WEBVTT

NOTE duration:"00:58:51"

NOTE recognizability:0.815

NOTE language:en-us

NOTE Confidence: 0.869160187272727

00:00:00.000 --> 00:00:01.292 So I'm Roy Herbst,

NOTE Confidence: 0.869160187272727

00:00:01.292 --> 00:00:03.720 Deputy Director here at the Cancer Center,

NOTE Confidence: 0.869160187272727

00:00:03.720 --> 00:00:05.730 and it's really my honor to

NOTE Confidence: 0.869160187272727

00:00:05.730 --> 00:00:08.680 introduce the Cal Brazy Lecture.

NOTE Confidence: 0.869160187272727

00:00:08.680 --> 00:00:10.105 And this year you'll you'll

NOTE Confidence: 0.869160187272727

00:00:10.105 --> 00:00:10.960 meet Doctor Pasiani,

NOTE Confidence: 0.869160187272727

00:00:10.960 --> 00:00:13.040 who will be introduced by our lung program,

NOTE Confidence: 0.869160187272727

00:00:13.040 --> 00:00:15.325 scientific leader Katie Poletti and

NOTE Confidence: 0.869160187272727

00:00:15.325 --> 00:00:16.710 clinical leader Sarah Goldberg.

NOTE Confidence: 0.869160187272727

00:00:16.710 --> 00:00:18.120 But first, I just want to

NOTE Confidence: 0.869160187272727

00:00:18.120 --> 00:00:19.398 say a word about Paul

NOTE Confidence: 0.769715758571428

00:00:21.680 --> 00:00:23.944 Paul. Cal Brazy is often referred to as

NOTE Confidence: 0.769715758571428

00:00:23.944 --> 00:00:26.156 the father of oncology and its influence

NOTE Confidence: 0.769715758571428

00:00:26.156 --> 00:00:28.483 here at Yale Cancer Center remains a

NOTE Confidence: 0.769715758571428

00:00:28.483 --> 00:00:30.181 former faculty member at Yale School

NOTE Confidence: 0.769715758571428

00:00:30.181 --> 00:00:31.811 of Medicine who was internationally

NOTE Confidence: 0.769715758571428

00:00:31.811 --> 00:00:33.983 recognized as an authority on the

NOTE Confidence: 0.769715758571428

00:00:33.983 --> 00:00:35.758 pharmacology of anti cancer agents.

NOTE Confidence: 0.769715758571428

00:00:35.760 --> 00:00:37.695 Doctor Calabrazi serves as director

NOTE Confidence: 0.769715758571428

00:00:37.695 --> 00:00:40.052 of the Yale Cancer Center's Advisory

NOTE Confidence: 0.769715758571428

00:00:40.052 --> 00:00:42.455 Board until 2003 and we honor him

NOTE Confidence: 0.769715758571428

00:00:42.455 --> 00:00:44.624 with a conference room WW2 O 8

NOTE Confidence: 0.769715758571428

00:00:44.624 --> 00:00:46.640 where his picture hangs and I bet

NOTE Confidence: 0.769715758571428

00:00:46.717 --> 00:00:49.037 almost everyone here has visited.

NOTE Confidence: 0.769715758571428

00:00:49.040 --> 00:00:51.028 You can see here's the conference room

NOTE Confidence: 0.769715758571428

00:00:51.028 --> 00:00:53.077 shown on the slide with a beautiful

NOTE Confidence: 0.769715758571428

00:00:53.077 --> 00:00:55.400 portrait of Paul and all the lecturers,

NOTE Confidence: 0.769715758571428

00:00:55.400 --> 00:00:57.744 the 13 who have given this lecture over

NOTE Confidence: 0.769715758571428

00:00:57.744 --> 00:01:00.240 the last 14 or 15 years have shown and

NOTE Confidence: 0.769715758571428

00:01:00.240 --> 00:01:02.160 Doctor Yanni's plaque is already there

NOTE Confidence: 0.769715758571428

00:01:02.160 --> 00:01:03.798 and you can see the outside of the room.

NOTE Confidence: 0.769715758571428

00:01:03.800 --> 00:01:04.920 So if you haven't been to the room,

NOTE Confidence: 0.769715758571428

00:01:04.920 --> 00:01:05.348 go visit.

NOTE Confidence: 0.769715758571428

00:01:05.348 --> 00:01:07.060 We were just there and it was just

NOTE Confidence: 0.769715758571428

00:01:07.118 --> 00:01:08.868 wonderful to be with the Cal Brazy

NOTE Confidence: 0.769715758571428

00:01:08.868 --> 00:01:10.926 family and I welcome them all here

NOTE Confidence: 0.769715758571428

00:01:10.926 --> 00:01:12.999 today and to take some photos.

NOTE Confidence: 0.769715758571428

00:01:13.000 --> 00:01:14.960 This is a list of the lecturers.

NOTE Confidence: 0.769715758571428

00:01:14.960 --> 00:01:17.078 This is a very important lecture.

NOTE Confidence: 0.769715758571428

00:01:17.080 --> 00:01:19.148 You know, Paul was you know who

NOTE Confidence: 0.769715758571428

00:01:19.148 --> 00:01:20.518 who here has AK12 award?

NOTE Confidence: 0.769715758571428

00:01:20.520 --> 00:01:23.928 Do we have any of our K12 awardees here?

NOTE Confidence: 0.769715758571428

00:01:23.928 --> 00:01:25.096 They'll be.

NOTE Confidence: 0.769715758571428

00:01:25.096 --> 00:01:27.160 Yep, Yep so. So we have.

NOTE Confidence: 0.769715758571428

00:01:27.160 --> 00:01:29.956 So K12 is the Calabresi award.

NOTE Confidence: 0.769715758571428

00:01:29.960 --> 00:01:31.240 Paul was all about mentorship,

NOTE Confidence: 0.769715758571428

00:01:31.240 --> 00:01:34.036 teaching, taking care of the patient.

NOTE Confidence: 0.769715758571428

00:01:34.040 --> 00:01:36.520 He was both a scientist and a clinician.

NOTE Confidence: 0.769715758571428

00:01:36.520 --> 00:01:38.123 The the true what we used to

NOTE Confidence: 0.769715758571428

00:01:38.123 --> 00:01:39.559 call the three legged stool.

NOTE Confidence: 0.769715758571428

00:01:39.560 --> 00:01:42.645 So we try to invite people to these lectures

NOTE Confidence: 0.769715758571428

00:01:42.645 --> 00:01:44.680 and you can see the list of lecturers.

NOTE Confidence: 0.769715758571428

00:01:44.680 --> 00:01:46.520 And the very first one was Eddie Chu,

NOTE Confidence: 0.769715758571428

00:01:46.520 --> 00:01:48.320 also a mentee of Paul.

NOTE Confidence: 0.769715758571428

00:01:48.320 --> 00:01:50.357 And last year we had Steven Rosenberg.

NOTE Confidence: 0.876615902222222

00:01:53.160 --> 00:01:55.959 And here are just some photos over the years.

NOTE Confidence: 0.876615902222222

00:01:55.960 --> 00:01:58.192 It's very special lectureship for me

NOTE Confidence: 0.876615902222222

00:01:58.192 --> 00:02:01.119 because I actually met Paul 44 years ago.

NOTE Confidence: 0.876615902222222

00:02:01.119 --> 00:02:03.357 And how did I meet Paul?

NOTE Confidence: 0.876615902222222

00:02:03.360 --> 00:02:04.416 I have a picture,

NOTE Confidence: 0.876615902222222

00:02:04.416 --> 00:02:06.771 I can only find 2 pictures on the left,

NOTE Confidence: 0.876615902222222

00:02:06.771 --> 00:02:08.313 that's Paul behind his wife Seal.

NOTE Confidence: 0.876615902222222

00:02:08.320 --> 00:02:10.132 And that's me at my friend

NOTE Confidence: 0.876615902222222

00:02:10.132 --> 00:02:11.056 Peter Calabresi's wedding,

NOTE Confidence: 0.876615902222222

00:02:11.056 --> 00:02:13.520 the only picture Janice could find for me.

NOTE Confidence: 0.876615902222222

00:02:13.520 --> 00:02:15.606 But Paul was mentoring me and how

NOTE Confidence: 0.876615902222222

00:02:15.606 --> 00:02:18.157 to walk and stand stand up straight.

NOTE Confidence: 0.876615902222222

00:02:18.160 --> 00:02:20.716 And then on the right Paul took this picture.

NOTE Confidence: 0.876615902222222

00:02:20.720 --> 00:02:21.600 There's another picture with

NOTE Confidence: 0.876615902222222

00:02:21.600 --> 00:02:22.920 Paul but I couldn't find it.

NOTE Confidence: 0.876615902222222

00:02:22.920 --> 00:02:25.088 But that's Peter and I just a few

NOTE Confidence: 0.876615902222222

00:02:25.088 --> 00:02:26.933 years ago probably around 1983.

NOTE Confidence: 0.876615902222222

00:02:26.933 --> 00:02:29.605 You can see I'm I'm drinking a tab but,

NOTE Confidence: 0.876615902222222

00:02:29.605 --> 00:02:31.880 but, but but Paul was a mentor

NOTE Confidence: 0.876615902222222

00:02:31.880 --> 00:02:33.718 to me as to so many.

NOTE Confidence: 0.876615902222222

00:02:33.720 --> 00:02:34.728 That's always so special

NOTE Confidence: 0.876615902222222

00:02:34.728 --> 00:02:36.240 for me to have this lecture.

NOTE Confidence: 0.876615902222222

00:02:36.240 --> 00:02:38.060 And here we have Paul's

NOTE Confidence: 0.876615902222222

00:02:38.060 --> 00:02:39.880 brother Guido in the audience.

NOTE Confidence: 0.876615902222222

00:02:39.880 --> 00:02:41.960 His wife Ann was with us last night.

NOTE Confidence: 0.876615902222222

00:02:41.960 --> 00:02:44.800 His sons Peter and Steven.

NOTE Confidence: 0.876615902222222

00:02:44.800 --> 00:02:46.772 His daughter Janice Mimi,

NOTE Confidence: 0.876615902222222

00:02:46.772 --> 00:02:48.388 who is Steven's wife.

NOTE Confidence: 0.876615902222222

00:02:48.388 --> 00:02:50.272 So it's just wonderful to have

NOTE Confidence: 0.876615902222222

00:02:50.272 --> 00:02:51.600 the Calabrazi family here.

NOTE Confidence: 0.876615902222222

00:02:51.600 --> 00:02:54.192 But now to introduce our guest of the day,

NOTE Confidence: 0.876615902222222

00:02:54.200 --> 00:02:54.650 our speaker,

NOTE Confidence: 0.876615902222222

00:02:54.650 --> 00:02:56.225 I'm going to invite Sarah Goldberg and

NOTE Confidence: 0.876615902222222

00:02:56.225 --> 00:02:57.840 Katie Paletti to introduce Doctor Yanni.

NOTE Confidence: 0.9634966

00:02:59.960 --> 00:03:00.030 Good

NOTE Confidence: 0.93304342875

00:03:06.230 --> 00:03:07.082 morning everyone.

NOTE Confidence: 0.93304342875

00:03:07.082 --> 00:03:10.490 So this is really so such so wonderful

NOTE Confidence: 0.93304342875

00:03:10.573 --> 00:03:13.244 to see everyone here and to meet and

NOTE Confidence: 0.93304342875

00:03:13.244 --> 00:03:15.393 get to know the the Calabrazi family.

NOTE Confidence: 0.93304342875

00:03:15.400 --> 00:03:16.877 But right now my my job is

NOTE Confidence: 0.93304342875

00:03:16.877 --> 00:03:17.960 to introduce our speaker.

NOTE Confidence: 0.93304342875

00:03:17.960 --> 00:03:20.004 So it is my absolute honor to

NOTE Confidence: 0.93304342875

00:03:20.004 --> 00:03:21.559 introduce my colleague and friend,

NOTE Confidence: 0.93304342875

00:03:21.560 --> 00:03:24.248 Doctor Pasiani as our guest lecturer for

NOTE Confidence: 0.93304342875

00:03:24.248 --> 00:03:27.040 the Paul Calabresi Memorial Lecture Series.

NOTE Confidence: 0.93304342875

00:03:27.040 --> 00:03:29.830 Doctor Yanni earned his MD as well as PhD

NOTE Confidence: 0.93304342875

00:03:29.830 --> 00:03:32.478 degrees from the University of Pennsylvania.

NOTE Confidence: 0.93304342875

00:03:32.480 --> 00:03:34.375 He then completed postgraduate training

NOTE Confidence: 0.93304342875

00:03:34.375 --> 00:03:36.641 in internal medicine at Brigham and

NOTE Confidence: 0.93304342875

00:03:36.641 --> 00:03:38.531 Women's Hospital and in Medical Oncology

NOTE Confidence: 0.93304342875

00:03:38.531 --> 00:03:40.440 at Dana Farber Cancer Institute.

NOTE Confidence: 0.93304342875

00:03:40.440 --> 00:03:42.234 He's currently the director of the

NOTE Confidence: 0.93304342875

00:03:42.234 --> 00:03:44.104 Lowe Center for Thoracic Oncology and

NOTE Confidence: 0.93304342875

00:03:44.104 --> 00:03:45.958 the scientific director of the Belfer

NOTE Confidence: 0.93304342875

00:03:45.958 --> 00:03:47.800 Center for Applied Cancer Science.

NOTE Confidence: 0.93304342875

00:03:47.800 --> 00:03:49.624 And he's also professor of Medicine

NOTE Confidence: 0.93304342875

00:03:49.624 --> 00:03:51.162 at Harvard Medical School and

NOTE Confidence: 0.93304342875

00:03:51.162 --> 00:03:52.238 the David M Livingston,

NOTE Confidence: 0.93304342875

00:03:52.240 --> 00:03:54.720 MD Chair at Dana Farber.

NOTE Confidence: 0.93304342875

00:03:54.720 --> 00:03:56.224 So it was at Dana Farber that I

NOTE Confidence: 0.93304342875

00:03:56.224 --> 00:03:57.835 first met posse when I was a fellow.

NOTE Confidence: 0.93304342875

00:03:57.840 --> 00:03:59.800 It was several years ago now as we

NOTE Confidence: 0.93304342875

00:03:59.800 --> 00:04:01.158 were reminiscing about last night,

NOTE Confidence: 0.93304342875

00:04:01.160 --> 00:04:03.040 I worked in his clinic and still now,

NOTE Confidence: 0.93304342875

00:04:03.040 --> 00:04:05.112 you know as we both see patients

NOTE Confidence: 0.93304342875

00:04:05.112 --> 00:04:06.000 with lung cancer,

NOTE Confidence: 0.93304342875

00:04:06.000 --> 00:04:08.478 we we sometimes still share patients.

NOTE Confidence: 0.93304342875

00:04:08.480 --> 00:04:10.307 And I can personally attest that he

NOTE Confidence: 0.93304342875

00:04:10.307 --> 00:04:12.552 really is a fantastic oncologist who goes

NOTE Confidence: 0.93304342875

00:04:12.552 --> 00:04:15.160 above and beyond for every single patient.

NOTE Confidence: 0.93304342875

00:04:15.160 --> 00:04:16.856 So I'm going to now turn over to

NOTE Confidence: 0.93304342875

00:04:16.856 --> 00:04:19.067 to Katie Politi to tell you a bit

NOTE Confidence: 0.93304342875

00:04:19.067 --> 00:04:20.223 about Doctor Yanni's remarkable

NOTE Confidence: 0.93304342875

00:04:20.281 --> 00:04:22.037 scientific contributions and PASI,

NOTE Confidence: 0.93304342875

00:04:22.040 --> 00:04:24.840 I'm really looking forward to your lecture.

NOTE Confidence: 0.93304342875

00:04:24.840 --> 00:04:26.625 Thank you, Sarah.

NOTE Confidence: 0.93304342875

00:04:26.625 --> 00:04:30.195 Bon giorno E benvenuti attuti specialmente

NOTE Confidence: 0.93304342875

00:04:30.195 --> 00:04:34.920 a la familia calabresi E aldotor pasi Yanni.

NOTE Confidence: 0.93304342875

00:04:34.920 --> 00:04:36.198 As I said,

NOTE Confidence: 0.93304342875

00:04:36.198 --> 00:04:39.151 good morning and welcome to everybody

NOTE Confidence: 0.93304342875

00:04:39.151 --> 00:04:41.936 and especially to the Calabrese

NOTE Confidence: 0.93304342875

00:04:41.936 --> 00:04:45.359 family and to Doctor Pasiyani Today.

NOTE Confidence: 0.93304342875

00:04:45.360 --> 00:04:47.436 The advances in lung cancer treatment

NOTE Confidence: 0.93304342875

00:04:47.436 --> 00:04:50.142 over the past 20 years have been

NOTE Confidence: 0.93304342875

00:04:50.142 --> 00:04:52.171 remarkable and are contributing to

NOTE Confidence: 0.93304342875

00:04:52.171 --> 00:04:54.433 a reduction in lung cancer deaths

NOTE Confidence: 0.93304342875

00:04:54.433 --> 00:04:56.637 that we've seen in recent years.

NOTE Confidence: 0.93304342875

00:04:56.640 --> 00:04:59.244 Doctor Yanni's research has played a

NOTE Confidence: 0.93304342875

00:04:59.244 --> 00:05:01.912 central and critical role in contributing

NOTE Confidence: 0.93304342875

00:05:01.912 --> 00:05:04.474 to the better outcomes for patients

NOTE Confidence: 0.93304342875

00:05:04.474 --> 00:05:07.157 with lung cancer that we see today.

NOTE Confidence: 0.93304342875

00:05:07.160 --> 00:05:09.565 His main research interests include

NOTE Confidence: 0.93304342875

00:05:09.565 --> 00:05:11.970 studying the therapeutic relevance of

NOTE Confidence: 0.93304342875

00:05:12.040 --> 00:05:14.480 oncogenic alterations in lung cancer.

NOTE Confidence: 0.93304342875

00:05:14.480 --> 00:05:17.104 He was one of the Co discoverers of

NOTE Confidence: 0.93304342875

00:05:17.104 --> 00:05:18.644 epidermal growth factor mutations

NOTE Confidence: 0.93304342875

00:05:18.644 --> 00:05:21.104 in lung cancer and has pioneered

NOTE Confidence: 0.93304342875

00:05:21.104 --> 00:05:22.847 the development of therapeutic

NOTE Confidence: 0.93304342875

00:05:22.847 --> 00:05:24.992 strategies for patients with EGF

NOTE Confidence: 0.93304342875

00:05:24.992 --> 00:05:26.727 receptor mutant lung cancer.

NOTE Confidence: 0.93304342875

00:05:26.727 --> 00:05:29.856 His lab based and clinical research has

NOTE Confidence: 0.93304342875

00:05:29.856 --> 00:05:32.703 also focused on other oncogenic driver

NOTE Confidence: 0.93304342875

00:05:32.703 --> 00:05:35.517 subsets like those for those patients

NOTE Confidence: 0.93304342875

00:05:35.597 --> 00:05:38.279 whose tumors harbor K Ras mutations.

NOTE Confidence: 0.93304342875

00:05:38.280 --> 00:05:39.640 As you will see today,

NOTE Confidence: 0.93304342875

00:05:39.640 --> 00:05:41.765 Doctor Yanni's laboratory research is

NOTE Confidence: 0.93304342875

00:05:41.765 --> 00:05:44.290 at the forefront of addressing major

NOTE Confidence: 0.93304342875

00:05:44.290 --> 00:05:46.312 challenges in lung cancer and sets

NOTE Confidence: 0.93304342875

00:05:46.312 --> 00:05:48.775 the stage for advancing approaches for

NOTE Confidence: 0.93304342875

00:05:48.775 --> 00:05:51.080 clinical treatment of the disease.

NOTE Confidence: 0.93304342875

00:05:51.080 --> 00:05:53.194 Thank you Pasi for being here today.

NOTE Confidence: 0.93304342875

00:05:53.200 --> 00:05:54.600 It's a pleasure to have you here

NOTE Confidence: 0.93304342875

00:05:54.600 --> 00:05:55.200 for this lecture.

NOTE Confidence: 0.60805017

00:05:59.000 --> 00:06:01.010 We're going to take a picture

NOTE Confidence: 0.60805017

00:06:01.010 --> 00:06:02.420 with a both Reef before

NOTE Confidence: 0.686923143076923

00:06:02.480 --> 00:06:04.184 we start because and for inviting

NOTE Confidence: 0.686923143076923

00:06:04.184 --> 00:06:05.672 child raising family to come up.

NOTE Confidence: 0.686923143076923

00:06:05.680 --> 00:06:07.157 I'm also going to ask Lori Pickens,

NOTE Confidence: 0.686923143076923

00:06:07.160 --> 00:06:08.876 our Senior Vice President from Smile,

NOTE Confidence: 0.686923143076923

00:06:08.880 --> 00:06:11.528 to join us and we'll take the obligate

NOTE Confidence: 0.686923143076923

00:06:11.528 --> 00:06:13.553 picture that will be in direct

NOTE Confidence: 0.686923143076923

00:06:13.553 --> 00:06:14.916 connect and we're how do you want us?

NOTE Confidence: 0.468812895

00:06:28.760 --> 00:06:29.940 How was he going to do that?

NOTE Confidence: 0.468812895

00:06:29.940 --> 00:06:31.760 So why have to come? The

NOTE Confidence: 0.16836825

00:06:34.640 --> 00:06:35.200 screen, by

NOTE Confidence: 0.50573885

00:06:38.840 --> 00:06:38.920 the

NOTE Confidence: 0.421193961666667

00:06:41.800 --> 00:06:42.676 way, went to a shoe up.

