WEBVTT

NOTE duration:"00:52:59.1440000"

NOTE language:en-us

NOTE Confidence: 0.80248904

00:00:00.000 --> 00:00:02.025 Daddy, thank you so much

NOTE Confidence: 0.80248904

00:00:02.025 --> 00:00:03.645 for joining us today.

NOTE Confidence: 0.80248904

00:00:03.650 --> 00:00:05.650 So for today's grand rounds,

NOTE Confidence: 0.80248904

00:00:05.650 --> 00:00:07.816 I am thrilled to present our

NOTE Confidence: 0.80248904

00:00:07.816 --> 00:00:10.234 speaker to Steve Hardy from the

NOTE Confidence: 0.80248904

00:00:10.234 --> 00:00:12.030 Dana Farber Cancer Institute.

NOTE Confidence: 0.80248904

00:00:12.030 --> 00:00:15.102 Runs the Melanoma program and he also runs

NOTE Confidence: 0.80248904

00:00:15.102 --> 00:00:18.405 the immuno Oncology program up at the Farber.

NOTE Confidence: 0.80248904

00:00:18.410 --> 00:00:20.405 He's a professor of medicine

NOTE Confidence: 0.80248904

00:00:20.405 --> 00:00:22.400 and has an endowed chair.

NOTE Confidence: 0.80248904

00:00:22.400 --> 00:00:24.400 He's the Sharon Crowley market.

NOTE Confidence: 0.80248904

00:00:24.400 --> 00:00:25.849 Share in Melanoma.

NOTE Confidence: 0.80248904

00:00:25.849 --> 00:00:28.747 I've known Steve for many years.

NOTE Confidence: 0.80248904

00:00:28.750 --> 00:00:30.675 He's been on the faculty

NOTE Confidence: 0.80248904

00:00:30.675 --> 00:00:32.600 at Dana Farber since 1995.

NOTE Confidence: 0.80248904

00:00:32.600 --> 00:00:33.755 After finishing his

NOTE Confidence: 0.80248904

00:00:33.755 --> 00:00:35.295 medical school at Cornell.

NOTE Confidence: 0.80248904

00:00:35.300 --> 00:00:37.335 Great in his graduate education

NOTE Confidence: 0.80248904

00:00:37.335 --> 00:00:38.963 between the University of

NOTE Confidence: 0.80248904

00:00:38.963 --> 00:00:40.298 Pennsylvania and the Farber,

NOTE Confidence: 0.80248904

00:00:40.300 --> 00:00:42.225 Steve has made major contributions

NOTE Confidence: 0.80248904

00:00:42.225 --> 00:00:43.765 to the Melanoma field.

NOTE Confidence: 0.80248904

00:00:43.770 --> 00:00:46.465 He's lead author or first author on

NOTE Confidence: 0.80248904

00:00:46.465 --> 00:00:48.440 multiple publications in major journals

NOTE Confidence: 0.80248904

00:00:48.440 --> 00:00:51.464 such as the New England Journal of Medicine,

NOTE Confidence: 0.80248904

00:00:51.470 --> 00:00:52.240 Lancet, Lancet,

NOTE Confidence: 0.80248904

00:00:52.240 --> 00:00:53.780 Onkologie, and the like.

NOTE Confidence: 0.80248904

00:00:53.780 --> 00:00:55.368 He's made some similar

NOTE Confidence: 0.80248904

00:00:55.368 --> 00:00:56.559 breakthroughs in clinical.

NOTE Confidence: 0.80248904

00:00:56.560 --> 00:00:59.144 And care as well as in Preclinical Research.

NOTE Confidence: 0.80248904

00:00:59.150 --> 00:01:00.426 He's pioneered two approaches

NOTE Confidence: 0.80248904

00:01:00.426 --> 00:01:02.340 that I recall that have really

NOTE Confidence: 0.80248904

00:01:02.395 --> 00:01:04.213 changed the landscape of what we're

NOTE Confidence: 0.80248904

00:01:04.213 --> 00:01:05.960 studying and doing in Melanoma.

NOTE Confidence: 0.80248904

00:01:05.960 --> 00:01:07.575 One is combination of angiogenic

NOTE Confidence: 0.80248904

00:01:07.575 --> 00:01:08.544 therapies and immunotherapy,

NOTE Confidence: 0.80248904

00:01:08.550 --> 00:01:10.194 and the other one is combinations

NOTE Confidence: 0.80248904

00:01:10.194 --> 00:01:12.439 of GM CSF with with immunotherapy,

NOTE Confidence: 0.80248904

00:01:12.440 --> 00:01:14.276 and I believe you'll be talking

NOTE Confidence: 0.80248904

00:01:14.276 --> 00:01:16.000 at least about the letter.

NOTE Confidence: 0.80248904

00:01:16.000 --> 00:01:18.544 He has a few other very novel gene

NOTE Confidence: 0.80248904

00:01:18.544 --> 00:01:20.208 therapy approaches that he's using,

NOTE Confidence: 0.80248904

00:01:20.210 --> 00:01:22.464 which I think he will be talking

NOTE Confidence: 0.80248904

00:01:22.464 --> 00:01:24.099 to us about as well,

NOTE Confidence: 0.80248904

00:01:24.100 --> 00:01:25.760 so we actually originally wanted

NOTE Confidence: 0.80248904

00:01:25.760 --> 00:01:27.780 Steve to come down last June.

NOTE Confidence: 0.80248904

00:01:27.780 --> 00:01:30.870 Marcus and I invited him as

NOTE Confidence: 0.80248904

00:01:30.870 --> 00:01:33.510 part of the skins for.

NOTE Confidence: 0.80248904

00:01:33.510 --> 00:01:34.136 Administrative core,

NOTE Confidence: 0.80248904

00:01:34.136 --> 00:01:35.075 but unfortunately wasn't

NOTE Confidence: 0.80248904

00:01:35.075 --> 00:01:36.640 able to come last June.

NOTE Confidence: 0.80248904

00:01:36.640 --> 00:01:38.887 Glad to have him here today and

NOTE Confidence: 0.80248904

00:01:38.887 --> 00:01:41.017 we look forward to seeing him in

NOTE Confidence: 0.80248904

00:01:41.020 --> 00:01:42.896 person sometime in the near future.

NOTE Confidence: 0.80248904

00:01:42.896 --> 00:01:44.148 So without further ado,

NOTE Confidence: 0.80248904

00:01:44.150 --> 00:01:46.040 I'd like Steve to take the

NOTE Confidence: 0.80248904

00:01:46.040 --> 00:01:47.909 screen over and take it away.

NOTE Confidence: 0.80248904

00:01:47.910 --> 00:01:50.406 And if you have any questions for Steve,

NOTE Confidence: 0.80248904

00:01:50.410 --> 00:01:52.594 please put them in the chat box.

NOTE Confidence: 0.8336587

00:01:55.620 --> 00:01:57.468 But thank you very much, Harry,

NOTE Confidence: 0.8336587

00:01:57.468 --> 00:01:59.008 for the very kind introduction.

NOTE Confidence: 0.8336587

00:01:59.010 --> 00:02:01.978 And I do hope that we get

NOTE Confidence: 0.8336587

00:02:01.978 --> 00:02:04.359 to see everybody very soon.

NOTE Confidence: 0.8336587

00:02:04.360 --> 00:02:08.077 Let me just get. And if you can verify,

NOTE Confidence: 0.8336587

00:02:08.080 --> 00:02:09.910 you can see slides and everything,

NOTE Confidence: 0.8336587

00:02:09.910 --> 00:02:11.418 OK, yes, we're seeing it.

NOTE Confidence: 0.8336587

00:02:11.418 --> 00:02:12.282 Well, great. Thanks.

NOTE Confidence: 0.8336587

00:02:12.282 --> 00:02:14.405 And I do hope we can all

NOTE Confidence: 0.8336587

00:02:14.405 --> 00:02:16.010 see each other again soon.

NOTE Confidence: 0.8336587

00:02:16.010 --> 00:02:18.264 Everyone is doing well so it's a

NOTE Confidence: 0.8336587

00:02:18.264 --> 00:02:20.646 pleasure to join you all today and I'm

NOTE Confidence: 0.8336587

00:02:20.646 --> 00:02:22.993 going to be kind of talking a little

NOTE Confidence: 0.8336587

00:02:22.993 --> 00:02:25.465 bit of leading up to some ways to

NOTE Confidence: 0.8336587

00:02:25.465 --> 00:02:26.990 think about rational combinations of

NOTE Confidence: 0.8336587

00:02:26.990 --> 00:02:28.210 combining with checkpoint blockade.

NOTE Confidence: 0.8336587

00:02:28.210 --> 00:02:29.730 So as a clinical investigator,

NOTE Confidence: 0.8336587

00:02:29.730 --> 00:02:31.305 think of of cancer therapeutics

NOTE Confidence: 0.8336587

00:02:31.305 --> 00:02:33.228 and such that cancer and people

NOTE Confidence: 0.8336587

00:02:33.228 --> 00:02:34.920 are present for a long time,

NOTE Confidence: 0.8336587

00:02:34.920 --> 00:02:36.288 so there's an opportunity

NOTE Confidence: 0.8336587

00:02:36.288 --> 00:02:37.314 for antigen recognition.

