also data in

 $00:50:36.759 \rightarrow 00:50:39.269$ 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

 $00:50:41.280 \rightarrow 00:50:43.720$ and they're using this degrader.

NOTE Confidence: 0.755040734

 $00:50:43.720 \dashrightarrow 00:50:45.834$ So this is original BCL XL degrader.

NOTE Confidence: 0.755040734

 $00:50:45.840 \longrightarrow 00:50:48.000$ This is like a next generation.

NOTE Confidence: 0.755040734

 $00{:}50{:}48.000 \dashrightarrow 00{:}50{:}50{.}648$ We showed us the cell lines that are NOTE Confidence: 0.755040734

 $00{:}50{:}50{.}648 \dashrightarrow 00{:}50{:}52{.}307$ 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

 $00{:}50{:}54{.}640 \dashrightarrow 00{:}50{:}57{.}520$ killed by this B cell cell degrader.

NOTE Confidence: 0.755040734

 $00{:}50{:}57{.}520 \dashrightarrow 00{:}50{:}59{.}963$ We also tested this in fuel primary

NOTE Confidence: 0.755040734

 $00{:}50{:}59{.}963 \dashrightarrow 00{:}51{:}02{.}902$ samples that you know failed all kind

NOTE Confidence: 0.755040734

 $00:51:02.902 \rightarrow 00:51:05.096$ 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

 $00{:}51{:}07{.}728 \dashrightarrow 00{:}51{:}10{.}078$ here and very nice response.

NOTE Confidence: 0.755040734

 $00:51:10.080 \rightarrow 00:51:12.360$ So again, this is preclinical work.

NOTE Confidence: 0.755040734

 $00:51:12.360 \rightarrow 00:51:15.204$ We're trying to get the drug if we get

- NOTE Confidence: 0.755040734
- $00:51:15.204 \rightarrow 00:51:17.798$ funding for the trials is still ongoing,
- NOTE Confidence: 0.755040734
- $00:51:17.800 \longrightarrow 00:51:20.680$ 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
- $00:51:23.861 \rightarrow 00:51:26.514$ just approved the nabito clocks
- NOTE Confidence: 0.755040734
- $00{:}51{:}26{.}514 \dashrightarrow 00{:}51{:}30{.}340$ for the subset of AL between MSK
- NOTE Confidence: 0.755040734
- $00{:}51{:}30{.}340 \dashrightarrow 00{:}51{:}32{.}560$ and the MD Anderson Cancer Center.
- NOTE Confidence: 0.755040734
- $00:51:32.560 \longrightarrow 00:51:34.464$ So there will be a small pilot
- NOTE Confidence: 0.755040734
- $00{:}51{:}34{.}464 \dashrightarrow 00{:}51{:}36{.}211$ trial at least testing the proof
- NOTE Confidence: 0.755040734
- $00{:}51{:}36{.}211 \dashrightarrow 00{:}51{:}38{.}646$ of principle that B cell XL is a
- NOTE Confidence: 0.755040734
- $00{:}51{:}38.646 \dashrightarrow 00{:}51{:}40.356$ driver in this horrible disease.
- NOTE Confidence: 0.755040734
- $00{:}51{:}40{.}360 \dashrightarrow 00{:}51{:}42{.}960$ 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
- $00{:}51{:}44{.}892 \dashrightarrow 00{:}51{:}46{.}640$ 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

 $00{:}51{:}51{.}720 \dashrightarrow 00{:}51{:}53{.}220$ so two dependent disease,

NOTE Confidence: 0.755040734

 $00{:}51{:}53{.}220 \dashrightarrow 00{:}51{:}55{.}778$ but then there's some subsets that are

NOTE Confidence: 0.755040734

 $00:51:55.778 \rightarrow 00:51:57.920$ 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

 $00{:}52{:}00{.}176 \dashrightarrow 00{:}52{:}02{.}278$ it kind of lowers the threshold.