NOTE Confidence: 0.638395336363636

00:06:49.730 --> 00:06:51.570 What invited speaker knows they

NOTE Confidence: 0.638395336363636

00:06:51.570 --> 00:06:53.890 only get 15 minutes to clock,

NOTE Confidence: 0.638395336363636

00:06:53.890 --> 00:06:54.414 but we will have.

NOTE Confidence: 0.638395336363636

00:06:54.414 --> 00:06:55.476 By the way, at the end,

NOTE Confidence: 0.638395336363636

00:06:55.476 --> 00:06:56.364 we're having mentorship testing.

NOTE Confidence: 0.638395336363636

00:06:56.370 --> 00:06:58.631 With any training you would like to

NOTE Confidence: 0.638395336363636

00:06:58.631 --> 00:06:59.835 say we're going to have all the images.

NOTE Confidence: 0.599663745

00:07:02.440 --> 00:07:03.520 Could we kill this just for a second?

NOTE Confidence: 0.599663745

00:07:03.520 --> 00:07:05.560 Just for a quick second? Sure. Thanks.

NOTE Confidence: 0.451984

00:07:22.550 --> 00:07:23.270 Good luck at lunch.

NOTE Confidence: 0.686743483333333

00:07:29.230 --> 00:07:31.070 Thank you so much. Thank you. I'll

NOTE Confidence: 0.69919418

00:07:36.310 --> 00:07:36.870 put it over here.

NOTE Confidence: 0.96965707

00:07:45.760 --> 00:07:48.733 Thank you for those wonderful

NOTE Confidence: 0.96965707

00:07:48.733 --> 00:07:51.319 introductions and thank you Roy and

NOTE Confidence: 0.96965707

00:07:51.320 --> 00:07:53.798 entire team for inviting me here.

NOTE Confidence: 0.96965707

00:07:53.800 --> 00:07:56.355 And thank you for the Calabrese family.

NOTE Confidence: 0.96965707

00:07:56.360 --> 00:08:00.256 It was lovely to meet all of you yesterday

NOTE Confidence: 0.96965707

00:08:00.256 --> 00:08:03.719 at dinner and and and and today as well.

NOTE Confidence: 0.96965707

00:08:03.720 --> 00:08:10.550 So I will focus my lecture today on

NOTE Confidence: 0.96965707

00:08:10.550 --> 00:08:14.736 on a specific area of lung Cancer

NOTE Confidence: 0.96965707

00:08:14.736 --> 00:08:18.784 Research that we call drug tolerant

NOTE Confidence: 0.96965707

00:08:18.784 --> 00:08:20.764 persisters and you'll see what

NOTE Confidence: 0.96965707

00:08:20.764 --> 00:08:23.920 that all means in a few moments.

NOTE Confidence: 0.96965707

00:08:23.920 --> 00:08:25.348 These are my disclosures.

NOTE Confidence: 0.96965707

00:08:25.348 --> 00:08:27.490 I work with lots of companies

NOTE Confidence: 0.96965707

00:08:27.563 --> 00:08:29.513 to try to develop new therapies

NOTE Confidence: 0.96965707

00:08:29.513 --> 00:08:33.360 and hence the disclosures. So as

NOTE Confidence: 0.87120651125

00:08:35.600 --> 00:08:37.895 Doctor Goldberg mentioned,

NOTE Confidence: 0.87120651125

00:08:37.895 --> 00:08:41.720 lung cancer therapies have changed

NOTE Confidence: 0.87120651125

00:08:41.720 --> 00:08:44.159 quite a bit and we think of lung cancer,

NOTE Confidence: 0.87120651125

00:08:44.160 --> 00:08:45.198 especially lung adenocarcinoma,

NOTE Confidence: 0.87120651125

00:08:45.198 --> 00:08:47.620 which is the most common form of

NOTE Confidence: 0.87120651125

00:08:47.684 --> 00:08:52.444 lung cancer today as as a cancer that

NOTE Confidence: 0.87120651125

00:08:52.444 --> 00:08:55.220 harbors potentially targetable genetic

NOTE Confidence: 0.87120651125

00:08:55.329 --> 00:08:59.090 alterations shown in this pie chart.

NOTE Confidence: 0.87120651125

00:08:59.090 --> 00:09:02.902 And if we actually look at what

NOTE Confidence: 0.87120651125

00:09:02.902 --> 00:09:06.212 has been approved as therapies

NOTE Confidence: 0.87120651125

00:09:06.212 --> 00:09:08.020 for these different alterations,

NOTE Confidence: 0.87120651125

00:09:08.020 --> 00:09:10.680 we actually have a large number of

NOTE Confidence: 0.87120651125

00:09:10.680 --> 00:09:13.417 therapies and more coming all the time

NOTE Confidence: 0.87120651125

00:09:13.417 --> 00:09:16.160 approved for specific subsets of lung cancer.

NOTE Confidence: 0.87120651125

00:09:16.160 --> 00:09:18.959 And so when we see patients in the clinic,

NOTE Confidence: 0.87120651125

00:09:18.960 --> 00:09:20.976 one of our first questions is to try

NOTE Confidence: 0.87120651125

00:09:20.976 --> 00:09:22.904 to understand does the cancer in that

NOTE Confidence: 0.87120651125

00:09:22.904 --> 00:09:24.588 individual harbor one of these genetic

NOTE Confidence: 0.87120651125

00:09:24.588 --> 00:09:26.464 alterations that we could then use one

NOTE Confidence: 0.87120651125

00:09:26.464 --> 00:09:28.615 of the therapies on the right hand

NOTE Confidence: 0.87120651125

00:09:28.615 --> 00:09:30.886 side or enroll that patient into a

NOTE Confidence: 0.87120651125

00:09:30.886 --> 00:09:32.944 clinical trial that may be evaluating a

NOTE Confidence: 0.87120651125

00:09:32.944 --> 00:09:35.476 new therapy or a therapeutic combination.

NOTE Confidence: 0.87120651125

00:09:35.480 --> 00:09:39.040 And the therapies are successful.

NOTE Confidence: 0.87120651125

00:09:39.040 --> 00:09:43.368 However, they still don't cure

NOTE Confidence: 0.87120651125

00:09:43.368 --> 00:09:46.078 patients with advanced lung cancer.

NOTE Confidence: 0.87120651125

00:09:46.080 --> 00:09:49.220 They're better than than what we

NOTE Confidence: 0.87120651125

00:09:49.220 --> 00:09:51.698 would have had 2025 years ago,

NOTE Confidence: 0.87120651125

00:09:51.698 --> 00:09:52.916 which is chemotherapy,

NOTE Confidence: 0.87120651125

00:09:52.920 --> 00:09:56.754 but we still need to continue to do better.

NOTE Confidence: 0.87120651125

00:09:56.760 --> 00:09:58.320 And So what typically happens,

NOTE Confidence: 0.87120651125

00:09:58.320 --> 00:10:00.632 and this is an example of a patient

NOTE Confidence: 0.87120651125

00:10:00.632 --> 00:10:03.048 with a lung cancer and he's treated

NOTE Confidence: 0.87120651125

00:10:03.048 --> 00:10:05.960 with a targeted therapy and you can see

NOTE Confidence: 0.87120651125

00:10:06.036 --> 00:10:08.556 almost all of the cancer disappears,

NOTE Confidence: 0.87120651125

00:10:08.560 --> 00:10:11.956 but then it ultimately comes back.

NOTE Confidence: 0.87120651125

00:10:11.960 --> 00:10:14.382 And what I'll focus my discussion today

NOTE Confidence: 0.87120651125

00:10:14.382 --> 00:10:17.117 and what my lab has focused a lot is

NOTE Confidence: 0.87120651125

00:10:17.120 --> 00:10:20.116 trying to understand why does it almost,

NOTE Confidence: 0.87120651125

00:10:20.120 --> 00:10:23.492 almost completely disappears,

NOTE Confidence: 0.87120651125

00:10:23.492 --> 00:10:25.676 but not completely disappear.

NOTE Confidence: 0.87120651125

00:10:25.680 --> 00:10:29.292 And if we made this sort of

NOTE Confidence: 0.87120651125

00:10:29.292 --> 00:10:31.840 intermediate state completely disappear,

NOTE Confidence: 0.87120651125

00:10:31.840 --> 00:10:35.800 would our therapies be more effective?

NOTE Confidence: 0.87120651125

00:10:35.800 --> 00:10:38.808 So let's look at it at a kind

NOTE Confidence: 0.87120651125

00:10:38.808 --> 00:10:41.450 of A at this level.

NOTE Confidence: 0.87120651125

00:10:41.450 --> 00:10:42.080 So,

NOTE Confidence: 0.87120651125

00:10:42.080 --> 00:10:44.304 so example of a cancer we call this

NOTE Confidence: 0.87120651125

00:10:44.304 --> 00:10:46.880 this sort of intermediate state the the

NOTE Confidence: 0.87120651125

00:10:46.880 --> 00:10:49.280 persistor state or the drug tolerant

NOTE Confidence: 0.87120651125

00:10:49.280 --> 00:10:51.637 persistor state out of which cancer

NOTE Confidence: 0.87120651125

00:10:51.637 --> 00:10:54.422 various resistance mechanisms that we

NOTE Confidence: 0.87120651125

00:10:54.422 --> 00:10:57.160 can detect clinically ultimately arise.

NOTE Confidence: 0.87120651125

00:10:57.160 --> 00:10:58.693 Sometimes resistance mechanisms

NOTE Confidence: 0.87120651125

00:10:58.693 --> 00:11:01.248 can pre-existing cancers and when

NOTE Confidence: 0.87120651125

00:11:01.248 --> 00:11:04.070 you treat them with therapies they

NOTE Confidence: 0.87120651125

00:11:04.070 --> 00:11:06.948 can out outgrow it and and and and

NOTE Confidence: 0.87120651125

00:11:06.948 --> 00:11:08.233 develop resistance in that way.

NOTE Confidence: 0.87120651125

00:11:08.240 --> 00:11:10.522 But this is definitely as as shown

NOTE Confidence: 0.87120651125

00:11:10.522 --> 00:11:12.671 in those scans before happens as

NOTE Confidence: 0.87120651125

00:11:12.671 --> 00:11:13.748 well and so how,

NOTE Confidence: 0.87120651125

00:11:13.748 --> 00:11:13.984 how,

NOTE Confidence: 0.87120651125

00:11:13.984 --> 00:11:15.800 how can we do better well we can

NOTE Confidence: 0.87120651125

00:11:15.800 --> 00:11:17.940 develop therapies that are more

NOTE Confidence: 0.87120651125

00:11:17.940 --> 00:11:20.080 effective at this initial therapy

NOTE Confidence: 0.87120651125

00:11:20.150 --> 00:11:22.816 stage to eliminate this intermediate

NOTE Confidence: 0.87120651125

00:11:22.816 --> 00:11:26.025 state or we can treat or figure out

NOTE Confidence: 0.87120651125

00:11:26.025 --> 00:11:28.675 what make what's unique about this

NOTE Confidence: 0.87120651125

00:11:28.675 --> 00:11:31.075 intermediate state and how could

NOTE Confidence: 0.87120651125

00:11:31.075 --> 00:11:34.144 we eliminate it and ultimately

NOTE Confidence: 0.87120651125

00:11:34.144 --> 00:11:36.764 delay or prevent resistance.

NOTE Confidence: 0.87120651125

00:11:36.764 --> 00:11:41.964 So one and and and as as as as you

NOTE Confidence: 0.87120651125

00:11:41.964 --> 00:11:43.045 heard from the introduction, I,

NOTE Confidence: 0.87120651125

00:11:43.045 --> 00:11:45.320 I focus on EGFR mutant lung cancer,

NOTE Confidence: 0.87120651125

00:11:45.320 --> 00:11:47.886 which in that pie chart is not

NOTE Confidence: 0.87120651125

00:11:47.886 --> 00:11:48.624 quite the biggest,

NOTE Confidence: 0.87120651125

00:11:48.624 --> 00:11:50.639 sort of the second biggest piece of the pie.

NOTE Confidence: 0.87120651125

00:11:50.640 --> 00:11:53.510 And we were involved in that initial

NOTE Confidence: 0.87120651125

00:11:53.510 --> 00:11:56.204 discovery and have subsequently tried

NOTE Confidence: 0.87120651125

00:11:56.204 --> 00:11:59.108 to develop therapies for patients who

NOTE Confidence: 0.87120651125

00:11:59.108 --> 00:12:01.276 are treated with EGFR inhibitors.

NOTE Confidence: 0.87120651125

00:12:01.276 --> 00:12:03.782 And one of the things that we're

NOTE Confidence: 0.87120651125

00:12:03.782 --> 00:12:05.558 recently involved in was asking

NOTE Confidence: 0.87120651125

00:12:05.560 --> 00:12:09.184 can we use another therapy such

NOTE Confidence: 0.87120651125

00:12:09.184 --> 00:12:11.600 as chemotherapy that we

NOTE Confidence: 0.854648556363636

00:12:11.600 --> 00:12:13.220 commonly use in lung cancer in

NOTE Confidence: 0.854648556363636

00:12:13.220 --> 00:12:14.840 combination with an EGFR inhibitor.

NOTE Confidence: 0.854648556363636

00:12:14.840 --> 00:12:17.864 And would that in fact lead to

NOTE Confidence: 0.854648556363636

00:12:17.864 --> 00:12:20.336 a better outcome for patients

NOTE Confidence: 0.854648556363636

00:12:20.336 --> 00:12:23.670 compared to an EGFR inhibitor alone.

NOTE Confidence: 0.854648556363636

00:12:23.670 --> 00:12:26.010 And that could be because it's

NOTE Confidence: 0.854648556363636

00:12:26.010 --> 00:12:27.559 more effective initially or it

NOTE Confidence: 0.854648556363636

00:12:27.560 --> 00:12:32.320 impacts this intermediate state.

NOTE Confidence: 0.854648556363636

00:12:32.320 --> 00:12:34.280 And so this is a clinical trial that

NOTE Confidence: 0.854648556363636

00:12:34.280 --> 00:12:36.058 those of you who treat lung cancer

NOTE Confidence: 0.854648556363636

00:12:36.058 --> 00:12:37.414 patients are probably familiar with

NOTE Confidence: 0.854648556363636

00:12:37.414 --> 00:12:39.516 called the FLORA two trial where

NOTE Confidence: 0.854648556363636

00:12:39.516 --> 00:12:41.850 the standard of care EGF inhibitor

NOTE Confidence: 0.854648556363636

00:12:41.925 --> 00:12:44.637 ASA mertnib also known as Tagrisso

NOTE Confidence: 0.854648556363636

00:12:44.637 --> 00:12:46.445 was combined with chemotherapy

NOTE Confidence: 0.854648556363636

00:12:46.515 --> 00:12:48.879 compared to the ASA mertnib alone.

NOTE Confidence: 0.854648556363636

00:12:48.880 --> 00:12:51.880 And patients got combination chemotherapy

NOTE Confidence: 0.854648556363636

00:12:51.880 --> 00:12:54.880 and then followed by maintenance

NOTE Confidence: 0.854648556363636

00:12:54.963 --> 00:12:57.638 chemotherapy and and ASA mertnib.

NOTE Confidence: 0.854648556363636

00:12:57.640 --> 00:12:59.662 And this trial turned out to

NOTE Confidence: 0.854648556363636

00:12:59.662 --> 00:13:03.360 be a positive in in terms of

NOTE Confidence: 0.854648556363636

00:13:03.360 --> 00:13:05.425 progression free survival sort of

NOTE Confidence: 0.854648556363636

00:13:05.425 --> 00:13:07.077 delaying the likelihood of

NOTE Confidence: 0.836114335

00:13:09.840 --> 00:13:14.536 recurrence from or disease growth from

NOTE Confidence: 0.836114335

00:13:14.536 --> 00:13:16.632 lung cancer significantly depending

NOTE Confidence: 0.836114335

00:13:16.632 --> 00:13:20.407 on how how it was looked at by the

NOTE Confidence: 0.836114335

00:13:20.407 --> 00:13:22.839 investigators or by blinded review.

NOTE Confidence: 0.836114335

00:13:22.840 --> 00:13:26.520 It delays that by about nine months which

NOTE Confidence: 0.836114335

00:13:26.520 --> 00:13:30.615 which has clinical implications as well.

NOTE Confidence: 0.836114335

00:13:30.615 --> 00:13:33.285 It was especially effective in patients

NOTE Confidence: 0.836114335

00:13:33.285 --> 00:13:35.524 who whose cancer had metastasized

NOTE Confidence: 0.836114335

00:13:35.524 --> 00:13:38.110 to the brain this this difference

NOTE Confidence: 0.836114335

00:13:38.183 --> 00:13:39.755 is larger but even in patients

NOTE Confidence: 0.836114335

00:13:39.755 --> 00:13:41.520 who where that wasn't the case,

NOTE Confidence: 0.836114335

00:13:41.520 --> 00:13:42.528 it was effective.

NOTE Confidence: 0.836114335

00:13:42.528 --> 00:13:44.880 And if we look at the common

NOTE Confidence: 0.836114335

00:13:44.958 --> 00:13:47.354 types of EGFR mutations about the

NOTE Confidence: 0.836114335

00:13:47.354 --> 00:13:49.342 of the common ones about 50% are

NOTE Confidence: 0.836114335

00:13:49.342 --> 00:13:51.394 these Exxon 19 deletions and 50%

NOTE Confidence: 0.836114335

00:13:51.400 --> 00:13:53.038 are these Li 58 arm mutations.

NOTE Confidence: 0.836114335

00:13:53.040 --> 00:13:56.431 And in both cases chemotherapy improved

NOTE Confidence: 0.836114335

00:13:56.431 --> 00:14:02.119 the outcome of of of of the patients.

NOTE Confidence: 0.836114335

00:14:02.120 --> 00:14:05.970 It's it's too early to know whether

NOTE Confidence: 0.836114335

00:14:05.970 --> 00:14:07.620 this improvement translates

NOTE Confidence: 0.836114335

00:14:07.713 --> 00:14:10.157 into patients living longer.

NOTE Confidence: 0.836114335

00:14:10.160 --> 00:14:11.995 We'll hopefully have some updates

NOTE Confidence: 0.836114335

00:14:11.995 --> 00:14:14.439 later on this year on on that.

NOTE Confidence: 0.836114335

00:14:14.440 --> 00:14:17.160 But it did delay the what we call

NOTE Confidence: 0.836114335

00:14:17.160 --> 00:14:18.760 the 2nd progression free survival.

NOTE Confidence: 0.836114335

00:14:18.760 --> 00:14:20.440 So the time

NOTE Confidence: 0.663055519090909

00:14:22.640 --> 00:14:25.004 of so patients who got chemotherapy

NOTE Confidence: 0.663055519090909

00:14:25.004 --> 00:14:28.180 and an EGFR inhibitor first even if

NOTE Confidence: 0.663055519090909

00:14:28.180 --> 00:14:31.130 they got subsequent therapy it's

NOTE Confidence: 0.663055519090909

00:14:31.130 --> 00:14:33.800 still that was still effective.

NOTE Confidence: 0.663055519090909

00:14:33.800 --> 00:14:36.920 They they had a longer durability

NOTE Confidence: 0.663055519090909

00:14:36.920 --> 00:14:39.872 of benefit than if they just

NOTE Confidence: 0.663055519090909

00:14:39.872 --> 00:14:41.840 started the EGFR inhibitor.

NOTE Confidence: 0.663055519090909

00:14:41.840 --> 00:14:44.424 Now if we look at kind of trying

NOTE Confidence: 0.663055519090909

00:14:44.424 --> 00:14:46.744 to understand what is what is

NOTE Confidence: 0.663055519090909

00:14:46.744 --> 00:14:49.249 chemotherapy doing now it turns out

NOTE Confidence: 0.663055519090909

00:14:49.249 --> 00:14:51.230 that the this is the EGFR inhibitor

NOTE Confidence: 0.663055519090909

00:14:51.291 --> 00:14:53.116 alone and this is chemotherapy,

NOTE Confidence: 0.663055519090909

00:14:53.120 --> 00:14:54.212 these look very similar.

NOTE Confidence: 0.663055519090909

00:14:54.212 --> 00:14:56.460 This is, these are all individual

NOTE Confidence: 0.663055519090909

00:14:56.460 --> 00:14:58.925 patients and the degree or or so

NOTE Confidence: 0.663055519090909

00:14:58.925 --> 00:15:00.710 this is what we call a waterfall

NOTE Confidence: 0.663055519090909

00:15:00.778 --> 00:15:03.305 plot and these are all patients were

NOTE Confidence: 0.663055519090909

00:15:03.305 --> 00:15:05.080 measuring their tumor shrinkage.

NOTE Confidence: 0.663055519090909

00:15:05.080 --> 00:15:08.800 And what was maybe disappointing

NOTE Confidence: 0.663055519090909

00:15:08.800 --> 00:15:12.440 is that even with the addition of

NOTE Confidence: 0.663055519090909

00:15:12.440 --> 00:15:15.800 chemotherapy the the maximum or

NOTE Confidence: 0.663055519090909

00:15:15.800 --> 00:15:19.136 median best tumor shrinkage was

NOTE Confidence: 0.663055519090909

00:15:19.136 --> 00:15:23.000 50% in the EGFR inhibitor and only

NOTE Confidence: 0.663055519090909

00:15:23.000 --> 00:15:26.000 52.6% when you added chemotherapy.