NOTE Confidence: 0.8336587

00:02:37.320 --> 00:02:39.203 There may be slightly different than what

NOTE Confidence: 0.8336587

00:02:39.203 --> 00:02:41.757 we see in the transplantable tumor models,

NOTE Confidence: 0.8336587

00:02:41.760 --> 00:02:43.024 the transplantable tumors being

NOTE Confidence: 0.8336587

00:02:43.024 --> 00:02:44.288 key to understanding mechanisms.

NOTE Confidence: 0.8336587

00:02:44.290 --> 00:02:46.208 But we've also found in most more

NOTE Confidence: 0.8336587

00:02:46.208 --> 00:02:47.831 recently that the translation into

NOTE Confidence: 0.8336587

00:02:47.831 --> 00:02:49.676 into people may be challenging.

NOTE Confidence: 0.8336587

00:02:49.680 --> 00:02:51.534 Some of the aspects really to

NOTE Confidence: 0.8336587

00:02:51.534 --> 00:02:53.102 agonist targets and other things

NOTE Confidence: 0.8336587

00:02:53.102 --> 00:02:54.992 in terms of the rate from ecology

NOTE Confidence: 0.8336587

00:02:54.992 --> 00:02:56.660 is also fairly challenging,

NOTE Confidence: 0.8336587

00:02:56.660 --> 00:02:58.564 so in the world in the world

NOTE Confidence: 0.8336587

00:02:58.564 --> 00:03:00.190 we're living in the checkpoint

NOTE Confidence: 0.8336587

00:03:00.190 --> 00:03:02.045 world that we're living in.

NOTE Confidence: 0.8336587

00:03:02.050 --> 00:03:04.530 Why do anti tumor responses are not do

NOTE Confidence: 0.8336587

00:03:04.530 --> 00:03:06.797 not happen in order to clear cancer,

NOTE Confidence: 0.8336587

00:03:06.800 --> 00:03:09.060 so they've either never developed?

NOTE Confidence: 0.8336587

00:03:09.060 --> 00:03:11.034 The immune cells are too few in

NOTE Confidence: 0.8336587

00:03:11.034 --> 00:03:12.780 number or there are exhausted,

NOTE Confidence: 0.8336587

00:03:12.780 --> 00:03:14.455 and this obviously the exhaustion

NOTE Confidence: 0.8336587

00:03:14.455 --> 00:03:16.130 is very important within the

NOTE Confidence: 0.8336587

00:03:16.186 --> 00:03:17.426 PD one we're living in,

NOTE Confidence: 0.8336587

00:03:17.430 --> 00:03:18.895 they could physically be excluded

NOTE Confidence: 0.8336587

00:03:18.895 --> 00:03:20.840 from the tumor or the antigen.

NOTE Confidence: 0.8336587

00:03:20.840 --> 00:03:22.375 Presenting machinery is somehow disrupted

NOTE Confidence: 0.8336587

00:03:22.375 --> 00:03:24.870 with engine loss or or the machine itself,

NOTE Confidence: 0.8336587

00:03:24.870 --> 00:03:26.006 such as MSE loss,

NOTE Confidence: 0.8336587

00:03:26.006 --> 00:03:28.280 which we're going to try to address.

NOTE Confidence: 0.8336587

00:03:28.280 --> 00:03:31.772 Most of these over the next hour or so.

NOTE Confidence: 0.8336587

00:03:31.780 --> 00:03:34.062 So in the beginning there was appealing

NOTE Confidence: 0.8336587

00:03:34.062 --> 00:03:35.943 map antisocial foreign just to use

NOTE Confidence: 0.8336587

00:03:35.943 --> 00:03:37.629 Melanoma as as the paradigm example.

NOTE Confidence: 0.8336587

00:03:37.630 --> 00:03:39.205 Traditionally Melanoma would have about

NOTE Confidence: 0.8336587

00:03:39.205 --> 00:03:41.330 11 months median survival for brain Mets,

NOTE Confidence: 0.8336587

00:03:41.330 --> 00:03:43.834 six months or less an now we have

NOTE Confidence: 0.8336587

00:03:43.834 --> 00:03:45.646 with hippie the 22% of patients

NOTE Confidence: 0.8336587

00:03:45.646 --> 00:03:47.524 now having a long term survival

NOTE Confidence: 0.8336587

00:03:47.524 --> 00:03:49.922 with over 10 years of follow up and

NOTE Confidence: 0.8336587

00:03:49.922 --> 00:03:51.747 notice on the survival curves that

NOTE Confidence: 0.8336587

00:03:51.747 --> 00:03:53.625 there's an inflection point or on

NOTE Confidence: 0.8336587

00:03:53.625 --> 00:03:55.790 the two and after three year point

NOTE Confidence: 0.8336587

00:03:55.790 --> 00:03:57.960 and then the flattening of the curve.

NOTE Confidence: 0.8336587

00:03:57.960 --> 00:04:00.382 But we also interesting we see with

NOTE Confidence: 0.8336587

00:04:00.382 --> 00:04:03.186 no volume app anti PD one this is the.

NOTE Confidence: 0.8336587

00:04:03.190 --> 00:04:04.534 Going to combine data,

NOTE Confidence: 0.8336587

00:04:04.534 --> 00:04:06.550 little bit of mixing apples and

NOTE Confidence: 0.8336587

00:04:06.620 --> 00:04:08.986 oranges in terms of dose and schedule.

NOTE Confidence: 0.8336587

00:04:08.990 --> 00:04:10.354 All previously treated patients

NOTE Confidence: 0.8336587

00:04:10.354 --> 00:04:11.718 then now those patients,

NOTE Confidence: 0.8336587

00:04:11.720 --> 00:04:13.848 about 35% are living long term with

NOTE Confidence: 0.8336587

00:04:13.848 --> 00:04:15.894 no volume AB monotherapy and then

NOTE Confidence: 0.8336587

00:04:15.894 --> 00:04:18.799 moving on to the most recent update of

NOTE Confidence: 0.8336587

00:04:18.799 --> 00:04:20.917 the Checkmate 067 trial in Melanoma,

NOTE Confidence: 0.8336587

00:04:20.920 --> 00:04:23.517 which was a phase three trial that

NOTE Confidence: 0.8336587

00:04:23.517 --> 00:04:25.600 combine Knievel plus it be and

NOTE Confidence: 0.8336587

00:04:25.600 --> 00:04:27.400 compared it to Epyx alone Evo.

NOTE Confidence: 0.8336587

00:04:27.400 --> 00:04:29.446 Plus it be compared to niveau.

NOTE Confidence: 0.8336587

00:04:29.450 --> 00:04:30.722 It was not designed.

NOTE Confidence: 0.8336587

00:04:30.722 --> 00:04:32.630 The caveat here not designed to

NOTE Confidence: 0.8336587

00:04:32.700 --> 00:04:33.620 compare Niveau.

NOTE Confidence: 0.8336587

00:04:33.620 --> 00:04:35.796 Happy to Nivo but now with six years

NOTE Confidence: 0.8336587

00:04:35.796 --> 00:04:37.661 of follow-up you again see this

NOTE Confidence: 0.8336587

00:04:37.661 --> 00:04:39.557 inflection point around 2:00 and after

NOTE Confidence: 0.78244525

00:04:39.618 --> 00:04:41.616 three years flattening of the curves

NOTE Confidence: 0.78244525

00:04:41.616 --> 00:04:43.832 with needle plus Tippy, now 56 percent,

NOTE Confidence: 0.78244525

00:04:43.832 --> 00:04:45.890 57% of patients to living a long

NOTE Confidence: 0.78244525

00:04:45.961 --> 00:04:47.616 long term with the disease.

NOTE Confidence: 0.78244525

00:04:47.620 --> 00:04:49.170 So so the question is,

NOTE Confidence: 0.78244525

00:04:49.170 --> 00:04:51.969 with this kind of as the the new baseline,

NOTE Confidence: 0.78244525

00:04:51.970 --> 00:04:55.274 how can we improve upon these results?

NOTE Confidence: 0.78244525

00:04:55.280 --> 00:04:58.576 And we look at very important biomarker data,

NOTE Confidence: 0.78244525

00:04:58.580 --> 00:05:00.902 so the the importance of CD

NOTE Confidence: 0.78244525

00:05:00.902 --> 00:05:03.130 8 and the invasive margin.

NOTE Confidence: 0.78244525

00:05:03.130 --> 00:05:05.190 So it's the tumor stromal

NOTE Confidence: 0.78244525

00:05:05.190 --> 00:05:06.838 interface and the proximity.

NOTE Confidence: 0.78244525

00:05:06.840 --> 00:05:09.675 The closeness to the PD one PD

NOTE Confidence: 0.78244525

00:05:09.675 --> 00:05:11.826 interaction is highly predictive of

NOTE Confidence: 0.78244525

00:05:11.826 --> 00:05:14.822 responses to anti PD one therapy again

NOTE Confidence: 0.78244525

00:05:14.822 --> 00:05:17.668 in Melanoma and also that PDL one

NOTE Confidence: 0.78244525

00:05:17.668 --> 00:05:20.842 is a mark biomarker in now with the

NOTE Confidence: 0.78244525

00:05:20.842 --> 00:05:24.189 numerous diseases that PD one is looked at.

NOTE Confidence: 0.78244525

00:05:24.190 --> 00:05:25.246 PD1PD1 target therapies.

