WEBVTT

NOTE duration: "01:01:33.226"

NOTE Confidence: 0.994584

00:00:01.280 --> 00:00:02.800 It's really pretty often that

NOTE Confidence: 0.994584

00:00:02.800 --> 00:00:04.019 we have experts

NOTE Confidence: 0.98760116

00:00:04.400 --> 00:00:06.080 from our own faculty who

NOTE Confidence: 0.98760116

00:00:06.080 --> 00:00:07.200 go around the world and

NOTE Confidence: 0.98760116

00:00:07.200 --> 00:00:08.559 give talks, and we never

NOTE Confidence: 0.98760116

00:00:08.559 --> 00:00:09.920 ask them to give talks

NOTE Confidence: 0.98760116

00:00:09.920 --> 00:00:10.420 here.

NOTE Confidence: 0.99546045

00:00:11.440 --> 00:00:13.039 So we're trying to fix

NOTE Confidence: 0.99546045

00:00:13.039 --> 00:00:13.780 that problem.

NOTE Confidence: 0.9342831

00:00:14.719 --> 00:00:16.805 And so our speaker today

NOTE Confidence: 0.9342831

00:00:16.945 --> 00:00:18.645 is Ian Cropp.

NOTE Confidence: 0.99848354

00:00:19.265 --> 00:00:20.225 I think many of you

NOTE Confidence: 0.99848354

00:00:20.225 --> 00:00:21.204 know Ian.

NOTE Confidence: 0.97586846

00:00:21.744 --> 00:00:22.965 Ian came here,

NOTE Confidence: 0.99625474

1

00:00:23.585 --> 00:00:25.125 a month after I did,

NOTE Confidence: 0.99378186

00:00:25.585 --> 00:00:27.825 three years ago from Dana

NOTE Confidence: 0.99378186

00:00:27.825 --> 00:00:28.325 Farber.

NOTE Confidence: 0.99149805

00:00:29.825 --> 00:00:30.325 He

NOTE Confidence: 0.99779046

00:00:31.320 --> 00:00:32.780 spent most of his life,

NOTE Confidence: 0.99363595

00:00:33.560 --> 00:00:34.940 up until about age,

NOTE Confidence: 0.9978245

00:00:35.320 --> 00:00:36.920 I don't know, somewhere in

NOTE Confidence: 0.9978245

00:00:36.920 --> 00:00:37.420 his

NOTE Confidence: 0.960174

00:00:37.800 --> 00:00:40.200 mid thirties at, Hopkins where

NOTE Confidence: 0.960174

00:00:40.200 --> 00:00:41.239 he went to college and

NOTE Confidence: 0.960174

00:00:41.239 --> 00:00:42.520 medical school and got his

NOTE Confidence: 0.960174

00:00:42.520 --> 00:00:43.659 PhD and trained,

NOTE Confidence: 0.99608403

00:00:44.120 --> 00:00:45.239 and then came to Dana

NOTE Confidence: 0.99608403

00:00:45.239 --> 00:00:46.280 Farber where he was a

NOTE Confidence: 0.99608403

00:00:46.280 --> 00:00:46.780 fellow

NOTE Confidence: 0.999384

00:00:47.265 --> 00:00:48.565 and stayed on the faculty

NOTE Confidence: 0.999384

00:00:48.704 --> 00:00:50.145 for quite a number of

NOTE Confidence: 0.999384

00:00:50.145 --> 00:00:50.645 years.

NOTE Confidence: 0.99366087

00:00:51.185 --> 00:00:53.184 He he is a breast

NOTE Confidence: 0.99366087

00:00:53.184 --> 00:00:54.165 cancer expert,

NOTE Confidence: 0.88964236

00:00:55.184 --> 00:00:55.684 of,

NOTE Confidence: 0.98733205

00:00:57.425 --> 00:00:58.805 known around the world.

NOTE Confidence: 0.9796658

00:00:59.750 --> 00:01:01.030 And for the purposes of

NOTE Confidence: 0.9796658

00:01:01.030 --> 00:01:01.750 today's talk,

NOTE Confidence: 0.9721699

00:01:02.390 --> 00:01:03.289 he's also,

NOTE Confidence: 0.99932814

00:01:03.989 --> 00:01:06.390 an expert in antibody drug

NOTE Confidence: 0.99932814

00:01:06.390 --> 00:01:06.890 conjugates.

NOTE Confidence: 0.99926573

00:01:07.590 --> 00:01:08.250 In fact,

NOTE Confidence: 0.92927253

00:01:08.709 --> 00:01:09.530 he ran,

NOTE Confidence: 0.99869794

00:01:10.950 --> 00:01:12.970 the first phase one trial

NOTE Confidence: 0.98850346

00:01:14.145 --> 00:01:16.305 of the first antibody drug

NOTE Confidence: 0.98850346

00:01:16.305 --> 00:01:17.744 conjugate that was approved in

NOTE Confidence: 0.98850346

00:01:17.744 --> 00:01:19.365 solid tumors, and that was,

NOTE Confidence: 0.83997744

00:01:20.064 --> 00:01:22.084 TDM one now back,

NOTE Confidence: 0.99944

00:01:22.704 --> 00:01:23.924 a number of years ago.

NOTE Confidence: 0.8758477

00:01:24.545 --> 00:01:25.024 So,

NOTE Confidence: 0.9435266

00:01:26.050 --> 00:01:27.650 I'll also mention that Ayan

NOTE Confidence: 0.9435266

00:01:27.650 --> 00:01:28.709 is the chief,

NOTE Confidence: 0.93370664

00:01:29.730 --> 00:01:31.250 chief scientific officer for the

NOTE Confidence: 0.93370664

00:01:31.250 --> 00:01:33.270 translational breast cancer research consortium.

NOTE Confidence: 0.9700801

00:01:33.890 --> 00:01:34.870 Here at Yale,

NOTE Confidence: 0.94656235

00:01:35.250 --> 00:01:36.390 he's our,

NOTE Confidence: 0.99799883

00:01:37.490 --> 00:01:39.190 chief clinical research officer

NOTE Confidence: 0.98820657

00:01:39.569 --> 00:01:41.525 and runs the the clinical

NOTE Confidence: 0.98820657

00:01:41.525 --> 00:01:42.425 trials office.

NOTE Confidence: 0.81921935

00:01:43.125 --> 00:01:44.265 So, Ian,

NOTE Confidence: 0.9934745

00:01:44.805 --> 00:01:45.305 please.

NOTE Confidence: 0.97630906

00:01:51.205 --> 00:01:51.945 Good afternoon.

NOTE Confidence: 0.9976174

00:01:52.645 --> 00:01:54.085 Thank you for that kind

NOTE Confidence: 0.9976174

00:01:54.085 --> 00:01:54.585 introduction.

NOTE Confidence: 0.9857878

00:01:58.900 --> 00:01:59.400 So,

NOTE Confidence: 0.96898127

00:01:59.939 --> 00:02:01.320 we're gonna be talking about

NOTE Confidence: 0.96898127

00:02:01.540 --> 00:02:03.299 antibody drug conjugates, which, you

NOTE Confidence: 0.96898127

00:02:03.299 --> 00:02:03.939 know, I think is a

NOTE Confidence: 0.96898127

00:02:04.100 --> 00:02:05.479 this is a particularly opportune

NOTE Confidence: 0.96898127

00:02:05.540 --> 00:02:07.220 time to have that discussion.

NOTE Confidence: 0.96898127

00:02:07.220 --> 00:02:08.260 This is an area that's

NOTE Confidence: 0.96898127

00:02:08.260 --> 00:02:10.360 moving very quickly. There's actually,

NOTE Confidence: 0.99333227

00:02:11.255 --> 00:02:13.255 been two FDA approvals of

NOTE Confidence: 0.99333227

00:02:13.255 --> 00:02:14.615 ADCs just in the last,

NOTE Confidence: 0.99333227

00:02:14.615 --> 00:02:16.135 like, eight or nine days,

NOTE Confidence: 0.99333227

00:02:16.135 --> 00:02:17.735 and that's just within breast

NOTE Confidence: 0.99333227

00:02:17.735 --> 00:02:18.235 cancer.

NOTE Confidence: 0.9893982

00:02:18.535 --> 00:02:19.415 So there's a lot going

NOTE Confidence: 0.9893982

00:02:19.415 --> 00:02:19.915 on.

NOTE Confidence: 0.98497415

00:02:21.015 --> 00:02:21.515 And

NOTE Confidence: 0.99674165

00:02:24.000 --> 00:02:24.959 what I thought I would

NOTE Confidence: 0.99674165

00:02:24.959 --> 00:02:26.000 do would be to talk

NOTE Confidence: 0.99674165

00:02:26.000 --> 00:02:27.540 about ADCs using

NOTE Confidence: 0.96945304

00:02:27.840 --> 00:02:29.439 HER2 positive breast cancer as

NOTE Confidence: 0.96945304

00:02:29.439 --> 00:02:30.639 kind of an example, and

NOTE Confidence: 0.96945304

00:02:30.639 --> 00:02:32.180 and the reasons for that,

NOTE Confidence: 0.9316423

00:02:32.639 --> 00:02:33.939 selection is because,

NOTE Confidence: 0.9361068

00:02:35.195 --> 00:02:37.215 HER2 positive disease is,

NOTE Confidence: 0.9640468

00:02:38.315 --> 00:02:39.355 an area where we've had

NOTE Confidence: 0.9640468

00:02:39.355 --> 00:02:40.875 the biggest clinical impact of

NOTE Confidence: 0.9640468

00:02:40.875 --> 00:02:42.315 of targeted therapy in general

NOTE Confidence: 0.9640468

00:02:42.315 --> 00:02:43.535 and ADCs specifically.

NOTE Confidence: 0.964635

00:02:44.555 --> 00:02:46.715 There's interestingly, there's a we

NOTE Confidence: 0.964635

00:02:46.715 --> 00:02:47.915 see a benefit of ADCs

NOTE Confidence: 0.964635

00:02:47.915 --> 00:02:49.115 across a very wide range

NOTE Confidence: 0.964635

00:02:49.115 --> 00:02:50.715 of target expression in in

NOTE Confidence: 0.964635

00:02:50.715 --> 00:02:52.709 this, subtype of breast cancer,

NOTE Confidence: 0.964635

00:02:52.709 --> 00:02:53.910 which I I think is

NOTE Confidence: 0.964635

00:02:53.910 --> 00:02:54.889 worth talking about.

NOTE Confidence: 0.98977864

00:02:55.430 --> 00:02:55.930 And,

NOTE Confidence: 0.8072351

00:02:56.550 --> 00:02:58.490 it's a there's a examples

NOTE Confidence: 0.9248949

00:02:58.950 --> 00:03:00.230 of basically all the key

NOTE Confidence: 0.9248949

00:03:00.230 --> 00:03:01.830 features of of ADCs are

NOTE Confidence: 0.9248949

00:03:01.830 --> 00:03:03.030 kind of manifest in HER2

NOTE Confidence: 0.9248949

00:03:03.030 --> 00:03:05.075 positive disease. And lastly,

NOTE Confidence: 0.9750537

00:03:05.775 --> 00:03:06.735 this is what I study,

NOTE Confidence: 0.9750537

00:03:06.735 --> 00:03:07.535 so I have most of

NOTE Confidence: 0.9750537

00:03:07.535 --> 00:03:09.135 the slides. So it was

NOTE Confidence: 0.9750537

00:03:09.135 --> 00:03:09.635 easier.

NOTE Confidence: 0.9927846

00:03:10.495 --> 00:03:10.995 So,

NOTE Confidence: 0.9984115

00:03:11.695 --> 00:03:12.495 just for those of you

NOTE Confidence: 0.9984115

00:03:12.495 --> 00:03:13.795 who don't treat breast cancer,

NOTE Confidence: 0.97917646

00:03:14.895 --> 00:03:16.590 HER2 positive disease makes up

NOTE Confidence: 0.97917646

00:03:16.590 --> 00:03:18.030 about fifteen to twenty percent

NOTE Confidence: 0.97917646

00:03:18.030 --> 00:03:19.389 of breast cancers, and these

NOTE Confidence: 0.97917646

00:03:19.389 --> 00:03:21.730 cancers have dramatic overexpression

NOTE Confidence: 0.9981534

00:03:22.110 --> 00:03:23.870 of of this cell surface

NOTE Confidence: 0.9981534

00:03:23.870 --> 00:03:24.370 protein

NOTE Confidence: 0.94836134

00:03:24.830 --> 00:03:26.530 tyrosine kinase called HER2.

NOTE Confidence: 0.9976084

00:03:27.070 --> 00:03:28.510 There's typically a million or

NOTE Confidence: 0.9976084

00:03:28.510 --> 00:03:29.870 even two million copies of

NOTE Confidence: 0.9976084

00:03:29.870 --> 00:03:31.710 HER2 protein on each cancer

NOTE Confidence: 0.9976084

00:03:31.710 --> 00:03:32.210 cell.

NOTE Confidence: 0.96213406

00:03:32.694 --> 00:03:34.615 These cancers are typically high

NOTE Confidence: 0.96213406

00:03:34.615 --> 00:03:36.375 grade, and they present with

NOTE Confidence: 0.96213406

00:03:36.375 --> 00:03:38.455 more advanced stage. They recur

NOTE Confidence: 0.96213406

00:03:38.455 --> 00:03:39.815 more frequently, and they have

NOTE Confidence: 0.96213406

00:03:39.815 --> 00:03:40.315 resistance,

NOTE Confidence: 0.84681773

00:03:41.175 --> 00:03:41.675 to,

NOTE Confidence: 0.9804595

00:03:42.055 --> 00:03:44.555 standard therapy. So these patients,

NOTE Confidence: 0.9995813

00:03:45.255 --> 00:03:46.635 had very poor prognosis

NOTE Confidence: 0.9997494

00:03:47.880 --> 00:03:49.100 prior to the realization

NOTE Confidence: 0.99029785

00:03:49.480 --> 00:03:50.840 that the reason these cancers

NOTE Confidence: 0.99029785

00:03:50.840 --> 00:03:52.360 were behaving so badly was

NOTE Confidence: 0.99029785

00:03:52.360 --> 00:03:54.300 because of this dramatic overexpression

NOTE Confidence: 0.99029785

00:03:54.440 --> 00:03:55.400 of HER2 and all the

NOTE Confidence: 0.99029785

00:03:55.400 --> 00:03:56.380 downstream signaling,

NOTE Confidence: 0.9995989

00:03:57.080 --> 00:03:58.440 that was happening because of

NOTE Confidence: 0.9995989

00:03:58.440 --> 00:03:58.940 that.

NOTE Confidence: 0.9635681

00:03:59.815 --> 00:04:00.855 So that led to the

NOTE Confidence: 0.9635681

00:04:00.855 --> 00:04:03.175 development of drugs targeting HER2,

NOTE Confidence: 0.9635681

00:04:03.175 --> 00:04:04.135 the first of which was

NOTE Confidence: 0.9635681

00:04:04.135 --> 00:04:04.875 an antibody

NOTE Confidence: 0.9522879

00:04:05.175 --> 00:04:05.995 called trastuzumab,

NOTE Confidence: 0.96765965

00:04:06.855 --> 00:04:07.975 and it was shown back

NOTE Confidence: 0.96765965

00:04:07.975 --> 00:04:09.334 in, I think, nineteen ninety

NOTE Confidence: 0.96765965

00:04:09.334 --> 00:04:10.715 eight or nineteen ninety nine,

NOTE Confidence: 0.9484665

00:04:11.175 --> 00:04:13.480 that the addition of paztuzumab

NOTE Confidence: 0.9973514

00:04:13.780 --> 00:04:14.439 to chemotherapy

NOTE Confidence: 0.9626232

00:04:14.739 --> 00:04:17.000 led to substantial improvements in

NOTE Confidence: 0.9626232

00:04:17.220 --> 00:04:19.220 in outcomes, progression free overall

NOTE Confidence: 0.9626232

00:04:19.220 --> 00:04:19.720 survival.

NOTE Confidence: 0.9802211

00:04:20.339 --> 00:04:20.839 And,

NOTE Confidence: 0.97528654

00:04:21.539 --> 00:04:22.419 if you use it in

NOTE Confidence: 0.97528654

00:04:22.419 --> 00:04:24.500 early stage disease, it increased

NOTE Confidence: 0.97528654

00:04:24.500 --> 00:04:25.539 the cure rate by about

NOTE Confidence: 0.97528654

00:04:25.539 --> 00:04:26.580 fifty percent. So it was

NOTE Confidence: 0.97528654

00:04:26.580 --> 00:04:27.380 a clear breakthrough,

NOTE Confidence: 0.9414148

00:04:29.587 --> 00:04:30.435 with the with this HER2

NOTE Confidence: 0.9414148

00:04:30.435 --> 00:04:31.735 targeted therapy introduction.

NOTE Confidence: 0.9794588

00:04:33.075 --> 00:04:34.275 And it really, in many

NOTE Confidence: 0.9794588

00:04:34.275 --> 00:04:35.555 ways, met this met the

NOTE Confidence: 0.9794588

00:04:35.555 --> 00:04:36.815 criteria of,

NOTE Confidence: 0.8419897

00:04:38.435 --> 00:04:40.295 the Nobel laureate Paul Ehrlich's,

NOTE Confidence: 0.9625053

00:04:40.835 --> 00:04:41.875 idea of a of a

NOTE Confidence: 0.9625053

00:04:41.875 --> 00:04:42.375 magic

NOTE Confidence: 0.7817173

00:04:43.350 --> 00:04:44.150 bullet, a a a drug

NOTE Confidence: 0.7817173

00:04:44.150 --> 00:04:45.130 that specifically

NOTE Confidence: 0.936007

00:04:45.430 --> 00:04:45.930 targets,

NOTE Confidence: 0.973109

00:04:46.630 --> 00:04:48.790 a pathogen by while sparing

NOTE Confidence: 0.973109

00:04:48.790 --> 00:04:50.790 normal tissues. And, actually, doctor

NOTE Confidence: 0.973109

00:04:50.790 --> 00:04:51.850 Ehrlich was thinking,

NOTE Confidence: 0.98390007

00:04:53.510 --> 00:04:55.690 about chemicals and chemical dyes,

NOTE Confidence: 0.9365901

00:04:56.135 --> 00:04:57.335 originally, but but we use

NOTE Confidence: 0.9365901

00:04:57.335 --> 00:04:58.775 it in terms of, thinking

NOTE Confidence: 0.9365901

00:04:58.775 --> 00:05:01.015 about antibody antibiotics and and

NOTE Confidence: 0.9365901

00:05:01.015 --> 00:05:01.515 antibodies,

NOTE Confidence: 0.9755736

00:05:01.975 --> 00:05:03.575 as well. So this feels

NOTE Confidence: 0.9755736

00:05:03.575 --> 00:05:04.935 like it it met those

NOTE Confidence: 0.9755736

00:05:04.935 --> 00:05:05.435 criteria.

NOTE Confidence: 0.989305

00:05:06.695 --> 00:05:07.595 But the problem,

NOTE Confidence: 0.9176836

00:05:08.130 --> 00:05:09.910 particularly in HER2 positive disease,

NOTE Confidence: 0.99971724

00:05:10.770 --> 00:05:11.590 was that

NOTE Confidence: 0.9886

00:05:12.690 --> 00:05:14.210 for trastuzumab really to work,

NOTE Confidence: 0.9886

00:05:14.210 --> 00:05:15.830 you need to have chemotherapy

NOTE Confidence: 0.9886

00:05:16.050 --> 00:05:16.930 around. You need to have

NOTE Confidence: 0.9886

00:05:16.930 --> 00:05:18.370 some type of cytotoxic agent,

NOTE Confidence: 0.9886

00:05:18.370 --> 00:05:19.570 and that's because one of

NOTE Confidence: 0.9886

00:05:19.570 --> 00:05:21.255 the things trastuzumab does is

NOTE Confidence: 0.9886

00:05:21.495 --> 00:05:22.235 helps encourage,

NOTE Confidence: 0.8733447

00:05:23.015 --> 00:05:24.535 apoptosis when you need something

NOTE Confidence: 0.8733447

00:05:24.535 --> 00:05:25.015 to,

NOTE Confidence: 0.9808693

00:05:25.495 --> 00:05:27.335 produce that apoptosis, and that's

NOTE Confidence: 0.9808693

00:05:27.335 --> 00:05:29.735 where chemotherapy comes in. But,

NOTE Confidence: 0.9808693

00:05:29.735 --> 00:05:30.535 you know, you have this

NOTE Confidence: 0.9808693

00:05:30.535 --> 00:05:31.355 very targeted

NOTE Confidence: 0.99373055

00:05:31.815 --> 00:05:32.315 antibody,

NOTE Confidence: 0.9862412

00:05:32.855 --> 00:05:34.339 the magic bullet, and then

NOTE Confidence: 0.9862412

00:05:34.339 --> 00:05:35.720 you throw in non targeted

NOTE Confidence: 0.9862412

00:05:35.779 --> 00:05:37.220 chemotherapy. So you lose some

NOTE Confidence: 0.9862412

00:05:37.220 --> 00:05:38.039 of your magicness,

NOTE Confidence: 0.97689116

00:05:38.900 --> 00:05:39.860 when you have to have

NOTE Confidence: 0.97689116

00:05:39.860 --> 00:05:41.300 chemotherapy around. So this was

NOTE Confidence: 0.97689116

00:05:41.300 --> 00:05:42.979 a perfect opportunity to take

NOTE Confidence: 0.97689116

00:05:42.979 --> 00:05:45.139 advantage of this then very

NOTE Confidence: 0.97689116

00:05:45.139 --> 00:05:47.139 new type of technology called

NOTE Confidence: 0.97689116

00:05:47.139 --> 00:05:48.520 an antibody drug conjugate,

NOTE Confidence: 0.9565972

00:05:49.220 --> 00:05:49.720 and,

NOTE Confidence: 0.91882885

00:05:50.285 --> 00:05:50.925 you know, this is a

NOTE Confidence: 0.91882885

00:05:50.925 --> 00:05:52.065 very simplified diagram,

NOTE Confidence: 0.77042973

00:05:52.365 --> 00:05:52.865 obviously,

NOTE Confidence: 0.9953025

00:05:53.565 --> 00:05:54.605 but the idea of an

NOTE Confidence: 0.9953025

00:05:54.605 --> 00:05:55.645 ADC is you have an

NOTE Confidence: 0.9953025

00:05:55.645 --> 00:05:57.565 antibody targeting some cell surface

NOTE Confidence: 0.9953025

00:05:57.565 --> 00:05:58.065 protein,

NOTE Confidence: 0.9952884

00:05:58.845 --> 00:06:00.285 and you have a very

14

NOTE Confidence: 0.9952884

00:06:00.285 --> 00:06:00.785 cytotoxic,

NOTE Confidence: 0.923013

00:06:01.964 --> 00:06:03.985 moiety, typically a potent chemotherapy,

NOTE Confidence: 0.923013

00:06:04.285 --> 00:06:05.665 and you attach them,

NOTE Confidence: 0.9786851

00:06:06.070 --> 00:06:07.930 with a linker that's typically

NOTE Confidence: 0.9426519

00:06:08.310 --> 00:06:10.150 cleaved once or the idea

NOTE Confidence: 0.9426519

00:06:10.150 --> 00:06:11.350 is that it's cleaved once

NOTE Confidence: 0.9426519

00:06:11.350 --> 00:06:11.850 the

NOTE Confidence: 0.95355743

00:06:12.630 --> 00:06:13.990 the conjugate gets inside of

NOTE Confidence: 0.95355743

00:06:13.990 --> 00:06:14.650 a cell.

NOTE Confidence: 0.9858006

00:06:15.029 --> 00:06:16.150 With the overall goal that

NOTE Confidence: 0.9858006

00:06:16.150 --> 00:06:17.610 you're gonna increase the efficacy,

NOTE Confidence: 0.981463

00:06:18.550 --> 00:06:20.205 of of the of the

NOTE Confidence: 0.981463

00:06:20.205 --> 00:06:22.045 cytotoxic drug while decreasing the

NOTE Confidence: 0.981463

00:06:22.045 --> 00:06:22.545 toxicity

NOTE Confidence: 0.9970787

00:06:23.005 --> 00:06:25.345 by selectively delivering this to,

NOTE Confidence: 0.97333044

00:06:25.725 --> 00:06:26.925 the cancer cells. So these

NOTE Confidence: 0.97333044

00:06:26.925 --> 00:06:28.765 are the conjugates you talk

NOTE Confidence: 0.97333044

00:06:28.765 --> 00:06:29.265 about,

NOTE Confidence: 0.9938754

00:06:30.125 --> 00:06:32.065 guided missiles, smart bombs,

NOTE Confidence: 0.71461916

00:06:33.389 --> 00:06:34.289 whatever warmongering,

NOTE Confidence: 0.917708

00:06:34.910 --> 00:06:36.430 terminology you wanna use, but

NOTE Confidence: 0.917708

00:06:36.430 --> 00:06:37.650 that's the general idea.

NOTE Confidence: 0.9934348

00:06:38.910 --> 00:06:39.729 And so

NOTE Confidence: 0.95523626

00:06:40.270 --> 00:06:41.470 the first of these, as

NOTE Confidence: 0.95523626

00:06:41.470 --> 00:06:43.250 Eric had mentioned, to really,

NOTE Confidence: 0.95915526

00:06:43.949 --> 00:06:46.029 become clinically useful in solid

NOTE Confidence: 0.95915526

00:06:46.029 --> 00:06:47.470 cancers was this one called

NOTE Confidence: 0.95915526

00:06:47.470 --> 00:06:48.705 trastuzumab emtansine,

NOTE Confidence: 0.98377866

00:06:49.404 --> 00:06:50.605 and the idea of ADCs

NOTE Confidence: 0.98377866

00:06:50.605 --> 00:06:51.645 actually had been around for

NOTE Confidence: 0.98377866

00:06:51.645 --> 00:06:52.845 decades. The problem is none

NOTE Confidence: 0.98377866

00:06:52.845 --> 00:06:54.365 of them really worked, and

NOTE Confidence: 0.98377866

00:06:54.365 --> 00:06:55.565 the main problem they were

NOTE Confidence: 0.98377866

00:06:55.565 --> 00:06:56.545 having in the past,

NOTE Confidence: 0.9410742

00:06:57.085 --> 00:06:59.425 was that was toxicity because

NOTE Confidence: 0.9862693

00:06:59.805 --> 00:07:01.770 the linker tended to break,

NOTE Confidence: 0.9364775

00:07:02.170 --> 00:07:02.570 in,

NOTE Confidence: 0.87099266

00:07:03.210 --> 00:07:05.050 in in blood. So you

NOTE Confidence: 0.87099266

00:07:05.050 --> 00:07:05.790 had disassociation,

NOTE Confidence: 0.89171654

00:07:06.170 --> 00:07:07.290 showed you had lots of

NOTE Confidence: 0.89171654

00:07:07.290 --> 00:07:08.350 free cytotoxic,

NOTE Confidence: 0.95712495

00:07:08.970 --> 00:07:10.170 drug floating around, and that

NOTE Confidence: 0.95712495

00:07:10.170 --> 00:07:11.950 was causing nonspecific toxicity.

NOTE Confidence: 0.8922796

00:07:12.890 --> 00:07:13.630 And so,

NOTE Confidence: 0.9781911

00:07:14.974 --> 00:07:16.495 what was different about TDM

NOTE Confidence: 0.9781911

00:07:16.495 --> 00:07:17.935 one, was that it it

NOTE Confidence: 0.9781911

17

00:07:17.935 --> 00:07:19.235 started with this trastuzumab

NOTE Confidence: 0.90824634

00:07:19.535 --> 00:07:20.035 monoclonal.

NOTE Confidence: 0.8802247

00:07:23.935 --> 00:07:25.074 Oh, it's a touch screen.

NOTE Confidence: 0.9811704

00:07:25.375 --> 00:07:26.754 It starts with this trastuzumab

NOTE Confidence: 0.9811704

00:07:26.974 --> 00:07:27.474 monoclonal,

NOTE Confidence: 0.9615276

00:07:28.930 --> 00:07:30.210 targeting HER2 that we talked

NOTE Confidence: 0.9615276

00:07:30.210 --> 00:07:31.830 about. It had a,

NOTE Confidence: 0.9350501

00:07:33.410 --> 00:07:35.650 microtubule inhibitor payload, and the

NOTE Confidence: 0.9350501

00:07:35.650 --> 00:07:36.690 linker in this case was

NOTE Confidence: 0.9350501

00:07:36.690 --> 00:07:38.370 actually not not cleavable. So

NOTE Confidence: 0.9350501

00:07:38.370 --> 00:07:39.409 I talked about the idea

NOTE Confidence: 0.9350501

00:07:39.409 --> 00:07:40.770 of general user cleavable. This

NOTE Confidence: 0.9350501

00:07:40.770 --> 00:07:41.750 one was not.

NOTE Confidence: 0.9938519

00:07:42.610 --> 00:07:43.110 And

NOTE Confidence: 0.9687788

00:07:43.885 --> 00:07:44.925 the story is kind of

NOTE Confidence: 0.9687788

00:07:44.925 --> 00:07:46.845 interesting how that came about,

NOTE Confidence: 0.9687788

00:07:46.845 --> 00:07:47.965 and I promise this is

NOTE Confidence: 0.9687788

00:07:47.965 --> 00:07:49.005 the only chemistry I will

NOTE Confidence: 0.9687788

00:07:49.005 --> 00:07:50.145 be talking about today.

NOTE Confidence: 0.9977537

00:07:51.085 --> 00:07:52.445 So when Genentech was trying

NOTE Confidence: 0.9977537

00:07:52.445 --> 00:07:53.665 to develop this drug,

NOTE Confidence: 0.98500836

00:07:54.285 --> 00:07:55.245 they were really trying to

NOTE Confidence: 0.98500836

00:07:55.245 --> 00:07:56.705 make for a more stable,

NOTE Confidence: 0.9714307

00:07:57.480 --> 00:07:58.840 linker. Because, again, the problem

NOTE Confidence: 0.9714307

00:07:58.840 --> 00:07:59.560 in the past would be

NOTE Confidence: 0.9714307

00:07:59.560 --> 00:08:00.680 the linkers weren't stable, and

NOTE Confidence: 0.9714307

00:08:00.680 --> 00:08:01.900 so you were getting toxicity.