NOTE Confidence: 0.663055519090909

00:15:26.000 --> 00:15:26.560 However,

NOTE Confidence: 0.663055519090909

00:15:26.560 --> 00:15:29.360 the durability of that shrinkage

NOTE Confidence: 0.663055519090909

00:15:29.360 --> 00:15:30.587 was much longer,

NOTE Confidence: 0.663055519090909

00:15:30.587 --> 00:15:33.041 about nine months longer if you

NOTE Confidence: 0.663055519090909

00:15:33.041 --> 00:15:35.422 had chemotherapy compared to the

NOTE Confidence: 0.663055519090909

00:15:35.422 --> 00:15:36.678 EGFR inhibited by itself.

NOTE Confidence: 0.663055519090909

00:15:36.680 --> 00:15:39.280 But it still means that there are

NOTE Confidence: 0.663055519090909

00:15:39.280 --> 00:15:42.400 cancer cells that are able to

NOTE Confidence: 0.663055519090909

00:15:42.400 --> 00:15:44.424 survive despite EGFR inhibition and

NOTE Confidence: 0.663055519090909

00:15:44.424 --> 00:15:47.503 and and and this is an area that we

NOTE Confidence: 0.663055519090909

00:15:47.503 --> 00:15:49.283 have focused pre clinically quite

NOTE Confidence: 0.663055519090909

00:15:49.283 --> 00:15:52.009 a bit and asked the question what

NOTE Confidence: 0.663055519090909

00:15:52.009 --> 00:15:54.391 sort of dictates the dichotomy of

NOTE Confidence: 0.663055519090909

00:15:54.400 --> 00:15:57.060 a of a of a of a cancer cell from

NOTE Confidence: 0.663055519090909

00:15:57.144 --> 00:15:59.616 dying versus surviving these cancers

NOTE Confidence: 0.663055519090909

00:15:59.616 --> 00:16:01.356 that have these EGFR mutations.

NOTE Confidence: 0.663055519090909

00:16:01.360 --> 00:16:02.560 This represents a cancer and

NOTE Confidence: 0.663055519090909

00:16:02.560 --> 00:16:03.520 these are individual cells.

NOTE Confidence: 0.663055519090909

00:16:03.520 --> 00:16:05.360 All of the individual cells

NOTE Confidence: 0.663055519090909

00:16:05.360 --> 00:16:06.832 have the EGFR mutation.

NOTE Confidence: 0.663055519090909

00:16:06.840 --> 00:16:08.872 So it's not like the ones that survive

NOTE Confidence: 0.663055519090909

00:16:08.872 --> 00:16:10.478 don't have the EGFR alteration,

NOTE Confidence: 0.663055519090909

00:16:10.480 --> 00:16:12.678 they do but they figure out ways

NOTE Confidence: 0.663055519090909

00:16:12.678 --> 00:16:14.359 to survive whereas others die.

NOTE Confidence: 0.663055519090909

00:16:14.360 --> 00:16:18.720 And several years ago we we

NOTE Confidence: 0.663055519090909

00:16:18.720 --> 00:16:21.504 recognize that one of the downstream

NOTE Confidence: 0.663055519090909

00:16:21.504 --> 00:16:23.360 pathways from EGFR map,

NOTE Confidence: 0.663055519090909

00:16:23.360 --> 00:16:26.312 kinase pathway are here as measured

NOTE Confidence: 0.663055519090909

00:16:26.312 --> 00:16:28.949 here by phosphorylation of URC is

NOTE Confidence: 0.663055519090909

00:16:28.949 --> 00:16:31.741 turned here it's on here it's off but

NOTE Confidence: 0.663055519090909

00:16:31.741 --> 00:16:34.146 within a few days it comes back on

NOTE Confidence: 0.663055519090909

00:16:34.146 --> 00:16:36.632 and if you block this pathway with

NOTE Confidence: 0.663055519090909

00:16:36.632 --> 00:16:39.080 a a MEC inhibitor here trimetinib,

NOTE Confidence: 0.663055519090909

00:16:39.080 --> 00:16:42.440 you can prevent that from happening.

NOTE Confidence: 0.663055519090909

00:16:42.440 --> 00:16:43.480 So why is that important?

NOTE Confidence: 0.663055519090909

00:16:43.480 --> 00:16:43.952 Well,

NOTE Confidence: 0.663055519090909

00:16:43.952 --> 00:16:46.784 the way EGFR inhibitors cause cancer

NOTE Confidence: 0.663055519090909

00:16:46.784 --> 00:16:50.109 cells to die is they down regulate

NOTE Confidence: 0.663055519090909

00:16:50.109 --> 00:16:53.232 this pathway as I've shown here that

NOTE Confidence: 0.663055519090909

00:16:53.232 --> 00:16:55.584 bath that leads to up regulation

NOTE Confidence: 0.663055519090909

00:16:55.584 --> 00:16:57.692 of a proipoptotic protein called

NOTE Confidence: 0.663055519090909

00:16:57.692 --> 00:17:00.118 BIM and then leads to cell death.

NOTE Confidence: 0.663055519090909

00:17:00.120 --> 00:17:02.843 And so now EGFR inhibition is decoupled

NOTE Confidence: 0.663055519090909

00:17:02.843 --> 00:17:05.119 from down regulating of this pathway.

NOTE Confidence: 0.663055519090909

00:17:05.120 --> 00:17:07.268 Now you've provided a a way

NOTE Confidence: 0.663055519090909

00:17:07.268 --> 00:17:09.440 for the cells to survive,

NOTE Confidence: 0.663055519090909

00:17:09.440 --> 00:17:14.456 turn this pathway on and and survive.

NOTE Confidence: 0.663055519090909

00:17:14.456 --> 00:17:17.194 And so here we can block it with a

NOTE Confidence: 0.663055519090909

00:17:17.194 --> 00:17:18.904 drug trimetinib, our MEC inhibitor.

NOTE Confidence: 0.663055519090909

00:17:18.904 --> 00:17:21.511 And we're trying to evaluate this in

NOTE Confidence: 0.663055519090909

00:17:21.511 --> 00:17:23.513 the clinic by doing a clinical trial

NOTE Confidence: 0.663055519090909

00:17:23.520 --> 00:17:25.705 combining an EGFR inhibitor here

NOTE Confidence: 0.663055519090909

00:17:25.705 --> 00:17:28.920 with a MEC inhibitor called solumettinib.

NOTE Confidence: 0.663055519090909

00:17:28.920 --> 00:17:32.372 And here we have to give it

NOTE Confidence: 0.663055519090909

00:17:32.372 --> 00:17:33.676 intermittently 4 days on,

NOTE Confidence: 0.663055519090909

00:17:33.680 --> 00:17:35.318 three days off because when these

NOTE Confidence: 0.663055519090909

00:17:35.318 --> 00:17:37.040 drugs are given by themselves,

NOTE Confidence: 0.663055519090909

00:17:37.040 --> 00:17:38.536 they have side effects,

NOTE Confidence: 0.663055519090909

00:17:38.536 --> 00:17:40.406 typically skin side effects and

NOTE Confidence: 0.663055519090909

00:17:40.406 --> 00:17:42.237 fevers and other side effects.

NOTE Confidence: 0.663055519090909

00:17:42.240 --> 00:17:45.032 And so we can't give both the EGFR

NOTE Confidence: 0.663055519090909

00:17:45.032 --> 00:17:47.839 inhibitor and the MEC inhibitor every day.

NOTE Confidence: 0.880460655454545

00:17:47.840 --> 00:17:49.828 Now whether this intermittent

NOTE Confidence: 0.880460655454545

00:17:49.828 --> 00:17:52.313 schedule achieves the same biologic

NOTE Confidence: 0.880460655454545

00:17:52.313 --> 00:17:55.645 outcome that we saw in the laboratory

NOTE Confidence: 0.880460655454545

00:17:55.645 --> 00:17:58.638 setting remains to be seen.

NOTE Confidence: 0.880460655454545

00:17:58.640 --> 00:18:02.760 Now despite doing those two therapies,

NOTE Confidence: 0.880460655454545

00:18:02.760 --> 00:18:06.920 if we look at cells under the microscope,

NOTE Confidence: 0.880460655454545

00:18:06.920 --> 00:18:08.720 they're still surviving cells

NOTE Confidence: 0.93936686125

00:18:11.280 --> 00:18:12.680 even when we add those

NOTE Confidence: 0.93936686125

00:18:12.680 --> 00:18:13.520 two combinations together.

NOTE Confidence: 0.93936686125

00:18:13.520 --> 00:18:15.879 And if we analyze the cells that

NOTE Confidence: 0.93936686125

00:18:15.880 --> 00:18:17.364 after one day of giving the drugs

NOTE Confidence: 0.93936686125

00:18:17.364 --> 00:18:19.159 or 21 days after giving the drugs,

NOTE Confidence: 0.93936686125

00:18:19.160 --> 00:18:21.023 we can see that all of the sort

NOTE Confidence: 0.93936686125

00:18:21.023 --> 00:18:23.081 of EGFR and pathways are turned

NOTE Confidence: 0.93936686125

00:18:23.081 --> 00:18:24.947 off including ERC because we're

NOTE Confidence: 0.93936686125

00:18:24.947 --> 00:18:27.239 using that the MEC inhibitor here.

NOTE Confidence: 0.93936686125

00:18:27.240 --> 00:18:28.716 If you withdraw those,

NOTE Confidence: 0.93936686125

00:18:28.716 --> 00:18:31.480 if you then wash out the drugs,

NOTE Confidence: 0.93936686125

00:18:31.480 --> 00:18:33.465 the cancer actually regrow regrows

NOTE Confidence: 0.93936686125

00:18:33.465 --> 00:18:36.038 that we call rebound cells and all

NOTE Confidence: 0.93936686125

00:18:36.038 --> 00:18:39.480 of those pathways are once again on.

NOTE Confidence: 0.93936686125

00:18:39.480 --> 00:18:43.736 And so we had wondered how is

NOTE Confidence: 0.93936686125

00:18:43.736 --> 00:18:46.908 it that they survive and they

NOTE Confidence: 0.93936686125

00:18:46.908 --> 00:18:49.216 survive through up regulating

NOTE Confidence: 0.93936686125

00:18:49.216 --> 00:18:51.120 another signaling pathway called

NOTE Confidence: 0.93936686125

00:18:51.120 --> 00:18:52.880 the Hippo signaling pathway,

NOTE Confidence: 0.93936686125

00:18:52.880 --> 00:18:57.660 namely a protein called Yap that

NOTE Confidence: 0.93936686125

00:18:57.660 --> 00:19:01.879 normally when it's turned on or

NOTE Confidence: 0.93936686125

00:19:01.879 --> 00:19:03.474 up regulated which happens in

NOTE Confidence: 0.93936686125

00:19:03.474 --> 00:19:05.720 response to EGFR and MEC inhibition,

NOTE Confidence: 0.93936686125

00:19:05.720 --> 00:19:10.277 it turns off the expression of A

NOTE Confidence: 0.93936686125

00:19:10.280 --> 00:19:12.840 pro apoptotic sensitizer called BMF.

NOTE Confidence: 0.93936686125

00:19:12.840 --> 00:19:15.440 And so if you now block this

NOTE Confidence: 0.93936686125

00:19:15.440 --> 00:19:17.440 in any way genetically deleted

NOTE Confidence: 0.93936686125

00:19:17.440 --> 00:19:19.680 or use drugs against this,

NOTE Confidence: 0.93936686125

00:19:19.680 --> 00:19:21.960 you now up regulate this protein.

NOTE Confidence: 0.93936686125

00:19:21.960 --> 00:19:25.777 It can release more of the apoptotic

NOTE Confidence: 0.93936686125

00:19:25.777 --> 00:19:28.262 proteins namely BIM from anti

NOTE Confidence: 0.93936686125

00:19:28.262 --> 00:19:30.747 apoptotic proteins and it can

NOTE Confidence: 0.93936686125

00:19:30.747 --> 00:19:33.237 shift cell survival to cell death.

NOTE Confidence: 0.93936686125

00:19:33.240 --> 00:19:34.784 And so that's another.

NOTE Confidence: 0.93936686125

00:19:34.784 --> 00:19:36.714 So it's basically another counter

NOTE Confidence: 0.93936686125

00:19:36.714 --> 00:19:38.051 regulatory mechanism by which

NOTE Confidence: 0.93936686125

00:19:38.051 --> 00:19:39.605 cancer is used to survive.

NOTE Confidence: 0.93936686125

00:19:39.605 --> 00:19:42.525 And this is just to prove that you

NOTE Confidence: 0.93936686125

00:19:42.525 --> 00:19:44.865 actually need if you if you use

NOTE Confidence: 0.93936686125

00:19:44.865 --> 00:19:47.120 genetic tools to knock out this BMF,

NOTE Confidence: 0.93936686125

00:19:47.120 --> 00:19:49.500 you don't see the the the increased

NOTE Confidence: 0.93936686125

00:19:49.500 --> 00:19:51.562 cell death here compared to if

NOTE Confidence: 0.93936686125

00:19:51.562 --> 00:19:53.512 it's if it's not knocked out.

NOTE Confidence: 0.93936686125

00:19:53.520 --> 00:19:55.992 And the good thing is there are now

NOTE Confidence: 0.93936686125

00:19:55.992 --> 00:19:58.760 companies that make TEED inhibitors.

NOTE Confidence: 0.93936686125

00:19:58.760 --> 00:20:01.611 This Yap protein interacts with

NOTE Confidence: 0.93936686125

00:20:01.611 --> 00:20:03.296 another protein called TEED and

NOTE Confidence: 0.93936686125

00:20:03.296 --> 00:20:04.989 there are multiple companies that

NOTE Confidence: 0.93936686125

00:20:04.989 --> 00:20:06.594 are making these inhibitors and

NOTE Confidence: 0.93936686125

00:20:06.594 --> 00:20:08.400 if we use these inhibitors.

NOTE Confidence: 0.93936686125

00:20:08.400 --> 00:20:09.960 Here if we measure cell death in red,

NOTE Confidence: 0.93936686125

00:20:09.960 --> 00:20:11.920 when we add one of these inhibitors,

NOTE Confidence: 0.93936686125

00:20:11.920 --> 00:20:13.320 they increase cell death from

NOTE Confidence: 0.93936686125

00:20:13.320 --> 00:20:15.950 blue to red and we hope that this

NOTE Confidence: 0.93936686125

00:20:15.950 --> 00:20:17.117 is clinically meaningful.

NOTE Confidence: 0.93936686125

00:20:17.120 --> 00:20:19.960 They're being mostly tested in

NOTE Confidence: 0.93936686125

00:20:19.960 --> 00:20:22.104 initially in malignant mesothelioma,

NOTE Confidence: 0.93936686125

00:20:22.104 --> 00:20:25.320 but they there are hopes that

NOTE Confidence: 0.93936686125

00:20:25.405 --> 00:20:27.555 these will move towards testing

NOTE Confidence: 0.93936686125

00:20:27.555 --> 00:20:30.200 in in lung cancers as well.

NOTE Confidence: 0.93936686125

00:20:30.200 --> 00:20:32.516 So I mentioned the two kind

NOTE Confidence: 0.93936686125

00:20:32.516 --> 00:20:33.674 of regulatory pathways.

NOTE Confidence: 0.93936686125

00:20:33.680 --> 00:20:35.780 We then wanted to ask another

NOTE Confidence: 0.93936686125

00:20:35.780 --> 00:20:37.803 question by studying this state and

NOTE Confidence: 0.93936686125

00:20:37.803 --> 00:20:39.682 ask is there something that we can

NOTE Confidence: 0.93936686125

00:20:39.682 --> 00:20:42.165 you know if we these are to enhance

NOTE Confidence: 0.93936686125

00:20:42.165 --> 00:20:44.193 the initial effect of the therapies.

NOTE Confidence: 0.93936686125

00:20:44.200 --> 00:20:46.504 I'll shift to talking about this

NOTE Confidence: 0.93936686125

00:20:46.504 --> 00:20:49.569 cell state and ask are these are

NOTE Confidence: 0.93936686125

00:20:49.569 --> 00:20:51.497 the unique vulnerabilities within

NOTE Confidence: 0.93936686125

00:20:51.497 --> 00:20:53.480 this actual cell state.

NOTE Confidence: 0.93936686125

00:20:53.480 --> 00:20:55.342 And when we did this prior study

NOTE Confidence: 0.93936686125

00:20:55.342 --> 00:20:55.874 where we

NOTE Confidence: 0.616356996

00:20:59.960 --> 00:21:02.440 found this Yap teed pathway,

NOTE Confidence: 0.616356996

00:21:02.440 --> 00:21:05.008 we recognize that the cells that

NOTE Confidence: 0.616356996

00:21:05.008 --> 00:21:07.150 survive in after a inhibition with

NOTE Confidence: 0.616356996

00:21:07.150 --> 00:21:09.367 an EGFR inhibitor or any other

NOTE Confidence: 0.616356996

00:21:09.367 --> 00:21:11.959 inhibitor in the right genetic context,

NOTE Confidence: 0.616356996

00:21:11.960 --> 00:21:15.560 they have features of cellular senescence,

NOTE Confidence: 0.616356996

00:21:15.560 --> 00:21:18.878 so aging cells and it it doesn't

NOTE Confidence: 0.616356996

00:21:18.880 --> 00:21:21.440 matter how you characterize them,

NOTE Confidence: 0.616356996

00:21:21.440 --> 00:21:23.078 they all have this is a,

NOTE Confidence: 0.616356996

00:21:23.080 --> 00:21:25.078 they're often they stain blue and

NOTE Confidence: 0.616356996

00:21:25.078 --> 00:21:26.410 this beta galactosidase stain

NOTE Confidence: 0.616356996

00:21:26.466 --> 00:21:28.050 and they have other features that

NOTE Confidence: 0.616356996

00:21:28.050 --> 00:21:29.799 are all found in these cells.

NOTE Confidence: 0.616356996

00:21:29.800 --> 00:21:32.332 Now it's not true cellular senescence

NOTE Confidence: 0.616356996

00:21:32.332 --> 00:21:34.880 because true senescence is irreversible

NOTE Confidence: 0.616356996

00:21:34.880 --> 00:21:38.359 unfortunately as all of us are aging.

NOTE Confidence: 0.616356996

00:21:38.360 --> 00:21:39.800 But this is a reversible state

NOTE Confidence: 0.616356996

00:21:39.800 --> 00:21:41.035 because as I mentioned earlier

NOTE Confidence: 0.616356996

00:21:41.035 --> 00:21:42.355 if you take the drugs off,

NOTE Confidence: 0.616356996

00:21:42.360 --> 00:21:45.384 the cancer cells will start to to grow.

NOTE Confidence: 0.616356996

00:21:45.384 --> 00:21:47.560 And and there is a whole field

NOTE Confidence: 0.616356996

00:21:47.560 --> 00:21:50.575 of developing drugs trying to

NOTE Confidence: 0.616356996

00:21:50.575 --> 00:21:53.590 treat senescent cells and they're

NOTE Confidence: 0.616356996

00:21:53.693 --> 00:21:56.758 often referred to as Senalytics.

NOTE Confidence: 0.616356996

00:21:56.760 --> 00:22:00.675 And what we so we wanted to do is

NOTE Confidence: 0.616356996

00:22:00.680 --> 00:22:03.590 first treat our cancer cells with

NOTE Confidence: 0.616356996

00:22:03.590 --> 00:22:06.834 an EGFR inhibitor and then treat him

NOTE Confidence: 0.616356996

00:22:06.834 --> 00:22:10.183 with another drug to ask can we in

NOTE Confidence: 0.616356996

00:22:10.183 --> 00:22:13.472 this red example can we find drugs

NOTE Confidence: 0.616356996

00:22:13.472 --> 00:22:15.314 that would specifically eliminate

NOTE Confidence: 0.616356996

00:22:15.314 --> 00:22:17.826 or be toxic to those cells that are

NOTE Confidence: 0.616356996

00:22:17.826 --> 00:22:20.355 in this state And and when we look

NOTE Confidence: 0.616356996

00:22:20.355 --> 00:22:22.718 through and and screened all of them,

NOTE Confidence: 0.616356996

00:22:22.720 --> 00:22:23.839 the ones that

NOTE Confidence: 0.854549174

00:22:26.440 --> 00:22:31.620 scored in the top are inhibitors of BCLXL

NOTE Confidence: 0.854549174

00:22:31.620 --> 00:22:36.860 which is an anti apoptotic protein.

NOTE Confidence: 0.854549174

00:22:36.860 --> 00:22:40.150 So by inhibiting that you can again

NOTE Confidence: 0.854549174

00:22:40.150 --> 00:22:43.156 shift cells more to dying as opposed

NOTE Confidence: 0.854549174

00:22:43.156 --> 00:22:45.573 to surviving and this is enriched

NOTE Confidence: 0.854549174

00:22:45.573 --> 00:22:48.440 in the in the senescent state.

NOTE Confidence: 0.9664974425

00:22:50.640 --> 00:22:51.680 So if that's true

NOTE Confidence: 0.906612749130435

00:22:51.680 --> 00:22:53.800 then we should be able to show that

NOTE Confidence: 0.906612749130435

00:22:53.800 --> 00:22:55.618 experimentally and so we first did this

NOTE Confidence: 0.906612749130435

00:22:55.618 --> 00:22:57.438 experiment where we took mice that have a

NOTE Confidence: 0.6015004

00:22:59.720 --> 00:23:02.160 carry a xenograft of an EGFR mutant cells.