NOTE Confidence: 0.78244525

00:05:25.246 --> 00:05:27.006 The back seat when expression

NOTE Confidence: 0.78244525

00:05:27.006 --> 00:05:28.819 on immune infiltrating cells.

NOTE Confidence: 0.78244525

00:05:28.820 --> 00:05:30.630 So the new cells themselves,

NOTE Confidence: 0.78244525

00:05:30.630 --> 00:05:31.440 mostly macrophages,

NOTE Confidence: 0.78244525

00:05:31.440 --> 00:05:33.870 are also predicted responses to hear

NOTE Confidence: 0.78244525

00:05:33.870 --> 00:05:36.470 anti PDL one because it was a mad

NOTE Confidence: 0.78244525

00:05:36.470 --> 00:05:38.850 in patients with lung cancer and now

NOTE Confidence: 0.78244525

00:05:38.850 --> 00:05:40.800 other countries with kidney cancer.

NOTE Confidence: 0.78244525

00:05:40.800 --> 00:05:43.086 So to briefly summarize other aspects

NOTE Confidence: 0.78244525

00:05:43.086 --> 00:05:45.701 that could be applied to improving upon

NOTE Confidence: 0.78244525

00:05:45.701 --> 00:05:48.420 those results quite a few years ago now,

NOTE Confidence: 0.78244525

00:05:48.420 --> 00:05:49.144 Glenn Dranoff,

NOTE Confidence: 0.78244525

00:05:49.144 --> 00:05:50.954 my longtime mentor and friend,

NOTE Confidence: 0.78244525

00:05:50.960 --> 00:05:53.939 and I did some anti slip or anybody trials

NOTE Confidence: 0.78244525

00:05:53.939 --> 00:05:56.516 looking specifically in patients who had.

NOTE Confidence: 0.78244525

00:05:56.520 --> 00:05:58.338 Received a prior GMC based vaccine,

NOTE Confidence: 0.78244525

00:05:58.340 --> 00:06:00.158 but notice pathologically when they received.

NOTE Confidence: 0.78244525

00:06:00.160 --> 00:06:01.675 If you limit map that

NOTE Confidence: 0.78244525

00:06:01.675 --> 00:06:03.190 there was this in panel,

NOTE Confidence: 0.78244525

00:06:03.190 --> 00:06:04.960 a area central necrosis with the

NOTE Confidence: 0.78244525

00:06:04.960 --> 00:06:06.820 room available to around the outside,

NOTE Confidence: 0.78244525

00:06:06.820 --> 00:06:08.764 and that room available tumor was

NOTE Confidence: 0.78244525

00:06:08.764 --> 00:06:10.459 heavily infiltrated with CD4CD8 CD 20s.

NOTE Confidence: 0.78244525

00:06:10.460 --> 00:06:12.104 But we notice throughout the tumor

NOTE Confidence: 0.78244525

00:06:12.104 --> 00:06:13.965 that there was an immune attack

NOTE Confidence: 0.78244525

00:06:13.965 --> 00:06:15.730 of the vascular vessels feeding

NOTE Confidence: 0.78244525

00:06:15.730 --> 00:06:17.428 the deposits depicted in panel F,

NOTE Confidence: 0.78244525

00:06:17.430 --> 00:06:19.470 and that this these lymphocytes were

NOTE Confidence: 0.78244525

00:06:19.470 --> 00:06:21.427 attacking the blood vessels when the

NOTE Confidence: 0.78244525

00:06:21.427 --> 00:06:23.324 product will be in the center and

NOTE Confidence: 0.78244525

00:06:23.324 --> 00:06:25.084 probably leading to this TNF like

NOTE Confidence: 0.78244525

00:06:25.084 --> 00:06:26.869 effect that we virtualized in pathology.

NOTE Confidence: 0.78244525

00:06:26.869 --> 00:06:29.661 And so it raises the question of the

NOTE Confidence: 0.78244525

00:06:29.661 --> 00:06:31.728 combination as he was alluding to

NOTE Confidence: 0.78244525

00:06:31.728 --> 00:06:33.383 of combining anti angiogenesis and

NOTE Confidence: 0.78244525

00:06:33.448 --> 00:06:35.518 immune checkpoint in the importance

NOTE Confidence: 0.78244525

00:06:35.518 --> 00:06:36.346 of hypoxemia.

NOTE Confidence: 0.78244525

00:06:36.350 --> 00:06:38.758 If 1A making veg F that not only

NOTE Confidence: 0.78244525

00:06:38.758 --> 00:06:40.788 involved into Genesis but Veg F

NOTE Confidence: 0.78244525

00:06:40.788 --> 00:06:42.488 being a very potent suppression

NOTE Confidence: 0.78244525

00:06:42.488 --> 00:06:44.470 of dentrix cell maturation.

NOTE Confidence: 0.78244525

00:06:44.470 --> 00:06:46.255 Another important myeloid as important

NOTE Confidence: 0.78244525

00:06:46.255 --> 00:06:48.350 suppressor cells that you might like.

NOTE Confidence: 0.78244525

00:06:48.350 --> 00:06:50.545 My Lloyd Wright suppressor cells

NOTE Confidence: 0.78244525

00:06:50.545 --> 00:06:52.301 also make important engineering

NOTE Confidence: 0.78244525

00:06:52.301 --> 00:06:54.564 factors such as Veg F that lead

NOTE Confidence: 0.78244525

00:06:54.564 --> 00:06:56.109 to also this suppressive feature

NOTE Confidence: 0.78244525

00:06:56.109 --> 00:06:58.293 and whether there was a role for.

NOTE Confidence: 0.78244525

00:06:58.300 --> 00:06:59.002 Andrew Genesis,

NOTE Confidence: 0.78244525

00:06:59.002 --> 00:07:01.459 in terms of not just being blocked

NOTE Confidence: 0.78244525

00:07:01.459 --> 00:07:03.630 for for blood vessel formation but

NOTE Confidence: 0.78244525

00:07:03.630 --> 00:07:06.002 also its role in immune activation

NOTE Confidence: 0.78244525

00:07:06.002 --> 00:07:07.658 and immune suppression.

NOTE Confidence: 0.78244525

00:07:07.660 --> 00:07:10.000 So we looked into this further

NOTE Confidence: 0.78244525

00:07:10.000 --> 00:07:12.390 summarizing some work from a few

NOTE Confidence: 0.78244525

00:07:12.390 --> 00:07:14.275 years ago of combining simplified

NOTE Confidence: 0.78244525

00:07:14.275 --> 00:07:16.638 paid with entry into Genesis based

NOTE Confidence: 0.78244525

00:07:16.638 --> 00:07:18.966 on the vasculopathy that we saw.

NOTE Confidence: 0.78244525

00:07:18.970 --> 00:07:20.675 I thought the pathologically the

NOTE Confidence: 0.78244525

00:07:20.675 --> 00:07:23.283 role of veg F and decrease in

NOTE Confidence: 0.78244525

00:07:23.283 --> 00:07:25.363 the Newcastle maturation work by

NOTE Confidence: 0.78244525

00:07:25.363 --> 00:07:27.160 George Lucas and others.

NOTE Confidence: 0.78244525

00:07:27.160 --> 00:07:28.174 Overcash Jenna natural.

NOTE Confidence: 0.78244525

00:07:28.174 --> 00:07:30.202 Also had shown that blocking Veg

NOTE Confidence: 0.78244525

00:07:30.202 --> 00:07:32.158 F and proved himself trafficking

NOTE Confidence: 0.78244525

00:07:32.158 --> 00:07:34.498 across Endothelia and we worked with

NOTE Confidence: 0.78244525

00:07:34.562 --> 00:07:36.620 Jed Walchak memorial looking at pre

NOTE Confidence: 0.78244525

00:07:36.620 --> 00:07:39.002 treatment levels of Veg F which were

NOTE Confidence: 0.78244525

00:07:39.002 --> 00:07:41.340 associated with the higher the bowls with

NOTE Confidence: 0.7596663

00:07:41.404 --> 00:07:42.270 poor outcomes.

NOTE Confidence: 0.7596663

00:07:42.270 --> 00:07:44.406 Both less responses and less reliable.

NOTE Confidence: 0.7596663

00:07:44.410 --> 00:07:46.546 Again guilt by discussed by association.

NOTE Confidence: 0.7596663

00:07:46.550 --> 00:07:49.175 Then Jeff may play a role with

NOTE Confidence: 0.7596663

00:07:49.175 --> 00:07:51.070 the new checkpoint blockade.

NOTE Confidence: 0.7596663

00:07:51.070 --> 00:07:54.150 So this is just kind of some summary of that.

NOTE Confidence: 0.7596663

00:07:54.150 --> 00:07:57.230 Here's a pet scan of a patient on the top.

NOTE Confidence: 0.7596663

00:07:57.230 --> 00:07:59.519 The CAT scan portion shows his liver

NOTE Confidence: 0.7596663

00:07:59.519 --> 00:08:01.895 metastasis and then that is lit up by pet

NOTE Confidence: 0.7596663

00:08:01.895 --> 00:08:04.292 and after just a few months of treatment

NOTE Confidence: 0.7596663

00:08:04.292 --> 00:08:06.464 delivery tasks hasn't changed in size,

NOTE Confidence: 0.7596663

00:08:06.470 --> 00:08:08.534 but it has become metabolically cold

NOTE Confidence: 0.7596663

00:08:08.534 --> 00:08:11.298 and this trial would it be alone had a

NOTE Confidence: 0.7596663

00:08:11.298 --> 00:08:13.758 response rate of about 35% and 50% of

NOTE Confidence: 0.7596663

00:08:13.758 --> 00:08:16.014 patients doing doing well with controlled

NOTE Confidence: 0.7596663

00:08:16.014 --> 00:08:18.547 the disease for six months or more.