NOTE Confidence: 0.9714307

00:08:02.040 --> 00:08:02.920 So they said, okay. Well,

NOTE Confidence: 0.9714307

00:08:02.920 --> 00:08:03.800 let's try to make this

NOTE Confidence: 0.9714307

00:08:03.800 --> 00:08:05.080 super stable. And so they

NOTE Confidence: 0.9714307

00:08:05.080 --> 00:08:06.600 were testing a number of

NOTE Confidence: 0.9714307

19

00:08:06.600 --> 00:08:07.100 different,

NOTE Confidence: 0.75640595

00:08:08.280 --> 00:08:10.360 chemical structures, looking different,

NOTE Confidence: 0.8251052

00:08:11.285 --> 00:08:11.945 link different,

NOTE Confidence: 0.99374896

00:08:12.645 --> 00:08:13.145 cleavable

NOTE Confidence: 0.9886522

00:08:13.525 --> 00:08:14.025 linker,

NOTE Confidence: 0.98095655

00:08:14.725 --> 00:08:16.805 chemistries and and distances between

NOTE Confidence: 0.98095655

00:08:16.805 --> 00:08:17.925 the antibody and the and

NOTE Confidence: 0.98095655

00:08:17.925 --> 00:08:18.585 the payload.

NOTE Confidence: 0.9782314

00:08:19.125 --> 00:08:20.165 And they threw in at

NOTE Confidence: 0.9782314

00:08:20.165 --> 00:08:21.785 the bottom of their experiments

NOTE Confidence: 0.9782314

00:08:21.845 --> 00:08:23.145 this, MCC

NOTE Confidence: 0.9802414

00:08:23.445 --> 00:08:24.990 linker, which is basically non

NOTE Confidence: 0.9802414

00:08:24.990 --> 00:08:26.030 cleavable. And they put that

NOTE Confidence: 0.9802414

00:08:26.030 --> 00:08:27.230 there as a negative control

NOTE Confidence: 0.9802414

00:08:27.230 --> 00:08:28.350 because, of course, this wasn't

NOTE Confidence: 0.9802414

00:08:28.350 --> 00:08:29.070 gonna work,

NOTE Confidence: 0.9825214

00:08:29.470 --> 00:08:30.110 because if you don't have

NOTE Confidence: 0.9825214

00:08:30.110 --> 00:08:31.550 a cleavable linker, then you

NOTE Confidence: 0.9825214

00:08:31.550 --> 00:08:32.830 can't release the drug to

NOTE Confidence: 0.9825214

00:08:32.830 --> 00:08:34.429 kill the cancer cell. So

NOTE Confidence: 0.9825214

00:08:34.429 --> 00:08:35.390 they throw that they threw

NOTE Confidence: 0.9825214

00:08:35.390 --> 00:08:36.270 that in there just as

NOTE Confidence: 0.9825214

00:08:36.270 --> 00:08:36.850 a control.

NOTE Confidence: 0.9670153

00:08:37.605 --> 00:08:38.885 And what they found was,

NOTE Confidence: 0.9670153

00:08:38.885 --> 00:08:41.605 as expected, that the the

NOTE Confidence: 0.9670153

00:08:41.605 --> 00:08:44.105 non cleavable linker, the MCC

NOTE Confidence: 0.9670153

00:08:44.165 --> 00:08:45.205 in blue there at the

NOTE Confidence: 0.9670153

00:08:45.205 --> 00:08:46.965 top, was very stable in

NOTE Confidence: 0.9670153

00:08:46.965 --> 00:08:48.245 plasma, the most stable, and

NOTE Confidence: 0.9670153

00:08:48.245 --> 00:08:50.485 it was, stable different ways

NOTE Confidence: 0.9670153

00:08:50.485 --> 00:08:51.385 looking at it.

NOTE Confidence: 0.8665641

00:08:52.860 --> 00:08:54.220 And it actually was pretty

NOTE Confidence: 0.8665641

00:08:54.220 --> 00:08:55.600 well tolerated because,

NOTE Confidence: 0.9500453

00:08:56.140 --> 00:08:57.340 you know, the there you

NOTE Confidence: 0.9500453

00:08:57.340 --> 00:08:59.200 weren't having this, disassociation

NOTE Confidence: 0.91005737

00:08:59.660 --> 00:09:01.500 in blood, but the surprise

NOTE Confidence: 0.91005737

00:09:01.500 --> 00:09:02.620 was is also was the

NOTE Confidence: 0.91005737

00:09:02.620 --> 00:09:03.360 most effective.

NOTE Confidence: 0.935747

00:09:03.900 --> 00:09:04.860 And so the blue line

NOTE Confidence: 0.935747

00:09:04.860 --> 00:09:05.900 at the bottom there is

NOTE Confidence: 0.935747

00:09:05.900 --> 00:09:07.420 the is the TDM one,

NOTE Confidence: 0.935747

00:09:07.420 --> 00:09:07.875 essentially.

NOTE Confidence: 0.9113395

00:09:13.715 --> 00:09:15.075 Conjugate, the TDM one binds

NOTE Confidence: 0.9113395

00:09:15.075 --> 00:09:16.135 to the cell surface,

NOTE Confidence: 0.9051717

00:09:16.595 --> 00:09:17.795 on the HERT the HERT

NOTE Confidence: 0.9051717

00:09:17.795 --> 00:09:19.335 two. It gets internalized

NOTE Confidence: 0.833535

00:09:19.875 --> 00:09:21.815 into lysosomes where the proteases

22

NOTE Confidence: 0.833535

00:09:22.035 --> 00:09:22.770 actually were

NOTE Confidence: 0.8312259

00:09:23.730 --> 00:09:26.230 would dissolve the antibody essentially,

NOTE Confidence: 0.95603013

00:09:26.610 --> 00:09:28.390 and so you you didn't

NOTE Confidence: 0.95603013

00:09:28.530 --> 00:09:29.590 break the linker.

NOTE Confidence: 0.9087149

00:09:29.970 --> 00:09:31.410 It's just the the amino

NOTE Confidence: 0.9087149

00:09:31.410 --> 00:09:32.690 acid, the lysine from the

NOTE Confidence: 0.9087149

00:09:32.690 --> 00:09:34.050 antibody where it's connected would

NOTE Confidence: 0.9087149

00:09:34.050 --> 00:09:34.790 just leave,

NOTE Confidence: 0.98053235

00:09:35.250 --> 00:09:36.530 with the with the with

NOTE Confidence: 0.98053235

00:09:36.530 --> 00:09:37.965 the drug attached to it.

NOTE Confidence: 0.9667171

00:09:38.445 --> 00:09:39.645 And so that's how this

NOTE Confidence: 0.9667171

00:09:39.645 --> 00:09:41.085 drug was working, and that's

NOTE Confidence: 0.9667171

00:09:41.085 --> 00:09:42.225 how you got this selective

NOTE Confidence: 0.9667171

00:09:42.285 --> 00:09:44.225 delivery of the DM one,

NOTE Confidence: 0.9605939

00:09:44.684 --> 00:09:46.045 was because the antibody was

NOTE Confidence: 0.9605939

00:09:46.045 --> 00:09:46.845 getting just,

NOTE Confidence: 0.98285687

00:09:47.805 --> 00:09:48.305 proteolyzed.

NOTE Confidence: 0.9787235

00:09:49.485 --> 00:09:51.405 So, as Eric mentioned, we

NOTE Confidence: 0.9787235

00:09:51.405 --> 00:09:52.605 were involved in this phase

NOTE Confidence: 0.9787235

00:09:52.605 --> 00:09:53.425 one trial,

NOTE Confidence: 0.95791054

00:09:54.290 --> 00:09:55.490 the phase first in human

NOTE Confidence: 0.95791054

00:09:55.490 --> 00:09:57.089 study of TDM one. We

NOTE Confidence: 0.95791054

00:09:57.089 --> 00:09:59.089 enrolled patients who had had

NOTE Confidence: 0.95791054

00:09:59.089 --> 00:10:01.330 already progressed on multiple, HER2

NOTE Confidence: 0.95791054

00:10:01.330 --> 00:10:02.309 directed therapies,

NOTE Confidence: 0.94723314

00:10:03.010 --> 00:10:04.770 and despite that and despite

NOTE Confidence: 0.94723314

00:10:04.770 --> 00:10:05.970 this being just the phase

NOTE Confidence: 0.94723314

00:10:05.970 --> 00:10:07.184 one, there was a lot

NOTE Confidence: 0.94723314

00:10:07.184 --> 00:10:08.785 of efficacy seen. So the

NOTE Confidence: 0.94723314

00:10:08.785 --> 00:10:10.645 forty four percent response rate,

NOTE Confidence: 0.9619588

00:10:11.505 --> 00:10:13.184 these were durable responses, the

NOTE Confidence: 0.9619588

00:10:13.184 --> 00:10:14.465 progression free survival is about

NOTE Confidence: 0.9619588

00:10:14.465 --> 00:10:15.985 ten months, and seventy three

NOTE Confidence: 0.9619588

00:10:15.985 --> 00:10:17.184 percent of patients had some

NOTE Confidence: 0.9619588

00:10:17.184 --> 00:10:17.684 benefit.

NOTE Confidence: 0.99181175

00:10:18.865 --> 00:10:20.165 And at the same time,

NOTE Confidence: 0.99181175

00:10:20.390 --> 00:10:21.690 not only was it efficacious,

NOTE Confidence: 0.9682525

00:10:22.710 --> 00:10:23.990 but it was very well

NOTE Confidence: 0.9682525

00:10:23.990 --> 00:10:25.830 tolerated. So we didn't see

NOTE Confidence: 0.9682525

00:10:25.830 --> 00:10:27.670 the usual chemotherapy side effects,

NOTE Confidence: 0.9682525

00:10:27.670 --> 00:10:29.270 people generally didn't get nauseous

NOTE Confidence: 0.9682525

00:10:29.270 --> 00:10:29.770 or,

NOTE Confidence: 0.9266493

00:10:30.150 --> 00:10:32.230 have neutropenia or neuropathy or

NOTE Confidence: 0.9266493

00:10:32.230 --> 00:10:32.890 hair loss,

NOTE Confidence: 0.97095937

00:10:34.295 --> 00:10:35.195 And so it

NOTE Confidence: 0.97471017

00:10:35.495 --> 00:10:36.535 it probably and and the

NOTE Confidence: 0.97471017

00:10:36.535 --> 00:10:37.355 reason why

NOTE Confidence: 0.97143644

00:10:37.735 --> 00:10:39.015 was because the amount of

NOTE Confidence: 0.97143644

00:10:39.015 --> 00:10:40.695 the free payload, which is

NOTE Confidence: 0.97143644

00:10:40.695 --> 00:10:42.295 in black here, was very

NOTE Confidence: 0.97143644

00:10:42.295 --> 00:10:43.735 low. It was negligible. So

NOTE Confidence: 0.97143644

00:10:43.735 --> 00:10:45.335 it really wasn't releasing that

NOTE Confidence: 0.97143644

00:10:45.335 --> 00:10:45.835 payload,

NOTE Confidence: 0.98470044

00:10:46.215 --> 00:10:47.434 very quickly as

NOTE Confidence: 0.97915673

00:10:47.735 --> 00:10:49.335 the hope, as as was

NOTE Confidence: 0.97915673

00:10:49.335 --> 00:10:49.835 hoped.

NOTE Confidence: 0.95760727

00:10:50.590 --> 00:10:51.710 We then moved to a

NOTE Confidence: 0.95760727

00:10:51.710 --> 00:10:53.230 phase two trial again in

NOTE Confidence: 0.95760727

00:10:53.230 --> 00:10:54.990 very heavily pretreated patients, and

NOTE Confidence: 0.95760727

00:10:54.990 --> 00:10:56.690 I'm just showing this because

NOTE Confidence: 0.95760727

00:10:56.750 --> 00:10:57.950 it's probably the first trial

NOTE Confidence: 0.95760727

00:10:57.950 --> 00:10:59.150 that that Eric,

NOTE Confidence: 0.9677108

00:10:59.630 --> 00:11:00.990 and Pat Larusso and I

NOTE Confidence: 0.9677108

00:11:00.990 --> 00:11:01.650 did together,

NOTE Confidence: 0.97855186

00:11:02.590 --> 00:11:03.570 back in the day.

NOTE Confidence: 0.93975

00:11:04.644 --> 00:11:05.524 And we saw the same

NOTE Confidence: 0.93975

00:11:05.524 --> 00:11:07.845 thing heavily pretreated patients, response

NOTE Confidence: 0.93975

00:11:07.845 --> 00:11:08.665 rate was

NOTE Confidence: 0.94728744

00:11:09.204 --> 00:11:10.885 was was reasonable, and and

NOTE Confidence: 0.94728744

00:11:10.885 --> 00:11:12.345 and, it was effective.

NOTE Confidence: 0.90690297

00:11:12.885 --> 00:11:13.925 And then we moved on

NOTE Confidence: 0.90690297

00:11:13.925 --> 00:11:15.144 to do a a registrational

NOTE Confidence: 0.9589143

00:11:15.445 --> 00:11:16.345 phase three,

NOTE Confidence: 0.9845607

00:11:16.725 --> 00:11:18.380 two phase three studies. This

NOTE Confidence: 0.9845607

00:11:18.380 --> 00:11:19.980 one, in patients who had

NOTE Confidence: 0.9845607

00:11:19.980 --> 00:11:21.820 already progressed on all standard

NOTE Confidence: 0.9845607

00:11:21.820 --> 00:11:22.320 therapies,

NOTE Confidence: 0.93878126

00:11:23.260 --> 00:11:24.779 showing that TDM one was

NOTE Confidence: 0.93878126

00:11:24.779 --> 00:11:26.460 better than the standard of

NOTE Confidence: 0.93878126

00:11:26.460 --> 00:11:27.740 care in terms of survival

NOTE Confidence: 0.93878126

00:11:27.740 --> 00:11:29.660 and PFS and was less

NOTE Confidence: 0.93878126

00:11:29.660 --> 00:11:30.160 toxic.

NOTE Confidence: 0.95076895

00:11:31.075 --> 00:11:31.654 And similarly,

NOTE Confidence: 0.8555104

00:11:32.355 --> 00:11:34.035 this is a earlier line

NOTE Confidence: 0.8555104

00:11:34.035 --> 00:11:34.934 trial again,

NOTE Confidence: 0.9808351

00:11:35.554 --> 00:11:36.695 showing better,

NOTE Confidence: 0.9530634

00:11:37.315 --> 00:11:39.554 efficacy and less toxicity compared

NOTE Confidence: 0.9530634

00:11:39.554 --> 00:11:40.834 to the standard of care.

NOTE Confidence: 0.9530634

00:11:40.834 --> 00:11:42.195 So these trials led to

NOTE Confidence: 0.9530634

00:11:42.195 --> 00:11:43.554 the approval of of PDM

NOTE Confidence: 0.9530634

00:11:43.554 --> 00:11:44.675 one as you heard, I

NOTE Confidence: 0.9530634

00:11:44.675 --> 00:11:46.054 think, in two thousand twelve,

NOTE Confidence: 0.9904747

00:11:46.640 --> 00:11:47.780 as the first ADC,

NOTE Confidence: 0.939806

00:11:48.160 --> 00:11:49.220 in solid cancers,

NOTE Confidence: 0.9138733

00:11:51.840 --> 00:11:52.420 and really,

NOTE Confidence: 0.9578809

00:11:53.760 --> 00:11:54.800 kind of it did a

NOTE Confidence: 0.9578809

00:11:54.800 --> 00:11:56.100 couple of things. It validated

NOTE Confidence: 0.9578809

00:11:56.240 --> 00:11:57.440 HER2 as a as a

NOTE Confidence: 0.9578809

00:11:57.440 --> 00:11:58.800 target for an antibody drug

NOTE Confidence: 0.9578809

00:11:58.800 --> 00:11:59.300 conjugate,

NOTE Confidence: 0.9355089

00:11:59.760 --> 00:12:00.740 but most importantly,

NOTE Confidence: 0.9994628

00:12:01.565 --> 00:12:03.024 as being the first success

NOTE Confidence: 0.9994628

00:12:03.084 --> 00:12:04.385 in a common cancer,

NOTE Confidence: 0.9992212

00:12:04.845 --> 00:12:06.065 it led to the widespread

NOTE Confidence: 0.96833163

00:12:06.524 --> 00:12:08.385 development of ADCs across,

NOTE Confidence: 0.99923617

00:12:08.765 --> 00:12:09.584 tumor types.

NOTE Confidence: 0.9793711

00:12:10.365 --> 00:12:12.045 So, at last check, there

NOTE Confidence: 0.9793711

00:12:12.045 --> 00:12:13.325 were three hundred and seventy

NOTE Confidence: 0.9793711

00:12:13.325 --> 00:12:14.865 ADCs in clinical development,

NOTE Confidence: 0.9775188

00:12:15.970 --> 00:12:17.890 again, spurred on by, by

NOTE Confidence: 0.9775188

00:12:17.890 --> 00:12:19.090 the success of of this

NOTE Confidence: 0.9775188

00:12:19.090 --> 00:12:19.590 drug.

NOTE Confidence: 0.9944831

00:12:20.690 --> 00:12:22.450 And it also inspired people

NOTE Confidence: 0.9944831

00:12:22.450 --> 00:12:23.570 to start looking at better

NOTE Confidence: 0.9944831

00:12:23.570 --> 00:12:25.490 technologies for for linkers and

NOTE Confidence: 0.9944831

00:12:25.490 --> 00:12:25.990 payloads,

NOTE Confidence: 0.9797646

00:12:26.450 --> 00:12:28.130 and that's probably been best

NOTE Confidence: 0.9797646

00:12:28.130 --> 00:12:30.309 exemplified by this next generation,

NOTE Confidence: 0.9006675

00:12:31.165 --> 00:12:33.245 drug targeting HER2, which is

NOTE Confidence: 0.9006675

00:12:33.245 --> 00:12:33.905 called trastuzumabdoroxican,

NOTE Confidence: 0.9801071

00:12:35.005 --> 00:12:36.045 which differs in a few

NOTE Confidence: 0.9801071

00:12:36.045 --> 00:12:37.965 ways. It's no longer it

NOTE Confidence: 0.9801071

00:12:37.965 --> 00:12:38.845 has a different class of

NOTE Confidence: 0.9801071

00:12:38.845 --> 00:12:40.225 payload. It's not a microtubule

30

NOTE Confidence: 0.9801071

00:12:40.285 --> 00:12:41.425 inhibitor. It's a topoisomerase

NOTE Confidence: 0.96810246

00:12:41.725 --> 00:12:42.225 inhibitor.

NOTE Confidence: 0.95939803

00:12:42.845 --> 00:12:44.205 But perhaps the most unique

NOTE Confidence: 0.95939803

00:12:44.205 --> 00:12:44.705 feature,

NOTE Confidence: 0.86851823

00:12:45.120 --> 00:12:46.720 was it it evidence this

NOTE Confidence: 0.86851823

00:12:46.720 --> 00:12:48.420 thing called bystander effect.

NOTE Confidence: 0.9656682

00:12:49.440 --> 00:12:50.400 And it had and the

NOTE Confidence: 0.9656682

00:12:50.400 --> 00:12:51.120 reason it did this is

NOTE Confidence: 0.9656682

00:12:51.120 --> 00:12:51.920 because it had a different

NOTE Confidence: 0.9656682

00:12:51.920 --> 00:12:53.780 linker that that was cleavable,

NOTE Confidence: 0.91989946

00:12:54.400 --> 00:12:55.700 by, proteases,

NOTE Confidence: 0.9319527

00:12:56.640 --> 00:12:58.080 inside the cell and that

NOTE Confidence: 0.9319527

00:12:58.080 --> 00:12:59.700 led to this bystander effect,

NOTE Confidence: 0.9319527

00:12:59.985 --> 00:13:00.485 which,

NOTE Confidence: 0.99231684

00:13:00.865 --> 00:13:02.165 I'll try to depict,

NOTE Confidence: 0.92611855

00:13:02.625 --> 00:13:04.225 here. So if you the

NOTE Confidence: 0.92611855

00:13:04.225 --> 00:13:06.545 conjugate now binds, again, binds

NOTE Confidence: 0.92611855

00:13:06.545 --> 00:13:07.505 to the surface of cell,

NOTE Confidence: 0.92611855

00:13:07.505 --> 00:13:09.605 gets internalized, the payload's released,

NOTE Confidence: 0.92611855

00:13:09.745 --> 00:13:11.745 and if you'll excuse my,

NOTE Confidence: 0.92611855

00:13:12.065 --> 00:13:13.445 grade school animation,

NOTE Confidence: 0.9659213

00:13:15.230 --> 00:13:16.590 that once that payload is

NOTE Confidence: 0.9659213

00:13:16.590 --> 00:13:17.410 in the cytoplasm,

NOTE Confidence: 0.96748286

00:13:17.950 --> 00:13:19.550 unlike TDM one, in this

NOTE Confidence: 0.96748286

00:13:19.550 --> 00:13:21.870 case there's no lysine attached

NOTE Confidence: 0.96748286

00:13:21.870 --> 00:13:23.650 to it, it's thus membrane

NOTE Confidence: 0.96748286

00:13:23.710 --> 00:13:25.150 permeable, and so it can

NOTE Confidence: 0.96748286

00:13:25.150 --> 00:13:26.830 diffuse outside the cell and

NOTE Confidence: 0.96748286

00:13:26.830 --> 00:13:28.590 kill neighboring cells, even if

NOTE Confidence: 0.96748286

00:13:28.590 --> 00:13:30.165 those neighboring cells don't have

NOTE Confidence: 0.96748286

00:13:30.165 --> 00:13:31.865 HER2 on their surface.

NOTE Confidence: 0.9462955

00:13:32.725 --> 00:13:34.325 Why is this important? Again,

NOTE Confidence: 0.9462955

00:13:34.325 --> 00:13:35.684 we're targeting a HER2 positive

NOTE Confidence: 0.9462955

00:13:35.684 --> 00:13:37.125 cancer. Why is it matter

NOTE Confidence: 0.9462955

00:13:37.125 --> 00:13:38.565 that this drug could work

NOTE Confidence: 0.9462955

00:13:38.565 --> 00:13:40.085 in cancers cells that don't

NOTE Confidence: 0.9462955

00:13:40.085 --> 00:13:41.385 have HER2 on them?

NOTE Confidence: 0.9439559

00:13:41.925 --> 00:13:42.425 Well,

NOTE Confidence: 0.94982296

00:13:42.929 --> 00:13:43.970 and I'm sorry. This and

NOTE Confidence: 0.94982296

00:13:43.970 --> 00:13:44.929 this just shows that this

NOTE Confidence: 0.94982296

00:13:44.929 --> 00:13:46.850 bystander effect really seems to

NOTE Confidence: 0.94982296

00:13:46.850 --> 00:13:47.350 work.

NOTE Confidence: 0.9828373

00:13:47.650 --> 00:13:48.870 So this is a xenograft,

NOTE Confidence: 0.9629165

00:13:50.130 --> 00:13:51.410 on the left of a

NOTE Confidence: 0.9629165

00:13:51.410 --> 00:13:53.010 combination of a HER2 positive

NOTE Confidence: 0.9629165

00:13:53.010 --> 00:13:54.290 cell line and HER2 negative

NOTE Confidence: 0.9629165

00:13:54.290 --> 00:13:55.970 cell line, HER2 positive stains

NOTE Confidence: 0.9629165

00:13:55.970 --> 00:13:56.470 brown,

NOTE Confidence: 0.7161095

00:13:57.010 --> 00:13:57.990 and by IHC.

NOTE Confidence: 0.90084183

00:13:59.115 --> 00:14:00.075 And if you treat with

NOTE Confidence: 0.90084183

00:14:00.075 --> 00:14:00.795 t d m one as

NOTE Confidence: 0.90084183

00:14:00.795 --> 00:14:01.755 shown in the middle,

NOTE Confidence: 0.9695701

00:14:02.155 --> 00:14:03.434 diagram, you kill off the

NOTE Confidence: 0.9695701

00:14:03.434 --> 00:14:04.715 HER2 positive cells, but you

NOTE Confidence: 0.9695701

00:14:04.715 --> 00:14:05.995 leave behind the HER2 negative

NOTE Confidence: 0.9695701

00:14:05.995 --> 00:14:07.675 cells. Again, because HER2 TDM

NOTE Confidence: 0.9695701

00:14:07.675 --> 00:14:09.054 one doesn't have this bystander

NOTE Confidence: 0.9695701

00:14:09.115 --> 00:14:10.395 effect. But on the right,

NOTE Confidence: 0.9695701

00:14:10.395 --> 00:14:11.215 you use TDXD

NOTE Confidence: 0.9533591

00:14:11.675 --> 00:14:13.115 with bystander effect, you kill

NOTE Confidence: 0.9533591

00:14:13.115 --> 00:14:14.260 off both cell lines. Okay.

NOTE Confidence: 0.9533591

00:14:14.260 --> 00:14:15.700 Again, why does that matter?

NOTE Confidence: 0.9533591

00:14:15.700 --> 00:14:16.899 This is a xenograph where

NOTE Confidence: 0.9533591

00:14:16.899 --> 00:14:18.440 you mix two cancers together.

NOTE Confidence: 0.9883789

00:14:18.980 --> 00:14:20.680 Obviously, people have one cancer,

NOTE Confidence: 0.955312

00:14:21.779 --> 00:14:23.700 and it's HER2 positive, so

NOTE Confidence: 0.955312

00:14:23.700 --> 00:14:24.820 there should be lots of

NOTE Confidence: 0.955312

00:14:24.820 --> 00:14:26.120 HER2 on all the cells.

NOTE Confidence: 0.955312

00:14:26.260 --> 00:14:27.964 Well, let's just for the

NOTE Confidence: 0.955312

00:14:27.964 --> 00:14:29.165 sake of argument say that's

NOTE Confidence: 0.955312

00:14:29.165 --> 00:14:30.125 not the case and that

NOTE Confidence: 0.955312

00:14:30.125 --> 00:14:31.345 there are heterogeneous,

NOTE Confidence: 0.9528449

00:14:32.285 --> 00:14:34.045 expression of HER2 in some

NOTE Confidence: 0.9528449

00:14:34.045 --> 00:14:36.125 cancers. The concern would be

NOTE Confidence: 0.9528449

00:14:36.125 --> 00:14:36.925 that if you have this

NOTE Confidence: 0.9528449

00:14:36.925 --> 00:14:38.705 heterogeneous cancer shown

NOTE Confidence: 0.9636179

00:14:40.200 --> 00:14:41.480 here where the blue cells

NOTE Confidence: 0.9636179

35

00:14:41.480 --> 00:14:42.600 are the HER2 positive and

NOTE Confidence: 0.9636179

00:14:42.600 --> 00:14:43.820 the red ones are not,

NOTE Confidence: 0.9636179

00:14:43.880 --> 00:14:44.840 you treat with a very

NOTE Confidence: 0.9636179

00:14:44.840 --> 00:14:45.980 targeted drug,

NOTE Confidence: 0.9720088

00:14:47.880 --> 00:14:49.320 you kill off the HER2

NOTE Confidence: 0.9720088

00:14:49.320 --> 00:14:50.440 positive cells, you leave behind

NOTE Confidence: 0.9720088

00:14:50.440 --> 00:14:51.640 the HER2 negative cells, and

NOTE Confidence: 0.9720088

00:14:51.640 --> 00:14:52.760 the HER2 negative cells then

NOTE Confidence: 0.9720088

00:14:52.760 --> 00:14:53.560 grow up, and now you

NOTE Confidence: 0.9720088

00:14:53.560 --> 00:14:54.860 have a resistant cancer

NOTE Confidence: 0.98329586

00:14:55.285 --> 00:14:56.645 similar to what was shown

NOTE Confidence: 0.98329586

00:14:56.645 --> 00:14:57.685 in in those in the

NOTE Confidence: 0.98329586

00:14:57.685 --> 00:14:58.985 xenograft I just showed.

NOTE Confidence: 0.9895037

00:15:00.325 --> 00:15:02.505 Is this clinically relevant? So,

NOTE Confidence: 0.78011066

00:15:03.125 --> 00:15:03.625 my,

NOTE Confidence: 0.9916874

00:15:04.885 --> 00:15:05.385 colleague,

NOTE Confidence: 0.9296983

00:15:06.485 --> 00:15:07.685 Otto Mesker and I did

NOTE Confidence: 0.9296983

00:15:07.685 --> 00:15:08.745 this IIT,

NOTE Confidence: 0.9769893

00:15:09.605 --> 00:15:11.760 to ask this seemingly pretty

NOTE Confidence: 0.9769893

00:15:11.760 --> 00:15:13.279 straightforward question, but at least

NOTE Confidence: 0.9769893

00:15:13.279 --> 00:15:14.000 as far as we knew

NOTE Confidence: 0.9769893

00:15:14.000 --> 00:15:15.360 that really hadn't been addressed

NOTE Confidence: 0.9769893

00:15:15.360 --> 00:15:16.420 before in the clinic.

NOTE Confidence: 0.95521164

00:15:17.360 --> 00:15:18.980 Are heterogeneous cancers

NOTE Confidence: 0.9966823

00:15:19.440 --> 00:15:21.300 less sensitive to targeted therapy?

NOTE Confidence: 0.98013633

00:15:22.400 --> 00:15:23.120 So the way we did

NOTE Confidence: 0.98013633

00:15:23.120 --> 00:15:24.115 this, we took a hundred

NOTE Confidence: 0.98013633

00:15:24.115 --> 00:15:25.235 and sixty four patients who

NOTE Confidence: 0.98013633

00:15:25.235 --> 00:15:26.915 had newly diagnosed HER2 positive

NOTE Confidence: 0.98013633

00:15:26.915 --> 00:15:27.415 disease,

NOTE Confidence: 0.99857885

00:15:28.195 --> 00:15:29.895 and before we started treatment,

NOTE Confidence: 0.988069

00:15:30.355 --> 00:15:31.555 we did a biopsy in

NOTE Confidence: 0.988069

00:15:31.555 --> 00:15:32.995 two different locations of their

NOTE Confidence: 0.988069

00:15:32.995 --> 00:15:33.495 cancer.