NOTE Confidence: 0.6015004

00:23:02.160 --> 00:23:04.613 We treated them with a control or

NOTE Confidence: 0.6015004

00:23:04.613 --> 00:23:06.851 with the EGFR and MEC inhibitor

NOTE Confidence: 0.6015004

00:23:06.851 --> 00:23:09.039 combination for three weeks and after

NOTE Confidence: 0.6015004

00:23:09.039 --> 00:23:11.488 three weeks we split half the mice

NOTE Confidence: 0.6015004

00:23:11.488 --> 00:23:13.952 to continue the EGFR MEC inhibitor or

NOTE Confidence: 0.6015004

00:23:13.952 --> 00:23:16.372 added a BCLXL inhibitor Nabita Clex.

NOTE Confidence: 0.6015004

00:23:16.372 --> 00:23:20.320 And then we treated for another three weeks

NOTE Confidence: 0.6015004

00:23:20.320 --> 00:23:22.040 and then we stopped all the drug treatments.

NOTE Confidence: 0.6015004

00:23:22.040 --> 00:23:25.678 And we asked is there is there a

NOTE Confidence: 0.6015004

00:23:25.678 --> 00:23:27.880 difference in growth regrowth of the of

NOTE Confidence: 0.6015004

00:23:27.880 --> 00:23:30.785 the cancer in the in the model that just

NOTE Confidence: 0.6015004

00:23:30.785 --> 00:23:33.333 got the EGFR MEC inhibitor compared to

NOTE Confidence: 0.6015004

00:23:33.409 --> 00:23:35.670 the one that got the BCLXL inhibitor.

NOTE Confidence: 0.6015004

00:23:35.670 --> 00:23:39.310 Because if we if if if our hypothesis

NOTE Confidence: 0.6015004

00:23:39.397 --> 00:23:41.615 is correct at this state that persistent

NOTE Confidence: 0.6015004

00:23:41.615 --> 00:23:43.304 state has been established and if

NOTE Confidence: 0.6015004

00:23:43.304 --> 00:23:44.876 they're sensitive to the nevita clax,

NOTE Confidence: 0.6015004

00:23:44.880 --> 00:23:47.112 we should eliminate more of the

NOTE Confidence: 0.6015004

00:23:47.112 --> 00:23:49.947 cells and then it should delay the

NOTE Confidence: 0.6015004

00:23:49.947 --> 00:23:51.639 regrowth of the tumor.

NOTE Confidence: 0.6015004

00:23:51.640 --> 00:23:54.175 And it does a little bit in green

NOTE Confidence: 0.6015004

00:23:54.175 --> 00:23:56.064 here although you could argue that

NOTE Confidence: 0.6015004

00:23:56.064 --> 00:23:57.594 this is probably pretty marginal.

NOTE Confidence: 0.6015004

00:23:57.600 --> 00:23:58.920 This is so the treatment,

NOTE Confidence: 0.6015004

00:23:58.920 --> 00:24:01.836 this is the day day 42 when we withdraw

NOTE Confidence: 0.6015004

00:24:01.836 --> 00:24:05.358 the the drugs and then compare growth.

NOTE Confidence: 0.6015004

00:24:05.360 --> 00:24:07.411 And here if you look at the

NOTE Confidence: 0.6015004

00:24:07.411 --> 00:24:07.997 individual animals,

NOTE Confidence: 0.6015004

00:24:08.000 --> 00:24:09.800 here's the the three drug combination,

NOTE Confidence: 0.6015004

00:24:09.800 --> 00:24:12.104 you can see that most of them still

NOTE Confidence: 0.6015004

00:24:12.104 --> 00:24:14.640 grow back although there are some

NOTE Confidence: 0.6015004

00:24:14.640 --> 00:24:16.600 that are completely eliminated.

NOTE Confidence: 0.6015004

00:24:16.600 --> 00:24:19.664 So we were wondering why may that be

NOTE Confidence: 0.6015004

00:24:19.664 --> 00:24:22.956 the the case and one possibility is,

NOTE Confidence: 0.6015004

00:24:22.960 --> 00:24:25.522 are we delivering the drugs to

NOTE Confidence: 0.6015004

00:24:25.522 --> 00:24:28.151 the to these persistent cells in

NOTE Confidence: 0.6015004

00:24:28.151 --> 00:24:29.835 in an efficient manner.

NOTE Confidence: 0.6015004

00:24:29.840 --> 00:24:32.560 And to get at that problem,

NOTE Confidence: 0.6015004

00:24:32.560 --> 00:24:34.796 we've worked with AbbVie,

NOTE Confidence: 0.6015004

00:24:34.796 --> 00:24:37.591 A pharmaceutical company that has

NOTE Confidence: 0.6015004

00:24:37.591 --> 00:24:40.345 developed an antibody against EGFR

NOTE Confidence: 0.6015004

00:24:40.345 --> 00:24:43.556 that's coupled to a BCLXL inhibitor.

NOTE Confidence: 0.6015004

00:24:43.556 --> 00:24:45.940 So this is a more of a targeted

NOTE Confidence: 0.6015004

00:24:46.006 --> 00:24:48.116 called an antibody drug conjugate.

NOTE Confidence: 0.6015004

00:24:48.120 --> 00:24:50.605 So it's a more targeted way of

NOTE Confidence: 0.6015004

00:24:50.605 --> 00:24:52.322 delivering the BCLXL inhibitor

NOTE Confidence: 0.6015004

00:24:52.322 --> 00:24:54.592 specifically to cells that express

NOTE Confidence: 0.6015004

00:24:54.592 --> 00:24:57.646 EGFR like the cancer cells that we're

NOTE Confidence: 0.6015004

00:24:57.646 --> 00:25:00.390 interested in And it and that has

NOTE Confidence: 0.6015004

00:25:00.390 --> 00:25:02.226 the advantage of avoiding potential

NOTE Confidence: 0.6015004

00:25:02.226 --> 00:25:03.756 systemic toxicities because if you

NOTE Confidence: 0.6015004

00:25:03.756 --> 00:25:05.479 just give the inhibitor by itself,

NOTE Confidence: 0.6015004

00:25:05.480 --> 00:25:07.202 one of the toxicities that's been

NOTE Confidence: 0.6015004

00:25:07.202 --> 00:25:08.891 seen in the clinic is thrombocytopenia

NOTE Confidence: 0.6015004

00:25:08.891 --> 00:25:10.746 or lowering of platelet counts

NOTE Confidence: 0.6015004

00:25:10.746 --> 00:25:12.650 because this protein is important

NOTE Confidence: 0.6015004

00:25:12.650 --> 00:25:14.480 for maturation of the platelets.

NOTE Confidence: 0.6015004

00:25:14.480 --> 00:25:16.505 And so if you give the drugs will there

NOTE Confidence: 0.6015004

00:25:16.505 --> 00:25:18.716 go to the tumor and to the bone marrow,

NOTE Confidence: 0.6015004

00:25:18.720 --> 00:25:20.620 you'll start to see patients

NOTE Confidence: 0.6015004

00:25:20.620 --> 00:25:21.760 platelet counts decrease.

NOTE Confidence: 0.845170085

00:25:24.040 --> 00:25:26.920 And this is just to show that in from ADVI,

NOTE Confidence: 0.845170085

00:25:26.920 --> 00:25:31.000 if they use a small molecule inhibitor,

NOTE Confidence: 0.845170085

00:25:31.000 --> 00:25:33.040 here's normal platelets, they go down.

NOTE Confidence: 0.845170085

00:25:33.040 --> 00:25:35.238 But if he uses antibody drug conjugate

NOTE Confidence: 0.845170085

00:25:35.238 --> 00:25:37.713 since the this is not cleaved normally

NOTE Confidence: 0.845170085

00:25:37.713 --> 00:25:40.280 except when it's internalized into the cell,

NOTE Confidence: 0.845170085

00:25:40.280 --> 00:25:42.020 you don't see that much

NOTE Confidence: 0.845170085

00:25:42.020 --> 00:25:46.040 of A platelet reduction.

NOTE Confidence: 0.845170085

00:25:46.040 --> 00:25:48.296 So and in ABB Vie's experiments

NOTE Confidence: 0.845170085

00:25:48.296 --> 00:25:50.795 when they've done given the EGFR

NOTE Confidence: 0.845170085

00:25:50.795 --> 00:25:53.110 inhibitor together with this antibody

NOTE Confidence: 0.845170085

00:25:53.110 --> 00:25:55.501 drug conjugate from the beginning,

NOTE Confidence: 0.845170085

00:25:55.501 --> 00:25:57.936 they can certainly delay the

NOTE Confidence: 0.845170085

00:25:57.936 --> 00:26:00.314 regrowth of cancer cancers in

NOTE Confidence: 0.845170085

00:26:00.314 --> 00:26:02.399 in these two different models.

NOTE Confidence: 0.845170085

00:26:02.400 --> 00:26:03.340 But that wasn't exactly the

NOTE Confidence: 0.845170085

00:26:03.340 --> 00:26:04.280 question that we were after.

NOTE Confidence: 0.845170085

00:26:04.280 --> 00:26:05.120 We were after this question,

NOTE Confidence: 0.845170085

00:26:05.120 --> 00:26:06.596 what happens in that persistent state.

NOTE Confidence: 0.845170085

00:26:06.600 --> 00:26:09.232 So we kind of redid that experiment here

NOTE Confidence: 0.845170085

00:26:09.232 --> 00:26:12.026 using the EGFR inhibitor alone where

NOTE Confidence: 0.845170085

00:26:12.026 --> 00:26:15.056 we then after 21 days half the mice

NOTE Confidence: 0.845170085

00:26:15.056 --> 00:26:16.959 will continue the EGFR inhibitor alone,

NOTE Confidence: 0.845170085

00:26:16.960 --> 00:26:18.844 half the mice will continue the

NOTE Confidence: 0.845170085

00:26:18.844 --> 00:26:21.960 EGFR inhibitor and get this e.g.

NOTE Confidence: 0.845170085

00:26:21.960 --> 00:26:24.020 FRBCLXL antibody drug conjugate for

NOTE Confidence: 0.845170085

00:26:24.020 --> 00:26:26.474 another three weeks and then we

NOTE Confidence: 0.845170085

00:26:26.474 --> 00:26:28.600 withdraw the drugs and follow outgrowth

NOTE Confidence: 0.845170085

00:26:28.600 --> 00:26:31.628 and here we see a much more dramatic

NOTE Confidence: 0.845170085

00:26:31.628 --> 00:26:34.196 difference and green is the the,

NOTE Confidence: 0.845170085

00:26:34.200 --> 00:26:36.200 the, the the double combination.

NOTE Confidence: 0.845170085

00:26:36.200 --> 00:26:38.314 You can see that here individual animals.

NOTE Confidence: 0.845170085

00:26:38.320 --> 00:26:41.134 So it's much more impressive than than

NOTE Confidence: 0.845170085

00:26:41.134 --> 00:26:44.088 the than using the nevitoclax alone and

NOTE Confidence: 0.845170085

00:26:44.088 --> 00:26:47.660 the and the animals tolerate it quite well.

NOTE Confidence: 0.845170085

00:26:47.660 --> 00:26:49.952 There are some some over

NOTE Confidence: 0.845170085

00:26:49.952 --> 00:26:51.520 long periods of time.

NOTE Confidence: 0.845170085

00:26:51.520 --> 00:26:54.804 This is like you know six months later

NOTE Confidence: 0.845170085

00:26:54.804 --> 00:26:57.520 we can look at the we can look at the,

NOTE Confidence: 0.845170085

00:26:57.520 --> 00:26:57.800 the,

NOTE Confidence: 0.845170085

00:26:57.800 --> 00:26:58.080 the,

NOTE Confidence: 0.845170085

00:26:58.080 --> 00:27:00.760 the animals and not all of them are cured.

NOTE Confidence: 0.845170085

00:27:00.760 --> 00:27:02.594 Some of them do regrow and we

NOTE Confidence: 0.845170085

00:27:02.594 --> 00:27:04.660 can detect the regrowth by using

NOTE Confidence: 0.845170085

00:27:04.660 --> 00:27:06.280 antibodies that specifically detect

NOTE Confidence: 0.845170085

00:27:06.280 --> 00:27:08.040 the mutiny GFR protein.

NOTE Confidence: 0.848916826

00:27:10.280 --> 00:27:13.680 Sometimes we see immune infiltrates

NOTE Confidence: 0.848916826

00:27:13.680 --> 00:27:16.360 and if he if you if we compare.

NOTE Confidence: 0.848916826

00:27:16.360 --> 00:27:18.048 So we can cure some of the animals

NOTE Confidence: 0.848916826

00:27:18.048 --> 00:27:19.558 with the EGFR inhibitor alone,

NOTE Confidence: 0.848916826

00:27:19.560 --> 00:27:21.426 but we can cure many more

NOTE Confidence: 0.848916826

00:27:21.426 --> 00:27:23.640 when we add this other agent.

NOTE Confidence: 0.848916826

00:27:23.640 --> 00:27:27.968 In the middle of treatment is

NOTE Confidence: 0.848916826

00:27:27.968 --> 00:27:29.608 another model that kind of

NOTE Confidence: 0.848916826

00:27:29.608 --> 00:27:31.752 shows the same same phenomenon.

NOTE Confidence: 0.848916826

00:27:31.752 --> 00:27:32.328 Unfortunately,

NOTE Confidence: 0.848916826

00:27:32.328 --> 00:27:35.784 they also do start to regrow

NOTE Confidence: 0.848916826

00:27:35.784 --> 00:27:38.598 after a period of time and so.

NOTE Confidence: 0.71174131875

00:27:40.760 --> 00:27:42.160 So we see that some mice are cured,

NOTE Confidence: 0.71174131875

00:27:42.160 --> 00:27:44.680 others are not and that could be for

NOTE Confidence: 0.71174131875

00:27:44.680 --> 00:27:46.920 lots of reasons, it's a duration of

NOTE Confidence: 0.71174131875

00:27:46.920 --> 00:27:48.120 treatment important in the clinic.

NOTE Confidence: 0.71174131875

00:27:48.120 --> 00:27:50.040 We would typically continue a second

NOTE Confidence: 0.71174131875

00:27:50.040 --> 00:27:52.219 therapy for much longer periods of time

NOTE Confidence: 0.71174131875

00:27:52.219 --> 00:27:54.193 than we did in the animal experiment.

NOTE Confidence: 0.71174131875

00:27:54.200 --> 00:27:57.320 And of course there are other proteins,

NOTE Confidence: 0.71174131875

00:27:57.320 --> 00:27:59.600 other antipoptotic proteins that

NOTE Confidence: 0.71174131875

00:27:59.600 --> 00:28:01.913 can sort of compensate for BCLXL

NOTE Confidence: 0.71174131875

00:28:01.913 --> 00:28:03.478 inhibition such as MCL one.

NOTE Confidence: 0.71174131875

00:28:03.480 --> 00:28:05.636 And that may be the reason that

NOTE Confidence: 0.71174131875

00:28:05.636 --> 00:28:07.758 we're seeing some of those relapses.

NOTE Confidence: 0.71174131875

00:28:07.760 --> 00:28:10.360 But ultimately we want to ask is this,

NOTE Confidence: 0.71174131875

00:28:10.360 --> 00:28:11.700 is this something that can

NOTE Confidence: 0.71174131875

00:28:11.700 --> 00:28:14.559 be applied in the clinic?

NOTE Confidence: 0.71174131875

00:28:14.560 --> 00:28:16.448 And this is, this is a drug that

NOTE Confidence: 0.71174131875

00:28:16.448 --> 00:28:18.199 is being tested in the clinic.

NOTE Confidence: 0.71174131875

00:28:18.200 --> 00:28:23.400 It's called a BVAB BV637 made by Avi.

NOTE Confidence: 0.71174131875

00:28:23.400 --> 00:28:24.564 And at this year,

NOTE Confidence: 0.71174131875

00:28:24.564 --> 00:28:26.496 this past year's ESMO meeting,

NOTE Confidence: 0.71174131875

00:28:26.496 --> 00:28:29.664 my colleague Julia Rotor from Dana

NOTE Confidence: 0.71174131875

00:28:29.664 --> 00:28:32.046 Farber presented the clinical data

NOTE Confidence: 0.71174131875

00:28:32.046 --> 00:28:34.944 of giving this agent by itself or

NOTE Confidence: 0.71174131875

00:28:35.029 --> 00:28:37.193 in combination with chemotherapy

NOTE Confidence: 0.71174131875

00:28:37.193 --> 00:28:39.234 or with with awesome mertinib.

NOTE Confidence: 0.71174131875

00:28:39.234 --> 00:28:41.460 So here it's given monthly and the

NOTE Confidence: 0.71174131875

00:28:41.522 --> 00:28:43.612 awesome mertinib is given every day.

NOTE Confidence: 0.71174131875

00:28:43.612 --> 00:28:46.380 And the good thing is that the combination

NOTE Confidence: 0.71174131875

00:28:46.446 --> 00:28:48.596 is actually quite well tolerated.

NOTE Confidence: 0.71174131875

00:28:48.600 --> 00:28:50.536 There's some liver function

NOTE Confidence: 0.71174131875

00:28:50.536 --> 00:28:52.956 abnormalities that you can see.

NOTE Confidence: 0.71174131875

00:28:52.960 --> 00:28:55.480 But no, there was no major interactions,

NOTE Confidence: 0.71174131875

00:28:55.480 --> 00:28:57.435 there's no major platelet decreases

NOTE Confidence: 0.71174131875

00:28:57.435 --> 00:28:59.989 as we'd expect from the preclinical

NOTE Confidence: 0.71174131875

00:28:59.989 --> 00:29:04.516 data and no bad toxicities that would

NOTE Confidence: 0.71174131875

00:29:04.516 --> 00:29:06.611 get us worried about potentially

NOTE Confidence: 0.71174131875

00:29:06.611 --> 00:29:07.956 moving this combination forward.

NOTE Confidence: 0.71174131875

00:29:07.956 --> 00:29:10.721 So our our plan is to try to move

NOTE Confidence: 0.71174131875

00:29:10.721 --> 00:29:13.165 that forward and use it in that same

NOTE Confidence: 0.71174131875

00:29:13.165 --> 00:29:15.319 scenario and patients that we saw in the

NOTE Confidence: 0.904953389

00:29:17.360 --> 00:29:18.960 in the mouse models.

NOTE Confidence: 0.904953389

00:29:18.960 --> 00:29:21.360 And in fact in that presentation,

NOTE Confidence: 0.904953389

00:29:21.360 --> 00:29:23.551 these were all patients that have been

NOTE Confidence: 0.904953389

00:29:23.551 --> 00:29:24.880 treated previously with Asamertinib

NOTE Confidence: 0.904953389

00:29:24.880 --> 00:29:27.246 and in some of those patients that

NOTE Confidence: 0.904953389

00:29:27.246 --> 00:29:28.778 combination actually led to tumor

NOTE Confidence: 0.904953389

00:29:28.778 --> 00:29:32.264 shrinkage which was very nice to see

NOTE Confidence: 0.904953389

00:29:32.264 --> 00:29:35.719 and encouraging to helps move that

NOTE Confidence: 0.904953389

00:29:35.719 --> 00:29:40.640 forward for clinical development.

NOTE Confidence: 0.904953389

00:29:40.640 --> 00:29:43.384 So another, so I talked about that

NOTE Confidence: 0.904953389

00:29:43.384 --> 00:29:45.800 vulnerability and then the other option,

NOTE Confidence: 0.904953389

00:29:45.800 --> 00:29:47.921 other thing that we're doing is asking

NOTE Confidence: 0.904953389

00:29:47.921 --> 00:29:50.200 of this sort of intermediate state,

NOTE Confidence: 0.904953389

00:29:50.200 --> 00:29:53.350 are there novel targets that could be

NOTE Confidence: 0.904953389

00:29:53.350 --> 00:29:56.014 expressed in this state that we could

NOTE Confidence: 0.904953389

00:29:56.014 --> 00:29:58.615 go after with therapies that are in

NOTE Confidence: 0.904953389

00:29:58.615 --> 00:30:01.051 the clinic or therapies that need to

NOTE Confidence: 0.904953389

00:30:01.124 --> 00:30:03.879 be developed for clinical application.

NOTE Confidence: 0.904953389

00:30:03.880 --> 00:30:06.589 And so we've done some RNA sequencing

NOTE Confidence: 0.904953389

00:30:06.589 --> 00:30:08.744 analysis and untreated cells and cells

NOTE Confidence: 0.904953389

00:30:08.744 --> 00:30:11.406 that are in this sort of persist or

NOTE Confidence: 0.904953389

00:30:11.406 --> 00:30:13.536 state focusing on specifically looking

NOTE Confidence: 0.904953389

00:30:13.536 --> 00:30:15.932 at cell surface proteins as targets.

NOTE Confidence: 0.904953389

00:30:15.932 --> 00:30:18.008 And for many cell surface proteins

NOTE Confidence: 0.904953389

00:30:18.008 --> 00:30:19.846 there are antibody drug conjugates

NOTE Confidence: 0.904953389

00:30:19.846 --> 00:30:22.359 which are that are in the clinic.

NOTE Confidence: 0.904953389

00:30:22.360 --> 00:30:25.360 So antibodies linked to not in the, not,

NOTE Confidence: 0.904953389

00:30:25.360 --> 00:30:27.920 not the BCL XL inhibitor that I showed,

NOTE Confidence: 0.904953389

00:30:27.920 --> 00:30:29.840 but to chemotherapy and so having

NOTE Confidence: 0.904953389

00:30:29.840 --> 00:30:32.510 a more sort of targeted way of

NOTE Confidence: 0.904953389

00:30:32.510 --> 00:30:34.715 delivering chemotherapy to two cells.