NOTE Confidence: 0.7596663

00:08:18.550 --> 00:08:20.220 So this is a background.

NOTE Confidence: 0.7596663

00:08:20.220 --> 00:08:22.341 I think the correlatives give you the

NOTE Confidence: 0.7596663

00:08:22.341 --> 00:08:24.538 basis for this for this combination,

NOTE Confidence: 0.7596663

00:08:24.540 --> 00:08:27.231 and that we look at the pre and on

NOTE Confidence: 0.7596663

00:08:27.231 --> 00:08:29.398 treatment on the left and comparing

NOTE Confidence: 0.7596663

00:08:29.398 --> 00:08:31.594 to patients who received it be

NOTE Confidence: 0.7596663

00:08:31.594 --> 00:08:33.876 alone on treatment on the right and

NOTE Confidence: 0.7596663

00:08:33.876 --> 00:08:35.862 some some control samples and the

NOTE Confidence: 0.7596663

00:08:35.862 --> 00:08:37.860 patients received Bevis is a map.

NOTE Confidence: 0.7596663

00:08:37.860 --> 00:08:40.408 Anti Veg F had changes in the

NOTE Confidence: 0.7596663

00:08:40.408 --> 00:08:42.189 endothelium as depicted by CD 31,

NOTE Confidence: 0.7596663

00:08:42.190 --> 00:08:43.860 where they morphologically look plumper,

NOTE Confidence: 0.7596663

00:08:43.860 --> 00:08:45.192 columnar and biochemically were

NOTE Confidence: 0.7596663

00:08:45.192 --> 00:08:47.190 activated with up regulation of E.

NOTE Confidence: 0.7596663

00:08:47.190 --> 00:08:47.534 Selectin.

NOTE Confidence: 0.7596663

00:08:47.534 --> 00:08:48.910 These morphologic and biochemical

NOTE Confidence: 0.7596663

00:08:48.910 --> 00:08:50.630 changes and then to filium.

NOTE Confidence: 0.7596663

00:08:50.630 --> 00:08:52.380 Were associated with kind of

NOTE Confidence: 0.7596663

00:08:52.380 --> 00:08:54.130 a robot robust in brisk,

NOTE Confidence: 0.7596663

00:08:54.130 --> 00:08:56.230 lymphocytic infiltrated on the larger insets.

NOTE Confidence: 0.7596663

00:08:56.230 --> 00:08:58.462 Here you can see that some red cells

NOTE Confidence: 0.7596663

00:08:58.462 --> 00:09:01.303 in the center of the endothelium and

NOTE Confidence: 0.7596663

00:09:01.303 --> 00:09:03.513 lymphocytes complete surrounding it in

NOTE Confidence: 0.7596663

00:09:03.582 --> 00:09:06.372 comparison to what we see with it be alone,

NOTE Confidence: 0.7596663

00:09:06.380 --> 00:09:08.130 which is really very little

NOTE Confidence: 0.7596663

00:09:08.130 --> 00:09:09.180 changes and aphelion.

NOTE Confidence: 0.7596663

00:09:09.180 --> 00:09:11.630 In addition, the endothelium with with veg.

NOTE Confidence: 0.7596663

00:09:11.630 --> 00:09:14.422 F blockade would be versus a mad had

NOTE Confidence: 0.7596663

00:09:14.422 --> 00:09:16.286 upregulation of other important anchor

NOTE Confidence: 0.7596663

00:09:16.286 --> 00:09:19.660 molecules such as the Cam and I Cam that

NOTE Confidence: 0.7596663

00:09:19.660 --> 00:09:22.327 you can see highlighted and Ethereum here.

NOTE Confidence: 0.7596663

00:09:22.330 --> 00:09:23.960 That also suggests that by

NOTE Confidence: 0.7596663

00:09:23.960 --> 00:09:26.190 blocking Veg F you can improve,

NOTE Confidence: 0.7596663

00:09:26.190 --> 00:09:28.215 potentially improve the trafficking of

NOTE Confidence: 0.7596663

00:09:28.215 --> 00:09:31.278 lymphocytes into the to my crime and in

NOTE Confidence: 0.7596663

00:09:31.278 --> 00:09:33.222 this approaching one of the concerns

NOTE Confidence: 0.7596663

00:09:33.222 --> 00:09:35.670 we had at the beginning of the talk,

NOTE Confidence: 0.7596663

00:09:35.670 --> 00:09:37.455 which was whether the lymphocytes

NOTE Confidence: 0.7596663

00:09:37.455 --> 00:09:39.240 immune cells can actually make

NOTE Confidence: 0.7596663

00:09:39.297 --> 00:09:40.577 it into my environment,

NOTE Confidence: 0.7596663

00:09:40.580 --> 00:09:42.340 or if they were excluded.

NOTE Confidence: 0.7596663

00:09:42.340 --> 00:09:44.251 So based on this then check went

NOTE Confidence: 0.7596663

00:09:44.251 --> 00:09:46.428 on to do some bevacizumab trials

NOTE Confidence: 0.7596663

00:09:46.428 --> 00:09:49.002 and they did something very smart.

NOTE Confidence: 0.7596663

00:09:49.010 --> 00:09:51.320 They gave a single dose of bevacizumab

NOTE Confidence: 0.7596663

00:09:51.320 --> 00:09:52.980 before combining with checkpoint.

NOTE Confidence: 0.7596663

00:09:52.980 --> 00:09:55.500 Did biopsies before and after above

NOTE Confidence: 0.7596663

00:09:55.500 --> 00:09:57.584 an fortunately showed that the

NOTE Confidence: 0.7596663

00:09:57.584 --> 00:09:59.908 Bev the Veg FA blockade by itself

NOTE Confidence: 0.7596663

00:09:59.908 --> 00:10:01.929 had changes in the endothelium.

NOTE Confidence: 0.7596663

00:10:01.930 --> 00:10:03.482 Ann had improved lymphocyte

NOTE Confidence: 0.7596663

00:10:03.482 --> 00:10:04.258 trafficking cross.

NOTE Confidence: 0.74153435

00:10:10.350 --> 00:10:12.934 Is your one and also the fact that

NOTE Confidence: 0.74153435

00:10:12.934 --> 00:10:15.600 the Arnie seek in the tumors that

NOTE Confidence: 0.74153435

00:10:15.600 --> 00:10:18.356 had a myeloid signature seems to do

NOTE Confidence: 0.74153435

00:10:18.356 --> 00:10:20.558 better when they receive this map.

NOTE Confidence: 0.74153435

00:10:20.560 --> 00:10:23.008 Again, tying in that myeloid suppressor

NOTE Confidence: 0.74153435

00:10:23.008 --> 00:10:26.341 function in the veg F function with the

NOTE Confidence: 0.74153435

00:10:26.341 --> 00:10:28.789 suppressive aspect of the immune system

NOTE Confidence: 0.74153435

00:10:28.858 --> 00:10:31.616 and that those patients who had those

NOTE Confidence: 0.74153435

00:10:31.616 --> 00:10:34.340 those myeloid cells there and receive Bev

NOTE Confidence: 0.74153435

00:10:34.340 --> 00:10:37.290 had a market improvement in their outcome.

NOTE Confidence: 0.74153435

00:10:37.290 --> 00:10:40.454 So this concept has very rapidly progressed

NOTE Confidence: 0.74153435

00:10:40.454 --> 00:10:43.152 and obviously in important issues such

NOTE Confidence: 0.74153435

00:10:43.152 --> 00:10:46.507 as kidney cancer that is driven by hip

NOTE Confidence: 0.74153435

00:10:46.507 --> 00:10:49.115 1A and in Genesis here is anti PDL,

NOTE Confidence: 0.74153435

00:10:49.120 --> 00:10:51.270 one to value map plus.

NOTE Confidence: 0.74153435

00:10:51.270 --> 00:10:53.114 XD Neb better far,

NOTE Confidence: 0.74153435

00:10:53.114 --> 00:10:55.419 123 inhibitor TKI showing that

NOTE Confidence: 0.74153435

00:10:55.419 --> 00:10:57.099 that combination improvement

NOTE Confidence: 0.74153435

00:10:57.099 --> 00:10:59.909 over soon to be alone.

NOTE Confidence: 0.74153435

00:10:59.910 --> 00:11:02.190 Another day to Pember Lism AB

NOTE Confidence: 0.74153435

00:11:02.190 --> 00:11:04.529 plus extended so anti PD 1 + 54.

NOTE Confidence: 0.74153435

00:11:04.530 --> 00:11:06.265 One 2-3 and innovation versus

NOTE Confidence: 0.74153435

00:11:06.265 --> 00:11:08.475 ended up having improvement in both

NOTE Confidence: 0.74153435

00:11:08.475 --> 00:11:10.545 progression free and overall survival.