NOTE Confidence: 0.9119549

00:15:34.435 --> 00:15:35.715 And then they treated with

NOTE Confidence: 0.9119549

00:15:35.715 --> 00:15:36.675 TBM one, we threw in

NOTE Confidence: 0.9119549

00:15:36.675 --> 00:15:37.895 another HER2 antibody,

NOTE Confidence: 0.9672322

00:15:38.275 --> 00:15:39.015 called pertuzumab,

NOTE Confidence: 0.9805381

00:15:40.160 --> 00:15:41.199 and and then they had

NOTE Confidence: 0.9805381

00:15:41.199 --> 00:15:42.880 surgery. And so we we

NOTE Confidence: 0.9805381

00:15:42.880 --> 00:15:44.000 took advantage of the fact

NOTE Confidence: 0.9805381

00:15:44.000 --> 00:15:44.720 that we did these two

NOTE Confidence: 0.9805381

00:15:44.720 --> 00:15:46.000 different biopsies, and so we

NOTE Confidence: 0.9805381

00:15:46.000 --> 00:15:47.360 had, and each of those

NOTE Confidence: 0.9805381

00:15:47.360 --> 00:15:49.279 biopsied had three different sections

NOTE Confidence: 0.9805381

00:15:49.279 --> 00:15:50.240 that we looked at. And

NOTE Confidence: 0.9805381

00:15:50.240 --> 00:15:51.519 we looked at whether there

NOTE Confidence: 0.9805381

00:15:51.519 --> 00:15:52.180 was heterogeneity,

NOTE Confidence: 0.98434466

00:15:53.155 --> 00:15:54.615 in terms of HER2 amplification

NOTE Confidence: 0.9745332

00:15:55.075 --> 00:15:56.295 in those different sections.

NOTE Confidence: 0.87935275

00:15:56.995 --> 00:15:58.695 And we scored those cancers,

NOTE Confidence: 0.97705686

00:16:01.475 --> 00:16:03.095 using a standard ASCO,

NOTE Confidence: 0.9614894

00:16:03.795 --> 00:16:05.735 cap definition of heterogeneity.

NOTE Confidence: 0.9882592

00:16:06.519 --> 00:16:07.399 And then we looked at

NOTE Confidence: 0.9882592

00:16:07.399 --> 00:16:08.540 how the heterogeneity

NOTE Confidence: 0.99615407

00:16:09.000 --> 00:16:10.200 played out in terms of,

NOTE Confidence: 0.99615407

00:16:10.519 --> 00:16:11.740 benefit to this treatment.

NOTE Confidence: 0.9942005

00:16:12.279 --> 00:16:13.480 And what we found was

NOTE Confidence: 0.9942005

00:16:13.480 --> 00:16:14.839 that in the cancers that

NOTE Confidence: 0.9942005

00:16:14.839 --> 00:16:16.600 were not heterogeneous, those cancers

NOTE Confidence: 0.9942005

00:16:16.600 --> 00:16:18.600 where there's pretty homogeneous expression

NOTE Confidence: 0.9942005

00:16:18.600 --> 00:16:20.140 or amplification of HER2,

NOTE Confidence: 0.9915651

00:16:20.774 --> 00:16:21.975 fifty five percent of those

NOTE Confidence: 0.9915651

00:16:21.975 --> 00:16:23.975 patients had complete eradication of

NOTE Confidence: 0.9915651

00:16:23.975 --> 00:16:25.675 their tumor just from the

NOTE Confidence: 0.9915651

00:16:25.894 --> 00:16:27.975 HER2 targeted therapy. So in

NOTE Confidence: 0.9915651

00:16:27.975 --> 00:16:29.115 in that situation,

NOTE Confidence: 0.932049

00:16:29.574 --> 00:16:30.855 this HER2 target therapy is

NOTE Confidence: 0.932049

00:16:30.855 --> 00:16:31.675 highly effective,

NOTE Confidence: 0.9841211

00:16:32.214 --> 00:16:33.514 and and well tolerated.

NOTE Confidence: 0.9883461

00:16:33.975 --> 00:16:35.170 But then when you looked

NOTE Confidence: 0.9883461

00:16:35.170 --> 00:16:36.130 at the cancers that were

NOTE Confidence: 0.9883461

00:16:36.130 --> 00:16:36.630 heterogeneous,

NOTE Confidence: 0.98126304

00:16:37.170 --> 00:16:38.210 none of them had a

NOTE Confidence: 0.98126304

00:16:38.210 --> 00:16:40.370 pathologic complete response. And so

NOTE Confidence: 0.98126304

00:16:40.370 --> 00:16:42.230 this was highly statistically significant,

NOTE Confidence: 0.9571037

00:16:42.770 --> 00:16:44.450 and it confirmed that actually

NOTE Confidence: 0.9571037

00:16:44.450 --> 00:16:46.050 heterogeneity matters, that if you

NOTE Confidence: 0.9571037

00:16:46.050 --> 00:16:46.870 have a heterogeneous

NOTE Confidence: 0.9559631

00:16:47.170 --> 00:16:48.770 cancer, you're not as likely

NOTE Confidence: 0.9559631

00:16:48.770 --> 00:16:51.085 to respond as completely to

NOTE Confidence: 0.9559631

00:16:51.085 --> 00:16:52.765 HER2 targeted therapy, or at

NOTE Confidence: 0.9559631

00:16:52.765 --> 00:16:54.205 least a HER2 targeted therapy

NOTE Confidence: 0.9559631

00:16:54.205 --> 00:16:55.665 that doesn't have this bystander

NOTE Confidence: 0.9559631

00:16:55.885 --> 00:16:57.565 effect, which TDM one does

NOTE Confidence: 0.9559631

00:16:57.565 --> 00:16:58.065 not.

NOTE Confidence: 0.9931549

00:16:58.525 --> 00:16:59.185 We actually

NOTE Confidence: 0.9897484

00:16:59.885 --> 00:17:01.325 went on to look a

NOTE Confidence: 0.9897484

00:17:01.325 --> 00:17:02.605 little bit more in-depth in

NOTE Confidence: 0.9897484

00:17:02.605 --> 00:17:03.665 collaboration with,

NOTE Confidence: 0.8645704

00:17:05.080 --> 00:17:06.619 a lab at Dana Farber

NOTE Confidence: 0.8645704

00:17:06.679 --> 00:17:08.119 led by Neli Polyak and

NOTE Confidence: 0.8645704

00:17:08.119 --> 00:17:09.179 and Francisca,

NOTE Confidence: 0.7683645

41

00:17:10.119 --> 00:17:10.619 Mihor,

NOTE Confidence: 0.9725625

00:17:11.080 --> 00:17:12.679 looking at at the single

NOTE Confidence: 0.9725625

00:17:12.679 --> 00:17:14.299 cell level by HER2 amplification,

NOTE Confidence: 0.99262613

00:17:14.600 --> 00:17:16.279 trying to understand what was

NOTE Confidence: 0.99262613

00:17:16.279 --> 00:17:17.259 actually driving,

NOTE Confidence: 0.97404677

00:17:17.639 --> 00:17:18.299 the resistance.

NOTE Confidence: 0.9847617

00:17:19.080 --> 00:17:19.820 And interestingly,

NOTE Confidence: 0.8731691

00:17:20.655 --> 00:17:22.115 at least interesting to me,

NOTE Confidence: 0.99284226

00:17:22.815 --> 00:17:24.095 it was actually the fraction

NOTE Confidence: 0.99284226

00:17:24.095 --> 00:17:26.095 of the non amplified cells

NOTE Confidence: 0.99284226

00:17:26.095 --> 00:17:26.595 within,

NOTE Confidence: 0.9997132

00:17:27.135 --> 00:17:27.795 the population

NOTE Confidence: 0.9470634

00:17:28.335 --> 00:17:30.095 that was strongly correlated with

NOTE Confidence: 0.9470634

00:17:30.095 --> 00:17:32.095 PACER. And it so, originally,

NOTE Confidence: 0.9470634

00:17:32.095 --> 00:17:32.895 we kind of had the

NOTE Confidence: 0.9470634

00:17:32.895 --> 00:17:35.135 idea, okay, a heterogeneous cancer

NOTE Confidence: 0.9470634

00:17:35.135 --> 00:17:36.240 is one where, you know,

NOTE Confidence: 0.9470634

00:17:36.240 --> 00:17:37.359 there's a big c of

NOTE Confidence: 0.9470634

00:17:37.359 --> 00:17:38.720 HER2 positive cells and then

NOTE Confidence: 0.9470634

00:17:38.720 --> 00:17:40.320 there's this little cluster of

NOTE Confidence: 0.9470634

00:17:40.320 --> 00:17:41.680 HER2 negative cells that was

NOTE Confidence: 0.9470634

00:17:41.680 --> 00:17:43.359 gonna stay behind and grow

NOTE Confidence: 0.9470634

00:17:43.359 --> 00:17:44.480 out. But, actually, that's not

NOTE Confidence: 0.9470634

00:17:44.480 --> 00:17:46.100 what we saw. It's actually

NOTE Confidence: 0.9869617

00:17:46.560 --> 00:17:47.060 fairly

NOTE Confidence: 0.9368856

00:17:47.440 --> 00:17:49.965 oftentimes relatively uniform distribution of

NOTE Confidence: 0.9368856

00:17:50.125 --> 00:17:51.645 HER2 positive and HER2 or

NOTE Confidence: 0.9368856

00:17:51.645 --> 00:17:53.005 HER2 amplified and HER2 non

NOTE Confidence: 0.9368856

00:17:53.005 --> 00:17:53.904 amplified cells,

NOTE Confidence: 0.96669006

00:17:54.284 --> 00:17:55.725 that was that was leading

NOTE Confidence: 0.96669006

00:17:55.725 --> 00:17:57.325 to heterogeneity. So you didn't

NOTE Confidence: 0.96669006

00:17:57.325 --> 00:17:58.365 actually have to do those

NOTE Confidence: 0.96669006

00:17:58.365 --> 00:17:58.865 six,

NOTE Confidence: 0.9351267

00:17:59.325 --> 00:18:00.924 biopsy sections. If you just

NOTE Confidence: 0.9351267

00:18:00.924 --> 00:18:02.044 look at one section and

NOTE Confidence: 0.9351267

00:18:02.044 --> 00:18:03.030 you quantitate,

NOTE Confidence: 0.84939826

00:18:04.450 --> 00:18:04.690 how,

NOTE Confidence: 0.9707269

00:18:05.250 --> 00:18:06.369 much how many of these

NOTE Confidence: 0.9707269

00:18:06.369 --> 00:18:08.130 HER2 non amplified cells are

NOTE Confidence: 0.9707269

00:18:08.130 --> 00:18:09.809 there, you can actually predict

NOTE Confidence: 0.9707269

00:18:09.809 --> 00:18:10.309 PCR,

NOTE Confidence: 0.7660967

00:18:11.330 --> 00:18:12.150 very strongly,

NOTE Confidence: 0.9773514

00:18:13.410 --> 00:18:14.230 which which is

NOTE Confidence: 0.9815133

00:18:14.585 --> 00:18:15.545 which is kind of interesting.

NOTE Confidence: 0.9815133

00:18:15.545 --> 00:18:16.045 And,

NOTE Confidence: 0.9789954

00:18:16.505 --> 00:18:18.744 we actually that our data

NOTE Confidence: 0.9789954

00:18:18.744 --> 00:18:20.585 was subsequently replicated a few

NOTE Confidence: 0.9789954

00:18:20.585 --> 00:18:21.945 years later, in a in

NOTE Confidence: 0.9789954

00:18:21.945 --> 00:18:23.305 a larger trial where they

NOTE Confidence: 0.9789954

00:18:23.305 --> 00:18:24.425 went back and looked at

NOTE Confidence: 0.9789954

00:18:24.425 --> 00:18:26.345 the same population patients treated

NOTE Confidence: 0.9789954

00:18:26.345 --> 00:18:27.565 with TDM one and pertuzumab.

NOTE Confidence: 0.96921855

00:18:28.185 --> 00:18:29.700 And, again, those who had

NOTE Confidence: 0.96921855

00:18:29.859 --> 00:18:30.359 heterogeneous

NOTE Confidence: 0.9208214

00:18:30.899 --> 00:18:32.580 positivity for HER2 had no

NOTE Confidence: 0.9208214

00:18:32.580 --> 00:18:34.100 pass ERs, whereas those that

NOTE Confidence: 0.9208214

00:18:34.100 --> 00:18:35.619 were homogeneous had a a

NOTE Confidence: 0.9208214

00:18:35.619 --> 00:18:36.899 over fifty percent pass ER

NOTE Confidence: 0.9208214

00:18:36.899 --> 00:18:37.399 rate.

NOTE Confidence: 0.9982163

00:18:38.340 --> 00:18:39.559 Okay. So

NOTE Confidence: 0.9691403

00:18:41.220 --> 00:18:42.679 getting back to TDXD,

NOTE Confidence: 0.9993789

00:18:43.380 --> 00:18:44.359 it's got this

NOTE Confidence: 0.9181617

00:18:44.835 --> 00:18:46.515 bystander effect, at least in

NOTE Confidence: 0.9181617

00:18:46.515 --> 00:18:47.015 vivo.

NOTE Confidence: 0.99812233

00:18:48.355 --> 00:18:49.475 Does that matter in terms

NOTE Confidence: 0.99812233

00:18:49.475 --> 00:18:50.695 of improving efficacy?

NOTE Confidence: 0.94738865

00:18:52.595 --> 00:18:53.494 So it does.

NOTE Confidence: 0.9059159

00:18:54.195 --> 00:18:55.794 Or at least somehow it

NOTE Confidence: 0.9059159

00:18:55.794 --> 00:18:57.075 has much better efficacy, whether

NOTE Confidence: 0.9059159

00:18:57.075 --> 00:18:58.135 how much of that's bystander

NOTE Confidence: 0.9059159

00:18:58.195 --> 00:18:59.075 effect or some of the

NOTE Confidence: 0.9059159

00:18:59.075 --> 00:18:59.575 other,

NOTE Confidence: 0.95580906

00:19:00.590 --> 00:19:01.790 aspects that we don't really

NOTE Confidence: 0.95580906

00:19:01.790 --> 00:19:02.670 know at this point. But

NOTE Confidence: 0.95580906

00:19:02.670 --> 00:19:03.390 this was the,

NOTE Confidence: 0.9345318

00:19:03.790 --> 00:19:05.310 phase two single arm study

NOTE Confidence: 0.9345318

00:19:05.310 --> 00:19:06.030 that that,

NOTE Confidence: 0.9586094

00:19:06.510 --> 00:19:07.810 we were involved with,

NOTE Confidence: 0.999218

00:19:09.550 --> 00:19:10.530 that demonstrated

NOTE Confidence: 0.9371244

00:19:10.910 --> 00:19:12.670 of in heavily pretreated patients,

NOTE Confidence: 0.9371244

00:19:12.670 --> 00:19:13.710 patients who had already had

NOTE Confidence: 0.9371244

00:19:13.710 --> 00:19:15.605 all the standard HER2 therapies,

NOTE Confidence: 0.9371244

00:19:15.605 --> 00:19:16.484 I think, the median of

NOTE Confidence: 0.9371244

00:19:16.484 --> 00:19:17.605 six prior lines. So these

NOTE Confidence: 0.9371244

00:19:17.605 --> 00:19:19.225 were seventh line metastatic

NOTE Confidence: 0.9286108

00:19:19.605 --> 00:19:21.125 patients, and the response rate

NOTE Confidence: 0.9286108

00:19:21.125 --> 00:19:22.725 to TDXD alone was over

NOTE Confidence: 0.9286108

00:19:22.725 --> 00:19:24.244 sixty percent. It was very

NOTE Confidence: 0.9286108

00:19:24.244 --> 00:19:25.544 durable. The patients,

NOTE Confidence: 0.87434304

00:19:25.924 --> 00:19:27.140 had a, a were on

NOTE Confidence: 0.87434304

00:19:27.140 --> 00:19:28.760 study for over twenty months,

NOTE Confidence: 0.97808754

00:19:29.299 --> 00:19:30.580 and virtually a hundred percent

NOTE Confidence: 0.97808754

00:19:30.580 --> 00:19:31.960 of patients had some benefit

NOTE Confidence: 0.9395061

00:19:32.260 --> 00:19:33.380 as shown in this waterfall

NOTE Confidence: 0.9395061

00:19:33.380 --> 00:19:33.880 plot.

NOTE Confidence: 0.97288346

00:19:35.619 --> 00:19:36.500 The trade off was that

NOTE Confidence: 0.97288346

00:19:36.500 --> 00:19:38.179 there was more toxicity. So

NOTE Confidence: 0.97288346

00:19:38.179 --> 00:19:39.559 unlike TDM one,

NOTE Confidence: 0.995012

00:19:40.020 --> 00:19:41.000 with this drug,

NOTE Confidence: 0.9757585

00:19:41.575 --> 00:19:43.355 most patients get some nausea,

NOTE Confidence: 0.9757585

00:19:43.494 --> 00:19:44.955 there's fatigue, there's,

NOTE Confidence: 0.8371376

00:19:47.095 --> 00:19:48.795 hair loss in some patients,

NOTE Confidence: 0.99648166

00:19:49.415 --> 00:19:49.915 and

NOTE Confidence: 0.97762054

00:19:50.215 --> 00:19:51.494 in ten to fifteen percent

NOTE Confidence: 0.97762054

00:19:51.494 --> 00:19:52.075 of patients,

NOTE Confidence: 0.99068826

00:19:52.775 --> 00:19:54.234 they get a serious complication

NOTE Confidence: 0.99068826

00:19:54.375 --> 00:19:55.895 called interstitial lung disease or

NOTE Confidence: 0.99068826

00:19:55.895 --> 00:19:56.395 pneumonitis,

NOTE Confidence: 0.96681213

00:19:57.809 --> 00:19:59.890 which is typically manageable, but

NOTE Confidence: 0.96681213

00:19:59.890 --> 00:20:00.929 it's definitely something that you

NOTE Confidence: 0.96681213

00:20:00.929 --> 00:20:01.890 have to pay attention to

NOTE Confidence: 0.96681213

00:20:01.890 --> 00:20:03.030 because it can be fatal.

NOTE Confidence: 0.8315493

00:20:03.809 --> 00:20:04.309 So,

NOTE Confidence: 0.94909394

00:20:06.210 --> 00:20:08.309 because of the incredible efficacy

NOTE Confidence: 0.94909394

00:20:08.450 --> 00:20:09.990 in very refractory patients,

NOTE Confidence: 0.9012558

00:20:10.315 --> 00:20:11.915 these data led to the

NOTE Confidence: 0.9012558

00:20:11.915 --> 00:20:13.195 the accelerated approval of of

NOTE Confidence: 0.9012558

00:20:13.195 --> 00:20:13.695 TDXD,

NOTE Confidence: 0.9520419

00:20:15.115 --> 00:20:16.175 in in this,

NOTE Confidence: 0.9644598

00:20:17.195 --> 00:20:18.655 kind of refractory setting.

NOTE Confidence: 0.958515

00:20:19.835 --> 00:20:20.715 But then we went on,

NOTE Confidence: 0.958515

00:20:20.715 --> 00:20:22.095 there were several other trials.

NOTE Confidence: 0.95889634

00:20:22.399 --> 00:20:23.519 This was a phase three

NOTE Confidence: 0.95889634

00:20:23.519 --> 00:20:24.019 style

NOTE Confidence: 0.9410416

49

00:20:24.320 --> 00:20:26.340 phase three trial looking specifically

NOTE Confidence: 0.9410416

00:20:26.399 --> 00:20:27.440 at patients who had already

NOTE Confidence: 0.9410416

00:20:27.440 --> 00:20:28.880 had the other ADC, TDM

NOTE Confidence: 0.9410416

00:20:28.880 --> 00:20:31.700 one, and comparing TDXD versus

NOTE Confidence: 0.9410416

00:20:31.840 --> 00:20:32.340 standard,

NOTE Confidence: 0.93565685

00:20:32.799 --> 00:20:33.700 HER2 therapy,

NOTE Confidence: 0.9801323

00:20:34.240 --> 00:20:36.179 and TDXD was much better.

NOTE Confidence: 0.9622426

00:20:37.605 --> 00:20:38.885 And this demonstrated,

NOTE Confidence: 0.9964126

00:20:41.125 --> 00:20:42.505 that you actually can

NOTE Confidence: 0.9578538

00:20:42.885 --> 00:20:44.645 have benefit from one antibody

NOTE Confidence: 0.9578538

00:20:44.645 --> 00:20:46.085 drug conjugate followed by another,

NOTE Confidence: 0.9578538

00:20:46.085 --> 00:20:46.965 even though they have the

NOTE Confidence: 0.9578538

00:20:46.965 --> 00:20:48.085 same target, but they have

NOTE Confidence: 0.9578538

00:20:48.085 --> 00:20:49.445 different payloads. So by switching

NOTE Confidence: 0.9578538

00:20:49.445 --> 00:20:50.484 payloads, you're able to,

NOTE Confidence: 0.95325124

00:20:51.490 --> 00:20:51.890 provide,

NOTE Confidence: 0.9420096

00:20:52.450 --> 00:20:53.429 more efficacy.

NOTE Confidence: 0.97053677

00:20:53.890 --> 00:20:54.929 And at least in my

NOTE Confidence: 0.97053677

00:20:54.929 --> 00:20:56.070 mind, this supports

NOTE Confidence: 0.9919634

00:20:56.450 --> 00:20:57.109 the paradigm,

NOTE Confidence: 0.9855313

00:20:57.730 --> 00:20:59.109 that you could treat patients

NOTE Confidence: 0.9855313

00:20:59.250 --> 00:21:01.250 with sequential ADCs with different

NOTE Confidence: 0.9855313

00:21:01.250 --> 00:21:02.690 payloads, and we'll we'll talk

NOTE Confidence: 0.9855313

00:21:02.690 --> 00:21:03.590 more about that,

NOTE Confidence: 0.99928194

00:21:04.049 --> 00:21:04.549 later.

NOTE Confidence: 0.9597696

00:21:08.185 --> 00:21:09.305 This went on to now

NOTE Confidence: 0.9597696

00:21:09.305 --> 00:21:10.505 look head to head at

NOTE Confidence: 0.9597696

00:21:10.505 --> 00:21:11.005 TDXD

NOTE Confidence: 0.9302776

00:21:11.305 --> 00:21:12.905 versus PDM one, so two

NOTE Confidence: 0.9302776

00:21:12.905 --> 00:21:15.145 ADCs against each other. Probably

NOTE Confidence: 0.9302776

00:21:15.145 --> 00:21:16.185 the only trial that's done

NOTE Confidence: 0.9302776

00:21:16.185 --> 00:21:16.685 that.

NOTE Confidence: 0.9590523

00:21:17.305 --> 00:21:19.225 And again, TDXD was was

NOTE Confidence: 0.9590523

00:21:19.225 --> 00:21:21.145 far superior to to TDM

NOTE Confidence: 0.9590523

00:21:21.145 --> 00:21:21.645 one,

NOTE Confidence: 0.90737617

00:21:22.490 --> 00:21:23.550 fourfold greater

NOTE Confidence: 0.9508183

00:21:23.930 --> 00:21:25.690 progression free survival, so almost

NOTE Confidence: 0.9508183

00:21:25.690 --> 00:21:27.210 twenty nine months progression free

NOTE Confidence: 0.9508183

00:21:27.210 --> 00:21:27.710 survival,

NOTE Confidence: 0.9451021

00:21:28.490 --> 00:21:29.450 a level that I don't

NOTE Confidence: 0.9451021

00:21:29.450 --> 00:21:30.570 think had ever been seen

NOTE Confidence: 0.9451021

00:21:30.570 --> 00:21:31.950 before in pretreated

NOTE Confidence: 0.9722887

00:21:32.410 --> 00:21:33.710 patients with breast cancer.

NOTE Confidence: 0.994174

00:21:34.250 --> 00:21:35.390 So very effective

NOTE Confidence: 0.9584633

00:21:35.815 --> 00:21:37.115 survival was also beneficial,

NOTE Confidence: 0.8988455

00:21:37.734 --> 00:21:39.655 and this established tDxD as

NOTE Confidence: 0.8988455

00:21:39.655 --> 00:21:40.395 the standard

NOTE Confidence: 0.847182

00:21:40.775 --> 00:21:41.835 care for patients,

NOTE Confidence: 0.88887644

00:21:43.015 --> 00:21:44.875 with her trophosid metastatic disease.

NOTE Confidence: 0.627298

00:21:47.335 --> 00:21:47.835 But

NOTE Confidence: 0.9404096

00:21:48.559 --> 00:21:49.520 there was a question at

NOTE Confidence: 0.9404096

00:21:49.520 --> 00:21:50.720 that time of what about

NOTE Confidence: 0.9404096

00:21:50.720 --> 00:21:52.320 patients with progressive brain mets?

NOTE Confidence: 0.9404096

00:21:52.320 --> 00:21:54.000 And, unfortunately, that's a big

NOTE Confidence: 0.9404096

00:21:54.000 --> 00:21:55.840 problem in HER2 positive disease

NOTE Confidence: 0.9404096

00:21:55.840 --> 00:21:56.340 because,

NOTE Confidence: 0.9583295

00:21:56.960 --> 00:21:58.559 for reasons that aren't completely

NOTE Confidence: 0.9583295

00:21:58.559 --> 00:22:00.340 clear, there's a strong predilection

NOTE Confidence: 0.9583295

00:22:00.480 --> 00:22:02.320 for HER2 positive breast cancer

NOTE Confidence: 0.9583295

00:22:02.320 --> 00:22:03.460 to go to the brain.

NOTE Confidence: 0.91226715

00:22:03.885 --> 00:22:05.165 It may partly, it may

NOTE Confidence: 0.91226715

00:22:05.165 --> 00:22:05.885 be because,

NOTE Confidence: 0.97498804

00:22:06.285 --> 00:22:07.085 or part of it may

NOTE Confidence: 0.97498804

00:22:07.085 --> 00:22:07.585 be

NOTE Confidence: 0.9412952

00:22:08.605 --> 00:22:10.765 the the conventional wisdom that

NOTE Confidence: 0.9412952

00:22:10.765 --> 00:22:12.445 that drugs like that we

NOTE Confidence: 0.9412952

00:22:12.445 --> 00:22:13.725 use in HER2 positive disease,

NOTE Confidence: 0.9412952

00:22:13.725 --> 00:22:15.505 like antibodies, antibody drug conjugates,

NOTE Confidence: 0.9412952

00:22:15.645 --> 00:22:17.005 don't get into the brain

NOTE Confidence: 0.9412952

00:22:17.085 --> 00:22:18.720 into into the the brain

NOTE Confidence: 0.9412952

00:22:18.720 --> 00:22:19.600 because of the blood brain

NOTE Confidence: 0.9412952

00:22:19.600 --> 00:22:20.640 barrier. So it's kind of

NOTE Confidence: 0.9412952

00:22:20.640 --> 00:22:22.080 a a sanctuary site, and

NOTE Confidence: 0.9412952

00:22:22.080 --> 00:22:23.040 that's why we see so

NOTE Confidence: 0.9412952

00:22:23.040 --> 00:22:23.920 much of it. But there's

NOTE Confidence: 0.9412952

00:22:23.920 --> 00:22:25.760 also some biology involved that

NOTE Confidence: 0.9412952

00:22:25.760 --> 00:22:26.960 these cancers are just have

NOTE Confidence: 0.9412952

00:22:26.960 --> 00:22:28.420 a tropism to the brain.

NOTE Confidence: 0.9903898

00:22:29.040 --> 00:22:30.179 But as I said,

NOTE Confidence: 0.9288873

00:22:30.480 --> 00:22:31.815 you know, the the idea

NOTE Confidence: 0.9288873

00:22:31.815 --> 00:22:33.335 was antibodies don't get into

NOTE Confidence: 0.9288873

00:22:33.335 --> 00:22:34.934 the brain, therefore, antibody drug

NOTE Confidence: 0.9288873

00:22:34.934 --> 00:22:35.895 conjugates don't get into the

NOTE Confidence: 0.9288873

00:22:35.895 --> 00:22:37.335 brain, so how are we

NOTE Confidence: 0.9288873

00:22:37.335 --> 00:22:38.455 gonna how could a drug

NOTE Confidence: 0.9288873

00:22:38.455 --> 00:22:39.115 like tDxD

NOTE Confidence: 0.9713826

00:22:39.575 --> 00:22:41.414 work in this very common

NOTE Confidence: 0.9713826

00:22:41.414 --> 00:22:41.914 situation?

NOTE Confidence: 0.97209376

00:22:43.095 --> 00:22:44.475 But it turns out that

NOTE Confidence: 0.97209376

00:22:44.570 --> 00:22:46.010 actually antibodies can get into

NOTE Confidence: 0.97209376

00:22:46.010 --> 00:22:47.309 the brain at least somewhat.

NOTE Confidence: 0.9155712

00:22:47.609 --> 00:22:49.230 This is a pet label,

NOTE Confidence: 0.9831402

00:22:50.170 --> 00:22:50.670 trastuzumab

NOTE Confidence: 0.96377766

00:22:51.130 --> 00:22:52.250 study, and you can see

NOTE Confidence: 0.96377766

00:22:52.250 --> 00:22:53.390 on the bottom there,

NOTE Confidence: 0.95479214

00:22:54.010 --> 00:22:56.730 that actually the antibody does

NOTE Confidence: 0.95479214

00:22:56.730 --> 00:22:57.690 get to the to the

NOTE Confidence: 0.95479214

00:22:57.690 --> 00:22:59.369 brain metastases at least to

NOTE Confidence: 0.95479214

00:22:59.369 --> 00:23:00.109 some level.

NOTE Confidence: 0.94078386

00:23:00.705 --> 00:23:01.525 Probably because

NOTE Confidence: 0.92750573

00:23:02.065 --> 00:23:03.184 the blood brain barrier breaks

NOTE Confidence: 0.92750573

00:23:03.184 --> 00:23:04.065 down a little bit when

NOTE Confidence: 0.92750573

00:23:04.065 --> 00:23:05.585 you have a cancer there

NOTE Confidence: 0.92750573

00:23:05.585 --> 00:23:07.184 and it's disrupting, you know,

NOTE Confidence: 0.92750573

00:23:07.184 --> 00:23:09.184 causes dysregulation of of vascular

NOTE Confidence: 0.92750573

00:23:09.184 --> 00:23:10.544 genesis, so the blood brain

NOTE Confidence: 0.92750573

00:23:10.544 --> 00:23:12.164 barrier isn't quite as intact.

NOTE Confidence: 0.9704683

00:23:13.150 --> 00:23:13.890 But regardless,

NOTE Confidence: 0.963996

00:23:14.990 --> 00:23:16.510 some antibody can get there.

NOTE Confidence: 0.963996

00:23:16.510 --> 00:23:17.790 And so we actually went

NOTE Confidence: 0.963996

00:23:17.790 --> 00:23:19.090 back and looked at,

NOTE Confidence: 0.9707772

00:23:19.790 --> 00:23:21.630 the the large studies I

NOTE Confidence: 0.9707772

00:23:21.630 --> 00:23:22.910 just had shown you, and

NOTE Confidence: 0.9707772

00:23:22.910 --> 00:23:24.030 there were a small number

NOTE Confidence: 0.9707772

00:23:24.030 --> 00:23:25.150 of patients on those studies

NOTE Confidence: 0.9707772

00:23:25.150 --> 00:23:26.510 that actually had progressive brain

NOTE Confidence: 0.9707772

00:23:26.510 --> 00:23:27.010 metastases

NOTE Confidence: 0.93539035

00:23:27.470 --> 00:23:28.130 at baseline.