NOTE Confidence: 0.904953389

00:30:34.720 --> 00:30:36.715 And these are just three of them.

NOTE Confidence: 0.904953389

00:30:36.720 --> 00:30:39.664 And we see them that they're both sort

NOTE Confidence: 0.904953389

00:30:39.664 --> 00:30:43.352 of enriched in that sort of state after

NOTE Confidence: 0.904953389

00:30:43.352 --> 00:30:46.164 treatment with an EGFR inhibitor here

NOTE Confidence: 0.904953389

00:30:46.164 --> 00:30:49.285 you can see them by by Western blotting.

NOTE Confidence: 0.904953389

00:30:49.285 --> 00:30:51.630 You can see in these EGFR mutant

NOTE Confidence: 0.904953389

00:30:51.700 --> 00:30:53.710 cancers this black band is this

NOTE Confidence: 0.904953389

00:30:53.710 --> 00:30:55.988 TROP 2 protein that's enriched after

NOTE Confidence: 0.904953389

00:30:55.988 --> 00:30:58.158 treatment with an EGFR inhibitor.

NOTE Confidence: 0.904953389

00:30:58.160 --> 00:31:00.904 This is full R1 which is a folate

NOTE Confidence: 0.904953389

00:31:00.904 --> 00:31:02.885 receptor that's also increased and

NOTE Confidence: 0.904953389

00:31:02.885 --> 00:31:04.355 it's not just limited to EGFR.

NOTE Confidence: 0.904953389

00:31:04.360 --> 00:31:06.118 Here are cells with other genetic

NOTE Confidence: 0.904953389

00:31:06.118 --> 00:31:07.840 alterations and ALK rearranged cell lines.

NOTE Confidence: 0.904953389

00:31:07.840 --> 00:31:09.238 We're treated with an ALK inhibitor.

NOTE Confidence: 0.904953389

00:31:09.240 --> 00:31:10.878 You can see the same thing,

NOTE Confidence: 0.904953389

00:31:10.880 --> 00:31:12.840 a Med amplified cell line treated with

NOTE Confidence: 0.904953389

00:31:12.840 --> 00:31:14.899 a Med inhibitor or K Ras mutant cell

NOTE Confidence: 0.904953389

00:31:14.899 --> 00:31:16.640 line treated with AK Ras inhibitor.

NOTE Confidence: 0.904953389

00:31:16.640 --> 00:31:18.838 You can see the the same things

NOTE Confidence: 0.9736366

00:31:21.040 --> 00:31:21.760 and

NOTE Confidence: 0.793071963333333

00:31:24.000 --> 00:31:25.716 again ALK and raw cell lines

NOTE Confidence: 0.793071963333333

00:31:25.716 --> 00:31:27.519 showing the showing the same thing.

NOTE Confidence: 0.793071963333333

00:31:27.520 --> 00:31:29.655 This is for the folate receptor and

NOTE Confidence: 0.793071963333333

00:31:29.655 --> 00:31:34.228 this is for trope trope too and we've

NOTE Confidence: 0.793071963333333

00:31:34.228 --> 00:31:36.006 also used our animal models and and

NOTE Confidence: 0.793071963333333

00:31:36.006 --> 00:31:37.880 and and some are cell line models,

NOTE Confidence: 0.793071963333333

00:31:37.880 --> 00:31:40.836 some are patient derived models to

NOTE Confidence: 0.793071963333333

00:31:40.836 --> 00:31:43.328 study that state that we I mentioned

NOTE Confidence: 0.793071963333333

00:31:43.328 --> 00:31:45.485 earlier in the presentation where

NOTE Confidence: 0.793071963333333

00:31:45.485 --> 00:31:48.016 we initially studied it from cells

NOTE Confidence: 0.793071963333333

00:31:48.016 --> 00:31:49.808 and grown in plastic but here we

NOTE Confidence: 0.793071963333333

00:31:49.808 --> 00:31:51.543 can study it from animals and here

NOTE Confidence: 0.793071963333333

00:31:51.543 --> 00:31:53.443 you can you can see the animals

NOTE Confidence: 0.793071963333333

00:31:53.443 --> 00:31:55.118 are treated with EGFR inhibitor,

NOTE Confidence: 0.793071963333333

00:31:55.120 --> 00:31:56.860 EGFR MEC inhibitor and they

NOTE Confidence: 0.793071963333333

00:31:56.860 --> 00:31:58.600 have these very nice responses.

NOTE Confidence: 0.793071963333333

00:31:58.600 --> 00:32:01.120 So the time of this maximum response

NOTE Confidence: 0.793071963333333

00:32:01.120 --> 00:32:03.604 we dissect out the kind of the

NOTE Confidence: 0.793071963333333

00:32:03.604 --> 00:32:05.720 residual area where the tumor is.

NOTE Confidence: 0.793071963333333

00:32:05.720 --> 00:32:07.256 We purify the tumor cells and

NOTE Confidence: 0.793071963333333

00:32:07.256 --> 00:32:09.280 can do all all different types of

NOTE Confidence: 0.793071963333333

00:32:09.280 --> 00:32:11.478 analysis on the tumor cells to ask.

NOTE Confidence: 0.793071963333333

00:32:11.480 --> 00:32:14.324 This has also happened in in in vivo as

NOTE Confidence: 0.793071963333333

00:32:14.324 --> 00:32:17.000 opposed to just in a tissue culture model.

NOTE Confidence: 0.793071963333333

00:32:17.000 --> 00:32:20.656 And so here's one example of different

NOTE Confidence: 0.793071963333333

00:32:20.656 --> 00:32:22.640 models treated with Asamertinib,

NOTE Confidence: 0.793071963333333

00:32:22.640 --> 00:32:24.160 Rasamertinib in the MEC inhibitor.

NOTE Confidence: 0.793071963333333

00:32:24.160 --> 00:32:26.040 This is the what the tumors look like

NOTE Confidence: 0.793071963333333

00:32:26.040 --> 00:32:28.002 when we dissect them out in the in

NOTE Confidence: 0.793071963333333

00:32:28.002 --> 00:32:29.799 the sort of minimal residual state.

NOTE Confidence: 0.793071963333333

00:32:29.800 --> 00:32:33.760 And if we look for expression of trope 2,

NOTE Confidence: 0.793071963333333

00:32:33.760 --> 00:32:35.839 we can see that it's a membrane

NOTE Confidence: 0.793071963333333

00:32:35.839 --> 00:32:36.433 bound protein.

NOTE Confidence: 0.793071963333333

00:32:36.440 --> 00:32:39.436 So you can see it expressed here

NOTE Confidence: 0.793071963333333

00:32:39.440 --> 00:32:41.108 more intensely than you see it

NOTE Confidence: 0.793071963333333

00:32:41.108 --> 00:32:43.359 in the in the untreated models,

NOTE Confidence: 0.793071963333333

00:32:43.360 --> 00:32:44.896 although you do see some expression

NOTE Confidence: 0.793071963333333

00:32:44.896 --> 00:32:45.920 in the untreated models.

NOTE Confidence: 0.793071963333333

00:32:45.920 --> 00:32:47.840 And if we quantify this,

NOTE Confidence: 0.793071963333333

00:32:47.840 --> 00:32:51.010 the models tend to have some baseline

NOTE Confidence: 0.793071963333333

00:32:51.010 --> 00:32:54.440 expression which is then enhanced with e.g.

NOTE Confidence: 0.793071963333333

00:32:54.440 --> 00:32:56.316 FREGFR MEC treatment and it kind of

NOTE Confidence: 0.793071963333333

00:32:56.316 --> 00:32:58.512 varies a little bit from model to model.

NOTE Confidence: 0.793071963333333

00:32:58.512 --> 00:32:59.992 This is the same experiment

NOTE Confidence: 0.793071963333333

00:32:59.992 --> 00:33:01.440 for this folate receptor.

NOTE Confidence: 0.793071963333333

00:33:01.440 --> 00:33:03.492 It seems to be much you don't

NOTE Confidence: 0.793071963333333

00:33:03.492 --> 00:33:06.064 find it in the untreated but you

NOTE Confidence: 0.793071963333333

00:33:06.064 --> 00:33:08.080 do find it in the treated one.

NOTE Confidence: 0.793071963333333

00:33:08.080 --> 00:33:11.343 So we like these kinds of examples

NOTE Confidence: 0.793071963333333

00:33:11.343 --> 00:33:14.024 because the hope would be that this

NOTE Confidence: 0.793071963333333

00:33:14.024 --> 00:33:15.674 is something that's specifically

NOTE Confidence: 0.793071963333333

00:33:15.674 --> 00:33:18.098 induced in the tumor cells and

NOTE Confidence: 0.793071963333333

00:33:18.098 --> 00:33:20.319 hence any therapeutic strategy

NOTE Confidence: 0.960245975

00:33:20.600 --> 00:33:22.440 should be should hopefully

NOTE Confidence: 0.862701431538462

00:33:22.440 --> 00:33:24.904 have a wider therapeutic index that it's

NOTE Confidence: 0.862701431538462

00:33:24.904 --> 00:33:27.382 targeting the tumor and not normal tissues.

NOTE Confidence: 0.862701431538462

00:33:27.382 --> 00:33:31.262 But wait to see that and here it's

NOTE Confidence: 0.862701431538462

00:33:31.262 --> 00:33:33.439 we look at it by RNA sequencing,

NOTE Confidence: 0.862701431538462

00:33:33.440 --> 00:33:35.575 same idea, we can look for these

NOTE Confidence: 0.862701431538462

00:33:35.575 --> 00:33:37.506 different cell surface proteins

NOTE Confidence: 0.862701431538462

00:33:37.506 --> 00:33:41.135 that are up regulated and for which

NOTE Confidence: 0.862701431538462

00:33:41.135 --> 00:33:43.560 there are antibody drug conjugates.

NOTE Confidence: 0.862701431538462

00:33:43.560 --> 00:33:46.066 And we also have a trial where

NOTE Confidence: 0.862701431538462

00:33:46.066 --> 00:33:47.196 we're trying to understand this.

NOTE Confidence: 0.862701431538462

00:33:47.200 --> 00:33:48.960 This actually happened in

NOTE Confidence: 0.862701431538462

00:33:48.960 --> 00:33:50.798 patients and so this is a trial,

NOTE Confidence: 0.862701431538462

00:33:50.800 --> 00:33:52.490 a very straightforward trial where

NOTE Confidence: 0.862701431538462

00:33:52.490 --> 00:33:54.180 newly diagnosed lung cancer patients

NOTE Confidence: 0.862701431538462

00:33:54.227 --> 00:33:55.559 were treated with Osamerton,

NOTE Confidence: 0.862701431538462

00:33:55.560 --> 00:33:58.157 they've been the EGFR inhibitor in the

NOTE Confidence: 0.862701431538462

00:33:58.157 --> 00:34:01.267 primary goal of the trial was to study

NOTE Confidence: 0.862701431538462

00:34:01.267 --> 00:34:03.400 how do cancers develop resistance to

NOTE Confidence: 0.862701431538462

00:34:03.400 --> 00:34:05.920 Asamerton when it's clinically visible.

NOTE Confidence: 0.862701431538462

00:34:05.920 --> 00:34:08.000 But what we built into this trial is

NOTE Confidence: 0.862701431538462

00:34:08.000 --> 00:34:10.142 that during the sort of maximal time that

NOTE Confidence: 0.862701431538462

00:34:10.142 --> 00:34:12.437 the person has had a response to therapy,

NOTE Confidence: 0.862701431538462

00:34:12.440 --> 00:34:15.192 we biopsy that area if we can find

NOTE Confidence: 0.862701431538462

00:34:15.192 --> 00:34:18.731 it and do analysis to see can we

NOTE Confidence: 0.862701431538462

00:34:18.731 --> 00:34:21.000 find these proteins expressed that

NOTE Confidence: 0.862701431538462

00:34:21.000 --> 00:34:23.358 I showed in the preclinical models.

NOTE Confidence: 0.862701431538462

00:34:23.360 --> 00:34:25.160 This is just an example of a patient.

NOTE Confidence: 0.862701431538462

00:34:25.160 --> 00:34:27.416 Here's two months of ASA Merton if not

NOTE Confidence: 0.862701431538462

00:34:27.416 --> 00:34:29.264 the most dramatic reduction but and

NOTE Confidence: 0.862701431538462

00:34:29.264 --> 00:34:32.240 here you may able to see the biopsy needle,

NOTE Confidence: 0.862701431538462

00:34:32.240 --> 00:34:35.040 we're biopsy in the individual and a

NOTE Confidence: 0.862701431538462

00:34:35.040 --> 00:34:37.680 study only has on treatment biopsy.

NOTE Confidence: 0.862701431538462

00:34:37.680 --> 00:34:39.591 So we don't have the pre treatment

NOTE Confidence: 0.862701431538462

00:34:39.591 --> 00:34:40.640 to compare it to.

NOTE Confidence: 0.862701431538462

00:34:40.640 --> 00:34:42.768 But at least by single cell RNA sequencing

NOTE Confidence: 0.862701431538462

00:34:42.768 --> 00:34:44.764 in the on treatment biopsies we can

NOTE Confidence: 0.862701431538462

00:34:44.764 --> 00:34:46.783 find a cluster of tumor cells that

NOTE Confidence: 0.862701431538462

00:34:46.783 --> 00:34:48.991 express trope here in this case trope 2.

NOTE Confidence: 0.862701431538462

00:34:49.000 --> 00:34:52.456 So at least we think that this is has

NOTE Confidence: 0.862701431538462

00:34:52.456 --> 00:34:56.605 some real relevance in patience and

NOTE Confidence: 0.862701431538462

00:34:56.605 --> 00:35:01.065 are trying to validate it further.

NOTE Confidence: 0.862701431538462

00:35:01.065 --> 00:35:03.040 So what is Trope 2?

NOTE Confidence: 0.862701431538462

00:35:03.040 --> 00:35:06.316 Trope 2's may be familiar for

NOTE Confidence: 0.862701431538462

00:35:06.320 --> 00:35:07.799 our clinical audience,

NOTE Confidence: 0.862701431538462

00:35:07.799 --> 00:35:10.400 but it's a intracellular calcium

NOTE Confidence: 0.862701431538462

00:35:10.400 --> 00:35:12.640 signal transducer that's over

NOTE Confidence: 0.862701431538462

00:35:12.640 --> 00:35:15.520 expressed in many epithelial cancers.

NOTE Confidence: 0.862701431538462

00:35:15.520 --> 00:35:18.397 There are agents that target trope 2.

NOTE Confidence: 0.862701431538462

00:35:18.400 --> 00:35:21.520 Here's an antibody linked to A

NOTE Confidence: 0.862701431538462

00:35:21.520 --> 00:35:24.305 chemotherapeutic agent in red here

NOTE Confidence: 0.862701431538462

00:35:24.305 --> 00:35:26.533 that's still infused intravenously

NOTE Confidence: 0.862701431538462

00:35:26.533 --> 00:35:29.405 and then binds the tumor cells and

NOTE Confidence: 0.862701431538462

00:35:29.405 --> 00:35:30.945 then this chemotherapeutic agent

NOTE Confidence: 0.862701431538462

00:35:30.945 --> 00:35:33.197 is internalized and cleaved in the

NOTE Confidence: 0.862701431538462

00:35:33.197 --> 00:35:35.440 tumor cells like a Trojan horse.

NOTE Confidence: 0.862701431538462

00:35:35.440 --> 00:35:38.900 And then specifically can can

NOTE Confidence: 0.862701431538462

00:35:38.900 --> 00:35:40.520 kill the tumor cells.

NOTE Confidence: 0.862701431538462

00:35:40.520 --> 00:35:42.344 And if we use this agent

NOTE Confidence: 0.862701431538462

00:35:42.344 --> 00:35:43.560 in lung cancer patients,

NOTE Confidence: 0.862701431538462

00:35:43.560 --> 00:35:45.744 you can see about 1/4 of patients

NOTE Confidence: 0.862701431538462

00:35:45.744 --> 00:35:48.083 have tumor shrinkage and some of them

NOTE Confidence: 0.862701431538462

00:35:48.083 --> 00:35:49.753 have more dramatic tumor shrinkage.

NOTE Confidence: 0.862701431538462

00:35:49.760 --> 00:35:52.056 This is given to a wide variety

NOTE Confidence: 0.862701431538462

00:35:52.056 --> 00:35:54.196 of patients with lung cancer.

NOTE Confidence: 0.862701431538462

00:35:54.200 --> 00:35:56.126 What we've learned over the last

NOTE Confidence: 0.862701431538462

00:35:56.126 --> 00:35:57.959 couple years is that it works

NOTE Confidence: 0.862701431538462

00:35:57.960 --> 00:36:00.320 perhaps particularly well in cancers

NOTE Confidence: 0.862701431538462

00:36:00.320 --> 00:36:02.680 that have the EGFR mutation.

NOTE Confidence: 0.862701431538462

00:36:02.680 --> 00:36:05.228 If we isolate this experiment to patients

NOTE Confidence: 0.862701431538462

00:36:05.228 --> 00:36:07.599 whose cancers have genetic alterations,

NOTE Confidence: 0.862701431538462

00:36:07.600 --> 00:36:09.220 about a third of them

NOTE Confidence: 0.862701431538462

00:36:09.220 --> 00:36:10.516 have real tumor shrinkage.

NOTE Confidence: 0.862701431538462

00:36:10.520 --> 00:36:12.518 And if you look at the specifics of them,

NOTE Confidence: 0.862701431538462

00:36:12.520 --> 00:36:14.501 most of these have EGFR mutant cancers

NOTE Confidence: 0.862701431538462

00:36:14.501 --> 00:36:16.596 although there are others in there as well.

NOTE Confidence: 0.862701431538462

00:36:16.600 --> 00:36:18.358 And but this year's ESMO meeting

NOTE Confidence: 0.862701431538462

00:36:18.358 --> 00:36:20.040 or last year's ESMO meeting,

NOTE Confidence: 0.862701431538462

00:36:20.040 --> 00:36:21.600 this was studied in more detail.

NOTE Confidence: 0.862701431538462

00:36:21.600 --> 00:36:24.400 And patients that have an EGFR mutation,

NOTE Confidence: 0.862701431538462

00:36:24.400 --> 00:36:26.710 they tend to have a greater response

NOTE Confidence: 0.862701431538462

00:36:26.710 --> 00:36:28.640 than cancers that have other

NOTE Confidence: 0.862701431538462

00:36:28.640 --> 00:36:30.380 genetic alterations for reasons

NOTE Confidence: 0.862701431538462

00:36:30.380 --> 00:36:32.120 that nobody understands yet.

NOTE Confidence: 0.814160468888889

00:36:32.120 --> 00:36:34.985 But it's something that we're

NOTE Confidence: 0.814160468888889

00:36:34.985 --> 00:36:37.277 keenly interested in investigating.

NOTE Confidence: 0.814160468888889

00:36:37.280 --> 00:36:39.296 So we then use that the same sort of

NOTE Confidence: 0.814160468888889

00:36:39.296 --> 00:36:41.477 in vivo model and ask the experiment

NOTE Confidence: 0.814160468888889

00:36:41.480 --> 00:36:44.035 if we now target this stroke two

NOTE Confidence: 0.814160468888889

00:36:44.035 --> 00:36:46.161 protein after this persistent state

NOTE Confidence: 0.814160468888889

00:36:46.161 --> 00:36:47.868 has been established, doesn't matter.

NOTE Confidence: 0.814160468888889

00:36:47.868 --> 00:36:50.360 So again treat the mice with asamertinib,

NOTE Confidence: 0.814160468888889

00:36:50.360 --> 00:36:53.678 some are, some continue on asamertinib

NOTE Confidence: 0.814160468888889

00:36:53.678 --> 00:36:56.770 and some are given this troph

NOTE Confidence: 0.814160468888889

00:36:56.770 --> 00:36:58.564 2 antibody drug conjugate which

NOTE Confidence: 0.814160468888889

00:36:58.564 --> 00:37:00.319 is approved in breast cancer,

NOTE Confidence: 0.814160468888889

00:37:00.320 --> 00:37:01.382 not lung cancer.

NOTE Confidence: 0.814160468888889

00:37:01.382 --> 00:37:03.860 And in fact the clinical trial and

NOTE Confidence: 0.814160468888889

00:37:03.929 --> 00:37:06.106 lung cancer just failed unfortunately

NOTE Confidence: 0.814160468888889

00:37:06.106 --> 00:37:09.837 and again treat him and then we

NOTE Confidence: 0.814160468888889

00:37:09.837 --> 00:37:11.970 withdraw the drugs and there is

NOTE Confidence: 0.814160468888889

00:37:11.970 --> 00:37:13.080 a little bit of a difference.

NOTE Confidence: 0.814160468888889

00:37:13.080 --> 00:37:13.947 It's not humongous,

NOTE Confidence: 0.814160468888889

00:37:13.947 --> 00:37:16.347 but there's a little bit of a difference

NOTE Confidence: 0.814160468888889

00:37:16.347 --> 00:37:18.538 in the tumors that got treated with

NOTE Confidence: 0.814160468888889

00:37:18.538 --> 00:37:20.760 a Trop 2 antibody drug conjugate.

NOTE Confidence: 0.814160468888889

00:37:20.760 --> 00:37:22.660 On the other hand,

NOTE Confidence: 0.814160468888889

00:37:22.660 --> 00:37:26.120 when we take this out longer days,

NOTE Confidence: 0.814160468888889

00:37:26.120 --> 00:37:27.320 they all start to regrow.