NOTE Confidence: 0.74153435

00:11:10.550 --> 00:11:13.007 And this kind of concept has expanded

NOTE Confidence: 0.74153435

00:11:13.007 --> 00:11:15.749 very quickly to non small cell lung

NOTE Confidence: 0.74153435

00:11:15.749 --> 00:11:18.173 cancer with some data showing improvement

NOTE Confidence: 0.74153435

00:11:18.247 --> 00:11:19.699 with angiogenesis combinations

NOTE Confidence: 0.74153435

00:11:19.699 --> 00:11:22.603 and either will or has probably

NOTE Confidence: 0.74153435

00:11:22.603 --> 00:11:25.175 checkpoint plus anti Andrew Genesis be

NOTE Confidence: 0.74153435

00:11:25.175 --> 00:11:26.843 approvals in hepatocellular carcinoma,

NOTE Confidence: 0.74153435

00:11:26.850 --> 00:11:29.868 anamitra carcinoma and with other many

NOTE Confidence: 0.74153435

00:11:29.868 --> 00:11:31.880 combinations being being developed.

NOTE Confidence: 0.74153435

00:11:31.880 --> 00:11:34.571 So one of the questions we had is what

NOTE Confidence: 0.74153435

00:11:34.571 --> 00:11:37.349 is the role of the immune system in

NOTE Confidence: 0.74153435

00:11:37.349 --> 00:11:40.204 this anti into Genesis in terms of the

NOTE Confidence: 0.74153435

00:11:40.204 --> 00:11:42.582 role of anti genesis and it distract

NOTE Confidence: 0.74153435

00:11:42.582 --> 00:11:45.070 effect on on immunity and so in some

NOTE Confidence: 0.74153435

00:11:45.143 --> 00:11:47.460 of our patients we have a banking

NOTE Confidence: 0.74153435

00:11:47.460 --> 00:11:49.688 aspect we collect from the biopsies,

NOTE Confidence: 0.74153435

00:11:49.690 --> 00:11:51.122 try isolate Melanoma cells.

NOTE Confidence: 0.74153435

00:11:51.122 --> 00:11:53.270 We also collect tumor associated fuel

NOTE Confidence: 0.74153435

00:11:53.334 --> 00:11:55.266 cells and also to associated comma stem

NOTE Confidence: 0.74153435

00:11:55.266 --> 00:11:57.419 cells in a very simple experiment,

NOTE Confidence: 0.74153435

00:11:57.420 --> 00:11:59.667 Western blot or mean blinding here looked

NOTE Confidence: 0.74153435

00:11:59.667 --> 00:12:01.920 at before and after treatment with.

NOTE Confidence: 0.74153435

00:12:01.920 --> 00:12:03.700 Anti introduces checkpoint combinations

NOTE Confidence: 0.74153435

00:12:03.700 --> 00:12:06.370 and found that patients post treatment

NOTE Confidence: 0.74153435

00:12:06.436 --> 00:12:08.524 from their human immunity had either

NOTE Confidence: 0.74153435

00:12:08.524 --> 00:12:10.323 recognized new an energy targets

NOTE Confidence: 0.74153435

00:12:10.323 --> 00:12:12.381 or had higher antibody titers to

NOTE Confidence: 0.74153435

00:12:12.381 --> 00:12:14.445 certain targets and just of note

NOTE Confidence: 0.74153435

00:12:14.445 --> 00:12:16.860 the bottom left hand corner is that

NOTE Confidence: 0.74153435

00:12:16.932 --> 00:12:19.157 these two are individual cells.

NOTE Confidence: 0.74153435

00:12:19.160 --> 00:12:21.666 Do make tube formation so they are

NOTE Confidence: 0.74153435

00:12:21.666 --> 00:12:24.221 functional that and so we were interested

NOTE Confidence: 0.74153435

00:12:24.221 --> 00:12:26.333 in trying to isolate what those

NOTE Confidence: 0.74153435

00:12:26.399 --> 00:12:28.949 targets are because they were seeing

NOTE Confidence: 0.74153435

00:12:28.949 --> 00:12:31.088 someone else somewhere seen actually

NOTE Confidence: 0.74153435

00:12:31.088 --> 00:12:33.278 on the endothelial cells themselves.

NOTE Confidence: 0.74153435

00:12:33.280 --> 00:12:34.705 Calls other medical mental illnesses

NOTE Confidence: 0.74153435

00:12:34.705 --> 00:12:36.517 and it comes stem cells within

NOTE Confidence: 0.74153435

00:12:36.517 --> 00:12:37.849 the tumor micro environment.

NOTE Confidence: 0.74153435

00:12:37.850 --> 00:12:39.796 So one of the factors that were

NOTE Confidence: 0.74153435

00:12:39.796 --> 00:12:42.602 found in in in doing our kind of

NOTE Confidence: 0.74153435

00:12:42.602 --> 00:12:44.126 Sidney expression library screening

NOTE Confidence: 0.74153435

00:12:44.126 --> 00:12:46.584 of endothelial cells with this other

NOTE Confidence: 0.74153435

00:12:46.584 --> 00:12:48.923 energetic factor in your put into

NOTE Confidence: 0.74153435

00:12:48.923 --> 00:12:51.587 an so it kind of shows that patients

NOTE Confidence: 0.74153435

00:12:51.587 --> 00:12:54.661 can at least make any bodies against

NOTE Confidence: 0.74153435

00:12:54.661 --> 00:12:57.358 another engine factory here at age 2

NOTE Confidence: 0.74153435

00:12:57.358 --> 00:12:59.687 and age 2 is involved with in Genesis

NOTE Confidence: 0.74153435

00:12:59.687 --> 00:13:02.186 through spreading and edit this on migration.

NOTE Confidence: 0.74153435

00:13:02.190 --> 00:13:04.200 It's involved with actually anchoring

NOTE Confidence: 0.74153435

00:13:04.200 --> 00:13:06.890 the ilium to parasites and kind of

NOTE Confidence: 0.74153435

00:13:06.890 --> 00:13:08.415 a scaffold of the deathly.

NOTE Confidence: 0.74153435

00:13:08.420 --> 00:13:10.320 For them to gain structure,

NOTE Confidence: 0.74153435

00:13:10.320 --> 00:13:13.092 and it's also been shown to be

NOTE Confidence: 0.74153435

00:13:13.092 --> 00:13:14.860 involved with resistance to bed.

NOTE Confidence: 0.74153435

00:13:14.860 --> 00:13:16.376 This is a map,

NOTE Confidence: 0.74153435

00:13:16.376 --> 00:13:18.650 so in many trials mostly chemotherapy.

NOTE Confidence: 0.74153435

00:13:18.650 --> 00:13:20.590 Those pieces who developed resistance

NOTE Confidence: 0.74153435

00:13:20.590 --> 00:13:22.530 had higher levels of Angel

NOTE Confidence: 0.78150344

00:13:22.593 --> 00:13:25.202 Queen too, as a kind of a resistant I

NOTE Confidence: 0.78150344

00:13:25.202 --> 00:13:28.264 now to tie in the Ender Genesis back

NOTE Confidence: 0.78150344

00:13:28.264 --> 00:13:30.880 with the potential for immune regulation

NOTE Confidence: 0.78150344

00:13:30.880 --> 00:13:33.743 and repeating 2 not only signals by

NOTE Confidence: 0.78150344

00:13:33.743 --> 00:13:36.086 that I receptor found on endothelium,

NOTE Confidence: 0.78150344

00:13:36.086 --> 00:13:38.360 but also tide to accept it,

NOTE Confidence: 0.78150344

00:13:38.360 --> 00:13:39.820 which can be found.

NOTE Confidence: 0.78150344

00:13:39.820 --> 00:13:42.010 Onto your training monocytes and macrophages.

NOTE Confidence: 0.78150344

00:13:42.010 --> 00:13:43.580 So again, the myeloid component

NOTE Confidence: 0.78150344

00:13:43.580 --> 00:13:45.959 here being tide in as well as

NOTE Confidence: 0.78150344

00:13:45.959 --> 00:13:47.459 the link between angiogenesis,

NOTE Confidence: 0.78150344

00:13:47.460 --> 00:13:49.506 an macrophage biology and immune suppression.

NOTE Confidence: 0.78150344

00:13:49.510 --> 00:13:52.138 So there could be a dual role for entropy

NOTE Confidence: 0.78150344

00:13:52.138 --> 00:13:54.477 into both in terms of the androgenic

NOTE Confidence: 0.78150344

00:13:54.477 --> 00:13:57.010 component as well as immune regulation,

NOTE Confidence: 0.78150344

00:13:57.010 --> 00:13:59.229 so we were further interest in just

NOTE Confidence: 0.78150344

00:13:59.229 --> 00:14:01.871 kind of taking a look at this and

NOTE Confidence: 0.78150344

00:14:01.871 --> 00:14:03.923 found for number of combinations that

NOTE Confidence: 0.78150344

00:14:03.923 --> 00:14:06.131 Angel Queen 2 levels were associated

NOTE Confidence: 0.78150344

00:14:06.131 --> 00:14:08.263 with outcomes to treatment so so

NOTE Confidence: 0.78150344

00:14:08.263 --> 00:14:09.968 patients who had higher levels.

NOTE Confidence: 0.78150344

00:14:09.970 --> 00:14:10.975 Andrew Queen 2.