NOTE Confidence: 0.97775817

00:23:29.135 --> 00:23:30.095 And we looked at the

NOTE Confidence: 0.97775817

00:23:30.095 --> 00:23:31.955 intracranial response of TDXD,

NOTE Confidence: 0.9588868

00:23:32.575 --> 00:23:33.695 and, actually, there there was

NOTE Confidence: 0.9588868

00:23:33.695 --> 00:23:34.654 some response. It was about

NOTE Confidence: 0.9588868

00:23:34.654 --> 00:23:36.174 a forty something percent response

NOTE Confidence: 0.9588868

00:23:36.174 --> 00:23:37.615 rate in the brain with

NOTE Confidence: 0.9588868

00:23:37.615 --> 00:23:39.455 this ADC, but the sample

NOTE Confidence: 0.9588868

00:23:39.455 --> 00:23:40.914 size was was pretty small.

NOTE Confidence: 0.84719825

00:23:41.580 --> 00:23:43.119 But just recently presented,

NOTE Confidence: 0.9714402

00:23:44.780 --> 00:23:46.140 at ESMO a few months

NOTE Confidence: 0.9714402

00:23:46.140 --> 00:23:48.059 ago was a prospective study

NOTE Confidence: 0.9714402

00:23:48.059 --> 00:23:49.020 of over two hundred and

NOTE Confidence: 0.9714402

00:23:49.020 --> 00:23:51.039 fifty patients with brain metastases,

NOTE Confidence: 0.94871426

00:23:51.740 --> 00:23:53.039 treating with tDxD.

NOTE Confidence: 0.97477216

00:23:54.155 --> 00:23:55.355 And as you can see,

NOTE Confidence: 0.99479115

00:23:55.835 --> 00:23:57.034 response rate in the brain

NOTE Confidence: 0.99479115

00:23:57.034 --> 00:23:58.715 with active brain metastases was

NOTE Confidence: 0.99479115

00:23:58.715 --> 00:24:00.155 over sixty percent. So I

NOTE Confidence: 0.99479115

00:24:00.155 --> 00:24:01.534 think we now have pretty,

NOTE Confidence: 0.9888765

00:24:02.075 --> 00:24:03.135 definitive data,

NOTE Confidence: 0.9672608

00:24:03.595 --> 00:24:05.434 that these ADCs actually are

NOTE Confidence: 0.9672608

00:24:05.434 --> 00:24:06.635 quite active in the brain.

NOTE Confidence: 0.9672608

00:24:06.635 --> 00:24:07.755 I think that's important to

NOTE Confidence: 0.9672608

00:24:07.755 --> 00:24:09.215 know since we obviously

NOTE Confidence: 0.9803328

00:24:09.660 --> 00:24:10.780 have a lot of cancer

NOTE Confidence: 0.9803328

00:24:10.780 --> 00:24:12.460 types that that have, brain

NOTE Confidence: 0.9803328

00:24:12.460 --> 00:24:14.160 metastases as a major problem.

NOTE Confidence: 0.997432

00:24:14.540 --> 00:24:15.500 And so this idea that

NOTE Confidence: 0.997432

00:24:15.500 --> 00:24:16.460 you have to use small

NOTE Confidence: 0.997432

00:24:16.460 --> 00:24:16.960 molecules,

NOTE Confidence: 0.99960446

00:24:17.580 --> 00:24:18.800 is probably not true.

NOTE Confidence: 0.99304974

00:24:21.260 --> 00:24:22.560 So as you might expect,

NOTE Confidence: 0.9730972

00:24:24.265 --> 00:24:25.865 with the efficacy of of

NOTE Confidence: 0.9730972

00:24:25.865 --> 00:24:27.304 of these conjugates in patients

NOTE Confidence: 0.9730972

00:24:27.304 --> 00:24:28.825 with metastatic disease, there was

NOTE Confidence: 0.9730972

00:24:28.825 --> 00:24:30.025 interest in seeing whether these

NOTE Confidence: 0.9730972

00:24:30.025 --> 00:24:31.244 conjugates could also,

NOTE Confidence: 0.9937965

00:24:32.905 --> 00:24:34.744 work in preventing recurrences in

NOTE Confidence: 0.9937965

00:24:34.744 --> 00:24:36.365 patients with early stage disease.

NOTE Confidence: 0.9715371

00:24:36.929 --> 00:24:38.129 And so there originally, there

NOTE Confidence: 0.9715371

00:24:38.129 --> 00:24:39.250 was a large trial that

NOTE Confidence: 0.9715371

00:24:39.250 --> 00:24:40.250 looked at patients who had

NOTE Confidence: 0.9715371

00:24:40.250 --> 00:24:41.649 a high risk early stage

NOTE Confidence: 0.9715371

00:24:41.649 --> 00:24:43.169 disease because their cancers did

NOTE Confidence: 0.9715371

00:24:43.169 --> 00:24:44.450 not respond all that well

NOTE Confidence: 0.9715371

00:24:44.450 --> 00:24:45.190 to neoadjuvant

NOTE Confidence: 0.9603665

00:24:45.570 --> 00:24:46.070 therapy,

NOTE Confidence: 0.9633596

00:24:46.769 --> 00:24:49.009 neoadjuvant HER2 therapy, and randomized

NOTE Confidence: 0.9633596

00:24:49.009 --> 00:24:50.289 those patients to either the

NOTE Confidence: 0.9633596

00:24:50.289 --> 00:24:51.490 standard back then, which was

NOTE Confidence: 0.9633596

00:24:51.490 --> 00:24:53.025 just continuing trastuzumab

NOTE Confidence: 0.8556442

00:24:53.484 --> 00:24:54.945 or using TDM one,

NOTE Confidence: 0.94074893

00:24:55.565 --> 00:24:57.905 and the TDM one showed

NOTE Confidence: 0.94074893

00:24:57.965 --> 00:24:59.165 about almost a fifty percent

NOTE Confidence: 0.94074893

00:24:59.165 --> 00:25:00.225 reduction in recurrences,

NOTE Confidence: 0.9902509

00:25:01.965 --> 00:25:03.565 compared to trastuzumab. So that's

NOTE Confidence: 0.9902509

00:25:03.565 --> 00:25:04.945 now the standard of care.

NOTE Confidence: 0.93455315

00:25:06.550 --> 00:25:07.910 One issue was that the

NOTE Confidence: 0.93455315

00:25:07.910 --> 00:25:08.810 brain metastases,

NOTE Confidence: 0.9586702

00:25:09.590 --> 00:25:11.830 actually was not significantly reduced

NOTE Confidence: 0.9586702

00:25:11.830 --> 00:25:12.710 with t d m one

NOTE Confidence: 0.9586702

00:25:12.710 --> 00:25:14.150 compared to trastuzumab, and I

NOTE Confidence: 0.9586702

00:25:14.150 --> 00:25:15.030 know that goes against a

NOTE Confidence: 0.9586702

00:25:15.030 --> 00:25:15.750 little bit about what I

NOTE Confidence: 0.9586702

00:25:15.750 --> 00:25:16.970 just said about brain metastases.

NOTE Confidence: 0.98577327

00:25:17.510 --> 00:25:18.310 And maybe we can talk

NOTE Confidence: 0.98577327

00:25:18.310 --> 00:25:19.609 about why that might be,

NOTE Confidence: 0.99700403

00:25:19.910 --> 00:25:20.475 in our

NOTE Confidence: 0.9503671

00:25:21.434 --> 00:25:23.355 very interesting question answer period

NOTE Confidence: 0.9503671

00:25:23.355 --> 00:25:25.135 that's gonna follow this talk.

NOTE Confidence: 0.94429535

00:25:27.035 --> 00:25:28.475 But it has led us

NOTE Confidence: 0.94429535

00:25:28.475 --> 00:25:30.234 to do this study in

NOTE Confidence: 0.94429535

00:25:30.234 --> 00:25:31.054 in the alliance

NOTE Confidence: 0.8888855

00:25:31.355 --> 00:25:32.335 where we're taking

NOTE Confidence: 0.98935944

00:25:32.650 --> 00:25:34.109 those patients who had,

NOTE Confidence: 0.9833363

00:25:35.690 --> 00:25:37.450 residual disease after neoadjuvant therapy

NOTE Confidence: 0.9833363

00:25:37.450 --> 00:25:38.890 and randomizing them to TDM

NOTE Confidence: 0.9833363

00:25:38.890 --> 00:25:40.510 one or TDM one plus

NOTE Confidence: 0.9833363

00:25:40.650 --> 00:25:42.730 this, potent HER2 tyrosine kinase

NOTE Confidence: 0.9833363

00:25:42.730 --> 00:25:44.410 inhibitor called tucatinib. And this

NOTE Confidence: 0.9833363

00:25:44.410 --> 00:25:45.630 study is underway

NOTE Confidence: 0.9579128

00:25:46.125 --> 00:25:47.565 here, at Yale, so you

NOTE Confidence: 0.9579128

00:25:47.565 --> 00:25:48.605 can put patients on this,

NOTE Confidence: 0.9579128

00:25:48.605 --> 00:25:49.725 and I will designate that

NOTE Confidence: 0.9579128

00:25:49.725 --> 00:25:51.484 by the handsome Dan icon

NOTE Confidence: 0.9579128

00:25:51.484 --> 00:25:52.285 as you'll see for the

NOTE Confidence: 0.9579128

00:25:52.285 --> 00:25:53.665 rest of the talk here.

NOTE Confidence: 0.98521584

00:25:54.525 --> 00:25:55.645 We also were looking at

NOTE Confidence: 0.98521584

00:25:55.645 --> 00:25:56.625 whether you can,

NOTE Confidence: 0.9899364

00:25:57.325 --> 00:25:59.005 use the the very well

NOTE Confidence: 0.9899364

00:25:59.005 --> 00:26:01.200 tolerated nature of TDM one

NOTE Confidence: 0.9899364

00:26:01.279 --> 00:26:01.859 to deescalate

NOTE Confidence: 0.9941268

00:26:02.240 --> 00:26:04.340 therapy in patients with earlier,

NOTE Confidence: 0.97174686

00:26:04.880 --> 00:26:06.480 or lower risk HER2 positive

NOTE Confidence: 0.97174686

00:26:06.480 --> 00:26:06.980 disease.

NOTE Confidence: 0.9155218

00:26:08.000 --> 00:26:09.519 So my then colleague at

NOTE Confidence: 0.9155218

00:26:09.519 --> 00:26:10.799 Dana Farber, Sarah Talaney, and

NOTE Confidence: 0.9155218

00:26:10.799 --> 00:26:13.380 I, did this, investigator initiated

NOTE Confidence: 0.9155218

00:26:13.519 --> 00:26:14.019 trial

NOTE Confidence: 0.9472453

63

00:26:14.399 --> 00:26:15.600 looking at patients with stage

NOTE Confidence: 0.9472453

00:26:15.600 --> 00:26:16.899 one HER2 positive cancers,

NOTE Confidence: 0.99443245

00:26:17.255 --> 00:26:18.635 randomizing them to,

NOTE Confidence: 0.9085021

00:26:19.015 --> 00:26:20.375 the previous standard that was

NOTE Confidence: 0.9085021

00:26:20.375 --> 00:26:22.215 actually established by Eric of

NOTE Confidence: 0.9085021

00:26:22.215 --> 00:26:24.695 paclitaxel and trastuzumab or TdM

NOTE Confidence: 0.9085021

00:26:24.695 --> 00:26:25.195 one,

NOTE Confidence: 0.97333

00:26:25.895 --> 00:26:27.335 and, the TdM one was

NOTE Confidence: 0.97333

00:26:27.335 --> 00:26:29.115 associated with incredibly good outcomes.

NOTE Confidence: 0.97333

00:26:29.175 --> 00:26:29.835 There was,

NOTE Confidence: 0.9995723

00:26:30.550 --> 00:26:31.210 less than

NOTE Confidence: 0.93582803

00:26:31.750 --> 00:26:33.590 one percent distant recurrence at

NOTE Confidence: 0.93582803

00:26:33.590 --> 00:26:34.330 five years.

NOTE Confidence: 0.8963836

00:26:34.790 --> 00:26:36.330 So clearly this was effective.

NOTE Confidence: 0.9820808

00:26:37.030 --> 00:26:38.070 We had assumed it was

NOTE Confidence: 0.9820808

00:26:38.070 --> 00:26:39.450 gonna be much better tolerated

NOTE Confidence: 0.9820808

00:26:39.590 --> 00:26:41.369 than the the the taxane,

NOTE Confidence: 0.97877425

00:26:42.150 --> 00:26:42.650 trastuzumab

NOTE Confidence: 0.933589

00:26:42.950 --> 00:26:43.450 regimen,

NOTE Confidence: 0.9427413

00:26:44.070 --> 00:26:45.425 and it turned out it

NOTE Confidence: 0.9427413

00:26:45.425 --> 00:26:46.625 it had less some of

NOTE Confidence: 0.9427413

00:26:46.625 --> 00:26:48.325 the standard chemotherapy toxicities,

NOTE Confidence: 0.9842276

00:26:48.785 --> 00:26:50.545 but people were discontinuing the

NOTE Confidence: 0.9842276

00:26:50.545 --> 00:26:51.665 TDM one, which was given

NOTE Confidence: 0.9842276

00:26:51.665 --> 00:26:52.545 for a year in this

NOTE Confidence: 0.9842276

00:26:52.545 --> 00:26:53.045 study,

NOTE Confidence: 0.98425347

00:26:53.665 --> 00:26:54.165 earlier,

NOTE Confidence: 0.9758548

00:26:54.625 --> 00:26:55.905 than they were discontinuing the

NOTE Confidence: 0.9758548

00:26:55.905 --> 00:26:57.105 trastuzumab in the in the

NOTE Confidence: 0.9758548

00:26:57.105 --> 00:26:58.260 other arm of the study.

NOTE Confidence: 0.8905601

00:26:59.220 --> 00:27:00.680 So, that's led,

NOTE Confidence: 0.97919005

00:27:02.100 --> 00:27:03.220 Sarah to go on to

NOTE Confidence: 0.97919005

00:27:03.220 --> 00:27:04.740 do this second version of

NOTE Confidence: 0.97919005

00:27:04.740 --> 00:27:05.480 the study,

NOTE Confidence: 0.9759287

00:27:06.020 --> 00:27:07.460 comparing just six cycles of

NOTE Confidence: 0.9759287

00:27:07.460 --> 00:27:08.580 TDM one, because we think

NOTE Confidence: 0.9759287

00:27:08.580 --> 00:27:09.460 that might be all you

NOTE Confidence: 0.9759287

00:27:09.460 --> 00:27:09.960 need,

NOTE Confidence: 0.9824363

00:27:10.420 --> 00:27:10.920 versus,

NOTE Confidence: 0.9774904

00:27:11.460 --> 00:27:12.280 the same

NOTE Confidence: 0.94397587

00:27:12.744 --> 00:27:14.105 control arm. Again, this is

NOTE Confidence: 0.94397587

00:27:14.105 --> 00:27:15.625 a study that's ongoing at

NOTE Confidence: 0.94397587

00:27:15.625 --> 00:27:16.205 at Yale,

NOTE Confidence: 0.9976562

00:27:16.664 --> 00:27:17.625 and it's actually a very

NOTE Confidence: 0.9976562

00:27:17.625 --> 00:27:19.484 good study for these patients,

NOTE Confidence: 0.99983335

00:27:20.345 --> 00:27:21.164 in my opinion.

NOTE Confidence: 0.98282117

00:27:21.865 --> 00:27:23.625 There's also studies going looking

NOTE Confidence: 0.98282117

00:27:23.625 --> 00:27:25.225 at TDXD, this more potent

NOTE Confidence: 0.98282117

00:27:25.225 --> 00:27:26.845 ADC. This is a study,

NOTE Confidence: 0.9359364

00:27:27.419 --> 00:27:28.700 actually comparing TDM one to

NOTE Confidence: 0.9359364

00:27:28.700 --> 00:27:30.139 TDXD in this adjuvant setting,

NOTE Confidence: 0.9359364

00:27:30.139 --> 00:27:31.279 and then there's a neoadjuvant

NOTE Confidence: 0.9359364

00:27:31.340 --> 00:27:32.159 file as well.

NOTE Confidence: 0.99658

00:27:32.460 --> 00:27:32.960 Okay.

NOTE Confidence: 0.8798

00:27:33.340 --> 00:27:33.840 So,

NOTE Confidence: 0.9705265

00:27:34.940 --> 00:27:36.220 switching gears a little bit,

NOTE Confidence: 0.9705265

00:27:36.379 --> 00:27:37.179 and this, I think, is

NOTE Confidence: 0.9705265

00:27:37.179 --> 00:27:38.480 where it gets really interesting.

NOTE Confidence: 0.9689061

00:27:41.205 --> 00:27:42.244 All the data I've showed

NOTE Confidence: 0.9689061

00:27:42.244 --> 00:27:43.285 you before is for these

NOTE Confidence: 0.9689061

00:27:43.285 --> 00:27:45.045 HER2 amplified cancers. These are

NOTE Confidence: 0.9689061

00:27:45.045 --> 00:27:46.984 the cancers that have incredibly

NOTE Confidence: 0.9689061

00:27:47.045 --> 00:27:48.185 high levels of HER2.

NOTE Confidence: 0.96321493

00:27:48.965 --> 00:27:50.565 In breast cancer, there's actually

NOTE Confidence: 0.96321493

00:27:50.565 --> 00:27:52.085 a continuum of HER2 expression.

NOTE Confidence: 0.96321493

00:27:52.085 --> 00:27:53.125 So you got these super

NOTE Confidence: 0.96321493

00:27:53.125 --> 00:27:53.625 high

NOTE Confidence: 0.9843146

00:27:53.970 --> 00:27:55.809 amplified cancers with a million

NOTE Confidence: 0.9843146

00:27:55.809 --> 00:27:56.850 or two million copies of

NOTE Confidence: 0.9843146

00:27:56.850 --> 00:27:58.390 HER2, and then you've got

NOTE Confidence: 0.9843146

00:27:58.609 --> 00:27:59.669 everything in between,

NOTE Confidence: 0.9438632

00:28:00.450 --> 00:28:02.369 moderate, lowish levels of HER2,

NOTE Confidence: 0.9438632

00:28:02.369 --> 00:28:03.990 a hundred thousand, fifty thousand

NOTE Confidence: 0.9438632

00:28:04.130 --> 00:28:05.890 HER2 proteins. And we call

NOTE Confidence: 0.9438632

00:28:05.890 --> 00:28:07.590 those HER2 low by immunohistochemistry.

NOTE Confidence: 0.98633784

00:28:08.049 --> 00:28:09.125 They're called one plus or

NOTE Confidence: 0.98633784

00:28:09.125 --> 00:28:10.085 two plus, but they're not

NOTE Confidence: 0.98633784

00:28:10.085 --> 00:28:10.585 amplified.

NOTE Confidence: 0.981475

00:28:10.885 --> 00:28:11.845 And then you have the

NOTE Confidence: 0.981475

00:28:11.845 --> 00:28:13.065 very negative,

NOTE Confidence: 0.9632773

00:28:13.445 --> 00:28:14.804 cancers, which we're gonna call

NOTE Confidence: 0.9632773

00:28:14.804 --> 00:28:15.625 HER2 negative.

NOTE Confidence: 0.9683304

00:28:17.524 --> 00:28:18.725 And it turns out that

NOTE Confidence: 0.9683304

00:28:18.725 --> 00:28:20.965 these lowish levels of HER2

NOTE Confidence: 0.9683304

00:28:20.965 --> 00:28:22.164 are actually very common. In

NOTE Confidence: 0.9683304

00:28:22.164 --> 00:28:23.730 fact, the majority of breast

NOTE Confidence: 0.9683304

00:28:23.730 --> 00:28:25.890 cancer has some level of

NOTE Confidence: 0.9683304

00:28:25.890 --> 00:28:26.790 HER2 expression.

NOTE Confidence: 0.97628504

00:28:28.690 --> 00:28:29.970 So given that, and given

NOTE Confidence: 0.97628504

00:28:29.970 --> 00:28:31.190 that we have this monoclonal

NOTE Confidence: 0.97628504

00:28:31.250 --> 00:28:32.390 antibody called trastuzumab

NOTE Confidence: 0.94086313

00:28:32.690 --> 00:28:33.750 that we know works,

NOTE Confidence: 0.9617853

00:28:34.530 --> 00:28:35.270 with chemotherapy,

NOTE Confidence: 0.78059983

00:28:36.765 --> 00:28:37.505 The NSABP,

NOTE Confidence: 0.98427093

00:28:38.765 --> 00:28:40.605 did this very large trial

NOTE Confidence: 0.98427093

00:28:40.605 --> 00:28:41.725 where they took patients with

NOTE Confidence: 0.98427093

00:28:41.725 --> 00:28:43.405 HER2 low early breast cancer,

NOTE Confidence: 0.98427093

00:28:43.405 --> 00:28:44.685 and they randomized them to

NOTE Confidence: 0.98427093

00:28:44.685 --> 00:28:46.545 chemotherapy with or without trastuzumab,

NOTE Confidence: 0.98427093

00:28:46.765 --> 00:28:47.725 the same thing that had

NOTE Confidence: 0.98427093

00:28:47.725 --> 00:28:49.025 shown to be very effective

NOTE Confidence: 0.98427093

00:28:49.165 --> 00:28:50.625 in HER2 amplified cancers.

NOTE Confidence: 0.95356876

00:28:51.710 --> 00:28:53.310 Unfortunately, this was completely not

NOTE Confidence: 0.95356876

00:28:53.310 --> 00:28:55.230 effective, so adding trastuzumab for

NOTE Confidence: 0.95356876

00:28:55.230 --> 00:28:56.830 these HER2 low cancers did

NOTE Confidence: 0.95356876

00:28:56.830 --> 00:28:57.810 absolutely nothing,

NOTE Confidence: 0.872733

00:28:58.350 --> 00:28:59.230 and you can see the

NOTE Confidence: 0.872733

00:28:59.230 --> 00:29:00.510 IDFS has a ratio is

NOTE Confidence: 0.872733

00:29:00.510 --> 00:29:02.290 point nine eight shows randomization

NOTE Confidence: 0.872733

00:29:02.510 --> 00:29:03.410 was very effective,

NOTE Confidence: 0.968991

00:29:04.030 --> 00:29:04.530 there,

NOTE Confidence: 0.99636555

00:29:05.150 --> 00:29:06.050 but no benefit.

NOTE Confidence: 0.90436745

00:29:07.445 --> 00:29:08.265 So then

NOTE Confidence: 0.8995647

00:29:11.125 --> 00:29:13.045 because trastuzumab works by, at

NOTE Confidence: 0.8995647

00:29:13.045 --> 00:29:14.325 least in part, by inhibiting

NOTE Confidence: 0.8995647

00:29:14.325 --> 00:29:15.145 HER2 signaling,

NOTE Confidence: 0.9575333

00:29:16.485 --> 00:29:18.165 it suggests that HER2 signaling

NOTE Confidence: 0.9575333

00:29:18.165 --> 00:29:19.285 really isn't important in these

NOTE Confidence: 0.9575333

00:29:19.285 --> 00:29:20.725 HER2 low cancers, so blocking

NOTE Confidence: 0.9575333

00:29:20.725 --> 00:29:21.785 it doesn't do anything.

NOTE Confidence: 0.9619348

00:29:22.830 --> 00:29:23.950 But it's still there. The

NOTE Confidence: 0.9619348

00:29:23.950 --> 00:29:24.910 HER2 is still there, and

NOTE Confidence: 0.9619348

00:29:24.910 --> 00:29:25.870 we have an antibody drug

NOTE Confidence: 0.9619348

00:29:25.870 --> 00:29:27.470 conjugate, which is basically looking

NOTE Confidence: 0.9619348

00:29:27.470 --> 00:29:28.669 for a target. And we

NOTE Confidence: 0.9619348

00:29:28.669 --> 00:29:30.289 use these antibody drug conjugates

NOTE Confidence: 0.9987006

00:29:30.669 --> 00:29:31.169 to

NOTE Confidence: 0.9975117

00:29:31.630 --> 00:29:32.910 to use the HER2 that's

NOTE Confidence: 0.9975117

00:29:32.910 --> 00:29:33.789 on the surface of these

NOTE Confidence: 0.9975117

00:29:33.789 --> 00:29:34.610 low cancers

NOTE Confidence: 0.9535528

00:29:34.924 --> 00:29:35.965 just as an address, a

NOTE Confidence: 0.9535528

00:29:35.965 --> 00:29:37.405 place, you know, a way

NOTE Confidence: 0.9535528

00:29:37.405 --> 00:29:39.664 to deliver our cytotoxic agent.

NOTE Confidence: 0.9751976

00:29:42.125 --> 00:29:43.804 So we now we had

NOTE Confidence: 0.9751976

00:29:43.804 --> 00:29:45.245 TDXD, and in the phase

NOTE Confidence: 0.9751976

00:29:45.245 --> 00:29:46.684 one trial of TDXD, we

NOTE Confidence: 0.9751976

00:29:46.684 --> 00:29:47.825 did have some cohorts

NOTE Confidence: 0.9640886

00:29:48.125 --> 00:29:49.745 of HER2 low cancers,

NOTE Confidence: 0.9386422

00:29:50.309 --> 00:29:51.190 and it actually looked like

NOTE Confidence: 0.9386422

00:29:51.190 --> 00:29:52.389 there was some activity in

NOTE Confidence: 0.9386422

00:29:52.389 --> 00:29:53.690 these HER2 low cancers.

NOTE Confidence: 0.90024996

00:29:54.070 --> 00:29:55.669 That prompted this very large

NOTE Confidence: 0.90024996

00:29:55.669 --> 00:29:56.169 trial

NOTE Confidence: 0.99709773

00:29:56.549 --> 00:29:57.049 of

NOTE Confidence: 0.98471016

00:29:57.429 --> 00:29:59.190 patients with metastatic HER2 low

NOTE Confidence: 0.98471016

00:29:59.190 --> 00:30:00.630 breast cancer. Again, the most

NOTE Confidence: 0.98471016

00:30:00.630 --> 00:30:02.090 common kind of breast cancer,

NOTE Confidence: 0.9768359

00:30:02.535 --> 00:30:03.975 there is sixty at least

NOTE Confidence: 0.9768359

00:30:03.975 --> 00:30:05.355 sixty percent of breast cancers,

NOTE Confidence: 0.92672604

00:30:06.055 --> 00:30:07.415 and randomized them to tDxD

NOTE Confidence: 0.92672604

00:30:07.415 --> 00:30:09.335 or chemotherapy because chemotherapy was

NOTE Confidence: 0.92672604

00:30:09.335 --> 00:30:10.935 a standard for these non

NOTE Confidence: 0.92672604

00:30:10.935 --> 00:30:12.315 HER2 amplified cancers,

NOTE Confidence: 0.98338205

00:30:12.695 --> 00:30:14.215 and tDxD was much better

NOTE Confidence: 0.98338205

00:30:14.215 --> 00:30:16.050 than chemotherapy in terms of

NOTE Confidence: 0.98338205

00:30:16.290 --> 00:30:16.790 survival,

NOTE Confidence: 0.90817577

00:30:17.410 --> 00:30:18.470 progression, response rate.

NOTE Confidence: 0.9665268

00:30:20.290 --> 00:30:21.170 And that led to the

NOTE Confidence: 0.9665268

00:30:21.170 --> 00:30:22.610 approval of tDxD in these

NOTE Confidence: 0.9665268

00:30:22.610 --> 00:30:24.370 HER2 low cancers, the first

NOTE Confidence: 0.9665268

00:30:24.370 --> 00:30:26.530 approval for of anything in

NOTE Confidence: 0.9665268

00:30:26.530 --> 00:30:27.590 HER2 low cancers,

NOTE Confidence: 0.95703566

00:30:27.970 --> 00:30:29.090 because it really wasn't a

NOTE Confidence: 0.95703566

00:30:29.090 --> 00:30:30.914 thing before the drug worked

NOTE Confidence: 0.95703566

00:30:30.914 --> 00:30:31.414 there.

NOTE Confidence: 0.96080273

00:30:32.274 --> 00:30:33.475 And it said, well, okay,

NOTE Confidence: 0.96080273

00:30:33.475 --> 00:30:34.674 if if it worked in

NOTE Confidence: 0.96080273

00:30:34.674 --> 00:30:36.115 these HER2 low cancers, and

NOTE Confidence: 0.96080273

00:30:36.115 --> 00:30:37.315 in fact, you know, I

NOTE Confidence: 0.96080273

00:30:37.315 --> 00:30:38.514 talked about that there's these

NOTE Confidence: 0.96080273

00:30:38.514 --> 00:30:39.875 one plus level and two

74

NOTE Confidence: 0.96080273

00:30:39.875 --> 00:30:40.695 plus levels.

NOTE Confidence: 0.9351204

00:30:42.034 --> 00:30:43.154 Two plus is more than

NOTE Confidence: 0.9351204

00:30:43.154 --> 00:30:43.815 one plus.

NOTE Confidence: 0.91171026

00:30:44.530 --> 00:30:45.890 If it in the trial,

NOTE Confidence: 0.91171026

00:30:45.890 --> 00:30:47.410 it actually the efficacy was

NOTE Confidence: 0.91171026

00:30:47.410 --> 00:30:48.610 pretty similar between the one

NOTE Confidence: 0.91171026

00:30:48.610 --> 00:30:49.490 plus and two plus. So

NOTE Confidence: 0.91171026

00:30:49.490 --> 00:30:50.610 that kind of begged the

NOTE Confidence: 0.91171026

00:30:50.610 --> 00:30:51.730 question, okay, well, can you

NOTE Confidence: 0.91171026

00:30:51.730 --> 00:30:53.170 go? How how low can

NOTE Confidence: 0.91171026

00:30:53.170 --> 00:30:53.830 you go?

NOTE Confidence: 0.9596975

00:30:54.130 --> 00:30:55.410 And in about twenty percent

NOTE Confidence: 0.9596975

00:30:55.410 --> 00:30:57.085 of cancers, there's, like, really

NOTE Confidence: 0.9596975

00:30:57.085 --> 00:30:59.404 marginal levels of HER2. So

NOTE Confidence: 0.9596975

00:30:59.404 --> 00:31:00.684 not even one plus, it's

NOTE Confidence: 0.9596975

00:31:00.684 --> 00:31:01.485 just like you can, you

NOTE Confidence: 0.9596975

00:31:01.485 --> 00:31:02.284 know, if you look real

NOTE Confidence: 0.9596975

00:31:02.284 --> 00:31:03.085 close, you can see a

NOTE Confidence: 0.9596975

00:31:03.085 --> 00:31:04.764 little smidgen of HER2 on

NOTE Confidence: 0.9596975

00:31:04.764 --> 00:31:05.965 the surface, but they're not

NOTE Confidence: 0.9596975

00:31:05.965 --> 00:31:06.465 completely

NOTE Confidence: 0.9830559

00:31:06.924 --> 00:31:08.304 stone cold zero.