NOTE Confidence: 0.755040734

 $00{:}52{:}02{.}280 \dashrightarrow 00{:}52{:}05{.}296$ So you can see the synergy with pretty

NOTE Confidence: 0.755040734

 $00{:}52{:}05{.}296 \dashrightarrow 00{:}52{:}07{.}871$ 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

 $00{:}52{:}11.000 \dashrightarrow 00{:}52{:}13.200$ But but this was really like you know

NOTE Confidence: 0.755040734

 $00{:}52{:}13.200 \dashrightarrow 00{:}52{:}15.808$ 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

 $00:52:17.800 \rightarrow 00:52:19.804$ with the hypermethylene agents,

NOTE Confidence: 0.755040734

 $00:52:19.804 \longrightarrow 00:52:22.309$ with thy ristine kinase inhibitors and

NOTE Confidence: 0.755040734

 $00:52:22.309 \rightarrow 00:52:25.434$ you know the fuel has really like

NOTE Confidence: 0.755040734

 $00{:}52{:}25{.}434 \dashrightarrow 00{:}52{:}28{.}037$ exploded using this drug as a sensitizer.

 $00:52:28.040 \rightarrow 00:52:30.600$ 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 the rapies 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

 $00:52:43.520 \rightarrow 00:52:45.585$ And you know I showed you what

NOTE Confidence: 0.755040734

 $00:52:45.585 \longrightarrow 00:52:47.440$ we're trying to do about that.

NOTE Confidence: 0.755040734

 $00{:}52{:}47{.}440 \dashrightarrow 00{:}52{:}50{.}184$ But then the subsets that are B cell

NOTE Confidence: 0.755040734

 $00{:}52{:}50{.}184 \dashrightarrow 00{:}52{:}52{.}212$ excel dependent and we are quite

NOTE Confidence: 0.755040734

 $00{:}52{:}52{.}212 \dashrightarrow 00{:}52{:}54{.}609$ excited about using this B cell excel

NOTE Confidence: 0.755040734

 $00{:}52{:}54{.}609 \dashrightarrow 00{:}52{:}57{.}159$ inhibitors or products in this setting.

NOTE Confidence: 0.755040734

 $00{:}52{:}57{.}160 \dashrightarrow 00{:}52{:}58{.}220$ 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

 $00{:}52{:}59{.}280 \dashrightarrow 00{:}53{:}02{.}235$ many Co workers collaborators from

 $00{:}53{:}02{.}235 \dashrightarrow 00{:}53{:}06{.}520$ both my MD Anderson lab that has now

NOTE Confidence: 0.755040734

 $00{:}53{:}06{.}520 \dashrightarrow 00{:}53{:}08{.}280$ 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

 $00:53:17.441 \longrightarrow 00:53:19.623$ of triplet combinations and many

NOTE Confidence: 0.755040734

 $00:53:19.623 \rightarrow 00:53:21.918$ 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

 $00:53:26.785 \dashrightarrow 00:53:29.438$ HMA event trial despite the fact that NOTE Confidence: 0.755040734

 $00:53:29.515 \rightarrow 00:53:31.999$ single agent was not as efficacious.

NOTE Confidence: 0.755040734

 $00{:}53{:}32{.}000 \dashrightarrow 00{:}53{:}34{.}640$ And a lot of collaborators from

NOTE Confidence: 0.755040734

 $00:53:34.640 \longrightarrow 00:53:35.520$ Montefiore Einstein,

NOTE Confidence: 0.755040734

 $00:53:35.520 \rightarrow 00:53:37.200$ we're developing this new programs

NOTE Confidence: 0.755040734

 $00:53:37.200 \longrightarrow 00:53:39.704$ that I showed to you and many

- NOTE Confidence: 0.755040734
- $00:53:39.704 \rightarrow 00:53:41.352$ collaborations with the companies
- NOTE Confidence: 0.755040734
- $00{:}53{:}41{.}352 \dashrightarrow 00{:}53{:}43{.}000$ but also a cademic 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
- $00:53:45.400 \longrightarrow 00:53:46.640$ who has been really like,
- NOTE Confidence: 0.956922252
- $00:53:46.640 \longrightarrow 00:53:48.765$ you know, developed this first
- NOTE Confidence: 0.956922252
- $00:53:48.765 \longrightarrow 00:53:51.630$ approach with me in the lab.
- NOTE Confidence: 0.956922252
- $00{:}53{:}51{.}630 \dashrightarrow 00{:}53{:}54{.}225$ And you know, we think that because of
- NOTE Confidence: 0.956922252
- $00{:}53{:}54{.}225 \dashrightarrow 00{:}53{:}56{.}933$ that work and algos really went into AML
- NOTE Confidence: 0.956922252
- $00{:}53{:}56{.}933 \dashrightarrow 00{:}53{:}59{.}077$ and we have collaboration with Andrew
- NOTE Confidence: 0.956922252
- $00:53:59.077 \rightarrow 00:54:01.376$ Way at Melbourne and with the Saint
- NOTE Confidence: 0.956922252
- $00{:}54{:}01{.}376 \dashrightarrow 00{:}54{:}04{.}000$ Jude team and Dao Hangzhou for the product.
- NOTE Confidence: 0.956922252
- $00{:}54{:}04{.}000 \dashrightarrow 00{:}54{:}04{.}960$ 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
- $00:54:06.380 \longrightarrow 00:54:07.560$ the end of the hour,
- NOTE Confidence: 0.956922252