NOTE Confidence: 0.814160468888889

00:37:27.320 --> 00:37:29.504 So we didn't really cure any of

NOTE Confidence: 0.814160468888889

00:37:29.504 --> 00:37:31.799 the mice here using this approach.

NOTE Confidence: 0.94540435

00:37:35.120 --> 00:37:38.415 So this Trop 2 protein expression

NOTE Confidence: 0.94540435

00:37:38.415 --> 00:37:40.315 increases following therapies that

NOTE Confidence: 0.94540435

00:37:40.315 --> 00:37:42.482 directed directed at the right

NOTE Confidence: 0.94540435

00:37:42.482 --> 00:37:44.512 genetic alteration in lung cancers.

NOTE Confidence: 0.94540435

00:37:44.520 --> 00:37:47.195 Adding this antibody drug conjugate

NOTE Confidence: 0.94540435

00:37:47.195 --> 00:37:50.419 once this tolerant state has been

NOTE Confidence: 0.94540435

00:37:50.419 --> 00:37:52.432 formed didn't really eradicate these

NOTE Confidence: 0.94540435

00:37:52.432 --> 00:37:54.372 cells because otherwise the cancers

NOTE Confidence: 0.94540435

00:37:54.372 --> 00:37:56.276 wouldn't have been able to grow back.

NOTE Confidence: 0.94540435

00:37:56.280 --> 00:38:00.398 And so where do we go from here?

NOTE Confidence: 0.94540435

00:38:00.400 --> 00:38:02.145 There are other antibody drug

NOTE Confidence: 0.94540435

00:38:02.145 --> 00:38:03.192 conjugates targeting this

NOTE Confidence: 0.94540435

00:38:03.192 --> 00:38:04.920 protein that may be more potent,

NOTE Confidence: 0.94540435

00:38:04.920 --> 00:38:06.036 which could be an issue here,

NOTE Confidence: 0.94540435

00:38:06.040 --> 00:38:10.416 one made by Dai Ichi and being developed

NOTE Confidence: 0.94540435

00:38:10.416 --> 00:38:14.626 by Dai Chi and AstraZeneca called DS1062A.

NOTE Confidence: 0.94540435

00:38:14.626 --> 00:38:16.222 Do we need to increase the

NOTE Confidence: 0.94540435

00:38:16.222 --> 00:38:17.600 duration of the treatment?

NOTE Confidence: 0.94540435

00:38:17.600 --> 00:38:20.578 Is that an issue here or can we

NOTE Confidence: 0.94540435

00:38:20.578 --> 00:38:22.008 develop some novel strategies here

NOTE Confidence: 0.94540435

00:38:22.008 --> 00:38:24.103 And and I'll I'll show you one

NOTE Confidence: 0.94540435

00:38:24.103 --> 00:38:25.713 novel strategy that we're evaluating

NOTE Confidence: 0.94540435

00:38:25.713 --> 00:38:28.513 that that and that is developing

NOTE Confidence: 0.94540435

00:38:28.513 --> 00:38:33.466 CAR T cells directed at trope 2.

NOTE Confidence: 0.94540435

00:38:33.466 --> 00:38:36.860 So chimeric antigen receptor T cell

NOTE Confidence: 0.94540435

00:38:36.860 --> 00:38:41.165 therapy type of immune therapy is being

NOTE Confidence: 0.94540435

00:38:41.165 --> 00:38:44.315 used in lots of hematologic malignancies

NOTE Confidence: 0.94540435

00:38:44.315 --> 00:38:48.956 and has done wonders there on a therapy.

NOTE Confidence: 0.94540435

00:38:48.960 --> 00:38:51.585 Just this strategy in general

NOTE Confidence: 0.94540435

00:38:51.585 --> 00:38:54.160 has struggled in solid tumors and

NOTE Confidence: 0.94540435

00:38:54.160 --> 00:38:56.851 part of the issue is that you're

NOTE Confidence: 0.94540435

00:38:56.851 --> 00:38:59.317 targeting you have to target a

NOTE Confidence: 0.94540435

00:38:59.317 --> 00:39:01.879 a specific cell surface protein.

NOTE Confidence: 0.94540435

00:39:01.880 --> 00:39:03.542 If that cell surface protein is

NOTE Confidence: 0.94540435

00:39:03.542 --> 00:39:05.120 also present in normal tissues,

NOTE Confidence: 0.94540435

00:39:05.120 --> 00:39:08.424 then you're then you're delivering this

NOTE Confidence: 0.94540435

00:39:08.424 --> 00:39:09.784 effective therapy to normal tissues

NOTE Confidence: 0.94540435

00:39:09.784 --> 00:39:11.836 and that can lead to a lot of toxicities.

NOTE Confidence: 0.94540435

00:39:11.840 --> 00:39:15.936 And so you need to try to

NOTE Confidence: 0.94540435

00:39:15.936 --> 00:39:17.520 identify two unique proteins,

NOTE Confidence: 0.94540435

00:39:17.520 --> 00:39:18.176 tumor antigens,

NOTE Confidence: 0.94540435

00:39:18.176 --> 00:39:20.144 proteins present on the surface of

NOTE Confidence: 0.94540435

00:39:20.144 --> 00:39:22.278 tumor cells that are not found on

NOTE Confidence: 0.94540435

00:39:22.278 --> 00:39:24.042 normal cells and that's remained a

NOTE Confidence: 0.94540435

00:39:24.042 --> 00:39:25.716 challenge in the solid tumor field.

NOTE Confidence: 0.94540435

00:39:25.720 --> 00:39:28.125 And this is work we've done with Eric

NOTE Confidence: 0.94540435

00:39:28.125 --> 00:39:31.800 Smith and Elliot Brea at Dana Farber.

NOTE Confidence: 0.94540435

00:39:31.800 --> 00:39:34.056 So this just shows you what

NOTE Confidence: 0.94540435

00:39:34.056 --> 00:39:36.360 these things look like.

NOTE Confidence: 0.94540435

00:39:36.360 --> 00:39:38.826 And so if we use these cells in again

NOTE Confidence: 0.94540435

00:39:38.826 --> 00:39:41.626 in a tissue culture model and we

NOTE Confidence: 0.94540435

00:39:41.626 --> 00:39:44.464 take those EGFR immune cancer cells

NOTE Confidence: 0.94540435

00:39:44.464 --> 00:39:46.720 and genetically remove trope 2.

NOTE Confidence: 0.94540435

00:39:46.720 --> 00:39:48.656 So the target of where the antibody is

NOTE Confidence: 0.94540435

00:39:48.656 --> 00:39:50.640 supposed to bind the the cells do nothing.

NOTE Confidence: 0.94540435

00:39:50.640 --> 00:39:53.790 Here in red and in green is a non

NOTE Confidence: 0.94540435

00:39:53.790 --> 00:39:57.015 specific or a a CAR T cell against the B

NOTE Confidence: 0.94540435

00:39:57.015 --> 00:39:59.640 cell antigen that isn't expressed at all.

NOTE Confidence: 0.94540435

00:39:59.640 --> 00:40:02.331 So if you knock it out or make a CAR

NOTE Confidence: 0.94540435

00:40:02.331 --> 00:40:04.113 T cell against an irrelevant protein,

NOTE Confidence: 0.94540435

00:40:04.120 --> 00:40:05.300 nothing happens.

NOTE Confidence: 0.94540435

00:40:05.300 --> 00:40:08.840 If you enter these knockout cells,

NOTE Confidence: 0.94540435

00:40:08.840 --> 00:40:12.277 replace the normal form of trope too,

NOTE Confidence: 0.94540435

00:40:12.280 --> 00:40:15.560 and now you can see less cells survive,

NOTE Confidence: 0.94540435

00:40:15.560 --> 00:40:16.920 or in the endogenous cells,

NOTE Confidence: 0.94540435

00:40:16.920 --> 00:40:19.620 less cell survives versus targeting

NOTE Confidence: 0.94540435

00:40:19.620 --> 00:40:23.200 AB cell antigen doesn't do anything.

NOTE Confidence: 0.94540435

00:40:23.200 --> 00:40:25.544 We of course wanted to make sure that

NOTE Confidence: 0.94540435

00:40:25.544 --> 00:40:27.283 the EGFR inhibitors weren't toxic

NOTE Confidence: 0.94540435

00:40:27.283 --> 00:40:29.824 to these CAR T cells and they're

NOTE Confidence: 0.94540435

00:40:29.888 --> 00:40:32.464 not except when you get to very

NOTE Confidence: 0.94540435

00:40:32.464 --> 00:40:33.200 high concentrations.

NOTE Confidence: 0.94540435

00:40:33.200 --> 00:40:35.344 So then we then we asked the experiment

NOTE Confidence: 0.94540435

00:40:35.344 --> 00:40:37.667 of first treating them with the EGFR

NOTE Confidence: 0.94540435

00:40:37.667 --> 00:40:39.799 inhibitor and tissue culture model and

NOTE Confidence: 0.94540435

00:40:39.799 --> 00:40:42.991 then to set up that drug tolerance state

NOTE Confidence: 0.94540435

00:40:42.991 --> 00:40:46.473 and then expose them to the CAR T cells.

NOTE Confidence: 0.94540435

00:40:46.480 --> 00:40:46.782 And.

NOTE Confidence: 0.94540435

00:40:46.782 --> 00:40:47.386 And similarly,

NOTE Confidence: 0.94540435

00:40:47.386 --> 00:40:49.198 if you've knocked out trope 2,

NOTE Confidence: 0.94540435

00:40:49.200 --> 00:40:50.160 nothing happens.

NOTE Confidence: 0.94540435

00:40:50.160 --> 00:40:53.472 And in the endogenous EGFR immune cells,

NOTE Confidence: 0.94540435

00:40:53.472 --> 00:40:54.876 they're very effective,

NOTE Confidence: 0.90106514125

00:40:54.880 --> 00:40:56.580 Very few cells survive.

NOTE Confidence: 0.90106514125

00:40:56.580 --> 00:40:58.573 And if you've replaced the

NOTE Confidence: 0.90106514125

00:40:58.573 --> 00:41:00.038 normal into this knockout cell,

NOTE Confidence: 0.90106514125

00:41:00.040 --> 00:41:01.797 replace the normal form of trope 2.

NOTE Confidence: 0.90106514125

00:41:01.800 --> 00:41:03.028 So now it's expressed.

NOTE Confidence: 0.90106514125

00:41:03.028 --> 00:41:04.563 Now they're once again effective

NOTE Confidence: 0.90106514125

00:41:04.563 --> 00:41:06.157 like in the normal situation.

NOTE Confidence: 0.90106514125

00:41:06.160 --> 00:41:09.625 So we do think it's doing what what we

NOTE Confidence: 0.90106514125

00:41:09.625 --> 00:41:12.840 expected to be doing at least in in vitro.

NOTE Confidence: 0.90106514125

00:41:12.840 --> 00:41:15.366 And we've now also again finally

NOTE Confidence: 0.90106514125

00:41:15.366 --> 00:41:17.437 taken the same experiment and

NOTE Confidence: 0.90106514125

00:41:17.437 --> 00:41:19.593 are starting to do it in vivo.

NOTE Confidence: 0.90106514125

00:41:19.600 --> 00:41:23.677 Treat the tumors for 10 days or 21 days.

NOTE Confidence: 0.90106514125

00:41:23.680 --> 00:41:27.796 Randomize them to continue EGFR inhibition.

NOTE Confidence: 0.90106514125

00:41:27.800 --> 00:41:30.122 Use the continue with EGFR inhibition

NOTE Confidence: 0.90106514125

00:41:30.122 --> 00:41:33.611 and the and the trope to antibody drug

NOTE Confidence: 0.90106514125

00:41:33.611 --> 00:41:36.810 conjugate or a CAR T cell against

NOTE Confidence: 0.90106514125

00:41:36.810 --> 00:41:40.283 the B cell antigen or against trope

NOTE Confidence: 0.90106514125

00:41:40.283 --> 00:41:43.320 to just delivered once and then

NOTE Confidence: 0.90106514125

00:41:43.320 --> 00:41:46.680 ask what happens to these animals.

NOTE Confidence: 0.90106514125

00:41:46.680 --> 00:41:48.416 So they're delivered here.

NOTE Confidence: 0.90106514125

00:41:48.416 --> 00:41:51.500 This is the schedule for the ADC

NOTE Confidence: 0.90106514125

00:41:51.500 --> 00:41:54.220 delivery and then the CAR T cells

NOTE Confidence: 0.90106514125

00:41:54.220 --> 00:41:56.756 are delivered also here at day 21.

NOTE Confidence: 0.90106514125

00:41:56.756 --> 00:41:59.300 And you can see that the ones that

NOTE Confidence: 0.90106514125

00:41:59.383 --> 00:42:01.933 are treated with the EGFR inhibitor

NOTE Confidence: 0.90106514125

00:42:01.933 --> 00:42:04.240 alone all managed to regrow.

NOTE Confidence: 0.90106514125

00:42:04.240 --> 00:42:06.956 The ones that are treated with the

NOTE Confidence: 0.90106514125

00:42:06.960 --> 00:42:08.912 targeting an irrelevant protein

NOTE Confidence: 0.90106514125

00:42:08.912 --> 00:42:11.840 also regrow and purple behind it.

NOTE Confidence: 0.90106514125

00:42:11.840 --> 00:42:13.792 And the ones that are treated with the

NOTE Confidence: 0.90106514125

00:42:13.792 --> 00:42:16.100 CAR T cell or in this case the ADC,

NOTE Confidence: 0.90106514125

00:42:16.100 --> 00:42:18.620 the Sazotuzumabe and Goba T can't

NOTE Confidence: 0.90106514125

00:42:18.620 --> 00:42:19.880 have the separation.

NOTE Confidence: 0.90106514125

00:42:19.880 --> 00:42:22.240 And if we look at this long term,

NOTE Confidence: 0.90106514125

00:42:22.240 --> 00:42:23.764 we certainly see that the ones

NOTE Confidence: 0.90106514125

00:42:23.764 --> 00:42:25.476 that receive the trope 2 CAR T

NOTE Confidence: 0.90106514125

00:42:25.476 --> 00:42:26.754 cell have a much better outcome.

NOTE Confidence: 0.90106514125

00:42:26.760 --> 00:42:28.235 There are some escapers here

NOTE Confidence: 0.90106514125

00:42:28.235 --> 00:42:29.710 and we're trying to understand

NOTE Confidence: 0.90106514125

00:42:29.767 --> 00:42:31.117 why do they escape therapy.

NOTE Confidence: 0.90106514125

00:42:31.120 --> 00:42:32.947 All of the ones treated with the ADC like

NOTE Confidence: 0.90106514125

00:42:32.947 --> 00:42:34.960 in our prior experiments start to regrow.

NOTE Confidence: 0.90106514125

00:42:34.960 --> 00:42:37.319 Similarly with the EGFR inhibitor by itself

NOTE Confidence: 0.90106514125

00:42:37.319 --> 00:42:39.960 and and also most of the ones that are,

NOTE Confidence: 0.90106514125

00:42:39.960 --> 00:42:42.081 there's one here most of the ones

NOTE Confidence: 0.90106514125

00:42:42.081 --> 00:42:43.712 that are treated with irrelevant

NOTE Confidence: 0.90106514125

00:42:43.712 --> 00:42:45.357 or B cell antigen CAR,

NOTE Confidence: 0.90106514125

00:42:45.360 --> 00:42:47.232 T cell also start to regrow

NOTE Confidence: 0.90106514125

00:42:47.232 --> 00:42:48.480 as as we'd expect.

NOTE Confidence: 0.8474694

00:42:51.120 --> 00:42:55.236 So I talked about this drug tolerant

NOTE Confidence: 0.8474694

00:42:55.236 --> 00:42:57.055 persistent state that can give rise

NOTE Confidence: 0.8474694

00:42:57.055 --> 00:42:59.102 to a broad range of actual drug

NOTE Confidence: 0.8474694

00:42:59.102 --> 00:43:00.906 resistance mechanisms and it's

NOTE Confidence: 0.8474694

00:43:00.906 --> 00:43:03.880 really one step why are one reason,

NOTE Confidence: 0.8474694

00:43:03.880 --> 00:43:06.988 not the only reason but one reason

NOTE Confidence: 0.8474694

00:43:06.988 --> 00:43:09.605 why are effective targeted therapies,

NOTE Confidence: 0.8474694

00:43:09.605 --> 00:43:13.013 precision therapies in lung cancer although

NOTE Confidence: 0.8474694

00:43:13.013 --> 00:43:15.678 effective they're not effective forever,

NOTE Confidence: 0.8474694

00:43:15.680 --> 00:43:18.240 they ultimately resistance happens

NOTE Confidence: 0.8474694

00:43:18.240 --> 00:43:21.731 in most if not all patients.

NOTE Confidence: 0.8474694

00:43:21.731 --> 00:43:22.604 And this state,

NOTE Confidence: 0.8474694

00:43:22.604 --> 00:43:24.696 what I'm trying to was trying to

NOTE Confidence: 0.8474694

00:43:24.696 --> 00:43:26.698 convince you is this state has some

NOTE Confidence: 0.8474694

00:43:26.698 --> 00:43:28.489 unique biologic properties and expressed

NOTE Confidence: 0.8474694

00:43:28.489 --> 00:43:30.424 potentially novel cell surface targets

NOTE Confidence: 0.8474694

00:43:30.424 --> 00:43:34.359 which can be leveraged therapeutically.

NOTE Confidence: 0.8474694

00:43:34.360 --> 00:43:36.896 And if we prevent the formation of this

NOTE Confidence: 0.8474694

00:43:36.896 --> 00:43:39.375 state or specifically treat the state,

NOTE Confidence: 0.8474694

00:43:39.375 --> 00:43:42.519 we may be able to extend the benefits of

NOTE Confidence: 0.8474694

00:43:42.520 --> 00:43:44.368 of our genotype directed therapies and

NOTE Confidence: 0.8474694

00:43:44.368 --> 00:43:46.520 lung cancers and maybe in other cancers.

NOTE Confidence: 0.8474694

00:43:46.520 --> 00:43:50.120 But this needs clinical validation and

NOTE Confidence: 0.8474694

00:43:50.120 --> 00:43:52.535 of course the issue that I mentioned

NOTE Confidence: 0.8474694

00:43:52.535 --> 00:43:54.361 that some of these proteins that are

NOTE Confidence: 0.8474694

00:43:54.361 --> 00:43:56.059 expressed in these drug tolerant states

NOTE Confidence: 0.8474694

00:43:56.059 --> 00:43:57.952 also expressed in normal tissues which

NOTE Confidence: 0.8474694

00:43:57.952 --> 00:44:01.024 may limit the therapeutic window and

NOTE Confidence: 0.8474694

00:44:01.024 --> 00:44:04.930 and again one reason why or 111 big

NOTE Confidence: 0.8474694

00:44:04.930 --> 00:44:08.200 reason why clinical validation is needed.

NOTE Confidence: 0.8474694

00:44:08.200 --> 00:44:10.278 So I just wanted to thank just acknowledge

NOTE Confidence: 0.8474694

00:44:10.278 --> 00:44:12.231 the many members of my laboratory who've

NOTE Confidence: 0.8474694

00:44:12.231 --> 00:44:14.040 been worked on these various projects.

NOTE Confidence: 0.8474694

00:44:14.040 --> 00:44:17.020 Here on the left hand side in the

NOTE Confidence: 0.8474694

00:44:17.020 --> 00:44:18.520 middle are my long term collaborators

NOTE Confidence: 0.8474694

00:44:18.520 --> 00:44:19.760 in the in this field,

NOTE Confidence: 0.8474694

00:44:19.760 --> 00:44:21.956 Nathaniel Gray who's a medicinal chemist,

NOTE Confidence: 0.8474694

00:44:21.960 --> 00:44:25.075 Mike Eck who is a structural biologist,

NOTE Confidence: 0.8474694

00:44:25.080 --> 00:44:27.150 biochemist and Kwak Wong who does

NOTE Confidence: 0.8474694

00:44:27.150 --> 00:44:29.040 animal models of lung cancer.

NOTE Confidence: 0.8474694

00:44:29.040 --> 00:44:29.990 We've worked,

NOTE Confidence: 0.8474694

00:44:29.990 --> 00:44:32.840 had the pleasure to work together

NOTE Confidence: 0.8474694

00:44:32.840 --> 00:44:35.072 for the last 10 years or so except

NOTE Confidence: 0.8474694

00:44:35.072 --> 00:44:36.734 during that time both Nathaniel

NOTE Confidence: 0.8474694

00:44:36.734 --> 00:44:38.474 and Kwak left Dana Farber.

NOTE Confidence: 0.8474694

00:44:38.480 --> 00:44:40.615 But we still continue to work together

NOTE Confidence: 0.8474694

00:44:40.615 --> 00:44:43.116 and still just submitted APO one together.

NOTE Confidence: 0.8474694

00:44:43.120 --> 00:44:46.120 So we'll hopefully be able to do this.

NOTE Confidence: 0.8474694

00:44:46.120 --> 00:44:46.954 The clinical,

NOTE Confidence: 0.8474694

00:44:46.954 --> 00:44:49.873 we have a lot of wonderful clinicians

NOTE Confidence: 0.8474694

00:44:49.873 --> 00:44:53.105 and clinical trialists who will run the

NOTE Confidence: 0.8474694

00:44:53.105 --> 00:44:55.800 clinical trials that I mentioned to you.