NOTE Confidence: 0.9317905

00:31:08.684 --> 00:31:09.424 And so,

NOTE Confidence: 0.92909163

00:31:10.480 --> 00:31:11.919 we just so there are

NOTE Confidence: 0.92909163

00:31:11.919 --> 00:31:13.360 just another trial that was

NOTE Confidence: 0.92909163

00:31:13.360 --> 00:31:14.899 just presented over the summer.

NOTE Confidence: 0.9804674

00:31:15.759 --> 00:31:17.200 Same almost the same trial

NOTE Confidence: 0.9804674

00:31:17.200 --> 00:31:18.080 as I just showed you,

NOTE Confidence: 0.9804674

00:31:18.080 --> 00:31:18.740 but now,

NOTE Confidence: 0.938314

00:31:19.679 --> 00:31:21.059 slightly different setting,

NOTE Confidence: 0.96139455

00:31:21.440 --> 00:31:23.039 but now this trial included

NOTE Confidence: 0.96139455

00:31:23.039 --> 00:31:24.565 a population of these ultra

NOTE Confidence: 0.96139455

00:31:25.045 --> 00:31:26.325 what we're now calling ultra

NOTE Confidence: 0.96139455

00:31:26.325 --> 00:31:28.245 low cancers. So just the

NOTE Confidence: 0.96139455

00:31:28.245 --> 00:31:29.785 smallest amount of HER2,

NOTE Confidence: 0.9850676

00:31:30.325 --> 00:31:31.285 not enough to be one

NOTE Confidence: 0.9850676

00:31:31.285 --> 00:31:31.785 plus.

NOTE Confidence: 0.91757077

00:31:33.045 --> 00:31:35.305 And what was seen, surprisingly

NOTE Confidence: 0.91757077

00:31:35.445 --> 00:31:35.945 somewhat,

NOTE Confidence: 0.8733977

00:31:36.645 --> 00:31:37.465 was that,

NOTE Confidence: 0.9457615

00:31:38.210 --> 00:31:39.570 actually, tDxD was much better

NOTE Confidence: 0.9457615

00:31:39.570 --> 00:31:41.010 than chemotherapy in these ultra

NOTE Confidence: 0.9457615

00:31:41.010 --> 00:31:42.050 low cancers. Seemed like the

NOTE Confidence: 0.9457615

00:31:42.050 --> 00:31:43.250 benefit was pretty similar to

NOTE Confidence: 0.9457615

00:31:43.250 --> 00:31:43.970 what we saw with the

NOTE Confidence: 0.9457615

00:31:43.970 --> 00:31:44.710 low cancers.

NOTE Confidence: 0.91219753

00:31:45.890 --> 00:31:47.090 Survival also seemed to be

NOTE Confidence: 0.91219753

00:31:47.090 --> 00:31:48.050 trending in the right direction,

NOTE Confidence: 0.91219753

00:31:48.050 --> 00:31:48.950 although immature.

NOTE Confidence: 0.94720834

00:31:49.410 --> 00:31:50.370 But I think what was

NOTE Confidence: 0.94720834

00:31:50.370 --> 00:31:52.035 particularly important or what was

NOTE Confidence: 0.94720834

00:31:52.035 --> 00:31:53.395 striking was that response rate

NOTE Confidence: 0.94720834

00:31:53.395 --> 00:31:54.595 in these ultra low cancers

NOTE Confidence: 0.94720834

00:31:54.595 --> 00:31:55.715 was sixty two percent. These

NOTE Confidence: 0.94720834

00:31:55.715 --> 00:31:56.855 were pretreated patients,

NOTE Confidence: 0.95936614

00:31:57.555 --> 00:31:58.055 and,

NOTE Confidence: 0.94342226

00:31:59.235 --> 00:32:00.435 you can see that it's

NOTE Confidence: 0.94342226

00:32:00.435 --> 00:32:01.555 actually the response rate in

NOTE Confidence: 0.94342226

00:32:01.555 --> 00:32:02.435 the ultra low is pretty

NOTE Confidence: 0.94342226

00:32:02.435 --> 00:32:03.955 similar to the HER2 low.

NOTE Confidence: 0.94342226

00:32:04.275 --> 00:32:05.315 And again, we can kinda

NOTE Confidence: 0.94342226

00:32:05.315 --> 00:32:06.510 talk about why that that

NOTE Confidence: 0.94342226

00:32:06.510 --> 00:32:07.250 might be,

NOTE Confidence: 0.9984202

00:32:07.710 --> 00:32:08.690 towards the end.

NOTE Confidence: 0.94733834

00:32:11.150 --> 00:32:12.510 It's funny, you know, when,

NOTE Confidence: 0.94733834

00:32:12.750 --> 00:32:14.030 in some of this original

NOTE Confidence: 0.94733834

00:32:14.030 --> 00:32:15.230 steering committee meetings of of

NOTE Confidence: 0.94733834

00:32:15.230 --> 00:32:15.730 TDXD,

NOTE Confidence: 0.90854234

00:32:16.350 --> 00:32:17.950 when the original ultra low

NOTE Confidence: 0.90854234

00:32:17.950 --> 00:32:18.750 date I'm sorry, when the

NOTE Confidence: 0.90854234

00:32:18.750 --> 00:32:20.110 original HER2 low data came

NOTE Confidence: 0.90854234

00:32:20.110 --> 00:32:20.610 out,

NOTE Confidence: 0.93317074

00:32:20.955 --> 00:32:22.154 people that I remember one

NOTE Confidence: 0.93317074

00:32:22.154 --> 00:32:23.235 specific person raising their hand

NOTE Confidence: 0.93317074

00:32:23.235 --> 00:32:23.995 and say, why don't we

NOTE Confidence: 0.93317074

00:32:23.995 --> 00:32:24.955 look at HER two zero

NOTE Confidence: 0.93317074

00:32:24.955 --> 00:32:25.914 cancers? And it was like,

NOTE Confidence: 0.93317074

00:32:25.914 --> 00:32:27.434 everybody kinda laughed because it's

NOTE Confidence: 0.93317074

00:32:27.434 --> 00:32:28.554 a HER two targeted drug.

NOTE Confidence: 0.93317074

00:32:28.554 --> 00:32:29.434 Of course, it's not gonna

NOTE Confidence: 0.93317074

00:32:29.434 --> 00:32:30.315 work in HER two zero

NOTE Confidence: 0.93317074

00:32:30.315 --> 00:32:30.815 cancers.

NOTE Confidence: 0.973676

00:32:31.914 --> 00:32:33.034 But it seems to work

NOTE Confidence: 0.973676

00:32:33.034 --> 00:32:34.075 in these ultra low cancers,

NOTE Confidence: 0.973676

00:32:34.075 --> 00:32:35.034 and now there's a question

NOTE Confidence: 0.973676

00:32:35.034 --> 00:32:36.270 of could it even work

NOTE Confidence: 0.973676

00:32:36.270 --> 00:32:37.870 with pretty undetectable levels of

NOTE Confidence: 0.973676

00:32:37.870 --> 00:32:38.370 HER2?

NOTE Confidence: 0.94859797

00:32:39.150 --> 00:32:41.250 And to test that, Adrianna

NOTE Confidence: 0.94859797

00:32:41.310 --> 00:32:42.370 Khan is doing,

NOTE Confidence: 0.99783623

00:32:42.830 --> 00:32:43.890 this IIT

NOTE Confidence: 0.88283587

00:32:44.270 --> 00:32:46.270 looking specifically at HER2 zero

NOTE Confidence: 0.88283587

00:32:46.270 --> 00:32:46.770 cancers,

NOTE Confidence: 0.95394397

00:32:47.070 --> 00:32:48.050 treating with TDXD,

NOTE Confidence: 0.94926125

00:32:48.350 --> 00:32:49.550 and then using some of

NOTE Confidence: 0.94926125

00:32:49.550 --> 00:32:50.385 David Rymm's,

NOTE Confidence: 0.8956775

00:32:51.025 --> 00:32:52.165 you know, very sophisticated,

NOTE Confidence: 0.9753584

00:32:53.345 --> 00:32:54.865 assays for HER2 to see

NOTE Confidence: 0.9753584

00:32:54.865 --> 00:32:55.985 if you can really identify

NOTE Confidence: 0.9753584

00:32:55.985 --> 00:32:57.365 whether there really is a

NOTE Confidence: 0.9753584

00:32:57.425 --> 00:32:59.505 threshold of HER2 expression below

NOTE Confidence: 0.9753584

00:32:59.505 --> 00:33:01.205 which you don't see activity.

NOTE Confidence: 0.9753584

00:33:01.425 --> 00:33:03.025 So that study hopefully will

NOTE Confidence: 0.9753584

00:33:03.025 --> 00:33:04.645 open, very soon.

NOTE Confidence: 0.9525379

00:33:05.630 --> 00:33:06.590 So what have we learned

NOTE Confidence: 0.9525379

00:33:06.590 --> 00:33:07.809 about HER2 ADCs?

NOTE Confidence: 0.98413444

00:33:08.909 --> 00:33:09.570 So clearly,

NOTE Confidence: 0.8544472

00:33:10.429 --> 00:33:12.669 they're superior to trastuzumab and

NOTE Confidence: 0.8544472

00:33:12.669 --> 00:33:13.169 chemotherapy,

NOTE Confidence: 0.98893124

00:33:13.630 --> 00:33:14.669 both in early stage and

NOTE Confidence: 0.98893124

00:33:14.669 --> 00:33:15.649 late stage disease.

NOTE Confidence: 0.96970177

00:33:17.149 --> 00:33:17.649 They've,

NOTE Confidence: 0.93259525

00:33:18.085 --> 00:33:19.945 TDXD is better, more efficacious

NOTE Confidence: 0.93259525

00:33:20.005 --> 00:33:21.205 at least than TDM one,

NOTE Confidence: 0.93259525

00:33:21.205 --> 00:33:22.165 but it also has more

NOTE Confidence: 0.93259525

00:33:22.165 --> 00:33:23.285 toxicity. And I think that

NOTE Confidence: 0.93259525

00:33:23.285 --> 00:33:25.205 like likely reflects the trade

NOTE Confidence: 0.93259525

00:33:25.205 --> 00:33:27.765 off, for these cleavable linkers

NOTE Confidence: 0.93259525

00:33:27.765 --> 00:33:29.385 versus non cleavable linkers.

NOTE Confidence: 0.993349

00:33:29.940 --> 00:33:31.480 You get the bystander effect,

NOTE Confidence: 0.993349

00:33:31.779 --> 00:33:33.299 but the bystander effect also

NOTE Confidence: 0.993349

00:33:33.299 --> 00:33:33.799 can,

NOTE Confidence: 0.94601643

00:33:35.059 --> 00:33:36.919 hit normal tissue, not just,

NOTE Confidence: 0.92860043

00:33:38.179 --> 00:33:39.480 to other tumor cells.

NOTE Confidence: 0.95867056

00:33:40.659 --> 00:33:41.700 And, you know, this very

NOTE Confidence: 0.95867056

00:33:41.700 --> 00:33:43.299 interesting finding of tDxD being

NOTE Confidence: 0.95867056

00:33:43.299 --> 00:33:44.925 affected even in minimal levels

NOTE Confidence: 0.95867056

00:33:44.925 --> 00:33:46.445 of HER2, which may be

NOTE Confidence: 0.95867056

00:33:46.445 --> 00:33:47.885 because of this bystander effect,

NOTE Confidence: 0.95867056

00:33:47.885 --> 00:33:49.345 although we haven't proven that.

NOTE Confidence: 0.9669518

00:33:50.685 --> 00:33:51.645 So I just wanna take

NOTE Confidence: 0.9669518

00:33:51.645 --> 00:33:52.225 a slight,

NOTE Confidence: 0.9452431

00:33:56.845 --> 00:33:58.890 divergence here and and and

NOTE Confidence: 0.9452431

00:33:58.890 --> 00:34:00.190 bring up this question,

NOTE Confidence: 0.9544178

00:34:00.570 --> 00:34:01.370 just because I think it's

NOTE Confidence: 0.9544178

00:34:01.370 --> 00:34:02.110 really cool,

NOTE Confidence: 0.97102666

00:34:02.650 --> 00:34:04.250 of the fact that given

NOTE Confidence: 0.97102666

00:34:04.250 --> 00:34:05.930 that we have these very

NOTE Confidence: 0.97102666

00:34:05.930 --> 00:34:07.450 effective HER2 therapies, you know,

NOTE Confidence: 0.97102666

00:34:07.450 --> 00:34:08.969 progression free survival of thirty

NOTE Confidence: 0.97102666

00:34:08.969 --> 00:34:10.994 months and, you know, very

NOTE Confidence: 0.97102666

00:34:10.994 --> 00:34:12.275 long durations of response. And

NOTE Confidence: 0.97102666

00:34:12.275 --> 00:34:13.795 we actually have there's actually

NOTE Confidence: 0.97102666

00:34:13.795 --> 00:34:15.075 eight drugs now approved for

NOTE Confidence: 0.97102666

00:34:15.075 --> 00:34:16.994 HER2 positive disease, different mechanism

NOTE Confidence: 0.97102666

00:34:16.994 --> 00:34:17.654 of action.

NOTE Confidence: 0.99775773

00:34:18.515 --> 00:34:19.635 So given all of these

NOTE Confidence: 0.99775773

00:34:19.635 --> 00:34:20.934 highly effective drugs,

NOTE Confidence: 0.9886516

00:34:22.610 --> 00:34:24.130 can we really move the

NOTE Confidence: 0.9886516

00:34:24.130 --> 00:34:25.570 needle of treating patients with

NOTE Confidence: 0.9886516

00:34:25.570 --> 00:34:27.010 metastatic disease and go away

NOTE Confidence: 0.9886516

00:34:27.010 --> 00:34:28.690 from treating in a non

NOTE Confidence: 0.9886516

00:34:28.690 --> 00:34:29.810 curative setting, which is the

NOTE Confidence: 0.9886516

00:34:29.810 --> 00:34:30.930 way we do it now,

NOTE Confidence: 0.9886516

00:34:31.170 --> 00:34:32.450 and move it, to a

NOTE Confidence: 0.9886516

00:34:32.450 --> 00:34:33.430 curative setting?

NOTE Confidence: 0.99352586

00:34:33.810 --> 00:34:35.250 And by for those of

NOTE Confidence: 0.99352586

00:34:35.250 --> 00:34:36.610 you who don't treat patients,

NOTE Confidence: 0.99352586

00:34:36.850 --> 00:34:38.150 with metastatic disease,

NOTE Confidence: 0.98007673

00:34:38.765 --> 00:34:40.125 nowadays, we treat with one

NOTE Confidence: 0.98007673

00:34:40.125 --> 00:34:41.165 treatment. We wait for the

NOTE Confidence: 0.98007673

00:34:41.165 --> 00:34:42.445 cancer to become resistant, and

NOTE Confidence: 0.98007673

00:34:42.445 --> 00:34:43.085 then we switch to the

NOTE Confidence: 0.98007673

00:34:43.085 --> 00:34:44.125 other drug. And we're we

NOTE Confidence: 0.98007673

00:34:44.125 --> 00:34:45.565 try to string along our

NOTE Confidence: 0.98007673

00:34:45.565 --> 00:34:46.065 treatments,

NOTE Confidence: 0.9787546

00:34:46.844 --> 00:34:49.005 to keep patients with disease

NOTE Confidence: 0.9787546

00:34:49.005 --> 00:34:50.205 control as long as possible

NOTE Confidence: 0.9787546

00:34:50.205 --> 00:34:50.925 because we know we can't

NOTE Confidence: 0.9787546

00:34:50.925 --> 00:34:52.210 cure them. So there's no

NOTE Confidence: 0.9787546

00:34:52.210 --> 00:34:53.330 use giving a lot of,

NOTE Confidence: 0.9787546

00:34:53.330 --> 00:34:54.610 you know, kind of piling

NOTE Confidence: 0.9787546

00:34:54.610 --> 00:34:56.130 on your therapies. You wanna

NOTE Confidence: 0.9787546

00:34:56.130 --> 00:34:57.010 stretch them out so they

NOTE Confidence: 0.9787546

00:34:57.010 --> 00:34:58.230 last as long as possible.

NOTE Confidence: 0.96718675

00:34:59.330 --> 00:35:01.170 But by doing that, generally,

NOTE Confidence: 0.96718675

00:35:01.170 --> 00:35:02.530 you're you're gonna get resistance

NOTE Confidence: 0.96718675

00:35:02.530 --> 00:35:03.570 because you're only giving one

NOTE Confidence: 0.96718675

00:35:03.570 --> 00:35:04.770 drug, and, eventually, the cancer

NOTE Confidence: 0.96718675

00:35:04.770 --> 00:35:05.650 is gonna learn to become

NOTE Confidence: 0.96718675

00:35:05.650 --> 00:35:07.335 resistant. And that's why metastatic

NOTE Confidence: 0.96718675

00:35:07.395 --> 00:35:08.835 disease is typically felt to

NOTE Confidence: 0.96718675

00:35:08.835 --> 00:35:09.735 be not curable.

NOTE Confidence: 0.9850716

00:35:10.114 --> 00:35:11.315 So maybe that's not true,

NOTE Confidence: 0.9850716

00:35:11.315 --> 00:35:12.915 though, given the fact that

NOTE Confidence: 0.9850716

00:35:12.915 --> 00:35:14.275 we have these highly effective

NOTE Confidence: 0.9850716

00:35:14.275 --> 00:35:14.775 drugs.

NOTE Confidence: 0.9305545

00:35:15.395 --> 00:35:16.135 And so,

NOTE Confidence: 0.9925322

00:35:17.955 --> 00:35:19.350 a trial that's gonna be

NOTE Confidence: 0.9925322

00:35:19.510 --> 00:35:21.190 launched here at Yale shortly

NOTE Confidence: 0.9925322

00:35:21.190 --> 00:35:22.710 that's being run-in this consortium

NOTE Confidence: 0.9925322

00:35:22.710 --> 00:35:23.530 called the TBCRC,

NOTE Confidence: 0.96927714

00:35:24.870 --> 00:35:26.150 is trying to address, can

NOTE Confidence: 0.96927714

00:35:26.150 --> 00:35:27.850 we cure HER2 positive metastatic

NOTE Confidence: 0.96927714

00:35:27.989 --> 00:35:28.489 disease?

NOTE Confidence: 0.96606797

00:35:29.190 --> 00:35:30.870 So to do this, we're

NOTE Confidence: 0.96606797

00:35:30.870 --> 00:35:32.310 gonna deviate from the normal

NOTE Confidence: 0.96606797

00:35:32.310 --> 00:35:34.150 practice and take newly diagnosed

NOTE Confidence: 0.96606797

00:35:34.150 --> 00:35:36.005 patients and treat them with,

NOTE Confidence: 0.96395886

00:35:37.344 --> 00:35:38.964 twelve weeks of of ataxane

NOTE Confidence: 0.96395886

00:35:39.105 --> 00:35:40.704 and and trastuzumab, and then

NOTE Confidence: 0.96395886

00:35:40.704 --> 00:35:42.625 give them TDXD for eighteen

NOTE Confidence: 0.96395886

00:35:42.625 --> 00:35:44.244 weeks, and then give TDM

NOTE Confidence: 0.96395886

00:35:44.305 --> 00:35:46.065 one with the kinase inhibitor,

NOTE Confidence: 0.96395886

00:35:46.065 --> 00:35:47.184 and then give more kinase

NOTE Confidence: 0.96395886

00:35:47.184 --> 00:35:47.684 inhibitor,

NOTE Confidence: 0.9583566

00:35:48.224 --> 00:35:49.344 for about a year, and

NOTE Confidence: 0.9583566

00:35:49.344 --> 00:35:50.730 then just stop treatment and

NOTE Confidence: 0.9583566

00:35:50.730 --> 00:35:52.730 just follow patients with c

NOTE Confidence: 0.9583566

00:35:52.730 --> 00:35:54.010 tDNA and c and CAT

NOTE Confidence: 0.9583566

00:35:54.010 --> 00:35:55.469 scans with the idea

NOTE Confidence: 0.9751693

00:35:55.930 --> 00:35:57.610 that we're gonna try to

NOTE Confidence: 0.9751693

00:35:57.610 --> 00:35:59.130 improve the percentage of patients

NOTE Confidence: 0.9751693

00:35:59.130 --> 00:36:00.650 who don't have progression after

NOTE Confidence: 0.9751693

00:36:00.650 --> 00:36:02.415 four years essentially are cured.

NOTE Confidence: 0.9353804

00:36:03.055 --> 00:36:04.355 You know, this is way

NOTE Confidence: 0.9353804

00:36:04.495 --> 00:36:06.175 leukemias are treated, lymphomas are

NOTE Confidence: 0.9353804

00:36:06.175 --> 00:36:07.455 treated, you pile on mass

NOTE Confidence: 0.9353804

00:36:07.614 --> 00:36:08.655 you know, lots of different

NOTE Confidence: 0.9353804

00:36:08.655 --> 00:36:09.155 drugs,

NOTE Confidence: 0.8219368

00:36:09.855 --> 00:36:10.655 you know, in a very

NOTE Confidence: 0.8219368

00:36:10.655 --> 00:36:11.715 intensive way,

NOTE Confidence: 0.96670616

00:36:12.175 --> 00:36:13.455 even though kind of leukemia

NOTE Confidence: 0.96670616

00:36:13.455 --> 00:36:14.515 is kind of metastatic,

NOTE Confidence: 0.99233776

00:36:15.279 --> 00:36:16.400 to begin with, but it

NOTE Confidence: 0.99233776

00:36:16.400 --> 00:36:17.680 it works. Can we do

NOTE Confidence: 0.99233776

00:36:17.680 --> 00:36:19.059 that for a solid cancer?

NOTE Confidence: 0.99233776

00:36:19.279 --> 00:36:20.239 In the past, we really

NOTE Confidence: 0.99233776

00:36:20.239 --> 00:36:21.519 just didn't have the effective

NOTE Confidence: 0.99233776

00:36:21.519 --> 00:36:22.960 therapies to do that. Now

NOTE Confidence: 0.99233776

00:36:22.960 --> 00:36:23.779 that we do,

NOTE Confidence: 0.9619982

00:36:24.559 --> 00:36:26.099 can we change the paradigm?

NOTE Confidence: 0.9619982

00:36:26.160 --> 00:36:27.279 So this is a trial

NOTE Confidence: 0.9619982

00:36:27.279 --> 00:36:28.480 that should open soon here,

NOTE Confidence: 0.9619982

00:36:28.480 --> 00:36:29.359 and and, again, I think

NOTE Confidence: 0.9619982

00:36:29.359 --> 00:36:30.614 it's really worth exploring. It

NOTE Confidence: 0.9619982

00:36:30.614 --> 00:36:31.895 may be wrong, may not

NOTE Confidence: 0.9619982

00:36:31.895 --> 00:36:33.355 work, but it's worth trying.

NOTE Confidence: 0.99870837

00:36:34.855 --> 00:36:35.355 Okay.

NOTE Confidence: 0.9254828

00:36:35.895 --> 00:36:36.875 Enough of HER2.

NOTE Confidence: 0.92049587

00:36:37.335 --> 00:36:39.755 Other HER2 there other targets.

NOTE Confidence: 0.92049587

00:36:39.975 --> 00:36:41.495 So I guess I didn't

NOTE Confidence: 0.92049587

00:36:41.495 --> 00:36:42.295 realize I have a slide

NOTE Confidence: 0.92049587

00:36:42.295 --> 00:36:44.395 on HER2 here. So when

NOTE Confidence: 0.96578425

00:36:44.850 --> 00:36:45.350 when,

NOTE Confidence: 0.9959257

00:36:45.810 --> 00:36:46.550 you know,

NOTE Confidence: 0.95190495

00:36:46.850 --> 00:36:48.310 when we were, you know,

NOTE Confidence: 0.95190495

00:36:48.450 --> 00:36:49.250 those of us in the

NOTE Confidence: 0.95190495

00:36:49.250 --> 00:36:50.930 field were working on HER2

NOTE Confidence: 0.95190495

00:36:50.930 --> 00:36:52.210 ADCs, we said, hey. This

NOTE Confidence: 0.95190495

00:36:52.210 --> 00:36:53.170 is great. These drugs are

NOTE Confidence: 0.95190495

00:36:53.170 --> 00:36:54.230 working really well,

NOTE Confidence: 0.9779715

00:36:55.250 --> 00:36:56.690 but it's probably just because

NOTE Confidence: 0.9779715

00:36:56.690 --> 00:36:58.290 HER2 is just this amazing

NOTE Confidence: 0.9779715

00:36:58.290 --> 00:36:59.430 target for an ADC.

NOTE Confidence: 0.985167

00:36:59.825 --> 00:37:00.945 Why is it amazing for

NOTE Confidence: 0.985167

00:37:00.945 --> 00:37:02.465 ADCs? Well, first, you have

NOTE Confidence: 0.985167

00:37:02.465 --> 00:37:03.265 tons of it on the

NOTE Confidence: 0.985167

00:37:03.265 --> 00:37:04.565 surface. And so the more

NOTE Confidence: 0.94553095

00:37:05.345 --> 00:37:06.145 protein you have on the

NOTE Confidence: 0.94553095

00:37:06.145 --> 00:37:08.065 surface, the more ADCs combined,

NOTE Confidence: 0.94553095

00:37:08.065 --> 00:37:09.665 and therefore, the more the

NOTE Confidence: 0.94553095

00:37:09.665 --> 00:37:10.545 more ADC you can get

NOTE Confidence: 0.94553095

00:37:10.545 --> 00:37:11.525 inside the cell.

NOTE Confidence: 0.98989034

00:37:12.640 --> 00:37:13.920 The normal tissue tended to

NOTE Confidence: 0.98989034

00:37:13.920 --> 00:37:14.960 have very low amounts of

NOTE Confidence: 0.98989034

00:37:14.960 --> 00:37:15.460 HER2.

NOTE Confidence: 0.9642385

00:37:15.840 --> 00:37:17.760 The internalization of HER2 is

NOTE Confidence: 0.9642385

00:37:17.760 --> 00:37:18.960 very fast, and it doesn't

NOTE Confidence: 0.9642385

00:37:18.960 --> 00:37:20.080 down regulate. And you can

NOTE Confidence: 0.9642385

00:37:20.080 --> 00:37:21.380 see in this photomicrograph,

NOTE Confidence: 0.95184755

00:37:21.840 --> 00:37:23.119 if you coat the cell

NOTE Confidence: 0.95184755

00:37:23.119 --> 00:37:24.994 with a fluorescent HER, trastuzumab

NOTE Confidence: 0.9644577

00:37:25.454 --> 00:37:26.414 and then wait a few

NOTE Confidence: 0.9644577

00:37:26.414 --> 00:37:27.775 hours, all of it gets

NOTE Confidence: 0.9644577

00:37:27.775 --> 00:37:28.974 inside the cell. So all

NOTE Confidence: 0.9644577

00:37:28.974 --> 00:37:30.994 those HER2s are getting internalized,

NOTE Confidence: 0.9644577

00:37:31.055 --> 00:37:32.255 which if there's a ADC

NOTE Confidence: 0.9644577

00:37:32.255 --> 00:37:33.535 attached, it'll bring it with

NOTE Confidence: 0.9644577

00:37:33.535 --> 00:37:35.295 it. So internalization is important

NOTE Confidence: 0.9644577

00:37:35.295 --> 00:37:37.350 for ADCs, and the tumors

NOTE Confidence: 0.9644577

00:37:37.350 --> 00:37:38.650 are addicted to their HER2.

NOTE Confidence: 0.9644577

00:37:38.710 --> 00:37:39.910 As I said, it's the

NOTE Confidence: 0.9644577

00:37:39.910 --> 00:37:41.430 HER2 that's driving these cells,

NOTE Confidence: 0.9644577

00:37:41.430 --> 00:37:42.550 so they really need the

NOTE Confidence: 0.9644577

00:37:42.550 --> 00:37:43.830 signaling. So it's really hard

NOTE Confidence: 0.9644577

00:37:43.830 --> 00:37:44.870 for them to down regulate

NOTE Confidence: 0.9644577

00:37:44.870 --> 00:37:45.930 as a way to escape

NOTE Confidence: 0.9644577

00:37:46.070 --> 00:37:47.030 the effects of a d

NOTE Confidence: 0.9644577

00:37:47.110 --> 00:37:47.850 of the ADC.

NOTE Confidence: 0.9780906

00:37:48.150 --> 00:37:49.430 So we thought, hey. It

NOTE Confidence: 0.9780906

00:37:49.430 --> 00:37:50.390 all makes sense that these

NOTE Confidence: 0.9780906

00:37:50.390 --> 00:37:51.350 drugs are gonna work in

NOTE Confidence: 0.9780906

00:37:51.350 --> 00:37:51.850 HER2,

NOTE Confidence: 0.98338526

00:37:52.385 --> 00:37:53.265 but they're probably not gonna

NOTE Confidence: 0.98338526

00:37:53.265 --> 00:37:54.545 work other with other targets

NOTE Confidence: 0.98338526

00:37:54.545 --> 00:37:55.585 because the other targets don't

NOTE Confidence: 0.98338526

00:37:55.585 --> 00:37:56.805 have all these great characteristics.

NOTE Confidence: 0.9374312

00:37:57.984 --> 00:37:59.585 Fortunately, I was wrong, as,

NOTE Confidence: 0.9374312

00:37:59.905 --> 00:38:01.204 as often is the case.

NOTE Confidence: 0.90342885

00:38:01.505 --> 00:38:03.285 We now have the twelve,

NOTE Confidence: 0.90342885

00:38:03.344 --> 00:38:05.285 I think, roughly twelve ADCs,

NOTE Confidence: 0.95638806

00:38:09.340 --> 00:38:10.460 that are FDA approved, and

NOTE Confidence: 0.95638806

00:38:10.460 --> 00:38:11.340 you can see across a

NOTE Confidence: 0.95638806

00:38:11.340 --> 00:38:12.800 wide range of targets.