 $00:54:07.560 \rightarrow 00:54:09.597$ 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

 $00{:}54{:}22.110 \dashrightarrow 00{:}54{:}23.310$ You have questions in Zoom

NOTE Confidence: 0.707469232222222

00:54:26.480 --> 00:54:27.746 a fantastic talk.

NOTE Confidence: 0.707469232222222

 $00:54:27.746 \dashrightarrow 00:54:29.856$ Very few people actually bridge

NOTE Confidence: 0.707469232222222

 $00{:}54{:}29{.}856 \dashrightarrow 00{:}54{:}32{.}188$ 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

 $00:54:34.040 \longrightarrow 00:54:34.931$ 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

 $00:54:37.920 \rightarrow 00:54:40.279$ but why would you think the metronomic

NOTE Confidence: 0.707469232222222

 $00{:}54{:}40{.}280 \dashrightarrow 00{:}54{:}44{.}012$ use of HMA with venetoclax would

NOTE Confidence: 0.707469232222222

 $00:54:44.012 \longrightarrow 00:54:47.050$ actually work for TP50 TP 53

NOTE Confidence: 0.707469232222222

 $00:54:47.050 \rightarrow 00:54:49.000$ while regular dosing would not?

NOTE Confidence: 0.851652816666666

 $00:54:49.840 \rightarrow 00:54:52.258$ 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: 0.8516528166666666
- $00:54:54.276 \rightarrow 00:54:56.899$ to the selection of P53 lost cells,
- NOTE Confidence: 0.851652816666666
- $00:54:56.899 \rightarrow 00:54:59.930$ so you kind of lose your hypermethylene
- NOTE Confidence: 0.851652816666666
- $00:55:00.012 \longrightarrow 00:55:01.961$ advantage, whatever that is.
- NOTE Confidence: 0.851652816666666
- $00:55:01.961 \rightarrow 00:55:04.670$ 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
- $00{:}55{:}06{.}680 \dashrightarrow 00{:}55{:}09{.}102$ but I think what happens with the
- NOTE Confidence: 0.8516528166666666
- $00:55:09.102 \rightarrow 00:55:10.625$ regular dosing, there's DNA damage,
- NOTE Confidence: 0.851652816666666
- $00{:}55{:}10.625 \dashrightarrow 00{:}55{:}12.000$ 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
- $00{:}55{:}13.644 \dashrightarrow 00{:}55{:}14.877$ And the cells,
- NOTE Confidence: 0.851652816666666
- $00:55:14.880 \longrightarrow 00:55:17.040$ they're just like being selected for.
- NOTE Confidence: 0.851652816666666
- $00{:}55{:}17.040 \dashrightarrow 00{:}55{:}18.916$ So all you get is selection of
- NOTE Confidence: 0.8516528166666666
- $00{:}55{:}18{.}916 \dashrightarrow 00{:}55{:}20{.}799$ cells that are like PHC mutated.
- NOTE Confidence: 0.851652816666666
- $00:55:20.800 \rightarrow 00:55:23.476$ They're resistant to DNA damaging drugs.
- NOTE Confidence: 0.851652816666666

 $00:55:23.480 \rightarrow 00:55:26.196$ And so there's very limited like advantage.