NOTE Confidence: 0.78150344

00:14:10.975 --> 00:14:13.320 Or changes in between 2 levels did

NOTE Confidence: 0.78150344

00:14:13.390 --> 00:14:16.042 worse and that patients who developed

NOTE Confidence: 0.78150344

00:14:16.042 --> 00:14:18.620 antibodies to interpret into did better,

NOTE Confidence: 0.78150344

00:14:18.620 --> 00:14:20.550 showing both for patients with

NOTE Confidence: 0.78150344

00:14:20.550 --> 00:14:22.950 it be on the bottom here.

NOTE Confidence: 0.78150344

00:14:22.950 --> 00:14:26.206 And for patients who received it be plus

NOTE Confidence: 0.78150344

00:14:26.206 --> 00:14:29.249 businesses map on the top right hand corner,

NOTE Confidence: 0.78150344

00:14:29.250 --> 00:14:31.620 which is the ratio of antibodies.

NOTE Confidence: 0.78150344

00:14:31.620 --> 00:14:33.978 Change two afterwards to pre levels.

NOTE Confidence: 0.78150344

00:14:33.980 --> 00:14:36.170 There are a couple of patients

NOTE Confidence: 0.78150344

00:14:36.170 --> 00:14:38.565 who had high titer antibodies and

NOTE Confidence: 0.78150344

00:14:38.565 --> 00:14:41.133 whether entropy to go up there.

NOTE Confidence: 0.78150344

00:14:41.140 --> 00:14:42.898 They had the highest danger point

NOTE Confidence: 0.78150344

00:14:42.898 --> 00:14:44.859 to any bodies that were present,

NOTE Confidence: 0.78150344

00:14:44.860 --> 00:14:46.841 so the one of the questions is

NOTE Confidence: 0.78150344

00:14:46.841 --> 00:14:48.466 whether the humoral immunity being

NOTE Confidence: 0.78150344

00:14:48.466 --> 00:14:50.251 developed is actually functional an

NOTE Confidence: 0.78150344

00:14:50.251 --> 00:14:52.489 we have some data that the patients

NOTE Confidence: 0.78150344

00:14:52.489 --> 00:14:54.465 who are making any bias to interpret

NOTE Confidence: 0.78150344

00:14:54.465 --> 00:14:56.295 into some of those antibodies can

NOTE Confidence: 0.78150344

00:14:56.295 --> 00:14:58.192 actually block Type 2 signaling both

NOTE Confidence: 0.78150344

00:14:58.192 --> 00:14:59.737 on endothelium and in macrophages,

NOTE Confidence: 0.78150344

00:14:59.740 --> 00:15:01.540 so so the immune system may be very

NOTE Confidence: 0.78150344

00:15:01.540 --> 00:15:03.603 smart in terms of actually making

NOTE Confidence: 0.78150344

00:15:03.603 --> 00:15:04.770 functional antibodies against

NOTE Confidence: 0.78150344

00:15:04.770 --> 00:15:06.250 an engineering factor here,

NOTE Confidence: 0.78150344

00:15:06.250 --> 00:15:08.590 such as interpreting 2.

NOTE Confidence: 0.78150344

00:15:08.590 --> 00:15:11.062 So here is some of the data showing

NOTE Confidence: 0.78150344

00:15:11.062 --> 00:15:13.451 that as a function of treatment

NOTE Confidence: 0.78150344

00:15:13.451 --> 00:15:15.571 patients get higher levels of

NOTE Confidence: 0.78150344

00:15:15.571 --> 00:15:18.300 agent into anybody's he both with

NOTE Confidence: 0.78150344

00:15:18.300 --> 00:15:20.530 patients received hippy dippy Bev.

NOTE Confidence: 0.78150344

00:15:20.530 --> 00:15:24.370 We have data showing anti PD one patients

NOTE Confidence: 0.78150344

00:15:24.370 --> 00:15:26.891 also developed any bias to injure

NOTE Confidence: 0.78150344

00:15:26.891 --> 00:15:30.050 Queen 2 as a function of treatment.

NOTE Confidence: 0.78150344

00:15:30.050 --> 00:15:32.360 So one of the questions again,

NOTE Confidence: 0.78150344

00:15:32.360 --> 00:15:34.295 maybe goodbye Sociation is is

NOTE Confidence: 0.78150344

00:15:34.295 --> 00:15:36.979 is the expression of a gene two,

NOTE Confidence: 0.78150344

00:15:36.980 --> 00:15:39.367 which seems to be suppressed by Veja

NOTE Confidence: 0.78150344

00:15:39.367 --> 00:15:41.619 blockade at times associated with these

NOTE Confidence: 0.78150344

00:15:41.619 --> 00:15:43.935 myeloid cells in the tumor microman

NOTE Confidence: 0.78150344

00:15:43.935 --> 00:15:46.217 now in preclinical animal models,

NOTE Confidence: 0.78150344

00:15:46.220 --> 00:15:48.915 people find M1 macrophages as more tumor.

NOTE Confidence: 0.78150344

00:15:48.920 --> 00:15:51.608 Sidell M2 is more suppressive in humans.

NOTE Confidence: 0.78150344

00:15:51.610 --> 00:15:53.458 It's a bit more challenging to

NOTE Confidence: 0.78150344

00:15:53.458 --> 00:15:56.259 define M1 versus 2 and it's really

NOTE Confidence: 0.78150344

00:15:56.259 --> 00:15:57.765 more functional characteristics,

NOTE Confidence: 0.78150344

00:15:57.770 --> 00:16:00.230 but he wanted to look at.

NOTE Confidence: 0.78150344

00:16:00.230 --> 00:16:03.326 Patients received if he alone would be Bev.

NOTE Confidence: 0.78150344

00:16:03.330 --> 00:16:05.946 So we had these samples to look at

NOTE Confidence: 0.78150344

00:16:05.946 --> 00:16:07.929 Angel Queen two expression before

NOTE Confidence: 0.78150344

00:16:07.929 --> 00:16:10.443 and after treatment and what we

NOTE Confidence: 0.78150344

00:16:10.443 --> 00:16:12.998 found is that with businesses amab,

NOTE Confidence: 0.78150344

00:16:13.000 --> 00:16:15.712 if you look both in the tumor and

NOTE Confidence: 0.78150344

00:16:15.712 --> 00:16:18.074 and acylium that you get decrease

NOTE Confidence: 0.78150344

00:16:18.074 --> 00:16:20.074 in entropy into expression as

NOTE Confidence: 0.78150344

00:16:20.074 --> 00:16:22.289 a function of the decade.

NOTE Confidence: 0.78150344

00:16:22.290 --> 00:16:24.220 But with hippie alone endocrine

NOTE Confidence: 0.78150344

00:16:24.220 --> 00:16:26.982 two seems to increase in both the

NOTE Confidence: 0.78150344

00:16:26.982 --> 00:16:29.256 tumor cells and in the endothelium.

NOTE Confidence: 0.7170105

00:16:29.260 --> 00:16:31.636 We then correlated the level of.

NOTE Confidence: 0.7170105

00:16:31.640 --> 00:16:33.670 Of Andrew Queen two that we could

NOTE Confidence: 0.7170105

00:16:33.670 --> 00:16:36.216 find in the ilium, to see 163 cells

NOTE Confidence: 0.7170105

00:16:36.216 --> 00:16:37.992 in the tumor marker firemint, CDC.

NOTE Confidence: 0.7170105

00:16:37.992 --> 00:16:40.260 Once we can be a marker for my Lord

NOTE Confidence: 0.7170105

00:16:40.327 --> 00:16:42.327 suppressor cells, or dendritic cells,

NOTE Confidence: 0.7170105

00:16:42.327 --> 00:16:45.297 and what we found in the dozen or so cases

NOTE Confidence: 0.7170105

00:16:45.297 --> 00:16:47.794 that there was a seems to be a correlation

NOTE Confidence: 0.7170105

00:16:47.794 --> 00:16:50.244 with age 2 expression in CD163 cells.

NOTE Confidence: 0.7170105

00:16:50.250 --> 00:16:52.080 So the higher the age 2,

NOTE Confidence: 0.7170105

00:16:52.080 --> 00:16:54.816 the more CD wants 3 cells that were noted.

NOTE Confidence: 0.7170105

00:16:54.820 --> 00:16:56.770 The tumor marker aren't these city

NOTE Confidence: 0.7170105

00:16:56.770 --> 00:16:59.211 wants 3 cells would be the cells that

NOTE Confidence: 0.7170105

00:16:59.211 --> 00:17:01.606 had the Type 2 receptors on them and

NOTE Confidence: 0.7170105

00:17:01.606 --> 00:17:03.724 would part of the myeloid suppression.

NOTE Confidence: 0.7170105

00:17:03.730 --> 00:17:06.146 And so there was kind of a correlation

NOTE Confidence: 0.7170105

00:17:06.146 --> 00:17:08.445 between that levels of age 2 in the

NOTE Confidence: 0.7170105

00:17:08.445 --> 00:17:10.369 my suppressor cells and tumor marker.

NOTE Confidence: 0.7170105

00:17:10.370 --> 00:17:12.603 Violent again giving data to suggest that

NOTE Confidence: 0.7170105

00:17:12.603 --> 00:17:14.899 maybe this would be an important target

NOTE Confidence: 0.7170105

00:17:14.899 --> 00:17:16.813 to consider from both an androgenic

NOTE Confidence: 0.7170105

00:17:16.875 --> 00:17:18.970 standpoint and from immune regulation.