NOTE Confidence: 0.99222106

00:38:13.580 --> 00:38:14.800 And I forgot to mention,

NOTE Confidence: 0.87189436

00:38:15.820 --> 00:38:16.320 TDXD,

NOTE Confidence: 0.99922085

00:38:17.340 --> 00:38:18.560 just got approved yesterday

NOTE Confidence: 0.9681767

00:38:18.940 --> 00:38:20.460 for treating those ultra low

NOTE Confidence: 0.9681767

00:38:20.460 --> 00:38:21.844 patients, so that's kind of

NOTE Confidence: 0.9681767

00:38:21.844 --> 00:38:23.444 exciting. Another group of cancers

NOTE Confidence: 0.9681767

00:38:23.444 --> 00:38:24.265 to be treated.

NOTE Confidence: 0.9661305

00:38:24.565 --> 00:38:25.364 But you can see we

NOTE Confidence: 0.9661305

00:38:25.364 --> 00:38:27.785 have, activity of ADCs across

NOTE Confidence: 0.9661305

00:38:27.844 --> 00:38:29.704 liquid tumors and solid tumors,

NOTE Confidence: 0.99941766

00:38:30.885 --> 00:38:32.344 with a broad range of

NOTE Confidence: 0.98090345

00:38:32.724 --> 00:38:34.025 of of, targets.

NOTE Confidence: 0.9648482

00:38:34.400 --> 00:38:35.520 So I'll talk of just

NOTE Confidence: 0.9648482

00:38:35.520 --> 00:38:36.800 a brief, in the last

NOTE Confidence: 0.9648482

00:38:36.800 --> 00:38:37.920 few minutes, some of the

NOTE Confidence: 0.9648482

00:38:37.920 --> 00:38:38.820 other targets.

NOTE Confidence: 0.86761296

00:38:40.080 --> 00:38:41.840 Trope two is being tested

NOTE Confidence: 0.86761296

00:38:41.840 --> 00:38:43.040 and is is is been

NOTE Confidence: 0.86761296

00:38:43.040 --> 00:38:44.320 validated in breast cancer. It's

NOTE Confidence: 0.86761296

00:38:44.320 --> 00:38:45.780 being tested in other cancers.

NOTE Confidence: 0.80239314

00:38:47.585 --> 00:38:48.944 So COP two is a,

NOTE Confidence: 0.95383483

00:38:49.344 --> 00:38:50.944 cell surface protein that's pretty

NOTE Confidence: 0.95383483

00:38:50.944 --> 00:38:52.305 widely expressed in breast cancer

NOTE Confidence: 0.95383483

00:38:52.305 --> 00:38:53.684 associated with the worst prognosis.

NOTE Confidence: 0.99174

00:38:54.625 --> 00:38:55.984 And there's a drug called

NOTE Confidence: 0.99174

00:38:55.984 --> 00:38:56.484 sacituzumab

NOTE Confidence: 0.9054693

00:38:56.785 --> 00:38:58.244 gobletikin, which is an ADC,

NOTE Confidence: 0.868559

00:38:59.184 --> 00:39:00.325 also with the topoisomerase

NOTE Confidence: 0.96589595

00:39:00.625 --> 00:39:02.305 pay payload, and it it's

NOTE Confidence: 0.96589595

00:39:02.305 --> 00:39:03.739 set up its linker a

NOTE Confidence: 0.96589595

00:39:03.739 --> 00:39:05.020 little differently. So in addition

NOTE Confidence: 0.96589595

00:39:05.020 --> 00:39:06.700 to being cleavable inside the

NOTE Confidence: 0.96589595

00:39:06.700 --> 00:39:08.319 cell, it's also cleavable

NOTE Confidence: 0.9897049

00:39:08.700 --> 00:39:09.200 by,

NOTE Confidence: 0.9527003

00:39:09.660 --> 00:39:11.500 low pH environments outside the

NOTE Confidence: 0.9527003

00:39:11.500 --> 00:39:13.020 cell, so it can it

NOTE Confidence: 0.9527003

00:39:13.020 --> 00:39:14.460 can release the payload both

NOTE Confidence: 0.9527003

00:39:14.460 --> 00:39:14.960 extracellularly

NOTE Confidence: 0.98157

00:39:15.260 --> 00:39:15.920 and intracellularly.

NOTE Confidence: 0.97482675

00:39:18.055 --> 00:39:19.495 And it's been tested in

NOTE Confidence: 0.97482675

00:39:19.495 --> 00:39:21.094 triple negative breast cancer compared

NOTE Confidence: 0.97482675

00:39:21.094 --> 00:39:22.695 to chemo where it's much

NOTE Confidence: 0.97482675

00:39:22.695 --> 00:39:24.215 better, and it's approved in

NOTE Confidence: 0.97482675

00:39:24.215 --> 00:39:24.955 that setting.

NOTE Confidence: 0.9482628

00:39:25.975 --> 00:39:27.735 And its toxicity profile is

NOTE Confidence: 0.9482628

00:39:27.735 --> 00:39:28.775 quite is different,

NOTE Confidence: 0.8906864

00:39:29.175 --> 00:39:30.075 than PDXDs.

NOTE Confidence: 0.95381755

00:39:30.880 --> 00:39:32.020 It's all myelosuppression

NOTE Confidence: 0.93535376

00:39:32.640 --> 00:39:34.099 and a little GI toxicity.

NOTE Confidence: 0.9446417

00:39:35.280 --> 00:39:36.020 And interestingly,

NOTE Confidence: 0.75959957

00:39:36.880 --> 00:39:37.380 datapodimab

NOTE Confidence: 0.83972394

97

00:39:37.920 --> 00:39:39.840 daroxetine, which is another trope

NOTE Confidence: 0.83972394

00:39:39.840 --> 00:39:40.580 two ADC,

NOTE Confidence: 0.90869004

00:39:41.280 --> 00:39:42.739 same antibody as sacituzumab,

NOTE Confidence: 0.9654208

00:39:43.415 --> 00:39:44.695 same class of payload as

NOTE Confidence: 0.9654208

00:39:44.695 --> 00:39:45.195 sacituzumab,

NOTE Confidence: 0.8563711

00:39:45.974 --> 00:39:47.035 but with a daroxican

NOTE Confidence: 0.99240255

00:39:47.655 --> 00:39:48.775 linker, which is a little

NOTE Confidence: 0.99240255

00:39:48.775 --> 00:39:49.275 different.

NOTE Confidence: 0.91022027

00:39:49.655 --> 00:39:50.635 It's it's

NOTE Confidence: 0.9764343

00:39:50.935 --> 00:39:53.355 purely protease cleavable. It's not

NOTE Confidence: 0.9764343

00:39:53.494 --> 00:39:54.474 pH cleavable.

NOTE Confidence: 0.96176136

00:39:55.494 --> 00:39:56.535 And this is an active

NOTE Confidence: 0.96176136

00:39:56.535 --> 00:39:58.020 drug. In our in the

NOTE Confidence: 0.96176136

00:39:58.020 --> 00:39:59.300 phase one trial, we showed

NOTE Confidence: 0.96176136

00:39:59.300 --> 00:40:00.760 that it was active and,

NOTE Confidence: 0.9633948

00:40:01.140 --> 00:40:02.020 even in patients who had

NOTE Confidence: 0.9633948

00:40:02.020 --> 00:40:03.540 already progressed on sacituzumab, there

NOTE Confidence: 0.9633948

00:40:03.540 --> 00:40:04.440 was some activity.

NOTE Confidence: 0.9558705

00:40:05.540 --> 00:40:07.880 But interestingly, again, same payload

NOTE Confidence: 0.9558705

00:40:08.100 --> 00:40:10.280 essentially, same antibody. The toxicity

NOTE Confidence: 0.9558705

00:40:10.420 --> 00:40:12.040 is completely different. So there's

NOTE Confidence: 0.9558705

00:40:12.204 --> 00:40:13.344 virtually no myelosuppression

NOTE Confidence: 0.83535784

00:40:13.964 --> 00:40:14.785 with dapotumab,

NOTE Confidence: 0.9455327

00:40:15.645 --> 00:40:17.805 stomatitis is the toxicity showing

NOTE Confidence: 0.9455327

00:40:17.805 --> 00:40:19.565 how important those linkers are

NOTE Confidence: 0.9455327

00:40:19.565 --> 00:40:21.184 in driving the the characteristics

NOTE Confidence: 0.9455327

00:40:21.244 --> 00:40:22.145 of these ADCs.

NOTE Confidence: 0.9617801

00:40:23.085 --> 00:40:23.585 Dapotumab

NOTE Confidence: 0.9830792

00:40:23.885 --> 00:40:25.085 actually just got approved last

NOTE Confidence: 0.9830792

00:40:25.085 --> 00:40:25.585 week,

NOTE Confidence: 0.9659461

00:40:25.910 --> 00:40:27.910 for hormone receptor positive breast

NOTE Confidence: 0.9659461

00:40:27.910 --> 00:40:29.370 cancer based on another study.

NOTE Confidence: 0.97830504

00:40:29.910 --> 00:40:30.810 And then lastly,

NOTE Confidence: 0.8225224

00:40:31.430 --> 00:40:31.930 HER3,

NOTE Confidence: 0.99541783

00:40:32.310 --> 00:40:33.290 which is another,

NOTE Confidence: 0.9650287

00:40:34.150 --> 00:40:35.989 tyrosine kinase. Actually, it's not

NOTE Confidence: 0.9650287

00:40:35.989 --> 00:40:37.190 a tyrosine kinase. It's it's

NOTE Confidence: 0.9650287

00:40:37.190 --> 00:40:38.390 related to the other tyrosine

NOTE Confidence: 0.9650287

00:40:38.390 --> 00:40:40.695 kinase, the HER2 tyros HER

NOTE Confidence: 0.9650287

00:40:40.695 --> 00:40:42.695 family tyrosine kinases. It itself

NOTE Confidence: 0.9650287

00:40:42.695 --> 00:40:44.075 doesn't have an active kinase,

NOTE Confidence: 0.9927115

00:40:44.855 --> 00:40:46.215 but it's important in in

NOTE Confidence: 0.9927115

00:40:46.215 --> 00:40:46.715 signaling,

NOTE Confidence: 0.95258415

00:40:47.175 --> 00:40:48.535 and is overexpressed in a

NOTE Confidence: 0.95258415

00:40:48.535 --> 00:40:49.675 number of breast cancers.

NOTE Confidence: 0.89115834

00:40:50.295 --> 00:40:52.295 And there's a a conjugate

NOTE Confidence: 0.89115834

00:40:52.295 --> 00:40:53.835 called HER3 DXD or pertitumab

NOTE Confidence: 0.89115834

00:40:53.975 --> 00:40:54.475 daroxetin,

NOTE Confidence: 0.97561055

00:40:55.030 --> 00:40:56.230 which we showed also has

NOTE Confidence: 0.97561055

00:40:56.230 --> 00:40:58.090 activity across breast cancers. But

NOTE Confidence: 0.97561055

00:40:58.230 --> 00:40:59.110 not really sure how this

NOTE Confidence: 0.97561055

00:40:59.110 --> 00:41:00.730 one's gonna develop get developed

NOTE Confidence: 0.97561055

00:41:00.790 --> 00:41:01.290 because,

NOTE Confidence: 0.9610411

00:41:02.230 --> 00:41:03.610 the field is getting crowded,

NOTE Confidence: 0.8960732

00:41:03.990 --> 00:41:04.710 lots of,

NOTE Confidence: 0.97814286

00:41:05.270 --> 00:41:06.710 antibodies with the same payload.

NOTE Confidence: 0.97814286

00:41:06.710 --> 00:41:07.990 So where this one's gonna

NOTE Confidence: 0.97814286

00:41:07.990 --> 00:41:09.050 fit in is unclear.

NOTE Confidence: 0.99199337

00:41:11.744 --> 00:41:13.765 So there are other conjugates

NOTE Confidence: 0.99199337

00:41:13.825 --> 00:41:14.724 being developed.

NOTE Confidence: 0.9347702

00:41:15.665 --> 00:41:17.605 There are ones with fancy

NOTE Confidence: 0.9347702

00:41:17.665 --> 00:41:19.665 new protein structures. So there's

NOTE Confidence: 0.9347702

101

00:41:19.665 --> 00:41:20.165 biparotropic

NOTE Confidence: 0.9680039

00:41:20.704 --> 00:41:22.145 ADCs that bind two different

NOTE Confidence: 0.9680039

00:41:22.145 --> 00:41:23.445 epitopes of the same,

NOTE Confidence: 0.97424066

00:41:23.825 --> 00:41:26.040 molecule. There's bispecific ADCs binding

NOTE Confidence: 0.97424066

00:41:26.040 --> 00:41:27.100 two different molecules.

NOTE Confidence: 0.98375326

00:41:27.400 --> 00:41:29.400 There's probody conjugates that get

NOTE Confidence: 0.98375326

00:41:29.400 --> 00:41:29.900 activated,

NOTE Confidence: 0.9934192

00:41:30.600 --> 00:41:31.420 in the microenvironment.

NOTE Confidence: 0.9974802

00:41:32.280 --> 00:41:33.420 There's new payloads

NOTE Confidence: 0.9665608

00:41:33.800 --> 00:41:36.200 beyond very potent cytotoxic drugs.

NOTE Confidence: 0.9665608

00:41:36.200 --> 00:41:37.420 There are targeted,

NOTE Confidence: 0.9592705

00:41:38.775 --> 00:41:40.214 therapy kinds of payloads like

NOTE Confidence: 0.9592705

00:41:40.214 --> 00:41:42.714 kinase inhibitors and apoptosis promoting

NOTE Confidence: 0.9592705

00:41:42.775 --> 00:41:44.315 drugs. There's immunomodulatory

NOTE Confidence: 0.9953583

00:41:45.174 --> 00:41:45.674 payloads,

NOTE Confidence: 0.9107342

00:41:46.295 --> 00:41:46.795 radionuclides,

NOTE Confidence: 0.97596335

00:41:47.255 --> 00:41:47.755 and,

NOTE Confidence: 0.9613646

00:41:48.535 --> 00:41:50.214 there are new antigens not

NOTE Confidence: 0.9613646

00:41:50.214 --> 00:41:51.414 targeting the tumor anymore, but

NOTE Confidence: 0.9613646

00:41:51.414 --> 00:41:53.114 actually targeting the the microenvironment.

NOTE Confidence: 0.9613646

00:41:53.414 --> 00:41:54.510 All of these things are,

NOTE Confidence: 0.9613646

00:41:54.750 --> 00:41:55.150 currently,

NOTE Confidence: 0.99401164

00:41:55.550 --> 00:41:56.850 in development. So

NOTE Confidence: 0.9545464

00:41:57.230 --> 00:41:58.510 lots to more to come.

NOTE Confidence: 0.9545464

00:41:58.510 --> 00:41:59.710 I just wanted to close

NOTE Confidence: 0.9545464

00:41:59.710 --> 00:42:01.150 by bringing up a few

NOTE Confidence: 0.9545464

00:42:01.150 --> 00:42:02.270 what I think are important

NOTE Confidence: 0.9545464

00:42:02.270 --> 00:42:03.250 unanswered questions.

NOTE Confidence: 0.9988214

00:42:03.790 --> 00:42:04.989 One is and this is

NOTE Confidence: 0.9988214

00:42:04.989 --> 00:42:05.570 a little

NOTE Confidence: 0.9322093

00:42:05.950 --> 00:42:06.930 wonky, I appreciate.

NOTE Confidence: 0.96941894

00:42:08.285 --> 00:42:09.565 Should we be making more

NOTE Confidence: 0.96941894

00:42:09.565 --> 00:42:11.985 ADCs with non cleavable linkers?

NOTE Confidence: 0.96941894

00:42:12.045 --> 00:42:13.085 Right now, TDM one is

NOTE Confidence: 0.96941894

00:42:13.085 --> 00:42:14.765 the only approved ADC with

NOTE Confidence: 0.96941894

00:42:14.765 --> 00:42:15.965 a non cleavable linker. All

NOTE Confidence: 0.96941894

00:42:15.965 --> 00:42:17.245 the other ones have different

NOTE Confidence: 0.96941894

00:42:17.245 --> 00:42:18.705 types of cleavable linkers.

NOTE Confidence: 0.984359

00:42:20.855 --> 00:42:21.355 And,

NOTE Confidence: 0.96449053

00:42:23.049 --> 00:42:24.410 you know, there's reasons for

NOTE Confidence: 0.96449053

00:42:24.410 --> 00:42:25.529 the cleavable linkers. You get

NOTE Confidence: 0.96449053

00:42:25.529 --> 00:42:26.670 the bystander effect,

NOTE Confidence: 0.96950984

00:42:27.289 --> 00:42:28.250 but you also get more

NOTE Confidence: 0.96950984

00:42:28.250 --> 00:42:29.930 toxicity. And I always wondered

NOTE Confidence: 0.96950984

00:42:29.930 --> 00:42:30.809 whether if you took a

NOTE Confidence: 0.96950984

00:42:30.809 --> 00:42:32.730 really potent cytotoxic drug and

NOTE Confidence: 0.96950984

00:42:32.730 --> 00:42:33.710 made it with a noncleavable

NOTE Confidence: 0.96950984

00:42:33.849 --> 00:42:34.809 linker, whether you could get

NOTE Confidence: 0.96950984

00:42:34.809 --> 00:42:35.930 efficacy and still keep the

NOTE Confidence: 0.96950984

00:42:35.930 --> 00:42:37.230 toxicity down. Because

NOTE Confidence: 0.96498936

00:42:37.545 --> 00:42:38.825 TDM one is still really

NOTE Confidence: 0.96498936

00:42:38.825 --> 00:42:39.864 the only drug with that

NOTE Confidence: 0.96498936

00:42:39.864 --> 00:42:40.684 really favorable,

NOTE Confidence: 0.97796094

00:42:41.625 --> 00:42:43.224 toxicity profile, which, again, was

NOTE Confidence: 0.97796094

00:42:43.224 --> 00:42:44.344 one of the original visions

NOTE Confidence: 0.97796094

00:42:44.344 --> 00:42:45.165 of an ADC.

NOTE Confidence: 0.98983675

00:42:47.145 --> 00:42:48.665 How should we sequence ADCs

NOTE Confidence: 0.98983675

00:42:48.665 --> 00:42:49.944 with different targets? So I

NOTE Confidence: 0.98983675

00:42:49.944 --> 00:42:50.525 I mentioned,

NOTE Confidence: 0.9708529

00:42:51.130 --> 00:42:52.010 we had a trial where

NOTE Confidence: 0.9708529

00:42:52.010 --> 00:42:53.609 we use the same target,

NOTE Confidence: 0.9708529

00:42:53.609 --> 00:42:55.290 but two different payloads, one

NOTE Confidence: 0.9708529

00:42:55.290 --> 00:42:56.810 ADC after another. What about

NOTE Confidence: 0.9708529

00:42:56.810 --> 00:42:57.950 the kind of the opposite?

NOTE Confidence: 0.9708529

00:42:58.170 --> 00:42:58.969 And now we have the

NOTE Confidence: 0.9708529

00:42:58.969 --> 00:43:00.090 tools to do that. So

NOTE Confidence: 0.9708529

00:43:00.090 --> 00:43:01.770 in the trade trial, which

NOTE Confidence: 0.9708529

00:43:01.770 --> 00:43:03.450 is gonna open here, hopefully

NOTE Confidence: 0.9708529

00:43:03.450 --> 00:43:03.950 soon,

NOTE Confidence: 0.94895935

00:43:04.955 --> 00:43:06.335 Patients are gonna be randomized

NOTE Confidence: 0.94895935

00:43:06.475 --> 00:43:08.495 to either tDxD or dapodimab,

NOTE Confidence: 0.7622658

00:43:08.875 --> 00:43:09.935 the trop two ADC,

NOTE Confidence: 0.9550717

00:43:10.235 --> 00:43:11.435 and then when they progress,

NOTE Confidence: 0.9550717

00:43:11.435 --> 00:43:12.395 they'll switch to the other

NOTE Confidence: 0.9550717

00:43:12.395 --> 00:43:13.675 one to see and then

NOTE Confidence: 0.9550717

00:43:13.675 --> 00:43:14.635 we'll try to figure out

NOTE Confidence: 0.9550717

00:43:14.635 --> 00:43:16.315 using biomarkers which is the

NOTE Confidence: 0.9550717

00:43:16.315 --> 00:43:18.175 best sequence for each individual

NOTE Confidence: 0.9914943

00:43:18.555 --> 00:43:19.675 answer. We don't know how

NOTE Confidence: 0.9914943

00:43:19.675 --> 00:43:20.655 to do that yet.

NOTE Confidence: 0.88484657

00:43:22.050 --> 00:43:22.770 And then,

NOTE Confidence: 0.97525245

00:43:23.489 --> 00:43:23.989 lastly,

NOTE Confidence: 0.9719373

00:43:24.610 --> 00:43:25.570 and this kinda gets back

NOTE Confidence: 0.9719373

00:43:25.570 --> 00:43:26.450 to the point I made

NOTE Confidence: 0.9719373

00:43:26.450 --> 00:43:27.190 at the beginning,

NOTE Confidence: 0.99730617

00:43:28.370 --> 00:43:30.050 can we get rid of

NOTE Confidence: 0.99730617

00:43:30.050 --> 00:43:31.750 conventional chemotherapy altogether?

NOTE Confidence: 0.98820865

00:43:32.770 --> 00:43:34.105 Ideally, why would you use

NOTE Confidence: 0.98820865

00:43:34.105 --> 00:43:36.265 conventional chemotherapy, which goes everywhere

NOTE Confidence: 0.98820865

00:43:36.265 --> 00:43:37.225 in the body and causes

NOTE Confidence: 0.98820865

00:43:37.225 --> 00:43:39.065 nonspecific toxicity? Why would you

NOTE Confidence: 0.98820865

00:43:39.065 --> 00:43:39.945 use that when you can

NOTE Confidence: 0.98820865

00:43:39.945 --> 00:43:40.985 link it to an antibody

NOTE Confidence: 0.98820865

00:43:40.985 --> 00:43:42.025 and deliver it to the

NOTE Confidence: 0.98820865

00:43:42.025 --> 00:43:42.844 cancer cell?

NOTE Confidence: 0.9042837

00:43:43.945 --> 00:43:44.985 To do that, you're gonna

NOTE Confidence: 0.9042837

00:43:44.985 --> 00:43:46.905 need anti ADCs with different

NOTE Confidence: 0.9042837

00:43:46.905 --> 00:43:47.405 payloads.

NOTE Confidence: 0.9645954

00:43:48.185 --> 00:43:49.405 Just like, you know, in

NOTE Confidence: 0.9645954

00:43:49.650 --> 00:43:51.329 practice with metastatic disease, we

NOTE Confidence: 0.9645954

00:43:51.329 --> 00:43:53.650 use chemotherapy a. Patients progress,

NOTE Confidence: 0.9645954

00:43:53.650 --> 00:43:55.329 we use chemotherapy b, and

NOTE Confidence: 0.9645954

00:43:55.329 --> 00:43:56.069 so on.

NOTE Confidence: 0.9500363

00:43:56.450 --> 00:43:57.890 You could do ADC a,

NOTE Confidence: 0.9500363

00:43:57.890 --> 00:44:00.210 ADC b, each just switching

NOTE Confidence: 0.9500363

00:44:00.210 --> 00:44:00.710 payloads.

NOTE Confidence: 0.97515976

00:44:01.329 --> 00:44:02.694 The problem is we don't

NOTE Confidence: 0.97515976

00:44:02.694 --> 00:44:04.375 have those drugs other than

NOTE Confidence: 0.97515976

00:44:04.375 --> 00:44:05.655 TDM one and TDXD I

NOTE Confidence: 0.97515976

00:44:05.655 --> 00:44:06.535 showed you. We don't have

NOTE Confidence: 0.97515976

00:44:06.535 --> 00:44:07.755 a lot of different payloads,

NOTE Confidence: 0.96706986

00:44:08.055 --> 00:44:09.815 and that's partly because the

NOTE Confidence: 0.96706986

00:44:09.815 --> 00:44:11.594 success of trastuzumab daroxetine

NOTE Confidence: 0.99709064

00:44:11.974 --> 00:44:13.035 was so high

NOTE Confidence: 0.9817437

00:44:13.335 --> 00:44:14.694 that everybody's jumping on the

NOTE Confidence: 0.9817437

00:44:14.694 --> 00:44:16.075 bandwagon of these topoisomerase

NOTE Confidence: 0.97079635

00:44:16.375 --> 00:44:17.275 inhibitor payloads.

NOTE Confidence: 0.98441076

00:44:17.840 --> 00:44:18.640 And you can see this

NOTE Confidence: 0.98441076

00:44:18.640 --> 00:44:19.120 is,

NOTE Confidence: 0.9946509

00:44:19.600 --> 00:44:20.640 from a review that just

NOTE Confidence: 0.9946509

00:44:20.640 --> 00:44:21.300 came out,

NOTE Confidence: 0.9955303

00:44:22.800 --> 00:44:24.719 showing, the different payloads that

NOTE Confidence: 0.9955303

00:44:24.719 --> 00:44:25.540 are being used.

NOTE Confidence: 0.982975

00:44:26.080 --> 00:44:27.460 There's a hundred and seven

109

NOTE Confidence: 0.982975

00:44:27.520 --> 00:44:29.219 in clinical development using,

NOTE Confidence: 0.89778095

00:44:29.775 --> 00:44:31.635 camptothecans or or basically topoisomerase

NOTE Confidence: 0.89778095

00:44:31.855 --> 00:44:32.755 inhibitor payloads.

NOTE Confidence: 0.94809055

00:44:33.295 --> 00:44:34.335 Almost all of them as

NOTE Confidence: 0.94809055

00:44:34.335 --> 00:44:35.535 shown in this graph are

NOTE Confidence: 0.94809055

00:44:35.535 --> 00:44:36.755 topoisomerase inhibitors.

NOTE Confidence: 0.9843567

00:44:37.214 --> 00:44:38.114 So they work,

NOTE Confidence: 0.93871367

00:44:39.055 --> 00:44:40.575 but we're getting very crowded,

NOTE Confidence: 0.93871367

00:44:40.575 --> 00:44:41.934 and you can imagine, and

NOTE Confidence: 0.93871367

00:44:41.934 --> 00:44:43.395 we have data now developing,

NOTE Confidence: 0.98775154

00:44:43.820 --> 00:44:45.340 that cancers can become resistant

NOTE Confidence: 0.98775154

00:44:45.340 --> 00:44:46.640 to the payload by,

NOTE Confidence: 0.9812666

00:44:47.180 --> 00:44:48.160 mutating topoisomerase.

NOTE Confidence: 0.9317063

00:44:50.540 --> 00:44:52.320 And then once you've got

NOTE Confidence: 0.9317063

00:44:52.540 --> 00:44:53.739 resistance to the payload, it

NOTE Confidence: 0.9317063

00:44:53.739 --> 00:44:55.340 doesn't matter which antibodies you

NOTE Confidence: 0.9317063

00:44:55.340 --> 00:44:56.145 hook up to it. It's

NOTE Confidence: 0.9317063

00:44:56.145 --> 00:44:57.505 it's not gonna work. So

NOTE Confidence: 0.9317063

00:44:57.505 --> 00:44:58.705 we need to diversify our

NOTE Confidence: 0.9317063

00:44:58.705 --> 00:44:59.205 payloads.

NOTE Confidence: 0.9929877

00:44:59.585 --> 00:45:00.945 So with that, I will

NOTE Confidence: 0.9929877

00:45:00.945 --> 00:45:02.545 stop. I'm happy to take

NOTE Confidence: 0.9929877

00:45:02.545 --> 00:45:03.045 questions.

NOTE Confidence: 0.6822139

00:45:09.660 --> 00:45:10.160 Oh,

NOTE Confidence: 0.7503681

00:45:11.180 --> 00:45:12.400 yep. Dan.

NOTE Confidence: 0.8804015

00:45:17.260 --> 00:45:18.619 Excellent talk, and I have

NOTE Confidence: 0.8804015

00:45:18.619 --> 00:45:19.280 two questions.

NOTE Confidence: 0.9703931

00:45:19.660 --> 00:45:20.480 Number one,

NOTE Confidence: 0.9593014

00:45:20.780 --> 00:45:22.400 I'm fascinated by this,

NOTE Confidence: 0.9363801

00:45:23.175 --> 00:45:25.495 observation about responses in brain

NOTE Confidence: 0.9363801

00:45:25.495 --> 00:45:25.995 metastases.

NOTE Confidence: 0.95283324

00:45:27.015 --> 00:45:28.475 It's known that in hyperprolisular

NOTE Confidence: 0.95283324

00:45:28.695 --> 00:45:30.535 vascular endothelium that HER-twoneu is

NOTE Confidence: 0.95283324

00:45:30.535 --> 00:45:32.055 expressed. Have you looked at

NOTE Confidence: 0.95283324

00:45:32.055 --> 00:45:33.415 the HER-twoneu expression in the

NOTE Confidence: 0.95283324

00:45:33.415 --> 00:45:34.395 vascular endothelium

NOTE Confidence: 0.98310393

00:45:34.855 --> 00:45:35.895 in addition to the tumor

NOTE Confidence: 0.98310393

00:45:35.895 --> 00:45:37.080 cells in those brain mets?

NOTE Confidence: 0.98310393

00:45:37.239 --> 00:45:38.280 Because it would certainly make

NOTE Confidence: 0.98310393

00:45:38.280 --> 00:45:39.640 sense if they have a

NOTE Confidence: 0.98310393

00:45:39.640 --> 00:45:40.760 bystander effect,

NOTE Confidence: 0.9594895

00:45:41.080 --> 00:45:42.040 that may that may be

NOTE Confidence: 0.9594895

00:45:42.040 --> 00:45:43.500 the actual mechanism of action.

NOTE Confidence: 0.9594895

00:45:43.640 --> 00:45:44.600 And the second question is

NOTE Confidence: 0.9594895

00:45:44.600 --> 00:45:46.040 about interstitial lumenitis. This is

NOTE Confidence: 0.9594895

00:45:46.040 --> 00:45:47.500 something we've seen with enfortumab

NOTE Confidence: 0.9594895

00:45:47.640 --> 00:45:48.140 vedotin.

00:45:49.175 --> 00:45:50.295 It's not really clear whether

00:45:50.295 --> 00:45:51.494 that's because of the interaction

00:45:51.494 --> 00:45:52.875 between checkpoints and enfortumab.

00:45:53.415 --> 00:45:54.215 But what do you think

00:45:54.215 --> 00:45:55.035 is the mechanism,

00:45:55.415 --> 00:45:56.855 with the HER2 targeted agents

00:45:56.855 --> 00:45:58.375 with that? Yeah. So both

00:45:58.375 --> 00:45:59.035 good questions.