NOTE Confidence: 0.851652816666666

 $00{:}55{:}26{.}200 \dashrightarrow 00{:}55{:}28{.}125$ 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

 $00{:}55{:}30{.}117 \dashrightarrow 00{:}55{:}31{.}719$ 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

 $00{:}55{:}37.080 \dashrightarrow 00{:}55{:}39.747$ but we are encouraged to see that

NOTE Confidence: 0.851652816666666

 $00{:}55{:}39{.}747 \dashrightarrow 00{:}55{:}41{.}656$ in the prospective trial with

NOTE Confidence: 0.851652816666666

 $00:55:41.656 \rightarrow 00:55:43.620$ the you know about 10 patients

NOTE Confidence: 0.851652816666666

 $00{:}55{:}43.620 \dashrightarrow 00{:}55{:}45.240$ treated that the data stand.

NOTE Confidence: 0.851652816666666

 $00{:}55{:}45{.}240 \dashrightarrow 00{:}55{:}47{.}368$ So this you know again they're going

NOTE Confidence: 0.851652816666666

 $00{:}55{:}47{.}368 \dashrightarrow 00{:}55{:}49{.}756$ 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

 $00:55:53.720 \rightarrow 00:55:56.360$ 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
- $00:55:57.560 \rightarrow 00:55:58.856$ 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
- $00{:}56{:}02.720 \dashrightarrow 00{:}56{:}04.582$ but we're hoping that you know this
- NOTE Confidence: 0.851652816666666
- $00{:}56{:}04{.}582 \dashrightarrow 00{:}56{:}06{.}560$ will stand, but again it's not curative.
- NOTE Confidence: 0.851652816666666
- $00:56:06.560 \rightarrow 00:56:08.040$ So we definitely need something
- NOTE Confidence: 0.8516528166666666
- $00{:}56{:}08{.}040 \dashrightarrow 00{:}56{:}09{.}520$ 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
- $00:56:18.790 \rightarrow 00:56:21.808$ about what's being done towards
- NOTE Confidence: 0.862851972857143
- $00{:}56{:}21.808 \dashrightarrow 00{:}56{:}25.118$ tissue specific MCL ONE inhibitors.
- NOTE Confidence: 0.862851972857143
- $00:56:25.120 \longrightarrow 00:56:27.598$ So in order to avoid the cardiotoxicity,
- NOTE Confidence: 0.862851972857143
- $00{:}56{:}27.600 \dashrightarrow 00{:}56{:}29.000$ you talk be autifully about BCL
- NOTE Confidence: 0.728932983333333
- 00:56:29.000 --> 00:56:32.153 XL for example. Unfortunately,
- NOTE Confidence: 0.728932983333333

 $00:56:32.153 \rightarrow 00:56:35.318$ nothing that I'm aware of.

NOTE Confidence: 0.728932983333333

 $00:56:35.320 \rightarrow 00:56:37.702$ I heard that there's some approaching

NOTE Confidence: 0.728932983333333

 $00:56:37.702 \rightarrow 00:56:39.600$ making approaches making the ADC.

NOTE Confidence: 0.867555357692308

 $00:56:41.880 \longrightarrow 00:56:44.064$ I haven't had yet chance to

NOTE Confidence: 0.867555357692308

 $00:56:44.064 \longrightarrow 00:56:46.439$ get any of those to my lab.

NOTE Confidence: 0.867555357692308

 $00:56:46.440 \dashrightarrow 00:56:48.918$ 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

 $00:56:52.106 \longrightarrow 00:56:53.440$ there's any like you know,

NOTE Confidence: 0.867555357692308

 $00:56:53.440 \rightarrow 00:56:55.156$ compound that is close to clinic,

NOTE Confidence: 0.867555357692308

 $00:56:55.160 \dashrightarrow 00:56:57.920$ but I think that would be the way to go.

NOTE Confidence: 0.867555357692308

 $00:56:57.920 \rightarrow 00:57:01.637$ Now the VHL is expressing the heart.

NOTE Confidence: 0.867555357692308

 $00:57:01.640 \longrightarrow 00:57:03.032$ So you know,

NOTE Confidence: 0.867555357692308

 $00:57:03.032 \dashrightarrow 00:57:05.784$ there's also effort by Stephen Fazek,

NOTE Confidence: 0.867555357692308

 $00{:}57{:}05{.}784 \dashrightarrow 00{:}57{:}09{.}088$ who is now at the Vanderbilt to look

NOTE Confidence: 0.867555357692308

 $00:57:09.088 \longrightarrow 00:57:11.076$ at all 600 ubiquitin ligase and try

 $00:57:11.076 \rightarrow 00:57:13.517$ to understand the tissue specificity.