NOTE Confidence: 0.7170105

00:17:18.970 --> 00:17:21.866 So moving on to some other plan today,

NOTE Confidence: 0.7170105

00:17:21.870 --> 00:17:24.396 working with Summer Amanar Group whose

NOTE Confidence: 0.7170105

00:17:24.396 --> 00:17:26.510 therapist in geologist we preceded

NOTE Confidence: 0.7170105

00:17:26.510 --> 00:17:29.044 with a Phase 1B study that tested

NOTE Confidence: 0.7170105

00:17:29.044 --> 00:17:31.568 the activity of PEMBLE is a map anti

NOTE Confidence: 0.7170105

00:17:31.568 --> 00:17:34.038 PD one with TRIBUTED which is in a

NOTE Confidence: 0.7170105

00:17:34.038 --> 00:17:36.000 Pepto body that blocks both Angel

NOTE Confidence: 0.7170105

00:17:36.078 --> 00:17:38.520 Green one and interpreting two now.

NOTE Confidence: 0.7170105

00:17:38.520 --> 00:17:41.327 The goal here would be hopefully to

NOTE Confidence: 0.7170105

00:17:41.327 --> 00:17:43.469 get the interpreting to blockade.

NOTE Confidence: 0.7170105

00:17:43.470 --> 00:17:45.432 Black entropy and one would maybe

NOTE Confidence: 0.7170105

00:17:45.432 --> 00:17:47.749 potentially do a slightly different effect,

NOTE Confidence: 0.7170105

00:17:47.750 --> 00:17:50.549 but we know that both veg F in this

NOTE Confidence: 0.7170105

00:17:50.549 --> 00:17:53.998 cartoon here as well as age 2 have some

NOTE Confidence: 0.7170105

00:17:53.998 --> 00:17:55.564 overlapping functions into distinct

NOTE Confidence: 0.7170105

00:17:55.564 --> 00:17:58.818 functions both on their veg F and H2 effects.

NOTE Confidence: 0.7170105

00:17:58.818 --> 00:18:00.250 On myeloid suppressor cells,

NOTE Confidence: 0.7170105

00:18:00.250 --> 00:18:02.085 making important factors of style

NOTE Confidence: 0.7170105

00:18:02.085 --> 00:18:04.658 10 and such the potential role for

NOTE Confidence: 0.7170105

00:18:04.658 --> 00:18:06.338 PDL 1 onto associated macrophages

NOTE Confidence: 0.7170105

00:18:06.338 --> 00:18:09.181 in the role that the entropy do in

NOTE Confidence: 0.7170105

00:18:09.181 --> 00:18:11.346 twin two increases that expression on

NOTE Confidence: 0.7170105

00:18:11.346 --> 00:18:13.276 tumor social macrophages went back

NOTE Confidence: 0.7170105

00:18:13.276 --> 00:18:14.820 to one day regional.

NOTE Confidence: 0.7170105

00:18:14.820 --> 00:18:16.540 Slide showing how PD one

NOTE Confidence: 0.7170105

00:18:16.540 --> 00:18:18.260 immune cells into my crime.

NOTE Confidence: 0.7170105

00:18:18.260 --> 00:18:20.374 It was predictive of a Tesla smab

NOTE Confidence: 0.7170105

00:18:20.374 --> 00:18:22.806 responses to in lung cancer and other

NOTE Confidence: 0.7170105

00:18:22.806 --> 00:18:24.990 myeloid cells such as neutrophils and

NOTE Confidence: 0.7170105

00:18:25.058 --> 00:18:27.170 that are becoming more highlighted in

NOTE Confidence: 0.7170105

00:18:27.170 --> 00:18:29.486 terms of their role in immune suppression.

NOTE Confidence: 0.7170105

00:18:29.486 --> 00:18:31.964 So we're going to show you the first

NOTE Confidence: 0.7170105

00:18:31.964 --> 00:18:33.806 group of patients that were rolled

NOTE Confidence: 0.7170105

00:18:33.806 --> 00:18:36.072 in this study were 17 microsatellite

NOTE Confidence: 0.7170105

00:18:36.072 --> 00:18:38.207 stable patients with clinical cancer.

NOTE Confidence: 0.7170105

00:18:38.210 --> 00:18:40.166 All had been heavily pretreated meeting

NOTE Confidence: 0.7170105

00:18:40.166 --> 00:18:42.680 time of 2.6 years since her diagnosis.

NOTE Confidence: 0.7170105

00:18:42.680 --> 00:18:45.432 In this trial there are no DLT's in

NOTE Confidence: 0.7170105

00:18:45.432 --> 00:18:48.120 that 30 mixture kid was was determined

NOTE Confidence: 0.7170105

00:18:48.120 --> 00:18:51.640 to be the MTD for the the Pepto body.

NOTE Confidence: 0.7170105

00:18:51.640 --> 00:18:53.920 There were some truly adverse events.

NOTE Confidence: 0.7170105

00:18:53.920 --> 00:18:54.660 Download distention,

NOTE Confidence: 0.7170105

00:18:54.660 --> 00:18:57.250 diarrhea of some some adima which has

NOTE Confidence: 0.7170105

00:18:57.250 --> 00:18:59.616 been shown with injury and inhibitors.

NOTE Confidence: 0.7170105

00:18:59.620 --> 00:19:02.732 That did you get a little bit of

NOTE Confidence: 0.7170105

00:19:02.732 --> 00:19:05.557 third spacing some level of Tita

NOTE Confidence: 0.7170105

00:19:05.557 --> 00:19:08.007 abnormalities but but nothing there

NOTE Confidence: 0.7170105

00:19:08.007 --> 00:19:10.617 was there was dose limiting.

NOTE Confidence: 0.7170105

00:19:10.620 --> 00:19:12.881 This is the dose escalation for those

NOTE Confidence: 0.7170105

00:19:12.881 --> 00:19:14.961 treated on the left with multiple

NOTE Confidence: 0.7170105

00:19:14.961 --> 00:19:17.397 different cancers and then on the on.

NOTE Confidence: 0.7170105

00:19:17.400 --> 00:19:19.766 The right is the colorectal cancer court.

NOTE Confidence: 0.7170105

00:19:19.770 --> 00:19:21.810 Specifically in the first quarter pants

NOTE Confidence: 0.7170105

00:19:21.810 --> 00:19:23.840 record, so in the dust escalation,

NOTE Confidence: 0.7170105

00:19:23.840 --> 00:19:25.880 a number of cancers were treated,

NOTE Confidence: 0.76763356

00:19:25.880 --> 00:19:26.894 including colorectal cancer,

NOTE Confidence: 0.76763356

00:19:26.894 --> 00:19:28.900 ovarian renal cell, showing that there

NOTE Confidence: 0.76763356

00:19:28.900 --> 00:19:31.210 were a couple of partial responses include

NOTE Confidence: 0.76763356

00:19:31.270 --> 00:19:33.328 rectal cancer and some stable disease,

NOTE Confidence: 0.76763356

00:19:33.330 --> 00:19:34.890 and the writer the spaghetti

NOTE Confidence: 0.76763356

00:19:34.890 --> 00:19:36.881 plots for spider plots showing the

NOTE Confidence: 0.76763356

00:19:36.881 --> 00:19:38.736 clinical activity in patients with

NOTE Confidence: 0.76763356

00:19:38.736 --> 00:19:40.220 colorectal cancer who received.

NOTE Confidence: 0.76763356

00:19:40.220 --> 00:19:41.635 This combination in the color

NOTE Confidence: 0.76763356

00:19:41.635 --> 00:19:43.050 took or hurt the meantime.

NOTE Confidence: 0.76763356

00:19:43.050 --> 00:19:44.706 Depression was 2.8 months that the

NOTE Confidence: 0.76763356

00:19:44.706 --> 00:19:46.449 meaning of survival of nine months.

NOTE Confidence: 0.76763356

00:19:46.450 --> 00:19:48.742 We're going to go through a

NOTE Confidence: 0.76763356

00:19:48.742 --> 00:19:50.750 little just now with this.

NOTE Confidence: 0.76763356

00:19:50.750 --> 00:19:53.518 So we applied site off which is looking

NOTE Confidence: 0.76763356

00:19:53.518 --> 00:19:56.882 at at staining immune cells in the from

NOTE Confidence: 0.76763356

00:19:56.882 --> 00:20:00.162 the purple blood using any bodies that

NOTE Confidence: 0.76763356

00:20:00.162 --> 00:20:02.617 have heavy metal conjugation which,

NOTE Confidence: 0.76763356

00:20:02.620 --> 00:20:05.170 as opposed to doing flow cytometry,

NOTE Confidence: 0.76763356

00:20:05.170 --> 00:20:07.290 are permitted to do 3540

NOTE Confidence: 0.76763356

00:20:07.290 --> 00:20:09.410 markers at at a time,

NOTE Confidence: 0.76763356

00:20:09.410 --> 00:20:11.888 and this is looking at patients with

NOTE Confidence: 0.76763356

00:20:11.888 --> 00:20:15.662 the 1st 12 weeks of cycles of therapy in

NOTE Confidence: 0.76763356

00:20:15.662 --> 00:20:17.970 specifically focusing on the colorectal

NOTE Confidence: 0.76763356

00:20:17.970 --> 00:20:21.337 cohort and in splitting up patients who.