00:45:59.734 --> 00:46:00.614 You know, when you look

00:46:00.614 --> 00:46:00.855 at the

00:46:01.580 --> 00:46:02.400 you know, I

00:46:03.180 --> 00:46:03.820 don't know

00:46:05.020 --> 00:46:06.380 I haven't seen data on

00:46:06.380 --> 00:46:07.980 looking at at the HER2

00:46:07.980 --> 00:46:09.200 expression on the vasculature,

NOTE Confidence: 0.94490355

00:46:11.020 --> 00:46:12.940 around tumors specifically in solid

NOTE Confidence: 0.94490355

00:46:12.940 --> 00:46:14.219 cancers. It's a great question

NOTE Confidence: 0.94490355

00:46:14.219 --> 00:46:14.719 and

NOTE Confidence: 0.9817763

00:46:15.215 --> 00:46:16.015 should be able to be

NOTE Confidence: 0.9817763

00:46:16.015 --> 00:46:17.055 looked at. We do enough,

NOTE Confidence: 0.9817763

00:46:17.055 --> 00:46:18.335 you know, resections of these

NOTE Confidence: 0.9817763

00:46:18.335 --> 00:46:18.835 cancers.

NOTE Confidence: 0.9850587

00:46:20.015 --> 00:46:20.815 You know, it's,

NOTE Confidence: 0.9632029

00:46:22.415 --> 00:46:23.535 you know, the the alternative

NOTE Confidence: 0.9632029

00:46:23.614 --> 00:46:24.335 you know, so if it's

NOTE Confidence: 0.9632029

00:46:24.335 --> 00:46:25.375 not just breakdown of the

NOTE Confidence: 0.9632029

00:46:25.375 --> 00:46:26.355 blood brain barrier,

NOTE Confidence: 0.9843833

00:46:27.135 --> 00:46:27.795 you know,

NOTE Confidence: 0.98739475

00:46:28.100 --> 00:46:29.219 is it released in the

NOTE Confidence: 0.98739475

00:46:29.219 --> 00:46:29.719 microenvironment?

NOTE Confidence: 0.9655115

00:46:30.580 --> 00:46:31.540 There are some data that

NOTE Confidence: 0.9655115

00:46:31.540 --> 00:46:32.580 I didn't have time to

NOTE Confidence: 0.9655115

00:46:32.580 --> 00:46:33.239 show you.

NOTE Confidence: 0.9261859

00:46:35.700 --> 00:46:36.980 But I think very provocative

NOTE Confidence: 0.9261859

00:46:36.980 --> 00:46:38.260 data that was presented at

NOTE Confidence: 0.9261859

00:46:38.260 --> 00:46:39.620 our San Antonio Breast Cancer

NOTE Confidence: 0.9261859

00:46:39.620 --> 00:46:41.205 meeting last month, just as

NOTE Confidence: 0.9261859

00:46:41.205 --> 00:46:42.325 a poster because I don't

NOTE Confidence: 0.9261859

00:46:42.325 --> 00:46:43.145 think people appreciated

NOTE Confidence: 0.9603503

00:46:43.845 --> 00:46:44.585 the impact,

NOTE Confidence: 0.99725986

00:46:46.405 --> 00:46:47.945 suggesting that it's actually

NOTE Confidence: 0.9136734

00:46:48.485 --> 00:46:50.025 cathepsins in the microenvironment.

NOTE Confidence: 0.9858144

00:46:50.325 --> 00:46:52.265 They're actually cleaving these conjugates,

NOTE Confidence: 0.9858144

00:46:52.405 --> 00:46:53.364 and that's why they work

NOTE Confidence: 0.9858144

00:46:53.364 --> 00:46:55.099 in, you know, potentially HER2

NOTE Confidence: 0.967241

00:46:55.559 --> 00:46:57.420 null or HER2 very low,

NOTE Confidence: 0.93488437

00:46:57.719 --> 00:46:58.680 because they're really they're hurt

NOTE Confidence: 0.93488437

00:46:58.760 --> 00:46:59.559 it's you don't need the

NOTE Confidence: 0.93488437

00:46:59.559 --> 00:47:01.579 HER2. It's just the microenvironment

NOTE Confidence: 0.96556586

00:47:02.039 --> 00:47:03.660 has enough cathepsins there,

NOTE Confidence: 0.99647164

00:47:04.279 --> 00:47:05.900 that you get selective cleavage

NOTE Confidence: 0.99647164

00:47:05.960 --> 00:47:06.940 around the tumor.

NOTE Confidence: 0.855186

00:47:07.464 --> 00:47:08.344 So that could be a

NOTE Confidence: 0.855186

00:47:08.344 --> 00:47:09.944 alternative explanation. But,

NOTE Confidence: 0.97741604

00:47:10.505 --> 00:47:12.045 also, if you had anchoring

NOTE Confidence: 0.97741604

00:47:12.105 --> 00:47:13.944 because of HER2 overexpression in

NOTE Confidence: 0.97741604

00:47:13.944 --> 00:47:14.605 the vasculature,

NOTE Confidence: 0.98313457

00:47:15.305 --> 00:47:16.605 you could imagine,

NOTE Confidence: 0.9994459

00:47:17.224 --> 00:47:18.605 having efficacy there

NOTE Confidence: 0.8644271

00:47:20.010 --> 00:47:20.750 and perhaps

NOTE Confidence: 0.97235715

00:47:21.290 --> 00:47:23.930 causing more disruption by causing

NOTE Confidence: 0.97235715

116

00:47:23.930 --> 00:47:25.790 some apoptosis of the endothelium,

NOTE Confidence: 0.97235715

00:47:25.930 --> 00:47:27.450 causing more disruption, allowing more

NOTE Confidence: 0.97235715

00:47:27.450 --> 00:47:28.489 ADC in there. So I

NOTE Confidence: 0.97235715

00:47:28.489 --> 00:47:29.530 think that's a great question,

NOTE Confidence: 0.97235715

00:47:29.530 --> 00:47:30.410 and I don't have a

NOTE Confidence: 0.97235715

00:47:30.410 --> 00:47:31.450 great answer for that. And

NOTE Confidence: 0.97235715

00:47:31.450 --> 00:47:32.590 in terms of the ILD,

NOTE Confidence: 0.94241256

00:47:34.475 --> 00:47:35.935 we we we don't know

NOTE Confidence: 0.94241256

00:47:36.075 --> 00:47:37.775 the the mechanism. It it,

NOTE Confidence: 0.98708856

00:47:38.635 --> 00:47:39.135 actually,

NOTE Confidence: 0.9561653

00:47:39.515 --> 00:47:40.715 Adriana Khan is looking at

NOTE Confidence: 0.9561653

00:47:40.715 --> 00:47:42.575 trying to do lung biopsies

NOTE Confidence: 0.9561653

00:47:42.635 --> 00:47:44.094 in patients who get pneumonitis

NOTE Confidence: 0.9561653

00:47:44.235 --> 00:47:45.355 or or who are getting

NOTE Confidence: 0.9561653

00:47:45.355 --> 00:47:46.655 these drugs and get pneumonitis,

NOTE Confidence: 0.93682736

00:47:47.380 --> 00:47:48.820 to try to kinda clarify

NOTE Confidence: 0.93682736

00:47:48.820 --> 00:47:49.320 that.

NOTE Confidence: 0.88943595

00:47:49.859 --> 00:47:51.060 You know, certainly, there is

NOTE Confidence: 0.88943595

00:47:51.060 --> 00:47:51.560 HER2,

NOTE Confidence: 0.9697744

00:47:52.260 --> 00:47:54.340 in in in some lung

NOTE Confidence: 0.9697744

00:47:54.340 --> 00:47:54.840 tissue,

NOTE Confidence: 0.95227695

00:47:56.820 --> 00:47:58.900 whether it's through direct target

NOTE Confidence: 0.95227695

00:47:58.900 --> 00:48:00.420 mediated, although as you pointed

NOTE Confidence: 0.95227695

00:48:00.420 --> 00:48:01.844 out, there are multiple targets

NOTE Confidence: 0.95227695

00:48:02.005 --> 00:48:02.965 that are that are seeing

NOTE Confidence: 0.95227695

00:48:02.965 --> 00:48:03.465 ILD.

NOTE Confidence: 0.99392545

00:48:04.005 --> 00:48:04.744 There are,

NOTE Confidence: 0.93652016

00:48:05.685 --> 00:48:07.705 you know, with TDM one,

NOTE Confidence: 0.93652016

00:48:07.844 --> 00:48:09.205 which is HER2 target, you

NOTE Confidence: 0.93652016

00:48:09.205 --> 00:48:10.484 don't you know, the ILD

NOTE Confidence: 0.93652016

00:48:10.484 --> 00:48:12.405 rate is is is very,

NOTE Confidence: 0.93652016

118

00:48:12.405 --> 00:48:13.305 very low.

NOTE Confidence: 0.9981122

00:48:13.765 --> 00:48:15.065 And so we have ILD

NOTE Confidence: 0.95466816

00:48:15.380 --> 00:48:16.820 in some drugs where you

NOTE Confidence: 0.95466816

00:48:16.820 --> 00:48:18.100 change the payload or change

NOTE Confidence: 0.95466816

00:48:18.100 --> 00:48:19.380 the linker and you you

NOTE Confidence: 0.95466816

00:48:19.380 --> 00:48:20.739 you change the ILD rate

NOTE Confidence: 0.95466816

00:48:20.739 --> 00:48:21.239 substantially.

NOTE Confidence: 0.92955965

00:48:22.739 --> 00:48:23.700 So we don't know. You

NOTE Confidence: 0.92955965

00:48:23.700 --> 00:48:25.000 you know, is it macrophage

NOTE Confidence: 0.92955965

00:48:25.140 --> 00:48:26.820 uptake because of FC receptors?

NOTE Confidence: 0.92955965

00:48:26.820 --> 00:48:27.540 I think there's a lot

NOTE Confidence: 0.92955965

00:48:27.540 --> 00:48:29.060 of hypotheses, but I don't

NOTE Confidence: 0.92955965

00:48:29.060 --> 00:48:30.280 think there's any definitive,

NOTE Confidence: 0.8663461

00:48:31.135 --> 00:48:31.635 data.

NOTE Confidence: 0.9906477

00:48:32.175 --> 00:48:33.375 And, you know, it is

NOTE Confidence: 0.9906477

00:48:33.375 --> 00:48:34.335 certainly a problem for some

NOTE Confidence: 0.9906477

00:48:34.335 --> 00:48:35.635 of these drugs that limits

NOTE Confidence: 0.99870765

00:48:35.935 --> 00:48:37.875 their their, you know, applicability.

NOTE Confidence: 0.99884367

00:48:38.575 --> 00:48:39.075 Thanks.

NOTE Confidence: 0.9892976

00:48:40.735 --> 00:48:41.235 Yeah.

NOTE Confidence: 0.99781346

00:48:45.860 --> 00:48:46.360 Okay.

NOTE Confidence: 0.98670465

00:48:47.140 --> 00:48:48.360 Thank you for your talk.

NOTE Confidence: 0.9323555

00:48:48.739 --> 00:48:50.020 I had a question about

NOTE Confidence: 0.9323555

00:48:50.020 --> 00:48:51.160 the brain mets.

NOTE Confidence: 0.98711634

00:48:51.620 --> 00:48:53.000 Have you seen any coexpression

NOTE Confidence: 0.9781136

00:48:53.380 --> 00:48:55.460 of cell adhesion molecules that

NOTE Confidence: 0.9781136

00:48:55.460 --> 00:48:56.500 you could then use as

NOTE Confidence: 0.9781136

00:48:56.500 --> 00:48:58.775 a, like, HER2 bispecific

NOTE Confidence: 0.96091336

00:48:59.315 --> 00:49:00.535 to increase internalization

NOTE Confidence: 0.9415512

00:49:00.915 --> 00:49:02.535 in those brain meds specifically

NOTE Confidence: 0.9415512

00:49:02.594 --> 00:49:03.954 or the potential Yeah. So,

NOTE Confidence: 0.9415512

00:49:03.954 --> 00:49:04.915 I mean, again, this gets

NOTE Confidence: 0.9415512

00:49:04.915 --> 00:49:06.835 back to, Dan's question and

NOTE Confidence: 0.9415512

00:49:06.835 --> 00:49:07.494 and then,

NOTE Confidence: 0.9962598

00:49:08.194 --> 00:49:08.855 you know,

NOTE Confidence: 0.9997093

00:49:09.315 --> 00:49:10.915 whether we can learn from

NOTE Confidence: 0.9997093

00:49:10.915 --> 00:49:11.815 some of these

NOTE Confidence: 0.9574404

00:49:12.890 --> 00:49:14.489 datasets where people are doing

NOTE Confidence: 0.9574404

00:49:14.489 --> 00:49:16.270 resections of of brain metastases

NOTE Confidence: 0.9574404

00:49:16.410 --> 00:49:18.110 and and looking at, dysregulation

NOTE Confidence: 0.9574404

00:49:18.250 --> 00:49:19.690 of adhesion molecules and as

NOTE Confidence: 0.9574404

00:49:19.690 --> 00:49:20.890 a way of potentially doing

NOTE Confidence: 0.9574404

00:49:20.890 --> 00:49:22.250 bispecifics. I mean, there have

NOTE Confidence: 0.9574404

00:49:22.250 --> 00:49:23.150 been some

NOTE Confidence: 0.94011956

00:49:24.414 --> 00:49:26.734 ADCs looking at at those

NOTE Confidence: 0.94011956

00:49:26.815 --> 00:49:28.414 at at adhesion molecules to

NOTE Confidence: 0.94011956

00:49:28.414 --> 00:49:29.295 try to get at the

NOTE Confidence: 0.94011956

00:49:29.295 --> 00:49:31.375 at the, microenvironment, but I

NOTE Confidence: 0.94011956

00:49:31.375 --> 00:49:32.174 I don't know of any

NOTE Confidence: 0.94011956

00:49:32.174 --> 00:49:33.855 of that with her too.

NOTE Confidence: 0.94011956

00:49:34.174 --> 00:49:35.055 But it's a good idea

NOTE Confidence: 0.94011956

00:49:35.055 --> 00:49:36.255 and and kinda looking at

NOTE Confidence: 0.94011956

00:49:36.255 --> 00:49:37.394 that. Because, again, the BRAINMET

NOTE Confidence: 0.94011956

00:49:37.454 --> 00:49:38.335 issue is a is a

NOTE Confidence: 0.94011956

00:49:38.335 --> 00:49:40.109 real problem. And, where we've

NOTE Confidence: 0.94011956

00:49:40.109 --> 00:49:41.549 seen we see benefit with

NOTE Confidence: 0.94011956

00:49:41.549 --> 00:49:42.750 ADCs in the brain as

NOTE Confidence: 0.94011956

00:49:42.750 --> 00:49:43.950 I showed you, but they're

NOTE Confidence: 0.94011956

00:49:43.950 --> 00:49:44.450 not,

NOTE Confidence: 0.98842204

00:49:44.750 --> 00:49:45.630 you know, they're not,

NOTE Confidence: 0.9752918

00:49:46.349 --> 00:49:48.430 eliminating the brain metastases. And,

NOTE Confidence: 0.9752918

00:49:48.430 --> 00:49:49.549 generally, what we see with

NOTE Confidence: 0.9752918

122

00:49:49.549 --> 00:49:51.469 our patients, once a patient

NOTE Confidence: 0.9752918

00:49:51.469 --> 00:49:52.450 has brain metastases,

NOTE Confidence: 0.99529684

00:49:53.390 --> 00:49:54.769 that's progressed after radiation,

NOTE Confidence: 0.94132596

00:49:55.230 --> 00:49:56.565 they always progress in the

NOTE Confidence: 0.94132596

00:49:56.565 --> 00:49:57.925 brain. And so it becomes

NOTE Confidence: 0.94132596

00:49:57.925 --> 00:49:59.945 the rate limiting step for

NOTE Confidence: 0.94132596

00:50:00.244 --> 00:50:01.205 a lot of patients. So

NOTE Confidence: 0.94132596

00:50:01.205 --> 00:50:02.325 we we need new treatments,

NOTE Confidence: 0.94132596

00:50:02.325 --> 00:50:03.705 but that's a good question.

NOTE Confidence: 0.94132596

00:50:03.765 --> 00:50:05.445 Yeah. Great talk, Ian. I'm

NOTE Confidence: 0.94132596

00:50:05.445 --> 00:50:06.585 one of the best molecular

NOTE Confidence: 0.94132596

00:50:06.805 --> 00:50:07.305 pathologist.

NOTE Confidence: 0.9115724

00:50:07.779 --> 00:50:09.380 The trial you presented, was

NOTE Confidence: 0.9115724

00:50:09.380 --> 00:50:11.299 AutoMedigar when you predicted the

NOTE Confidence: 0.9115724

00:50:11.299 --> 00:50:12.900 pathologic complete response by the

NOTE Confidence: 0.9115724

00:50:12.900 --> 00:50:13.400 heterogeneity

NOTE Confidence: 0.92515594

00:50:13.779 --> 00:50:14.839 Yeah. In HER2.

NOTE Confidence: 0.91271585

00:50:15.380 --> 00:50:17.059 I we encounter heterogeneity on

NOTE Confidence: 0.91271585

00:50:17.059 --> 00:50:18.180 IHC all the time. And

NOTE Confidence: 0.91271585

00:50:18.180 --> 00:50:19.299 sometime when we go for

NOTE Confidence: 0.91271585

00:50:19.299 --> 00:50:20.900 fish, it doesn't translate to

NOTE Confidence: 0.91271585

00:50:20.900 --> 00:50:22.665 heterogeneity in fish in this

NOTE Confidence: 0.91271585

00:50:22.825 --> 00:50:24.685 area. But also on FISH,

NOTE Confidence: 0.9927094

00:50:24.985 --> 00:50:26.425 any FISH I review, there

NOTE Confidence: 0.9927094

00:50:26.425 --> 00:50:27.705 is negative cells in the

NOTE Confidence: 0.9927094

00:50:27.705 --> 00:50:28.205 FISH.

NOTE Confidence: 0.94988877

00:50:28.905 --> 00:50:29.945 Can how can we make

NOTE Confidence: 0.94988877

00:50:29.945 --> 00:50:31.165 this clinically applicable?

NOTE Confidence: 0.9477374

00:50:31.625 --> 00:50:33.385 And can this patient go

NOTE Confidence: 0.9477374

00:50:33.385 --> 00:50:35.065 instead of going getting new

NOTE Confidence: 0.9477374

00:50:35.065 --> 00:50:36.910 adjuvant antibody drug conjugate? Because

NOTE Confidence: 0.9477374

124

00:50:36.910 --> 00:50:38.450 they're not gonna achieve BCR

NOTE Confidence: 0.9477374

00:50:38.590 --> 00:50:40.350 with the regular regimen. Thank

NOTE Confidence: 0.9477374

00:50:40.350 --> 00:50:40.850 you.

NOTE Confidence: 0.9445479

00:50:41.310 --> 00:50:42.910 Yeah. So, I mean, with

NOTE Confidence: 0.9445479

00:50:42.910 --> 00:50:45.570 TBM one, we've definitely seen

NOTE Confidence: 0.9445479

00:50:45.790 --> 00:50:46.530 in in

NOTE Confidence: 0.95960575

00:50:46.989 --> 00:50:48.030 in both of the studies

NOTE Confidence: 0.95960575

00:50:48.030 --> 00:50:49.150 I showed you and and

NOTE Confidence: 0.95960575

00:50:49.150 --> 00:50:50.430 pretty much every study of

NOTE Confidence: 0.95960575

00:50:50.430 --> 00:50:52.235 TBM one, which, again, non

NOTE Confidence: 0.95960575

00:50:52.235 --> 00:50:53.835 cleavable link are very dependent

NOTE Confidence: 0.95960575

00:50:53.835 --> 00:50:54.975 on HER2 expression,

NOTE Confidence: 0.9945505

00:50:55.435 --> 00:50:57.535 that you see less substantially

NOTE Confidence: 0.9945505

00:50:57.594 --> 00:50:59.035 less activity as you go

NOTE Confidence: 0.9945505

00:50:59.035 --> 00:51:00.635 down to either lower expression

NOTE Confidence: 0.9945505

00:51:00.635 --> 00:51:02.015 levels of HER2 or heterogeneity.

NOTE Confidence: 0.94645244

00:51:02.795 --> 00:51:03.995 But in truth, we don't

NOTE Confidence: 0.94645244

00:51:03.995 --> 00:51:05.114 use TDM one in the

NOTE Confidence: 0.94645244

00:51:05.114 --> 00:51:06.719 neoadjuvant setting. It's not it's

NOTE Confidence: 0.94645244

00:51:06.719 --> 00:51:07.380 it's not clinically

NOTE Confidence: 0.9597503

00:51:08.319 --> 00:51:08.819 used.

NOTE Confidence: 0.9730716

00:51:10.000 --> 00:51:10.500 And

NOTE Confidence: 0.9558946

00:51:11.280 --> 00:51:12.880 as Eric has been potting

NOTE Confidence: 0.9558946

00:51:12.880 --> 00:51:13.859 me for years

NOTE Confidence: 0.9457678

00:51:14.160 --> 00:51:15.359 to go back and redo

NOTE Confidence: 0.9457678

00:51:15.359 --> 00:51:16.960 that trial of heterogeneity with

NOTE Confidence: 0.9457678

00:51:16.960 --> 00:51:18.239 one of these conjugates that

NOTE Confidence: 0.9457678

00:51:18.239 --> 00:51:20.000 has by standard effect to

NOTE Confidence: 0.9457678

00:51:20.000 --> 00:51:22.185 see whether we eliminate that

NOTE Confidence: 0.9457678

00:51:22.505 --> 00:51:23.005 disparity.

NOTE Confidence: 0.9307345

00:51:24.025 --> 00:51:25.305 You would expect we would

NOTE Confidence: 0.9307345

00:51:25.305 --> 00:51:26.925 if the hypothesis was correct,

NOTE Confidence: 0.9741073

00:51:27.545 --> 00:51:28.585 but we haven't proven it.

NOTE Confidence: 0.9741073

00:51:28.585 --> 00:51:29.785 But one of the as

NOTE Confidence: 0.9741073

00:51:29.785 --> 00:51:30.825 I said, there's a big

NOTE Confidence: 0.9741073

00:51:30.825 --> 00:51:32.425 trial that's just been it's

NOTE Confidence: 0.9741073

00:51:32.425 --> 00:51:33.545 been completed. We're waiting for

NOTE Confidence: 0.9741073

00:51:33.545 --> 00:51:34.585 the results. We should get

NOTE Confidence: 0.9741073

00:51:34.585 --> 00:51:35.945 it sometime this year of

NOTE Confidence: 0.9741073

00:51:35.945 --> 00:51:36.445 neoadjuvant

NOTE Confidence: 0.8919727

00:51:36.745 --> 00:51:37.245 TDXD,

NOTE Confidence: 0.9812144

00:51:37.860 --> 00:51:39.080 the one with the payload,

NOTE Confidence: 0.9689232

00:51:39.860 --> 00:51:40.900 spreading, the one with,

NOTE Confidence: 0.9337611

00:51:41.860 --> 00:51:42.920 bystander effect.

NOTE Confidence: 0.8049592

00:51:44.260 --> 00:51:45.239 And, hopefully,

NOTE Confidence: 0.9728249

00:51:46.980 --> 00:51:47.780 I'm not involved in that

NOTE Confidence: 0.9728249

00:51:47.780 --> 00:51:48.680 trial, but, hopefully,

NOTE Confidence: 0.9175464

00:51:49.220 --> 00:51:50.420 they'll look at that question

NOTE Confidence: 0.9175464

00:51:50.420 --> 00:51:52.065 and and and hope and,

NOTE Confidence: 0.9175464

00:51:52.065 --> 00:51:53.344 hopefully, we won't see that

NOTE Confidence: 0.9175464

00:51:53.344 --> 00:51:54.325 just big disparity

NOTE Confidence: 0.92149884

00:51:54.705 --> 00:51:55.925 by HER2 level,

NOTE Confidence: 0.9991467

00:51:56.465 --> 00:51:57.665 because of the unique features

NOTE Confidence: 0.9991467

00:51:57.665 --> 00:51:58.565 of this conjugate.

NOTE Confidence: 0.96577424

00:51:59.105 --> 00:52:00.145 But if we do, then,

NOTE Confidence: 0.96577424

00:52:00.145 --> 00:52:01.185 again, it brings up your

NOTE Confidence: 0.96577424

00:52:01.185 --> 00:52:02.625 point and says, hey. You

NOTE Confidence: 0.96577424

00:52:02.625 --> 00:52:03.744 know, a a one size

NOTE Confidence: 0.96577424

00:52:03.744 --> 00:52:05.289 fits all approach is not

NOTE Confidence: 0.96577424

00:52:05.289 --> 00:52:06.809 right, and the heterogeneous cancer

NOTE Confidence: 0.96577424

00:52:06.809 --> 00:52:08.010 should be treated in different

NOTE Confidence: 0.96577424

00:52:08.010 --> 00:52:08.510 ways,

NOTE Confidence: 0.99198693

00:52:09.770 --> 00:52:10.890 which probably is

NOTE Confidence: 0.97852546

00:52:11.529 --> 00:52:13.049 you know? I didn't have

NOTE Confidence: 0.97852546

00:52:13.049 --> 00:52:14.170 time to talk about resistance

NOTE Confidence: 0.97852546

00:52:14.170 --> 00:52:14.910 or biomarkers,

NOTE Confidence: 0.9962648

00:52:16.170 --> 00:52:17.505 but we're not good at

NOTE Confidence: 0.9962648

00:52:17.505 --> 00:52:18.545 figuring out either one of

NOTE Confidence: 0.9962648

00:52:18.545 --> 00:52:19.045 those,

NOTE Confidence: 0.9990063

00:52:19.585 --> 00:52:20.704 areas right now. We need

NOTE Confidence: 0.9990063

00:52:20.704 --> 00:52:21.664 a lot more work on

NOTE Confidence: 0.9990063

00:52:21.664 --> 00:52:22.164 identifying

NOTE Confidence: 0.991664

00:52:22.785 --> 00:52:24.065 whether there are biomarkers that

NOTE Confidence: 0.991664

00:52:24.065 --> 00:52:25.105 predict benefit of any of

NOTE Confidence: 0.991664

00:52:25.105 --> 00:52:26.384 these drugs. We haven't been

NOTE Confidence: 0.991664

00:52:26.384 --> 00:52:27.184 able to figure that out

NOTE Confidence: 0.991664

00:52:27.184 --> 00:52:27.984 yet. Eric, do you have

NOTE Confidence: 0.991664

00:52:27.984 --> 00:52:28.565 a follow-up?

NOTE Confidence: 0.964721

00:52:30.400 --> 00:52:31.540 Question from online.

NOTE Confidence: 0.8943226

00:52:32.080 --> 00:52:33.700 So this is the limitation

NOTE Confidence: 0.8943226

00:52:33.840 --> 00:52:34.500 of PCR

NOTE Confidence: 0.8465879

00:52:34.880 --> 00:52:36.020 versus long term.

NOTE Confidence: 0.96406966

00:52:36.719 --> 00:52:38.719 Because just because someone doesn't

NOTE Confidence: 0.96406966

00:52:38.719 --> 00:52:39.700 achieve a PCR

NOTE Confidence: 0.65669197

00:52:40.320 --> 00:52:42.400 doesn't necessarily mean for going

NOTE Confidence: 0.65669197

00:52:42.400 --> 00:52:43.540 to have a good

NOTE Confidence: 0.9520136

00:52:43.840 --> 00:52:44.340 answer.

NOTE Confidence: 0.84442

00:52:44.645 --> 00:52:46.085 So some of those cells

NOTE Confidence: 0.84442

00:52:46.085 --> 00:52:47.045 that may be first and

NOTE Confidence: 0.84442

00:52:47.045 --> 00:52:47.545 negatives

NOTE Confidence: 0.85325694

00:52:48.085 --> 00:52:50.105 may also be ER positive

NOTE Confidence: 0.85325694

00:52:50.165 --> 00:52:51.785 in response to anything therapy,

NOTE Confidence: 0.85325694

00:52:51.844 --> 00:52:52.744 maybe biologically

NOTE Confidence: 0.98965275

00:52:53.125 --> 00:52:53.864 less aggressive.

NOTE Confidence: 0.9991655

00:52:54.565 --> 00:52:56.025 So it's it's not

NOTE Confidence: 0.8736976

00:52:57.080 --> 00:52:58.280 absolutely the case when you

NOTE Confidence: 0.8736976

00:52:58.280 --> 00:52:59.880 have to eradicate every single

NOTE Confidence: 0.8736976

00:52:59.880 --> 00:53:00.700 one of their

NOTE Confidence: 0.92255014

00:53:01.080 --> 00:53:02.540 cell. The question

NOTE Confidence: 0.7009845

00:53:04.520 --> 00:53:05.020 online,

NOTE Confidence: 0.98604643

00:53:05.800 --> 00:53:06.300 was,

NOTE Confidence: 0.9722866

00:53:06.920 --> 00:53:07.880 do you think it would

NOTE Confidence: 0.9722866

00:53:07.880 --> 00:53:10.360 be possible using antibody drug

NOTE Confidence: 0.9722866

00:53:10.360 --> 00:53:10.860 conjugate

NOTE Confidence: 0.92130375

00:53:11.255 --> 00:53:13.755 technology to deliver non chemotherapy

NOTE Confidence: 0.867363

00:53:14.215 --> 00:53:15.195 agents like,

NOTE Confidence: 0.9765433

00:53:16.855 --> 00:53:17.835 immune checkpoints

NOTE Confidence: 0.9485687

00:53:18.135 --> 00:53:19.114 or such?

NOTE Confidence: 0.930881

00:53:19.895 --> 00:53:21.094 Yeah. So, yeah, so it's

NOTE Confidence: 0.930881

00:53:21.094 --> 00:53:22.055 a great question, and then

NOTE Confidence: 0.930881

00:53:22.055 --> 00:53:22.855 there's been a lot of

NOTE Confidence: 0.930881

00:53:22.855 --> 00:53:25.350 interest in in in delivering

NOTE Confidence: 0.930881

00:53:25.410 --> 00:53:26.469 everything with that,

NOTE Confidence: 0.9636701

00:53:27.090 --> 00:53:27.590 antisense,

NOTE Confidence: 0.97324103

00:53:28.530 --> 00:53:29.830 you know, as I said,

NOTE Confidence: 0.7119164

00:53:30.210 --> 00:53:31.190 DNA damage,

NOTE Confidence: 0.962941

00:53:32.369 --> 00:53:34.070 inhibit you know, repair inhibitors,

NOTE Confidence: 0.9772008

00:53:35.650 --> 00:53:36.850 I think you name it.