NOTE Confidence: 0.867555357692308

 $00:57:13.520 \longrightarrow 00:57:14.680$ Obviously, if I'm so one,

NOTE Confidence: 0.867555357692308

 $00:57:14.680 \longrightarrow 00:57:16.516$ we have to avoid the heart.

NOTE Confidence: 0.867555357692308

 $00{:}57{:}16{.}520 \dashrightarrow 00{:}57{:}18{.}152$ I think that effort is still

NOTE Confidence: 0.867555357692308

 $00{:}57{:}18.152 \dashrightarrow 00{:}57{:}20.079$ ongoing as far as the products,

NOTE Confidence: 0.867555357692308

 $00{:}57{:}20.080 \dashrightarrow 00{:}57{:}24.770$ but I think perhaps using the antibodrap

NOTE Confidence: 0.867555357692308

 $00:57:24.770 \longrightarrow 00:57:27.480$ conugate maybe is the way to go.

NOTE Confidence: 0.867555357692308

 $00{:}57{:}27{.}480 \dashrightarrow 00{:}57{:}30{.}536$ You know there was the B7 HCB cell Excel

NOTE Confidence: 0.867555357692308

 $00:57:30.536 \rightarrow 00:57:33.560$ 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

 $00{:}57{:}36{.}170 \dashrightarrow 00{:}57{:}37{.}960$ perhaps can be used in Amo,

NOTE Confidence: 0.867555357692308

 $00{:}57{:}37{.}960 \dashrightarrow 00{:}57{:}39{.}760$ but nothing close to clinic yet.

NOTE Confidence: 0.867555357692308

 $00{:}57{:}40{.}640 \dashrightarrow 00{:}57{:}40{.}960$ Thank you.

NOTE Confidence: 0.4894056025

 $00{:}57{:}44{.}120 \dashrightarrow 00{:}57{:}47{.}520$ Thank you for that. Thank you.

 $00:57:47.520 \longrightarrow 00:57:49.092$ 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

 $00:57:53.120 \rightarrow 00:57:55.640$ 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

 $00{:}57{:}59{.}720 \dashrightarrow 00{:}58{:}02{.}840$ ASA one curves don't separate after

NOTE Confidence: 0.4894056025

 $00:58:02.840 \rightarrow 00:58:05.620$ 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

 $00:58:09.400 \longrightarrow 00:58:11.120$ I think what are we doing there

NOTE Confidence: 0.808251238

 $00{:}58{:}11.760 \dashrightarrow 00{:}58{:}14.364$ I think the probably the people don't NOTE Confidence: 0.808251238

 $00{:}58{:}14{.}364 \dashrightarrow 00{:}58{:}16{.}732$ die with ASA after first month either. NOTE Confidence: 0.808251238

NOTE Confidence. 0.808251258

 $00{:}58{:}16.732 \dashrightarrow 00{:}58{:}19.281$ So they still you know this well with NOTE Confidence: 0.808251238

 $00:58:19.281 \dashrightarrow 00:58:21.395$ ASA side is about nine months right.