NOTE Confidence: 0.8474694

00:44:55.800 --> 00:44:57.984 That couldn't be done without our

NOTE Confidence: 0.8474694

00:44:57.984 --> 00:44:59.992 clinical research staff and patients

NOTE Confidence: 0.8474694

00:44:59.992 --> 00:45:02.986 and families who participate in clinical

NOTE Confidence: 0.8474694

00:45:02.986 --> 00:45:05.154 trials or translational research

NOTE Confidence: 0.8474694

00:45:05.160 --> 00:45:07.680 undergoing on treatment biopsies which

NOTE Confidence: 0.8474694

00:45:07.680 --> 00:45:11.148 may not benefit them directly but may

NOTE Confidence: 0.8474694

00:45:11.148 --> 00:45:13.247 ultimately help develop new therapies.

NOTE Confidence: 0.8474694

00:45:13.247 --> 00:45:16.183 We use a lot of bioinformatics in our

NOTE Confidence: 0.8474694

00:45:16.183 --> 00:45:18.808 analysis and with that couldn't be

NOTE Confidence: 0.8474694

00:45:18.808 --> 00:45:20.556 done without the bioinformaticians,

NOTE Confidence: 0.8474694

00:45:20.560 --> 00:45:22.674 the Belfer Centre that I helped run.

NOTE Confidence: 0.8474694

00:45:22.680 --> 00:45:24.465 These are many of the members are

NOTE Confidence: 0.8474694

00:45:24.465 --> 00:45:26.921 there and of course we need to have

NOTE Confidence: 0.8474694

00:45:26.921 --> 00:45:28.556 collaborators in the pharma industry

NOTE Confidence: 0.8474694

00:45:28.613 --> 00:45:30.419 who are developing many of these

NOTE Confidence: 0.8474694

00:45:30.419 --> 00:45:31.720 drugs to be able to

NOTE Confidence: 0.781017591

00:45:34.280 --> 00:45:35.988 to carry them out and hear some

NOTE Confidence: 0.781017591

00:45:35.988 --> 00:45:36.720 collaborators from AstraZeneca,

NOTE Confidence: 0.781017591

00:45:36.720 --> 00:45:39.880 Daiichi Sanchio and AbbVie.

NOTE Confidence: 0.781017591

00:45:39.880 --> 00:45:43.010 My collaborator Dave Barbie on

NOTE Confidence: 0.781017591

00:45:43.010 --> 00:45:45.960 the and Eric Smith and Elliot

NOTE Confidence: 0.781017591

00:45:45.960 --> 00:45:48.762 Abrea works with Eric and Dave

NOTE Confidence: 0.781017591

00:45:48.762 --> 00:45:51.834 on the on the car T cell studies.

NOTE Confidence: 0.781017591

00:45:51.840 --> 00:45:53.040 I just want to acknowledge them.

NOTE Confidence: 0.781017591

00:45:53.040 --> 00:45:55.588 And of course, none of the work

NOTE Confidence: 0.781017591

00:45:55.588 --> 00:45:57.599 would be possible without funding.

NOTE Confidence: 0.781017591

00:45:57.599 --> 00:45:59.513 And these are many of the

NOTE Confidence: 0.781017591

00:45:59.513 --> 00:46:00.760 funding agencies that have

NOTE Confidence: 0.883675986666667

00:46:03.520 --> 00:46:05.680 supported the work over the years.

NOTE Confidence: 0.883675986666667

00:46:05.680 --> 00:46:08.032 So I will stop there and happy to

NOTE Confidence: 0.883675986666667

00:46:08.032 --> 00:46:10.039 take any questions. Thank you again

NOTE Confidence: 0.883675986666667

00:46:10.039 --> 00:46:11.317 for the invitation to be here.

NOTE Confidence: 0.891138492

00:46:22.180 --> 00:46:23.380 Thank you so much, Posse,

NOTE Confidence: 0.891138492

00:46:23.380 --> 00:46:25.908 for really a fantastic talk.

NOTE Confidence: 0.891138492

00:46:25.908 --> 00:46:28.420 It was so clinically relevant

NOTE Confidence: 0.731016719

00:46:28.420 --> 00:46:29.560 and you're doing amazing work

NOTE Confidence: 0.731016719

00:46:29.560 --> 00:46:30.700 to really advance this field.

NOTE Confidence: 0.888756576666667

00:46:30.740 --> 00:46:32.228 So thank you again for all

NOTE Confidence: 0.888756576666667

00:46:32.228 --> 00:46:33.940 of that and for being here.

NOTE Confidence: 0.888756576666667

00:46:33.940 --> 00:46:34.960 So as is tradition,

NOTE Confidence: 0.888756576666667

00:46:34.960 --> 00:46:36.235 the first question goes back

NOTE Confidence: 0.888756576666667

00:46:36.235 --> 00:46:37.500 to Vito Calabrese. I don't

NOTE Confidence: 0.427580245

00:46:41.140 --> 00:46:41.580 know. All right. OK.

NOTE Confidence: 0.598923358333333

00:46:42.360 --> 00:46:44.238 Additionally, I asked a first question,

NOTE Confidence: 0.598923358333333

00:46:44.240 --> 00:46:46.914 even if I have nothing to say.

NOTE Confidence: 0.598923358333333

00:46:46.920 --> 00:46:50.595 But I was wondering whether in other

NOTE Confidence: 0.598923358333333

00:46:50.595 --> 00:46:54.226 types of cancers like Melanoma which

NOTE Confidence: 0.598923358333333

00:46:54.226 --> 00:46:58.200 got treated from nothing and then had

NOTE Confidence: 0.598923358333333

00:46:58.200 --> 00:47:00.710 the same intermediate stage developed

NOTE Confidence: 0.598923358333333

00:47:00.710 --> 00:47:03.132 where there were some cells of this

NOTE Confidence: 0.598923358333333

00:47:03.132 --> 00:47:05.433 sort and they found ways of going

NOTE Confidence: 0.598923358333333

00:47:05.433 --> 00:47:08.209 after them or whether there there was a

NOTE Confidence: 0.598923358333333

00:47:08.209 --> 00:47:12.560 total treatment from the first time. So

NOTE Confidence: 0.924440378888889

00:47:12.560 --> 00:47:14.513 depends a little bit on the type of therapy.

NOTE Confidence: 0.924440378888889

00:47:14.520 --> 00:47:16.698 But this sort of intermediate state

NOTE Confidence: 0.924440378888889

00:47:16.698 --> 00:47:19.330 does exist in other cancers if they're

NOTE Confidence: 0.924440378888889

00:47:19.330 --> 00:47:21.280 especially if they're treated with the

NOTE Confidence: 0.924440378888889

00:47:21.280 --> 00:47:22.799 targeted therapies that I mentioned.

NOTE Confidence: 0.924440378888889

00:47:22.800 --> 00:47:24.240 I think the difference in

NOTE Confidence: 0.924440378888889

00:47:24.240 --> 00:47:26.040 Melanoma is that it's a very,

NOTE Confidence: 0.924440378888889

00:47:26.040 --> 00:47:28.770 it's a cancer that we can effectively

NOTE Confidence: 0.924440378888889

00:47:28.770 --> 00:47:30.917 treat with immune therapies that

NOTE Confidence: 0.924440378888889

00:47:30.917 --> 00:47:33.270 are already exist and were developed

NOTE Confidence: 0.924440378888889

00:47:33.270 --> 00:47:34.920 in Melanoma and other cancers.

NOTE Confidence: 0.924440378888889

00:47:34.920 --> 00:47:36.800 They do work in lung cancers as well.

NOTE Confidence: 0.924440378888889

00:47:36.800 --> 00:47:38.728 They just don't work in the lung cancers

NOTE Confidence: 0.924440378888889

00:47:38.728 --> 00:47:40.295 that have these genetic alterations

NOTE Confidence: 0.924440378888889

00:47:40.295 --> 00:47:42.353 where we use these targeted therapies.

NOTE Confidence: 0.924440378888889

00:47:42.360 --> 00:47:43.836 And so that's why we need

NOTE Confidence: 0.924440378888889

00:47:43.840 --> 00:47:44.502 different approaches.

NOTE Confidence: 0.924440378888889

00:47:44.502 --> 00:47:46.157 But it isn't this example.

NOTE Confidence: 0.924440378888889

00:47:46.160 --> 00:47:47.760 This sort of pattern isn't

NOTE Confidence: 0.924440378888889

00:47:47.760 --> 00:47:49.040 unique to lung cancer,

NOTE Confidence: 0.924440378888889

00:47:49.040 --> 00:47:51.000 does happen in other cancers as well.

NOTE Confidence: 0.614070866

00:47:53.080 --> 00:47:55.735 Hi, I'm. I'm Steve Calabresi, Dr.

NOTE Confidence: 0.614070866

00:47:55.735 --> 00:47:58.640 Calabresi's son. And I'm a law professor.

NOTE Confidence: 0.614070866

00:47:58.640 --> 00:48:01.356 So this question may not be

NOTE Confidence: 0.614070866

00:48:01.356 --> 00:48:04.536 thoroughly relevant, but my father

NOTE Confidence: 0.614070866

00:48:04.536 --> 00:48:09.117 had a cancer of the tongue in 1975

NOTE Confidence: 0.614070866

00:48:09.117 --> 00:48:11.973 on the left side of the tongue and

NOTE Confidence: 0.614070866

00:48:11.973 --> 00:48:15.400 was given a 15% chance of surviving.

NOTE Confidence: 0.614070866

00:48:15.400 --> 00:48:17.492 He ended up living another 25 years.

NOTE Confidence: 0.614070866

00:48:17.492 --> 00:48:20.471 The way he treated the cancer of the

NOTE Confidence: 0.614070866

00:48:20.471 --> 00:48:22.921 tongue was to have surgery on his

NOTE Confidence: 0.614070866

00:48:22.921 --> 00:48:25.226 tongue and to have the glands on

NOTE Confidence: 0.614070866

00:48:25.226 --> 00:48:27.960 the left side of his neck removed,

NOTE Confidence: 0.614070866

00:48:27.960 --> 00:48:29.900 which turned out to have cancer

NOTE Confidence: 0.614070866

00:48:29.900 --> 00:48:32.920 cells in them. He had chemotherapy,

NOTE Confidence: 0.614070866

00:48:32.920 --> 00:48:35.133 He had radiation therapy with

NOTE Confidence: 0.614070866

00:48:35.133 --> 00:48:37.139 radioactive needles in his tongue,

NOTE Confidence: 0.614070866

00:48:37.139 --> 00:48:39.966 and he even used, in 1975,

NOTE Confidence: 0.614070866

00:48:39.966 --> 00:48:42.596 a primitive form of immunotherapy.

NOTE Confidence: 0.614070866

00:48:42.600 --> 00:48:45.200 And his idea was to throw everything,

NOTE Confidence: 0.614070866

00:48:45.200 --> 00:48:47.073 everything at it, basically.

NOTE Confidence: 0.614070866

00:48:47.073 --> 00:48:49.539 And so I wondered with these

NOTE Confidence: 0.614070866

00:48:49.539 --> 00:48:50.601 persistent can cancers,

NOTE Confidence: 0.614070866

00:48:50.601 --> 00:48:53.489 can you once you reduce the size of

NOTE Confidence: 0.614070866

00:48:53.489 --> 00:48:56.119 the cancer to a smaller location,

NOTE Confidence: 0.614070866

00:48:56.120 --> 00:48:58.280 is there any chance of gaining

NOTE Confidence: 0.614070866

00:48:58.280 --> 00:48:59.960 anything by surgically removing it.

NOTE Confidence: 0.614070866

00:48:59.960 --> 00:49:01.680 Obviously microscopic cancer cells

NOTE Confidence: 0.614070866

00:49:01.680 --> 00:49:03.976 might remain but maybe those would

NOTE Confidence: 0.614070866

00:49:03.976 --> 00:49:05.959 could be targeted by chemotherapy or

NOTE Confidence: 0.720138036

00:49:05.960 --> 00:49:07.200 yeah so in in the,

NOTE Confidence: 0.720138036

00:49:07.200 --> 00:49:09.888 in the EGFR example and Roy knows

NOTE Confidence: 0.720138036

00:49:09.888 --> 00:49:12.898 is very well since he led the the,

NOTE Confidence: 0.720138036

00:49:12.898 --> 00:49:15.094 the, the trials patients who have

NOTE Confidence: 0.720138036

00:49:15.094 --> 00:49:17.558 earlier stage lung cancer which we

NOTE Confidence: 0.720138036

00:49:17.558 --> 00:49:19.588 can potentially cure with surgery

NOTE Confidence: 0.720138036

00:49:19.662 --> 00:49:21.557 although it can still recur.

NOTE Confidence: 0.720138036

00:49:21.560 --> 00:49:25.228 We now use these effective like the

NOTE Confidence: 0.720138036

00:49:25.228 --> 00:49:27.910 the EGFR inhibitor as an adjuvant.

NOTE Confidence: 0.720138036

00:49:27.910 --> 00:49:30.130 So after surgery patients may get

NOTE Confidence: 0.720138036

00:49:30.130 --> 00:49:32.362 chemotherapy and then they get the EGFR

NOTE Confidence: 0.720138036

00:49:32.362 --> 00:49:34.235 inhibitor for multiple years there.

NOTE Confidence: 0.720138036

00:49:34.235 --> 00:49:37.731 We know that that not only reduces the

NOTE Confidence: 0.720138036

00:49:37.731 --> 00:49:40.395 likelihood of the cancer coming back,

NOTE Confidence: 0.720138036

00:49:40.400 --> 00:49:43.316 but it makes people live longer.

NOTE Confidence: 0.720138036

00:49:43.320 --> 00:49:45.045 Now whether whether it ultimately

NOTE Confidence: 0.720138036

00:49:45.045 --> 00:49:46.080 cures those cancers,

NOTE Confidence: 0.720138036

00:49:46.080 --> 00:49:47.238 I think we don't know yet,

NOTE Confidence: 0.720138036

00:49:47.240 --> 00:49:49.354 but at least the early signs are

NOTE Confidence: 0.720138036

00:49:49.354 --> 00:49:51.679 all going in the right direction.

NOTE Confidence: 0.720138036

00:49:51.680 --> 00:49:52.800 So yes,

NOTE Confidence: 0.720138036

00:49:52.800 --> 00:49:55.600 absolutely we're trying trying to

NOTE Confidence: 0.720138036

00:49:55.600 --> 00:49:57.490 take what we learn in studying

NOTE Confidence: 0.720138036

00:49:57.490 --> 00:49:59.181 patients with advanced lung cancer

NOTE Confidence: 0.720138036

00:49:59.181 --> 00:50:01.056 and moving the effective therapies

NOTE Confidence: 0.720138036

00:50:01.056 --> 00:50:03.190 into earlier settings where we can

NOTE Confidence: 0.720138036

00:50:03.190 --> 00:50:04.428 hopefully cure more patients with

NOTE Confidence: 0.720138036

00:50:04.428 --> 00:50:06.102 the with the disease as as long

NOTE Confidence: 0.720138036

00:50:06.102 --> 00:50:07.694 as we can find the the cancers in

NOTE Confidence: 0.720138036

00:50:07.694 --> 00:50:09.179 the earlier stage which remains

NOTE Confidence: 0.720138036

00:50:09.179 --> 00:50:10.120 a challenge still

NOTE Confidence: 0.88103646

00:50:12.720 --> 00:50:14.800 really nice talk. I'm wondering if

NOTE Confidence: 0.88103646

00:50:14.800 --> 00:50:17.346 drug therapy is acquired through

NOTE Confidence: 0.88103646

00:50:17.346 --> 00:50:19.320 somatic mutations or if there are

NOTE Confidence: 0.831825115

00:50:19.800 --> 00:50:21.904 pre-existing cells that then

NOTE Confidence: 0.831825115

00:50:21.904 --> 00:50:24.920 grow out that account for the.

NOTE Confidence: 0.831825115

00:50:24.920 --> 00:50:26.816 Yeah, both can happen and there's

NOTE Confidence: 0.831825115

00:50:26.816 --> 00:50:29.247 and and and and certainly there are

NOTE Confidence: 0.831825115

00:50:29.247 --> 00:50:31.449 examples in lung cancer and then

NOTE Confidence: 0.831825115

00:50:31.449 --> 00:50:33.755 EJFR space where you can find the,

NOTE Confidence: 0.831825115

00:50:33.760 --> 00:50:35.904 you know, you know one in a million

NOTE Confidence: 0.831825115

00:50:35.904 --> 00:50:38.124 cells you can find the resistance

NOTE Confidence: 0.831825115

00:50:38.124 --> 00:50:40.149 mechanism cancer with a resistance

NOTE Confidence: 0.831825115

00:50:40.149 --> 00:50:42.592 mechanism already there and then

NOTE Confidence: 0.831825115

00:50:42.592 --> 00:50:45.640 over time it gets selected for.

NOTE Confidence: 0.831825115

00:50:45.640 --> 00:50:48.180 But the other way around,

NOTE Confidence: 0.831825115

00:50:48.180 --> 00:50:49.710 the other other is also true

NOTE Confidence: 0.831825115

00:50:49.764 --> 00:50:51.036 that you may not find it,

NOTE Confidence: 0.831825115

00:50:51.040 --> 00:50:54.477 but it's this intermediate state for

NOTE Confidence: 0.831825115

00:50:54.477 --> 00:50:57.013 whatever reason then is denied us for many

NOTE Confidence: 0.831825115

00:50:57.013 --> 00:50:58.926 different resistance things to evolve,

NOTE Confidence: 0.831825115

00:50:58.926 --> 00:51:00.624 and part of the reason to

NOTE Confidence: 0.831825115

00:51:00.624 --> 00:51:02.679 to of course go after that.

NOTE Confidence: 0.831825115

00:51:02.680 --> 00:51:04.680 But both do exist.

NOTE Confidence: 0.831825115

00:51:04.680 --> 00:51:08.160 Both both paths to resistance are possible.

NOTE Confidence: 0.831825115

00:51:08.160 --> 00:51:09.918 Doesn't mean they can't coexist either.

NOTE Confidence: 0.658929428571429

00:51:14.760 --> 00:51:16.608 Hi, Pasi, it's good to see

NOTE Confidence: 0.658929428571429

00:51:16.608 --> 00:51:17.976 you and thanks for coming.

NOTE Confidence: 0.658929428571429

00:51:17.976 --> 00:51:20.000 It's beautiful work.

NOTE Confidence: 0.658929428571429

00:51:20.000 --> 00:51:22.300 I wondered if in the studies

NOTE Confidence: 0.658929428571429

00:51:22.300 --> 00:51:24.842 that you use the combination of

NOTE Confidence: 0.658929428571429

00:51:24.842 --> 00:51:26.688 your BCLXADC and ASA Mertonib,

NOTE Confidence: 0.658929428571429

00:51:26.688 --> 00:51:29.020 did you add, did you do any

NOTE Confidence: 0.658929428571429

00:51:29.020 --> 00:51:30.320 studies combining that with the

NOTE Confidence: 0.658929428571429

00:51:30.320 --> 00:51:31.773 MEC inhibitor because it looks

NOTE Confidence: 0.658929428571429

00:51:31.773 --> 00:51:32.945 like that's your preclinical

NOTE Confidence: 0.658929428571429

00:51:32.945 --> 00:51:34.479 data with support that triplet.

NOTE Confidence: 0.646076198333333

00:51:34.600 --> 00:51:36.958 Yeah, We we didn't, we didn't.

NOTE Confidence: 0.646076198333333

00:51:36.960 --> 00:51:39.480 And part of it is that it's,

NOTE Confidence: 0.646076198333333

00:51:39.480 --> 00:51:42.126 it's tough to take the MEC inhibitor

NOTE Confidence: 0.646076198333333

00:51:42.126 --> 00:51:43.260 combinations forward clinically

NOTE Confidence: 0.646076198333333

00:51:43.323 --> 00:51:45.435 because of the MEC inhibitor toxicity.

NOTE Confidence: 0.646076198333333

00:51:45.440 --> 00:51:48.560 And so we wanted to stick to strategies

NOTE Confidence: 0.646076198333333

00:51:48.560 --> 00:51:50.976 that we could ultimately test in the

NOTE Confidence: 0.646076198333333

00:51:50.976 --> 00:51:53.679 clinic in the form of a clinical trial.

NOTE Confidence: 0.646076198333333

00:51:53.680 --> 00:51:54.704 And as you said,

NOTE Confidence: 0.646076198333333

00:51:54.704 --> 00:51:56.240 we're doing a trial of ASA,

NOTE Confidence: 0.646076198333333

00:51:56.240 --> 00:51:57.904 Merton and Ben Celimetin,

NOTE Confidence: 0.646076198333333

00:51:57.904 --> 00:52:01.127 but even that and even giving it an

NOTE Confidence: 0.646076198333333

00:52:01.127 --> 00:52:03.200 intermediate or intermittent dose levels,

NOTE Confidence: 0.646076198333333

00:52:03.200 --> 00:52:04.840 not everybody can tolerate it.

NOTE Confidence: 0.646076198333333

00:52:04.840 --> 00:52:10.072 The MEC inhibitor toxicity adds up over time.

NOTE Confidence: 0.646076198333333

00:52:10.072 --> 00:52:10.520 Thanks.

NOTE Confidence: 0.881945735454545

00:52:12.360 --> 00:52:13.770 I'm going to ask a question

NOTE Confidence: 0.881945735454545

00:52:13.770 --> 00:52:15.241 as I walk over here POSI.

NOTE Confidence: 0.881945735454545

00:52:15.241 --> 00:52:17.169 I think you know one of the studies

NOTE Confidence: 0.881945735454545

00:52:17.169 --> 00:52:19.086 that I was really struck by is the

NOTE Confidence: 0.881945735454545

00:52:19.086 --> 00:52:20.750 the study that you did where you

NOTE Confidence: 0.881945735454545

00:52:20.750 --> 00:52:22.400 buy up did on treatment biopsies.