NOTE Confidence: 0.9772008

00:53:36.850 --> 00:53:38.390 I think the the problem

NOTE Confidence: 0.9928721

00:53:39.195 --> 00:53:40.875 the the concern people have

NOTE Confidence: 0.9928721

00:53:40.875 --> 00:53:42.335 with going that direction,

NOTE Confidence: 0.975631

00:53:43.035 --> 00:53:43.995 not that it's not being

NOTE Confidence: 0.975631

00:53:43.995 --> 00:53:45.114 tried, but the concern is

NOTE Confidence: 0.975631

00:53:45.114 --> 00:53:46.735 just gonna be, you know,

NOTE Confidence: 0.9585555

00:53:48.795 --> 00:53:50.235 the amount of ADC that

NOTE Confidence: 0.9585555

00:53:50.235 --> 00:53:51.594 actually gets the tumor cell

NOTE Confidence: 0.9585555

00:53:51.594 --> 00:53:52.495 is very low,

NOTE Confidence: 0.9540519

00:53:53.289 --> 00:53:54.489 because they get taken up.

NOTE Confidence: 0.9540519

00:53:54.489 --> 00:53:55.230 Even though,

NOTE Confidence: 0.9710372

00:53:56.170 --> 00:53:57.049 you know, we talk about

NOTE Confidence: 0.9710372

00:53:57.049 --> 00:53:58.270 it being a guided missile,

NOTE Confidence: 0.998506

00:53:58.650 --> 00:53:59.930 most of the drug actually

NOTE Confidence: 0.998506

00:53:59.930 --> 00:54:00.989 ends up in just

NOTE Confidence: 0.9540679

00:54:02.329 --> 00:54:03.770 random tissue just because it

NOTE Confidence: 0.9540679

00:54:03.849 --> 00:54:05.710 just antibodies get stuck places.

NOTE Confidence: 0.9540679

00:54:05.930 --> 00:54:07.724 So, you know, data suggests

NOTE Confidence: 0.9540679

00:54:07.724 --> 00:54:08.765 that, like, one percent of

NOTE Confidence: 0.9540679

00:54:08.765 --> 00:54:09.724 the dose that you give

NOTE Confidence: 0.9540679

00:54:09.724 --> 00:54:10.924 actually gets to the tumor.

NOTE Confidence: 0.9540679

00:54:10.924 --> 00:54:12.125 So you don't really getting

NOTE Confidence: 0.9540679

00:54:12.125 --> 00:54:13.325 a whole lot of of

NOTE Confidence: 0.9540679

00:54:13.325 --> 00:54:15.164 the payload to the cancer

NOTE Confidence: 0.9540679

00:54:15.164 --> 00:54:16.065 cell. And so

NOTE Confidence: 0.9987168

00:54:16.684 --> 00:54:17.885 there's been a push to

NOTE Confidence: 0.9987168

00:54:17.885 --> 00:54:19.664 get very high potency

NOTE Confidence: 0.9985857

00:54:20.760 --> 00:54:21.260 payloads

NOTE Confidence: 0.97036713

00:54:21.719 --> 00:54:22.520 with the idea that you

NOTE Confidence: 0.97036713

00:54:22.520 --> 00:54:23.320 can get away with that

NOTE Confidence: 0.97036713

00:54:23.320 --> 00:54:24.860 because they're being somewhat selectively

NOTE Confidence: 0.97036713

00:54:24.920 --> 00:54:25.420 delivered,

NOTE Confidence: 0.98670846

00:54:26.280 --> 00:54:27.400 because you you we're not

NOTE Confidence: 0.98670846

00:54:27.400 --> 00:54:28.360 getting a whole lot into

NOTE Confidence: 0.98670846

00:54:28.360 --> 00:54:29.480 the cancer, so you you

NOTE Confidence: 0.98670846

00:54:29.480 --> 00:54:30.280 want what you get in

NOTE Confidence: 0.98670846

00:54:30.280 --> 00:54:31.660 there to be very potent.

NOTE Confidence: 0.98670846

134

00:54:31.719 --> 00:54:32.840 And the problem with most

NOTE Confidence: 0.98670846

00:54:32.840 --> 00:54:34.460 of these small molecules,

NOTE Confidence: 0.99449575

00:54:35.685 --> 00:54:36.965 is that they're not as

NOTE Confidence: 0.99449575

00:54:36.965 --> 00:54:38.725 potent as as they need

NOTE Confidence: 0.99449575

00:54:38.725 --> 00:54:40.085 to be or the concern

NOTE Confidence: 0.99449575

00:54:40.085 --> 00:54:40.885 is they're not as potent

NOTE Confidence: 0.99449575

00:54:40.885 --> 00:54:41.605 as they need to be.

NOTE Confidence: 0.99449575

00:54:41.605 --> 00:54:42.485 We'll see. I mean, again,

NOTE Confidence: 0.99449575

00:54:42.485 --> 00:54:43.285 there's a lot of them

NOTE Confidence: 0.99449575

00:54:43.285 --> 00:54:44.645 in development, but that's the

NOTE Confidence: 0.99449575

00:54:44.645 --> 00:54:45.545 problem with,

NOTE Confidence: 0.92173445

00:54:46.565 --> 00:54:47.765 with your payload is if

NOTE Confidence: 0.92173445

00:54:47.765 --> 00:54:48.425 it's not

NOTE Confidence: 0.99966073

00:54:48.930 --> 00:54:49.670 quite potent,

NOTE Confidence: 0.9671221

00:54:50.609 --> 00:54:51.890 it may not be effective

NOTE Confidence: 0.9671221

00:54:51.890 --> 00:54:52.950 enough even if

NOTE Confidence: 0.9994446

00:54:53.489 --> 00:54:54.150 the general

NOTE Confidence: 0.9954277

00:54:54.450 --> 00:54:55.650 hypothesis is a good one

NOTE Confidence: 0.9954277

00:54:55.650 --> 00:54:56.609 of of of doing that.

NOTE Confidence: 0.9954277

00:54:56.609 --> 00:54:57.969 So but, you know, none

NOTE Confidence: 0.9954277

00:54:57.969 --> 00:54:58.930 of them have been approved

NOTE Confidence: 0.9954277

00:54:58.930 --> 00:54:59.890 as far as I know.

NOTE Confidence: 0.9954277

00:54:59.890 --> 00:55:00.770 We'll have to we'll have

NOTE Confidence: 0.9954277

00:55:00.770 --> 00:55:01.730 to see as they pan

NOTE Confidence: 0.9954277

00:55:01.730 --> 00:55:02.530 out. It's a it's a

NOTE Confidence: 0.9954277

00:55:02.530 --> 00:55:03.190 good idea.

NOTE Confidence: 0.9335475

00:55:03.569 --> 00:55:04.545 Did did you have a

NOTE Confidence: 0.9335475

00:55:04.625 --> 00:55:05.125 question?

NOTE Confidence: 0.97098863

00:55:06.224 --> 00:55:06.724 Yeah.

NOTE Confidence: 0.9015487

00:55:17.200 --> 00:55:19.200 Is is autoimmune, like is

NOTE Confidence: 0.9015487

00:55:19.200 --> 00:55:19.700 autoimmune

NOTE Confidence: 0.9931744

00:55:20.080 --> 00:55:20.580 toxicity?

NOTE Confidence: 0.9479253

00:55:21.680 --> 00:55:24.000 So well, autoimmune meaning anti

NOTE Confidence: 0.9479253

00:55:24.000 --> 00:55:24.500 antibody.

NOTE Confidence: 0.92439127

00:55:25.120 --> 00:55:26.719 Yeah. So so,

NOTE Confidence: 0.81073403

00:55:32.005 --> 00:55:34.105 antihuman antibodies or anti

NOTE Confidence: 0.97260547

00:55:34.725 --> 00:55:35.705 conjugate antibodies

NOTE Confidence: 0.96418935

00:55:36.085 --> 00:55:37.205 don't seem to be a

NOTE Confidence: 0.96418935

00:55:37.205 --> 00:55:38.565 big problem with these. It's

NOTE Confidence: 0.96418935

00:55:38.565 --> 00:55:39.765 it's a good question because

NOTE Confidence: 0.96418935

00:55:39.765 --> 00:55:40.885 you would expect you've, you

NOTE Confidence: 0.96418935

00:55:40.885 --> 00:55:41.844 know, you've got a a

NOTE Confidence: 0.96418935

00:55:41.844 --> 00:55:44.350 humanized antibody. You've got derivation

NOTE Confidence: 0.96418935

00:55:44.489 --> 00:55:45.469 of that antibody.

NOTE Confidence: 0.9988389

00:55:45.770 --> 00:55:46.830 Could that be immunogenic?

NOTE Confidence: 0.96594995

00:55:48.410 --> 00:55:49.930 It's it hasn't been a

NOTE Confidence: 0.96594995

00:55:49.930 --> 00:55:50.670 a problem.

NOTE Confidence: 0.99360245

00:55:52.570 --> 00:55:53.950 You don't see much hypersensitivity

NOTE Confidence: 0.9202275

00:55:54.410 --> 00:55:55.070 with these.

NOTE Confidence: 0.8636359

00:55:55.770 --> 00:55:56.650 I mean, you can't at,

NOTE Confidence: 0.8636359

00:55:56.650 --> 00:55:57.710 you know, low percentages.

NOTE Confidence: 0.9814002

00:55:58.570 --> 00:56:00.545 But but antibody you know,

NOTE Confidence: 0.9814002

00:56:00.545 --> 00:56:02.625 anti ADC antibodies haven't been

NOTE Confidence: 0.9814002

00:56:02.625 --> 00:56:03.605 clinically significant,

NOTE Confidence: 0.9827094

00:56:04.145 --> 00:56:05.585 and autoimmune disease really hasn't

NOTE Confidence: 0.9827094

00:56:05.585 --> 00:56:06.545 been. You know, whether the

NOTE Confidence: 0.9827094

00:56:06.545 --> 00:56:07.825 the pneumonitis that we see

NOTE Confidence: 0.9827094

00:56:07.825 --> 00:56:09.265 could be an autoimmune reaction

NOTE Confidence: 0.9827094

00:56:09.265 --> 00:56:10.944 is certainly possible, but but

NOTE Confidence: 0.9827094

00:56:10.944 --> 00:56:12.385 we other than that, we

NOTE Confidence: 0.9827094

00:56:12.385 --> 00:56:13.605 really haven't seen it.

NOTE Confidence: 0.96399003

00:56:24.769 --> 00:56:26.390 Yeah. So, you know, meaning

NOTE Confidence: 0.96399003

00:56:26.450 --> 00:56:28.130 if the ADC bot is

NOTE Confidence: 0.96399003

00:56:28.130 --> 00:56:29.845 is encounters an immune cell,

NOTE Confidence: 0.96399003

00:56:29.845 --> 00:56:30.885 it kills it because of

NOTE Confidence: 0.96399003

00:56:30.885 --> 00:56:31.625 the cytotoxic

NOTE Confidence: 0.9441903

00:56:31.925 --> 00:56:33.285 moiety. Yeah. I think that

NOTE Confidence: 0.9441903

00:56:33.285 --> 00:56:35.625 that's that's certainly possible.

NOTE Confidence: 0.980385

00:56:36.805 --> 00:56:37.205 But,

NOTE Confidence: 0.9054052

00:56:37.605 --> 00:56:38.905 and then that's a good

NOTE Confidence: 0.9054052

00:56:39.045 --> 00:56:39.545 thought.

NOTE Confidence: 0.90857244

00:56:40.085 --> 00:56:41.364 Fortunately, I said clinically, it

NOTE Confidence: 0.90857244

00:56:41.364 --> 00:56:42.405 just really hasn't been an

NOTE Confidence: 0.90857244

00:56:42.405 --> 00:56:42.905 issue.

NOTE Confidence: 0.4563213

00:56:49.680 --> 00:56:50.160 Pan,

NOTE Confidence: 0.796416

00:56:51.200 --> 00:56:52.319 I had, like, twenty questions,

NOTE Confidence: 0.796416

00:56:52.319 --> 00:56:54.020 but I'll Absolutely. Eliminate them.

NOTE Confidence: 0.987937

00:56:55.040 --> 00:56:55.619 So so

NOTE Confidence: 0.97009665

00:56:56.305 --> 00:56:57.585 with with the ultra low,

NOTE Confidence: 0.97009665

00:56:57.585 --> 00:56:58.705 you're you're assuming that you're

NOTE Confidence: 0.97009665

00:56:58.705 --> 00:56:59.844 dealing with with

NOTE Confidence: 0.9561364

00:57:00.225 --> 00:57:01.665 probably a small percentage of

NOTE Confidence: 0.9561364

00:57:01.665 --> 00:57:03.045 cells that are actually expressing.

NOTE Confidence: 0.91358006

00:57:04.225 --> 00:57:05.585 By definition. And I guess

NOTE Confidence: 0.91358006

00:57:05.585 --> 00:57:06.625 the I understand the idea

NOTE Confidence: 0.91358006

00:57:06.625 --> 00:57:07.825 of cathepsins doing this. But

NOTE Confidence: 0.91358006

00:57:07.825 --> 00:57:08.705 I guess the other question

NOTE Confidence: 0.91358006

00:57:08.705 --> 00:57:10.325 is for the spreading effect,

NOTE Confidence: 0.91358006

00:57:10.599 --> 00:57:11.079 do we think this is

NOTE Confidence: 0.91358006

00:57:11.079 --> 00:57:12.440 apoptotic cell death, or do

NOTE Confidence: 0.91358006

00:57:12.440 --> 00:57:13.079 we think this is cell

NOTE Confidence: 0.91358006

00:57:13.079 --> 00:57:14.760 death that's actually messier? And

NOTE Confidence: 0.91358006

00:57:14.760 --> 00:57:15.420 if so,

NOTE Confidence: 0.9976842

00:57:16.440 --> 00:57:18.140 has anyone thought of immune

NOTE Confidence: 0.9764181

00:57:19.000 --> 00:57:19.740 in combination,

NOTE Confidence: 0.80875677

00:57:20.119 --> 00:57:21.640 you know, like p one?

NOTE Confidence: 0.80875677

00:57:21.640 --> 00:57:22.760 So I didn't talk about

NOTE Confidence: 0.80875677

00:57:22.760 --> 00:57:23.880 biomarkers. I'm sorry. I was

NOTE Confidence: 0.80875677

00:57:23.880 --> 00:57:24.599 just last night. I don't

NOTE Confidence: 0.80875677

00:57:24.599 --> 00:57:25.725 wanna forget. Forget. Brady and

NOTE Confidence: 0.80875677

00:57:25.725 --> 00:57:27.405 Anna's thing. I know David

NOTE Confidence: 0.80875677

00:57:27.405 --> 00:57:28.705 Brim is gonna be doing,

NOTE Confidence: 0.95770425

00:57:29.165 --> 00:57:30.525 QIF. Are you also gonna

NOTE Confidence: 0.95770425

00:57:30.525 --> 00:57:31.485 be doing IHC at the

NOTE Confidence: 0.95770425

00:57:31.485 --> 00:57:32.285 same time? Because I think

NOTE Confidence: 0.95770425

00:57:32.285 --> 00:57:33.325 you sort of I go

NOTE Confidence: 0.95770425

00:57:33.325 --> 00:57:34.305 on and do both

NOTE Confidence: 0.96031785

00:57:34.925 --> 00:57:36.285 because I mean, at least

NOTE Confidence: 0.96031785

00:57:36.285 --> 00:57:37.485 David's not here. Right? He's

141

NOTE Confidence: 0.96031785

00:57:37.485 --> 00:57:38.145 been testing,

NOTE Confidence: 0.99489754

00:57:39.730 --> 00:57:40.230 you

NOTE Confidence: 0.8530746

00:57:42.850 --> 00:57:44.370 know, Yeah. We're we're actually

NOTE Confidence: 0.8530746

00:57:44.690 --> 00:57:45.410 see if it's covered because

NOTE Confidence: 0.8530746

00:57:45.490 --> 00:57:46.850 Yeah. So the actual correlate.

NOTE Confidence: 0.8530746

00:57:46.850 --> 00:57:48.630 Yeah. Yeah. The actual analysis

NOTE Confidence: 0.8530746

00:57:48.770 --> 00:57:49.970 plan is to do multiple

NOTE Confidence: 0.8530746

00:57:49.970 --> 00:57:51.430 HER2 assays, both

NOTE Confidence: 0.9982893

00:57:51.744 --> 00:57:52.724 protein and genomics

NOTE Confidence: 0.9503128

00:57:53.105 --> 00:57:53.984 to try to come up

NOTE Confidence: 0.9503128

00:57:53.984 --> 00:57:55.105 with, you know, the best

NOTE Confidence: 0.9503128

00:57:55.105 --> 00:57:55.605 predictor.

NOTE Confidence: 0.923928

00:57:56.705 --> 00:57:58.244 So good question.

NOTE Confidence: 0.9774887

00:57:59.984 --> 00:58:01.685 In terms of of immunogenic

NOTE Confidence: 0.9774887

00:58:01.825 --> 00:58:02.865 cell death, it certainly looks

NOTE Confidence: 0.9774887

00:58:02.865 --> 00:58:04.244 like these are causing immunogenic

NOTE Confidence: 0.9774887

00:58:04.385 --> 00:58:05.125 cell death.

NOTE Confidence: 0.95738256

00:58:06.000 --> 00:58:07.920 You know, again, the payloads

NOTE Confidence: 0.95738256

00:58:07.920 --> 00:58:10.080 are standard chemotherapies, essentially, and

NOTE Confidence: 0.95738256

00:58:10.080 --> 00:58:10.720 you're getting a lot of

NOTE Confidence: 0.95738256

00:58:10.720 --> 00:58:11.760 it. You know, they're they're

NOTE Confidence: 0.95738256

00:58:11.760 --> 00:58:13.120 potent. So there's there are

NOTE Confidence: 0.95738256

00:58:13.120 --> 00:58:14.480 actually some interesting papers that

NOTE Confidence: 0.95738256

00:58:14.480 --> 00:58:16.580 you get particularly good immunogenic

NOTE Confidence: 0.95738256

00:58:16.720 --> 00:58:17.840 cell death for reasons that

NOTE Confidence: 0.95738256

00:58:17.840 --> 00:58:18.640 I I don't know how

NOTE Confidence: 0.95738256

00:58:18.640 --> 00:58:20.155 well they they've been validated.

NOTE Confidence: 0.9789109

00:58:21.255 --> 00:58:22.795 And there there are combinations

NOTE Confidence: 0.9565772

00:58:23.255 --> 00:58:23.755 of,

NOTE Confidence: 0.8050108

00:58:24.295 --> 00:58:26.474 ADCs plus checkpoint inhibitors,

NOTE Confidence: 0.971712

00:58:26.775 --> 00:58:28.395 which have shown some promise.

NOTE Confidence: 0.94778115

00:58:30.295 --> 00:58:31.770 In smaller studies, there's some

NOTE Confidence: 0.94778115

00:58:31.770 --> 00:58:33.210 studies that have shown incredible,

NOTE Confidence: 0.94778115

00:58:33.210 --> 00:58:34.490 you know, response rates, eighty,

NOTE Confidence: 0.94778115

00:58:34.490 --> 00:58:35.310 ninety percent,

NOTE Confidence: 0.95298046

00:58:36.570 --> 00:58:37.850 and with and there have

NOTE Confidence: 0.95298046

00:58:37.850 --> 00:58:39.610 been some small randomized trials

NOTE Confidence: 0.95298046

00:58:39.610 --> 00:58:41.150 of of TDM one plus,

NOTE Confidence: 0.9344907

00:58:41.930 --> 00:58:43.550 checkpoint inhibitors, which show

NOTE Confidence: 0.9195554

00:58:44.244 --> 00:58:46.025 a signal, but not overwhelming

NOTE Confidence: 0.9195554

00:58:46.165 --> 00:58:47.785 signal. So I think,

NOTE Confidence: 0.98327994

00:58:49.925 --> 00:58:51.065 we'll have to wait,

NOTE Confidence: 0.99908936

00:58:51.765 --> 00:58:52.265 for

NOTE Confidence: 0.8945533

00:58:52.645 --> 00:58:54.085 there are randomized trials right

NOTE Confidence: 0.8945533

00:58:54.085 --> 00:58:55.845 now with the FOC two

NOTE Confidence: 0.8945533

00:58:55.845 --> 00:58:57.480 ADCs ADCs with or without,

NOTE Confidence: 0.9864527

00:58:58.100 --> 00:58:59.000 checkpoint inhibitors,

NOTE Confidence: 0.9924315

00:58:59.540 --> 00:59:00.040 being,

NOTE Confidence: 0.9413259

00:59:01.140 --> 00:59:02.340 being conducted, and we should

NOTE Confidence: 0.9413259

00:59:02.340 --> 00:59:03.460 have the results actually pretty

NOTE Confidence: 0.9413259

00:59:03.460 --> 00:59:03.960 quickly.

NOTE Confidence: 0.993603

00:59:04.420 --> 00:59:05.380 The hope is that those

NOTE Confidence: 0.993603

00:59:05.380 --> 00:59:06.900 are gonna be, you know,

NOTE Confidence: 0.993603

00:59:06.900 --> 00:59:07.380 really,

NOTE Confidence: 0.876835

00:59:07.780 --> 00:59:08.920 impressive combinations,

NOTE Confidence: 0.9902297

00:59:09.460 --> 00:59:11.060 both because we know that,

NOTE Confidence: 0.9902297

00:59:11.060 --> 00:59:11.640 you know,

NOTE Confidence: 0.941445

00:59:11.975 --> 00:59:13.975 checkpoint inhibitors plus chemotherapy work

NOTE Confidence: 0.941445

00:59:13.975 --> 00:59:15.495 well in triple negative breast

NOTE Confidence: 0.941445

00:59:15.495 --> 00:59:17.655 cancer, but particularly because of

NOTE Confidence: 0.941445

00:59:17.655 --> 00:59:18.935 the the the having an

NOTE Confidence: 0.941445

00:59:18.935 --> 00:59:20.615 antibody there, maybe you're getting

NOTE Confidence: 0.941445

00:59:20.615 --> 00:59:21.115 more,

NOTE Confidence: 0.95162326

00:59:21.815 --> 00:59:23.575 antigen presentation, maybe you're getting

NOTE Confidence: 0.95162326

00:59:23.575 --> 00:59:24.855 more immunogenic cell death that

NOTE Confidence: 0.95162326

00:59:24.855 --> 00:59:25.975 it's really gonna be,

NOTE Confidence: 0.98901457

00:59:27.200 --> 00:59:28.720 truly synergistic. So it's a

NOTE Confidence: 0.98901457

00:59:28.720 --> 00:59:29.920 great question, and we'll have

NOTE Confidence: 0.98901457

00:59:29.920 --> 00:59:30.720 data by the end of

NOTE Confidence: 0.98901457

00:59:30.720 --> 00:59:31.380 this year

NOTE Confidence: 0.9984144

00:59:31.680 --> 00:59:32.339 on that.

NOTE Confidence: 0.8824676

00:59:33.359 --> 00:59:33.859 Barbara?

NOTE Confidence: 0.9458466

00:59:39.325 --> 00:59:41.565 Wonderful talk. And I'm so

NOTE Confidence: 0.9458466

00:59:41.565 --> 00:59:43.885 fascinated by the HER2 low

NOTE Confidence: 0.9458466

00:59:43.885 --> 00:59:44.865 because, I guess,

NOTE Confidence: 0.9707919

00:59:45.405 --> 00:59:46.205 I think we have some

NOTE Confidence: 0.9707919

00:59:46.205 --> 00:59:47.165 head and neck cancers that

NOTE Confidence: 0.9707919

00:59:47.165 --> 00:59:48.625 are like that. But so,

NOTE Confidence: 0.9707919

00:59:48.765 --> 00:59:49.565 you know, in the in

NOTE Confidence: 0.9707919

00:59:49.565 --> 00:59:50.305 the amplified,

NOTE Confidence: 0.95731205

00:59:50.845 --> 00:59:51.645 you always have the same

NOTE Confidence: 0.95731205

00:59:51.645 --> 00:59:52.760 target, and you're just changing

NOTE Confidence: 0.95731205

00:59:52.760 --> 00:59:53.800 your payload, you're changing your

NOTE Confidence: 0.95731205

00:59:53.800 --> 00:59:54.680 link area, and it keeps

NOTE Confidence: 0.95731205

00:59:54.680 --> 00:59:55.579 working for years.

NOTE Confidence: 0.9834628

00:59:56.040 --> 00:59:57.260 And in the HER2

NOTE Confidence: 0.99285215

00:59:57.640 --> 00:59:58.140 low,

NOTE Confidence: 0.96799016

00:59:59.079 --> 01:00:00.359 I'm assuming that to the

NOTE Confidence: 0.96799016

01:00:00.359 --> 01:00:01.740 extent that that HER2

NOTE Confidence: 0.99887335

01:00:02.040 --> 01:00:03.420 is doing something biologically,

NOTE Confidence: 0.9781745

01:00:03.720 --> 01:00:04.540 it's heterodimerizing

NOTE Confidence: 0.96402425

01:00:05.079 --> 01:00:07.635 with EGFR or HER3. Right?

NOTE Confidence: 0.9385328

01:00:08.035 --> 01:00:09.635 And so I wondered either

147

NOTE Confidence: 0.9385328

01:00:09.635 --> 01:00:11.415 with a panHER kinase inhibitor

NOTE Confidence: 0.9801036

01:00:12.035 --> 01:00:12.535 or,

NOTE Confidence: 0.9713469

01:00:12.995 --> 01:00:14.595 you know, cetuximab or something

NOTE Confidence: 0.9713469

01:00:14.595 --> 01:00:15.795 like that, have there been

NOTE Confidence: 0.9713469

01:00:15.795 --> 01:00:17.335 attempts to kinda cotarget

NOTE Confidence: 0.94699407

01:00:18.355 --> 01:00:20.130 what HER2 is is hanging

NOTE Confidence: 0.94699407

01:00:20.130 --> 01:00:21.170 out with in the in

NOTE Confidence: 0.94699407

01:00:21.170 --> 01:00:22.770 those cancers? Yeah. So great

NOTE Confidence: 0.94699407

01:00:22.770 --> 01:00:23.990 question as always, Barbara.

NOTE Confidence: 0.9857225

01:00:25.010 --> 01:00:26.529 So as I was gonna

NOTE Confidence: 0.9857225

01:00:26.529 --> 01:00:27.410 tell Mike, you know, so

NOTE Confidence: 0.9857225

01:00:27.410 --> 01:00:29.109 we didn't talk about biomarkers

NOTE Confidence: 0.9857225

01:00:29.170 --> 01:00:30.450 or resistance. We also didn't

NOTE Confidence: 0.9857225

01:00:30.450 --> 01:00:31.349 talk about combinations.

NOTE Confidence: 0.9769732

01:00:32.865 --> 01:00:34.465 Combining things with ADCs has

NOTE Confidence: 0.9769732

01:00:34.465 --> 01:00:35.745 been more complicated than we

NOTE Confidence: 0.9769732

01:00:35.745 --> 01:00:37.185 would like. The the checkpoint

NOTE Confidence: 0.9769732

01:00:37.185 --> 01:00:38.645 inhibitors actually are an exception.

NOTE Confidence: 0.99231464

01:00:40.145 --> 01:00:41.505 There have been studies looking

NOTE Confidence: 0.99231464

01:00:41.505 --> 01:00:43.185 at kinase inhibitors for the

NOTE Confidence: 0.99231464

01:00:43.185 --> 01:00:44.485 reason you talked about.

NOTE Confidence: 0.9790307

01:00:46.040 --> 01:00:47.320 So far, the data don't

NOTE Confidence: 0.9790307

01:00:47.320 --> 01:00:48.140 look great.

NOTE Confidence: 0.9438835

01:00:50.760 --> 01:00:51.720 It's funny you bring that

NOTE Confidence: 0.9438835

01:00:51.720 --> 01:00:53.080 up. Jingde and I are

NOTE Confidence: 0.9438835

01:00:53.080 --> 01:00:53.560 just,

NOTE Confidence: 0.9540246

01:00:53.960 --> 01:00:55.500 in the process of submitting,

NOTE Confidence: 0.8342963

01:00:56.609 --> 01:00:57.109 a

NOTE Confidence: 0.52796936

01:00:58.455 --> 01:00:58.955 concept

NOTE Confidence: 0.973918

01:00:59.255 --> 01:00:59.755 for,

NOTE Confidence: 0.9405926

01:01:00.775 --> 01:01:02.055 the combination of a HER2

NOTE Confidence: 0.9405926

01:01:02.055 --> 01:01:04.055 ADC plus the HER3 ADC

NOTE Confidence: 0.9405926

01:01:04.055 --> 01:01:05.195 that you're working on,

NOTE Confidence: 0.96484464

01:01:05.735 --> 01:01:07.255 for that very reason. Also,

NOTE Confidence: 0.96484464

01:01:07.255 --> 01:01:08.715 knowing that HER3 gets upregulated

NOTE Confidence: 0.96484464

01:01:08.855 --> 01:01:09.915 when you block HER2,

NOTE Confidence: 0.991449

01:01:10.480 --> 01:01:11.440 can you, you know, can

NOTE Confidence: 0.991449

01:01:11.440 --> 01:01:12.960 you leverage that by combining

NOTE Confidence: 0.991449

01:01:12.960 --> 01:01:13.860 those two ADCs?

NOTE Confidence: 0.9943261

01:01:14.560 --> 01:01:15.300 But just

NOTE Confidence: 0.9830502

01:01:16.240 --> 01:01:18.000 from lots of unfortunate personal

NOTE Confidence: 0.9830502

01:01:18.000 --> 01:01:19.760 experience, combining ADCs with other

NOTE Confidence: 0.9830502

01:01:19.760 --> 01:01:20.640 drugs has not been as

NOTE Confidence: 0.9830502

01:01:20.640 --> 01:01:21.541 easy as we would have

NOTE Confidence: 0.9830502

01:01:21.701 --> 01:01:22.201 thought.

NOTE Confidence: 0.9666532

01:01:22.741 --> 01:01:23.941 Even TDM one, which, you

NOTE Confidence: 0.9666532

01:01:23.941 --> 01:01:25.301 know, is such a good

NOTE Confidence: 0.9666532

01:01:25.301 --> 01:01:27.321 toxicity profile, it's been hard.

NOTE Confidence: 0.9791586

01:01:28.021 --> 01:01:28.521 So

NOTE Confidence: 0.8430106

01:01:30.901 --> 01:01:32.441 Alright. Thank you very