NOTE Confidence: 0.808251238

 $00:58:21.400 \longrightarrow 00:58:23.850$ So they even though they don't get

NOTE Confidence: 0.808251238

 $00:58:23.850 \rightarrow 00:58:25.520$ intermission, they are still, you know,

- NOTE Confidence: 0.808251238
- $00:58:25.520 \rightarrow 00:58:27.860$ alive and they continue on study
- NOTE Confidence: 0.808251238
- $00{:}58{:}27{.}860 \dashrightarrow 00{:}58{:}30{.}679$ 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
- $00{:}58{:}33{.}000 \dashrightarrow 00{:}58{:}35{.}107$ You know, remissions happen after one to
- NOTE Confidence: 0.808251238
- $00{:}58{:}35{.}107 \dashrightarrow 00{:}58{:}37{.}451$ two months with the vanilla clocks and
- NOTE Confidence: 0.808251238
- $00{:}58{:}37{.}451 \dashrightarrow 00{:}58{:}39{.}917$ 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
- $00{:}58{:}42{.}545 \dashrightarrow 00{:}58{:}45{.}412$ kind of able to maintain people alive with
- NOTE Confidence: 0.808251238
- $00{:}58{:}45{.}412 \dashrightarrow 00{:}58{:}47{.}116$ all our supportive care and everything.
- NOTE Confidence: 0.808251238
- $00:58:47.120 \longrightarrow 00:58:49.520$ They they are still there.
- NOTE Confidence: 0.808251238
- $00:58:49.520 \longrightarrow 00:58:51.038$ 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
- $00{:}58{:}53{.}496 \dashrightarrow 00{:}58{:}54{.}946$ that paper that you're a part of the
- NOTE Confidence: 0.623632461
- $00{:}58{:}54{.}946 \dashrightarrow 00{:}58{:}56{.}656$ Curtis paper that frankly presented
- NOTE Confidence: 0.623632461
- $00{:}58{:}56{.}656 \dashrightarrow 00{:}58{:}58{.}960$ at the older NPM on positive.
- NOTE Confidence: 0.623632461

 $00:58:58.960 \rightarrow 00:59:00.647$ I have a feeling when Nick presents

NOTE Confidence: 0.623632461

 $00{:}59{:}00{.}647 \dashrightarrow 00{:}59{:}02{.}240$ the data after that combination,

NOTE Confidence: 0.623632461

 $00{:}59{:}02{.}240 \dashrightarrow 00{:}59{:}04{.}844$ they're highly choosing NPM on positive

NOTE Confidence: 0.623632461

 $00:59:04.844 \rightarrow 00:59:06.771$ patients that is chemosensitive

NOTE Confidence: 0.623632461

 $00{:}59{:}06{.}771 \dashrightarrow 00{:}59{:}08{.}759$ or mild suppression sensitive.

NOTE Confidence: 0.623632461

 $00{:}59{:}08{.}760 \dashrightarrow 00{:}59{:}10{.}664$ And then they're tagging it up with

NOTE Confidence: 0.623632461

 $00:59:10.664 \rightarrow 00:59:12.515$ 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

 $00{:}59{:}14.585 \dashrightarrow 00{:}59{:}16.072$ 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

 $00{:}59{:}17.600 \dashrightarrow 00{:}59{:}20.948$ drop and we know what addition of three

NOTE Confidence: 0.623632461

 $00:59:20.948 \rightarrow 00:59:22.556$ class of frequently liberals done too.

NOTE Confidence: 0.623632461

 $00{:}59{:}22{.}560 \dashrightarrow 00{:}59{:}22{.}800$ And

NOTE Confidence: 0.471341158

 $00:59:24.880 \rightarrow 00:59:28.240$ the point being is AML being all legal

NOTE Confidence: 0.471341158

 $00{:}59{:}28{.}240 \dashrightarrow 00{:}59{:}30{.}734$ flow now, how much emphasis can we

NOTE Confidence: 0.471341158

 $00:59:30.734 \rightarrow 00:59:33.303$ give just the BCL component in looking

 $00{:}59{:}33{.}303 \dashrightarrow 00{:}59{:}35{.}413$ 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

 $00:59:37.279 \rightarrow 00:59:39.192$ for three to six months, very good.

NOTE Confidence: 0.471341158

 $00:59:39.192 \longrightarrow 00:59:40.984$ We don't have anything to that extent

NOTE Confidence: 0.471341158

 $00:59:40.984 \rightarrow 00:59:44.200$ compared to cytotoxic in the past.

NOTE Confidence: 0.471341158

 $00:59:44.200 \longrightarrow 00:59:46.132$ Garcia within a recently in the post

NOTE Confidence: 0.471341158

 $00{:}59{:}46.132 \dashrightarrow 00{:}59{:}48.119$ transplant period in the other one has

NOTE Confidence: 0.471341158

 $00{:}59{:}48.119 \dashrightarrow 00{:}59{:}49.775$ maintenance even there the curves first

NOTE Confidence: 0.471341158

 $00{:}59{:}49{.}830 \dashrightarrow 00{:}59{:}51{.}475$ three to six months and then drop,

NOTE Confidence: 0.471341158

 $00:59:51.480 \longrightarrow 00:59:53.292$ drop, drop, you don't have a

NOTE Confidence: 0.471341158

 $00:59:53.292 \rightarrow 00:59:54.920$ leukemia there at that stage.