NOTE Confidence: 0.881945735454545

00:52:22.400 --> 00:52:24.609 I think it's something we a lot of

NOTE Confidence: 0.881945735454545

00:52:24.609 --> 00:52:26.067 trials have them as optional biopsies

NOTE Confidence: 0.881945735454545

00:52:26.067 --> 00:52:27.936 and I think sometimes we feel it's hard

NOTE Confidence: 0.881945735454545

00:52:27.936 --> 00:52:29.880 to to have patients go through that.

NOTE Confidence: 0.881945735454545

00:52:29.880 --> 00:52:31.548 I'm just curious your experience in

NOTE Confidence: 0.881945735454545

00:52:31.548 --> 00:52:33.254 the clinic because it's such important

NOTE Confidence: 0.881945735454545

00:52:33.254 --> 00:52:35.137 samples how how it was talking to

NOTE Confidence: 0.881945735454545

00:52:35.137 --> 00:52:36.873 patients about that and getting those

NOTE Confidence: 0.881945735454545

00:52:36.873 --> 00:52:38.080 samples and the importance of those

NOTE Confidence: 0.867367971111111

00:52:39.400 --> 00:52:42.910 most most patients that this

NOTE Confidence: 0.867367971111111

00:52:42.910 --> 00:52:46.564 trial and other trials as you

NOTE Confidence: 0.867367971111111

00:52:46.564 --> 00:52:48.674 mentioned require on study biopsies.

NOTE Confidence: 0.867367971111111

00:52:48.680 --> 00:52:52.905 And I think we're most of our patients

NOTE Confidence: 0.867367971111111

00:52:52.905 --> 00:52:55.578 are willing to assuming it's safe and

NOTE Confidence: 0.867367971111111

00:52:55.578 --> 00:52:57.992 the tumors in a location that can be

NOTE Confidence: 0.867367971111111

00:52:57.992 --> 00:53:00.080 biopsied are willing to undergo that.

NOTE Confidence: 0.867367971111111

00:53:00.080 --> 00:53:03.580 You know after we explain to them and you

NOTE Confidence: 0.867367971111111

00:53:03.580 --> 00:53:05.960 know although it may not help them directly,

NOTE Confidence: 0.867367971111111

00:53:05.960 --> 00:53:07.934 it'll help the development of medicines

NOTE Confidence: 0.867367971111111

00:53:07.934 --> 00:53:09.855 that we're trying to develop and

NOTE Confidence: 0.867367971111111

00:53:09.855 --> 00:53:11.773 it'll help others in the future and

NOTE Confidence: 0.867367971111111

00:53:11.773 --> 00:53:14.034 we do we we are have been able to

NOTE Confidence: 0.867367971111111

00:53:14.034 --> 00:53:16.845 be successful in that but it is it,

NOTE Confidence: 0.867367971111111

00:53:16.845 --> 00:53:19.515 it is optional in most cases

NOTE Confidence: 0.867367971111111

00:53:19.515 --> 00:53:21.640 optional typically means not done.

NOTE Confidence: 0.867367971111111

00:53:21.640 --> 00:53:27.240 So so yeah it it remains a challenge

NOTE Confidence: 0.867367971111111

00:53:27.240 --> 00:53:28.080 a really great talk

NOTE Confidence: 0.683729291111111

00:53:29.440 --> 00:53:30.168 as a radiation oncologist.

NOTE Confidence: 0.683729291111111

00:53:30.168 --> 00:53:31.314 One thing I worry about is,

NOTE Confidence: 0.683729291111111

00:53:31.314 --> 00:53:32.933 is there evidence of the senesa state

NOTE Confidence: 0.683729291111111

00:53:32.933 --> 00:53:34.653 being more or less ready resistant

NOTE Confidence: 0.683729291111111

00:53:34.653 --> 00:53:37.008 initial tumor and clinically it might

NOTE Confidence: 0.683729291111111

00:53:37.008 --> 00:53:38.580 be relevant patients got you know

NOTE Confidence: 0.683729291111111

00:53:38.632 --> 00:53:40.081 a handful of brain Mets and right

NOTE Confidence: 0.683729291111111

00:53:40.081 --> 00:53:41.486 now if they have an EGFR option

NOTE Confidence: 0.683729291111111

00:53:41.486 --> 00:53:42.626 do we do radiosurgery upfront,

NOTE Confidence: 0.683729291111111

00:53:42.626 --> 00:53:44.536 do we just do EGFR therapy and then

NOTE Confidence: 0.683729291111111

00:53:44.536 --> 00:53:45.880 watch wait for it to come back.

NOTE Confidence: 0.683729291111111

00:53:45.880 --> 00:53:47.020 When's the right time to kind

NOTE Confidence: 0.683729291111111

00:53:47.020 --> 00:53:47.400 of incorporate

NOTE Confidence: 0.632910193333333

00:53:47.400 --> 00:53:48.600 right. And there there there is,

NOTE Confidence: 0.632910193333333

00:53:48.600 --> 00:53:50.340 there are studies that are looking

NOTE Confidence: 0.632910193333333

00:53:50.340 --> 00:53:52.639 at this you know for EGFR therapies,

NOTE Confidence: 0.632910193333333

00:53:52.640 --> 00:53:55.226 you know patients who have sort

NOTE Confidence: 0.632910193333333

00:53:55.226 --> 00:53:57.240 of maximal response radiating the

NOTE Confidence: 0.632910193333333

00:53:57.240 --> 00:53:58.822 sort of the remaining areas and and

NOTE Confidence: 0.632910193333333

00:53:58.822 --> 00:54:00.376 and there are some studies that

NOTE Confidence: 0.632910193333333

00:54:00.376 --> 00:54:02.032 suggest that that may be beneficial.

NOTE Confidence: 0.632910193333333

00:54:02.040 --> 00:54:06.644 And we typically have a radiation

NOTE Confidence: 0.632910193333333

00:54:06.644 --> 00:54:08.184 oncologist see our patients have

NOTE Confidence: 0.632910193333333

00:54:08.184 --> 00:54:10.007 that they've had a maximal response

NOTE Confidence: 0.632910193333333

00:54:10.007 --> 00:54:11.447 to whatever targeted therapy to

NOTE Confidence: 0.632910193333333

00:54:11.447 --> 00:54:12.362 ask is it feasible,

NOTE Confidence: 0.632910193333333

00:54:12.362 --> 00:54:14.616 is it in a location that can

NOTE Confidence: 0.632910193333333

00:54:14.616 --> 00:54:16.777 you know that that is can be

NOTE Confidence: 0.632910193333333

00:54:16.777 --> 00:54:18.840 done in terms of brain lesions.

NOTE Confidence: 0.96419372

00:54:21.840 --> 00:54:23.654 I think as medical oncologists

NOTE Confidence: 0.96419372

00:54:23.654 --> 00:54:25.744 we prefer to have pharmacologic

NOTE Confidence: 0.96419372

00:54:25.744 --> 00:54:27.879 approaches to treat brain lesions,

NOTE Confidence: 0.96419372

00:54:27.880 --> 00:54:30.448 although we rely heavily on our

NOTE Confidence: 0.96419372

00:54:30.448 --> 00:54:31.732 radiation oncology colleagues

NOTE Confidence: 0.96419372

00:54:31.732 --> 00:54:32.754 for stereotactic radiation.

NOTE Confidence: 0.96419372

00:54:32.754 --> 00:54:34.833 But if we can avoid things like

NOTE Confidence: 0.96419372

00:54:34.833 --> 00:54:36.348 whole brain radiation with

NOTE Confidence: 0.96419372

00:54:36.348 --> 00:54:37.515 using pharmacologic agents,

NOTE Confidence: 0.96419372

00:54:37.520 --> 00:54:40.400 I think that would be preferable.

NOTE Confidence: 0.96419372

00:54:40.400 --> 00:54:43.045 But not all of our agents as you know

NOTE Confidence: 0.96419372

00:54:43.045 --> 00:54:44.120 across the blood brain barriers.

NOTE Confidence: 0.782650837111111

00:54:45.640 --> 00:54:46.860 Posse, thanks so much for

NOTE Confidence: 0.782650837111111

00:54:46.860 --> 00:54:47.836 being our visiting professor.

NOTE Confidence: 0.782650837111111

00:54:47.840 --> 00:54:48.876 As you know as well as anyone,

NOTE Confidence: 0.782650837111111

00:54:48.880 --> 00:54:51.176 it's now 20 years since the EGF

NOTE Confidence: 0.782650837111111

00:54:51.176 --> 00:54:52.160 reputations were discovered.

NOTE Confidence: 0.782650837111111

00:54:52.160 --> 00:54:53.875 Your lab was of course one of

NOTE Confidence: 0.782650837111111

00:54:53.875 --> 00:54:55.842 the key labs in that and it's so

NOTE Confidence: 0.782650837111111

00:54:55.842 --> 00:54:57.147 tantalizing to have these oral

NOTE Confidence: 0.782650837111111

00:54:57.147 --> 00:54:58.519 agents and patients live longer.

NOTE Confidence: 0.782650837111111

00:54:58.520 --> 00:54:59.868 But as you mentioned,

NOTE Confidence: 0.782650837111111

00:54:59.868 --> 00:55:01.553 no one's ever really cured.

NOTE Confidence: 0.782650837111111

00:55:01.560 --> 00:55:03.247 So now you've described to us adding

NOTE Confidence: 0.782650837111111

00:55:03.247 --> 00:55:04.799 different agents in that add toxicity.

NOTE Confidence: 0.782650837111111

00:55:04.800 --> 00:55:06.256 So my question is going to be

NOTE Confidence: 0.782650837111111

00:55:06.256 --> 00:55:07.731 about that it really does change

NOTE Confidence: 0.782650837111111

00:55:07.731 --> 00:55:09.374 the course of a patient's life as

NOTE Confidence: 0.782650837111111

00:55:09.374 --> 00:55:11.103 you start adding in some of these

NOTE Confidence: 0.782650837111111

00:55:11.103 --> 00:55:13.020 toxicities with you have to come in

NOTE Confidence: 0.782650837111111

00:55:13.020 --> 00:55:14.164 for intravenous infusions exactly.

NOTE Confidence: 0.782650837111111

00:55:14.164 --> 00:55:15.872 So my specific question is going to

NOTE Confidence: 0.782650837111111

00:55:15.872 --> 00:55:17.480 be something we're interested in here,

NOTE Confidence: 0.782650837111111

00:55:17.480 --> 00:55:19.244 some of the the pulmonary toxicity we

NOTE Confidence: 0.782650837111111

00:55:19.244 --> 00:55:20.980 see with these antibody drug targets.

NOTE Confidence: 0.782650837111111

00:55:20.980 --> 00:55:22.480 Is there anything that's known

NOTE Confidence: 0.782650837111111

00:55:22.480 --> 00:55:23.963 about structure function and will

NOTE Confidence: 0.782650837111111

00:55:23.963 --> 00:55:25.397 there be ways to ameliorate that?

NOTE Confidence: 0.782650837111111

00:55:25.400 --> 00:55:26.504 Because certainly you take

NOTE Confidence: 0.782650837111111

00:55:26.504 --> 00:55:28.160 someone with a long life span,

NOTE Confidence: 0.782650837111111

00:55:28.160 --> 00:55:29.441 but you if they end up having

NOTE Confidence: 0.782650837111111

00:55:29.441 --> 00:55:30.479 a pulmonary crisis that could

NOTE Confidence: 0.782650837111111

00:55:30.479 --> 00:55:31.594 be of course very devastating.

NOTE Confidence: 0.946696772

00:55:31.800 --> 00:55:36.696 Yeah. I don't think we as a field

NOTE Confidence: 0.946696772

00:55:36.696 --> 00:55:39.420 completely understand why some of

NOTE Confidence: 0.946696772

00:55:39.420 --> 00:55:41.420 these antibody drug conjugates

NOTE Confidence: 0.946696772

00:55:41.420 --> 00:55:44.240 give a rise to pulmonary toxicity.

NOTE Confidence: 0.946696772

00:55:44.240 --> 00:55:48.300 Or of course it is the the, the one of

NOTE Confidence: 0.946696772

00:55:48.300 --> 00:55:52.474 the more feared toxicities because A,

NOTE Confidence: 0.946696772

00:55:52.474 --> 00:55:54.112 that can be symptomatic and B typically

NOTE Confidence: 0.946696772

00:55:54.112 --> 00:55:56.158 means you have to stop using that treatment,

NOTE Confidence: 0.946696772

00:55:56.160 --> 00:55:58.022 even though if it's if it's been

NOTE Confidence: 0.946696772

00:55:58.022 --> 00:55:59.560 effective because you don't want to,

NOTE Confidence: 0.946696772

00:55:59.560 --> 00:56:01.000 you know, make the toxicity worse.

NOTE Confidence: 0.946696772

00:56:01.000 --> 00:56:04.330 But our mechanistic understanding of

NOTE Confidence: 0.946696772

00:56:04.330 --> 00:56:07.328 what gives rise to that I think is at

NOTE Confidence: 0.946696772

00:56:07.328 --> 00:56:09.773 its infancy still and I think something

NOTE Confidence: 0.946696772

00:56:09.773 --> 00:56:12.160 that we should continue to work on.

NOTE Confidence: 0.946696772

00:56:12.160 --> 00:56:15.888 And they're not great models like mice don't

NOTE Confidence: 0.946696772

00:56:15.888 --> 00:56:18.280 get interstitial lung disease from that.

NOTE Confidence: 0.946696772

00:56:18.280 --> 00:56:19.477 So you have to have a good

NOTE Confidence: 0.946696772

00:56:19.477 --> 00:56:20.799 model to be able to study in.

NOTE Confidence: 0.893544244545455

00:56:22.200 --> 00:56:23.768 I think we have time for one and

NOTE Confidence: 0.893544244545455

00:56:23.768 --> 00:56:25.480 maybe two questions. So just

NOTE Confidence: 0.806565596666667

00:56:25.480 --> 00:56:27.760 my question come from pathology NGS,

NOTE Confidence: 0.806565596666667

00:56:27.760 --> 00:56:29.400 so this persistent cells.

NOTE Confidence: 0.806565596666667

00:56:29.400 --> 00:56:31.020 So when we get that tumor treated

NOTE Confidence: 0.806565596666667

00:56:31.020 --> 00:56:32.960 and recurrent, we see additional

NOTE Confidence: 0.806565596666667

00:56:32.960 --> 00:56:35.160 mutation in GFR amplification,

NOTE Confidence: 0.806565596666667

00:56:35.160 --> 00:56:36.410 some tumor exchange to become

NOTE Confidence: 0.806565596666667

00:56:36.410 --> 00:56:37.546 neuron decrin and squamous.

NOTE Confidence: 0.806565596666667

00:56:37.546 --> 00:56:39.476 These persistent tumor cells where

NOTE Confidence: 0.806565596666667

00:56:39.476 --> 00:56:42.440 they are located in in these pathways

NOTE Confidence: 0.7271285

00:56:43.720 --> 00:56:46.260 typically as I showed you pre

NOTE Confidence: 0.7271285

00:56:46.260 --> 00:56:47.680 clinically typically if we take

NOTE Confidence: 0.803133007333333

00:56:47.742 --> 00:56:49.034 one of these persistent

NOTE Confidence: 0.803133007333333

00:56:49.034 --> 00:56:50.400 cells and do NGS on them,

NOTE Confidence: 0.803133007333333

00:56:50.400 --> 00:56:52.386 they don't have any other genetic

NOTE Confidence: 0.803133007333333

00:56:52.386 --> 00:56:54.200 alterations compared to the parental

NOTE Confidence: 0.803133007333333

00:56:54.200 --> 00:56:55.544 because they're basically just

NOTE Confidence: 0.803133007333333

00:56:55.544 --> 00:56:57.560 rewired to be able to survive.

NOTE Confidence: 0.803133007333333

00:56:57.560 --> 00:56:59.810 And if you in that preclinical

NOTE Confidence: 0.803133007333333

00:56:59.810 --> 00:57:02.238 experiment if you take off the drug

NOTE Confidence: 0.803133007333333

00:57:02.240 --> 00:57:04.166 they regrow and they're the signaling

NOTE Confidence: 0.803133007333333

00:57:04.166 --> 00:57:05.997 pathways look like look the same

NOTE Confidence: 0.803133007333333

00:57:05.997 --> 00:57:07.712 as they do in the parental cells.

NOTE Confidence: 0.803133007333333

00:57:07.720 --> 00:57:11.040 So it's it's it's sort of an adapt,

NOTE Confidence: 0.803133007333333

00:57:11.040 --> 00:57:13.420 it would fall under sort of an

NOTE Confidence: 0.803133007333333

00:57:13.420 --> 00:57:14.944 adaptive resistance that allows

NOTE Confidence: 0.803133007333333

00:57:14.944 --> 00:57:17.086 survival but not necessarily driven

NOTE Confidence: 0.803133007333333

00:57:17.086 --> 00:57:19.240 by a specific genomic mechanism. OK,

NOTE Confidence: 0.674707294

00:57:21.440 --> 00:57:22.400 David, I think this will

NOTE Confidence: 0.608082976

00:57:22.400 --> 00:57:25.760 be the last question from pathology.

NOTE Confidence: 0.608082976

00:57:25.760 --> 00:57:27.704 So the protein expression of

NOTE Confidence: 0.608082976

00:57:27.704 --> 00:57:29.912 both trope 2 and EGFR spans

NOTE Confidence: 0.608082976

00:57:29.912 --> 00:57:31.957 about a two log dynamic range.

NOTE Confidence: 0.608082976

00:57:31.960 --> 00:57:33.745 Have you ever looked at the levels

NOTE Confidence: 0.608082976

00:57:33.745 --> 00:57:35.057 of protein expression to correlate

NOTE Confidence: 0.608082976

00:57:35.057 --> 00:57:36.560 with your ADADC effects that you see?

NOTE Confidence: 0.956039637142857

00:57:37.240 --> 00:57:39.950 So clinically that's been looked

NOTE Confidence: 0.956039637142857

00:57:39.950 --> 00:57:42.525 at and disappointingly has no

NOTE Confidence: 0.956039637142857

00:57:42.525 --> 00:57:45.000 correlation with the efficacy of

NOTE Confidence: 0.956039637142857

00:57:45.000 --> 00:57:47.440 Trope 2AD CS or her three AD CS.

NOTE Confidence: 0.956039637142857

00:57:47.440 --> 00:57:50.080 Now maybe it's because we don't

NOTE Confidence: 0.956039637142857

00:57:50.080 --> 00:57:54.392 have the right assets to look at.

NOTE Confidence: 0.956039637142857

00:57:54.392 --> 00:57:56.784 Maybe it's because other things you

NOTE Confidence: 0.956039637142857

00:57:56.784 --> 00:57:59.360 you need the expression of the target,

NOTE Confidence: 0.956039637142857

00:57:59.360 --> 00:58:00.320 but you need other things.

NOTE Confidence: 0.956039637142857

00:58:00.320 --> 00:58:02.637 The antibody has to bind the target.

NOTE Confidence: 0.956039637142857

00:58:02.640 --> 00:58:03.800 It has to be internalized.

NOTE Confidence: 0.956039637142857

00:58:03.800 --> 00:58:06.016 It has to be transported to the right

NOTE Confidence: 0.956039637142857

00:58:06.016 --> 00:58:07.600 cell compartment where then the the,

NOTE Confidence: 0.956039637142857

00:58:07.600 --> 00:58:10.050 the the conjugate is cleaved and and

NOTE Confidence: 0.956039637142857

00:58:10.050 --> 00:58:12.677 and then can kill the tumor cells.

NOTE Confidence: 0.956039637142857

00:58:12.680 --> 00:58:14.969 So maybe maybe there are other things

NOTE Confidence: 0.956039637142857

00:58:14.969 --> 00:58:17.159 that are important in that in that

NOTE Confidence: 0.956039637142857

00:58:17.159 --> 00:58:19.350 overall efficacy as well not just the

NOTE Confidence: 0.956039637142857

00:58:19.350 --> 00:58:21.958 expression of the of the of the target.

NOTE Confidence: 0.63022959

00:58:24.400 --> 00:58:26.165 Great. Well possibly.

NOTE Confidence: 0.63022959

00:58:26.165 --> 00:58:28.445 Again, thank you so much for really a

NOTE Confidence: 0.63022959

00:58:28.445 --> 00:58:30.239 fantastic talk and for coming to visit.

NOTE Confidence: 0.63022959

00:58:30.240 --> 00:58:31.698 I will just make one announcement

NOTE Confidence: 0.63022959

00:58:31.698 --> 00:58:33.491 which is after this in the next

NOTE Confidence: 0.63022959

00:58:33.491 --> 00:58:35.033 couple minutes we're going to gather

NOTE Confidence: 0.63022959

00:58:35.033 --> 00:58:36.508 outside and and the fellows and

NOTE Confidence: 0.63022959

00:58:36.508 --> 00:58:38.300 other trainees are going to have a

NOTE Confidence: 0.63022959

00:58:38.300 --> 00:58:40.385 chance to ask you more questions and

NOTE Confidence: 0.63022959

00:58:40.385 --> 00:58:41.960 really look forward to that as well.

NOTE Confidence: 0.63022959

00:58:41.960 --> 00:58:42.560 Thank you again.

NOTE Confidence: 0.76574013

00:58:44.320 --> 00:58:44.760 Thank you.