NOTE Confidence: 0.471341158

 $00:59:54.920 \rightarrow 00:59:57.240$ So now when I'm going to fight stem cells,

NOTE Confidence: 0.471341158

 $00{:}59{:}57{.}240 \dashrightarrow 00{:}59{:}59{.}080$ what do you think the resistance is in

NOTE Confidence: 0.471341158

 $00{:}59{:}59{.}080 \dashrightarrow 01{:}00{:}00{.}390$ that context when you're using either

NOTE Confidence: 0.471341158

 $01:00:00.390 \rightarrow 01:00:01.920$ one in the post transplant context?

- $01:00:02.560 \longrightarrow 01:00:04.436$ Oh I I don't think I'm able
- NOTE Confidence: 0.854454804545455
- $01{:}00{:}04.436 \dashrightarrow 01{:}00{:}06.480$ to answer that question. So
- NOTE Confidence: 0.825061614
- $01:00:08.520 \rightarrow 01:00:11.760$ I'm not sure what the you know.
- NOTE Confidence: 0.825061614
- $01:00:11.760 \rightarrow 01:00:13.632$ I don't think that this is just mouse
- NOTE Confidence: 0.825061614
- $01{:}00{:}13.632 \dashrightarrow 01{:}00{:}14.720$ suppression causing people to die,
- NOTE Confidence: 0.825061614
- $01:00:14.720 \rightarrow 01:00:17.800$ but there's really like relapses going on,
- NOTE Confidence: 0.825061614
- $01:00:17.800 \longrightarrow 01:00:19.893$ right? And I assume that this is
- NOTE Confidence: 0.825061614
- $01:00:19.893 \rightarrow 01:00:22.220$ still escape of some of the clones
- NOTE Confidence: 0.825061614
- $01{:}00{:}22.220 \dashrightarrow 01{:}00{:}23.920$ that are not being eliminated.
- NOTE Confidence: 0.825061614
- $01{:}00{:}23.920 \dashrightarrow 01{:}00{:}26.720$ But I don't know the data that well.
- NOTE Confidence: 0.825061614
- $01:00:26.720 \longrightarrow 01:00:28.407$ 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
- $01:00:31.800 \longrightarrow 01:00:33.000$ As far as like you know,
- NOTE Confidence: 0.825061614
- $01:00:33.000 \longrightarrow 01:00:34.180$ there's a lot of discussion
- NOTE Confidence: 0.825061614
- $01:00:34.180 \longrightarrow 01:00:35.823$ if you have MP1 free, St.
- NOTE Confidence: 0.825061614
- $01:00:35.823 \rightarrow 01:00:38.138$ Commutative clone can be eliminated

- NOTE Confidence: 0.825061614
- $01:00:38.138 \longrightarrow 01:00:40.360$ with Venetoclax alone or not.
- NOTE Confidence: 0.825061614
- $01{:}00{:}40{.}360 \dashrightarrow 01{:}00{:}41{.}758$ 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
- $01:00:43.734 \rightarrow 01:00:45.480$ we know that Flixtree mutated
- NOTE Confidence: 0.825061614
- $01:00:45.480 \rightarrow 01:00:48.000$ 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
- $01{:}00{:}49.032 \dashrightarrow 01{:}00{:}51.598$ 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
- $01{:}00{:}53.946 \dashrightarrow 01{:}00{:}56.398$ for those who have only MPN 1.
- NOTE Confidence: 0.825061614
- $01{:}00{:}56{.}400 \dashrightarrow 01{:}00{:}57{.}935$ So there's still that contribution
- NOTE Confidence: 0.825061614
- $01:00:57.935 \longrightarrow 01:00:59.866$ 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
- $01:01:01.240 \longrightarrow 01:01:03.396$ 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
- $01:01:05.320 \longrightarrow 01:01:06.684$ 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

 $01:01:13.408 \longrightarrow 01:01:15.727$ that sense that it will target the

NOTE Confidence: 0.825061614

 $01{:}01{:}15{.}727 \dashrightarrow 01{:}01{:}18{.}132$ 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

 $01{:}01{:}19{.}320 \dashrightarrow 01{:}01{:}20{.}280$ I don't have data to that.

NOTE Confidence: 0.752345258

 $01:01:22.040 \longrightarrow 01:01:24.400$ 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

 $01{:}01{:}26.794 \dashrightarrow 01{:}01{:}29.448$ development in AML and you alluded to

NOTE Confidence: 0.752345258

 $01{:}01{:}29{.}448 \dashrightarrow 01{:}01{:}32{.}104$ the Twitter wars on some of these data.

NOTE Confidence: 0.752345258

 $01:01:32.104 \longrightarrow 01:01:34.168$ I think one big question that

NOTE Confidence: 0.752345258

 $01:01:34.168 \longrightarrow 01:01:36.854$ 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

 $01:01:38.440 \longrightarrow 01:01:41.160$ does it can it have realistically a chance

NOTE Confidence: 0.752345258

 $01:01:41.160 \rightarrow 01:01:43.839$ 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 $\operatorname{-->}$ 01:01:48.396 but actually Vinito clacks as you
- NOTE Confidence: 0.752345258
- $01:01:48.396 \rightarrow 01:01:49.959$ 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
- $01:01:52.426 \longrightarrow 01:01:54.328$ some people took a Victory lab
- NOTE Confidence: 0.752345258
- $01{:}01{:}54{.}328 \dashrightarrow 01{:}01{:}55{.}893$ 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
- $01:01:58.966 \longrightarrow 01:02:00.320$ 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
- $01:02:07.040 \longrightarrow 01:02:08.800$ 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

 $01:02:12.880 \longrightarrow 01:02:15.092$ I would probably be very worried about

NOTE Confidence: 0.7396741875

 $01:02:15.092 \rightarrow 01:02:17.340$ going to phase three with a drug

NOTE Confidence: 0.7396741875

 $01:02:17.340 \longrightarrow 01:02:19.200$ that has no single agent activity.

NOTE Confidence: 0.7396741875

 $01:02:19.200 \longrightarrow 01:02:21.351$ 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

 $01{:}02{:}23.558 \dashrightarrow 01{:}02{:}26.566$ and the the data also in the front line

NOTE Confidence: 0.7396741875

 $01:02:26.566 \rightarrow 01:02:29.240$ 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

10112 Communice: 0.1550141015

01:02:31.436 --> 01:02:33.821 just single agent and they did bone

NOTE Confidence: 0.7396741875

 $01{:}02{:}33{.}821 \dashrightarrow 01{:}02{:}35{.}830$ marrow that was done in Australia and

NOTE Confidence: 0.7396741875

 $01{:}02{:}35{.}891 \dashrightarrow 01{:}02{:}38{.}173$ they also showed reduction or even like

NOTE Confidence: 0.7396741875

 $01{:}02{:}38{.}173 \dashrightarrow 01{:}02{:}40{.}012$ remission in about 50% of patients.

NOTE Confidence: 0.7396741875

 $01:02:40.012 \rightarrow 01:02:42.000$ So it does have single agent activity

NOTE Confidence: 0.7396741875

 $01:02:42.058 \rightarrow 01:02:43.928$ but also like different mechanistically

NOTE Confidence: 0.7396741875

 $01:02:43.928 \rightarrow 01:02:46.046$ 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
- $01:02:47.280 \longrightarrow 01:02:48.888$ think that even if you didn't
- NOTE Confidence: 0.7396741875
- $01{:}02{:}48.888 \dashrightarrow 01{:}02{:}50.335$ have that single agent activity
- NOTE Confidence: 0.7396741875
- $01:02:50.335 \rightarrow 01:02:52.237$ in combination you might have had.
- NOTE Confidence: 0.7396741875
- $01{:}02{:}52{.}240 \dashrightarrow 01{:}02{:}54{.}376$ 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
- $01:02:56.300 \rightarrow 01:02:58.748$ I'm not sure I would develop the drug that
- NOTE Confidence: 0.7396741875
- $01{:}02{:}58.748 \dashrightarrow 01{:}03{:}01{.}094$ 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
- $01:03:04.080 \rightarrow 01:03:05.000$ I might be wrong.
- NOTE Confidence: 0.94450996
- $01:03:06.200 \longrightarrow 01:03:06.960$ Thank you so much.
- NOTE Confidence: 0.94904423
- $01:03:07.560 \longrightarrow 01:03:09.000$ Thank you everybody.