NOTE Confidence: 0.76763356

00:20:21.340 --> 00:20:23.030 Received clinical benefit as defined

NOTE Confidence: 0.76763356

00:20:23.030 --> 00:20:25.190 as either response or stable disease,

NOTE Confidence: 0.76763356

00:20:25.190 --> 00:20:28.020 lasting six months or more.

NOTE Confidence: 0.76763356

00:20:28.020 --> 00:20:30.162 What we found is that there were

NOTE Confidence: 0.76763356

00:20:30.162 --> 00:20:31.940 certainly higher CC-3 positive cells

NOTE Confidence: 0.76763356

00:20:31.940 --> 00:20:33.925 in patients with clinical benefit

NOTE Confidence: 0.76763356

00:20:33.925 --> 00:20:36.089 following their first mission therapy.

NOTE Confidence: 0.76763356

00:20:36.090 --> 00:20:38.070 Both C4G8 cells decrease in patients

NOTE Confidence: 0.76763356

00:20:38.070 --> 00:20:40.499 that did not have clinical benefit.

NOTE Confidence: 0.76763356

00:20:40.500 --> 00:20:41.964 CD 8 effector cell,

NOTE Confidence: 0.76763356

00:20:41.964 --> 00:20:42.330 specifically,

NOTE Confidence: 0.76763356

00:20:42.330 --> 00:20:44.220 the memory phenotypes decrease the

NOTE Confidence: 0.76763356

00:20:44.220 --> 00:20:46.498 patients that do not have clinical

NOTE Confidence: 0.76763356

00:20:46.498 --> 00:20:48.745 benefit in both the CD four and

NOTE Confidence: 0.76763356

00:20:48.745 --> 00:20:50.639 8603 cells decreased in patients

NOTE Confidence: 0.76763356

00:20:50.639 --> 00:20:52.609 who had no clinical benefit.

NOTE Confidence: 0.76763356

00:20:52.610 --> 00:20:53.394 In particular,

NOTE Confidence: 0.76763356

00:20:53.394 --> 00:20:56.138 was noted in patients who had rapid

NOTE Confidence: 0.76763356

00:20:56.138 --> 00:20:58.488 progressive disease that these cells were.

NOTE Confidence: 0.76763356

00:20:58.490 --> 00:21:01.696 Were quite were quite low in decreased,

NOTE Confidence: 0.76763356

00:21:01.700 --> 00:21:04.469 almost non detectable.

NOTE Confidence: 0.76763356

00:21:04.470 --> 00:21:05.950 We're looking at other phenotypes

NOTE Confidence: 0.76763356

00:21:05.950 --> 00:21:08.309 in terms of an NK cell analysis.

NOTE Confidence: 0.76763356

00:21:08.310 --> 00:21:10.230 Those and we're going to think

NOTE Confidence: 0.76763356

00:21:10.230 --> 00:21:11.510 further discussed the potential

NOTE Confidence: 0.76763356

00:21:11.562 --> 00:21:13.107 role for innate immunity here.

NOTE Confidence: 0.76763356

00:21:13.110 --> 00:21:15.214 So this is going to be the first

NOTE Confidence: 0.76763356

00:21:15.214 --> 00:21:17.291 kind of hinted that there are

NOTE Confidence: 0.76763356

00:21:17.291 --> 00:21:19.505 trends that increases in the city.

NOTE Confidence: 0.76763356

00:21:19.510 --> 00:21:20.706 Fix ceases, Dim CD,

NOTE Confidence: 0.76763356

00:21:20.706 --> 00:21:22.201 60 negative cells in patients

NOTE Confidence: 0.76763356

00:21:22.201 --> 00:21:23.668 with no clinical benefit,

NOTE Confidence: 0.76763356

00:21:23.670 --> 00:21:25.590 and that is in the CD.

NOTE Confidence: 0.76763356

00:21:25.590 --> 00:21:27.510 16 positive cells were higher in

NOTE Confidence: 0.76763356

00:21:27.510 --> 00:21:28.790 patients with clinical benefit,

NOTE Confidence: 0.76763356

00:21:28.790 --> 00:21:30.710 which goes along with the potential

NOTE Confidence: 0.76763356

00:21:30.710 --> 00:21:31.350 indeed aspects.

NOTE Confidence: 0.76763356

00:21:31.350 --> 00:21:33.312 There are no differences in the

NOTE Confidence: 0.76763356

00:21:33.312 --> 00:21:34.293 CD fix excels.

NOTE Confidence: 0.76763356

00:21:34.300 --> 00:21:37.065 According to the cycle or clinical benefits,

NOTE Confidence: 0.76763356

00:21:37.070 --> 00:21:39.324 it didn't seem that it was had

NOTE Confidence: 0.76763356

00:21:39.324 --> 00:21:41.670 to do with timing over treatment

NOTE Confidence: 0.76763356

00:21:41.670 --> 00:21:44.694 and the CD 56 positive cells were

NOTE Confidence: 0.76763356

00:21:44.780 --> 00:21:46.865 higher in patients clinical benefit

NOTE Confidence: 0.76763356

00:21:46.865 --> 00:21:50.060 as well as the NK marker Pete 3056

NOTE Confidence: 0.76763356

00:21:50.060 --> 00:21:51.910 positive cells were higher in

NOTE Confidence: 0.76763356

00:21:51.910 --> 00:21:53.699 patients received clinical benefit.

NOTE Confidence: 0.76763356

00:21:53.700 --> 00:21:55.670 This was consistent across really

NOTE Confidence: 0.76763356

00:21:55.670 --> 00:21:58.106 all of the patients with the

NOTE Confidence: 0.76763356

00:21:58.106 --> 00:22:00.440 significance look in my Lloyd cells,

NOTE Confidence: 0.76763356

00:22:00.440 --> 00:22:03.044 which you would assume that the Pepto

NOTE Confidence: 0.76763356

00:22:03.044 --> 00:22:05.700 body might be affecting my itself.

NOTE Confidence: 0.76763356

00:22:05.700 --> 00:22:07.570 That Mila cells increased in

NOTE Confidence: 0.76763356

00:22:07.570 --> 00:22:09.440 patients with no clinical benefit,

NOTE Confidence: 0.76763356

00:22:09.440 --> 00:22:11.350 but the myeloid derived suppressor

NOTE Confidence: 0.76763356

00:22:11.350 --> 00:22:13.260 cell phenotypes seems to increase

NOTE Confidence: 0.76763356

00:22:13.321 --> 00:22:15.116 in patients with no clinical

NOTE Confidence: 0.76763356

00:22:15.116 --> 00:22:16.911 benefit in the classical monocytes.

NOTE Confidence: 0.76763356

00:22:16.920 --> 00:22:17.293 Also,

NOTE Confidence: 0.76763356

00:22:17.293 --> 00:22:19.158 increasing patient clinical benefit these.

NOTE Confidence: 0.76763356

00:22:19.160 --> 00:22:20.672 The M2 like macrophages,

NOTE Confidence: 0.76763356

00:22:20.672 --> 00:22:22.940 which the markers again are not

NOTE Confidence: 0.76763356

00:22:23.013 --> 00:22:24.768 as well defined in humans,

NOTE Confidence: 0.76763356

00:22:24.770 --> 00:22:26.700 trended to be higher inpatient

NOTE Confidence: 0.76763356

00:22:26.700 --> 00:22:28.630 clinical benefit but did not

NOTE Confidence: 0.76763356

00:22:28.700 --> 00:22:30.728 reach statistical significance.

NOTE Confidence: 0.76763356

00:22:30.730 --> 00:22:32.599 So the activity of anti PD one

NOTE Confidence: 0.76763356

00:22:32.599 --> 00:22:33.400 plus the end

NOTE Confidence: 0.76873326

00:22:33.470 --> 00:22:35.490 two pepta body probando combination

NOTE Confidence: 0.76873326

00:22:35.490 --> 00:22:37.884 may be hindered by increasing the

NOTE Confidence: 0.76873326

00:22:37.884 --> 00:22:40.019 price of my life cells leading to

NOTE Confidence: 0.76873326

00:22:40.019 --> 00:22:41.620 decrease in memory and effector

NOTE Confidence: 0.76873326

00:22:41.620 --> 00:22:42.940 T cell populations interesting.

NOTE Confidence: 0.76873326

00:22:42.940 --> 00:22:44.590 There was an association between

NOTE Confidence: 0.76873326

00:22:44.590 --> 00:22:45.910 baseline NK cell activity,

NOTE Confidence: 0.76873326

00:22:45.910 --> 00:22:47.926 an expansion of the cytolytic NK

NOTE Confidence: 0.76873326

00:22:47.926 --> 00:22:50.270 cells and think that the role of

NOTE Confidence: 0.76873326

00:22:50.270 --> 00:22:52.136 the of checkpoint and other things

NOTE Confidence: 0.76873326

00:22:52.136 --> 00:22:54.490 on a native beauty needs to be

NOTE Confidence: 0.76873326

00:22:54.490 --> 00:22:56.102 fully explored will talk about

NOTE Confidence: 0.76873326

00:22:56.102 --> 00:22:58.146 it a bit and we're currently in

NOTE Confidence: 0.76873326

00:22:58.146 --> 00:23:00.099 the midst of another enrolling.

NOTE Confidence: 0.76873326

00:23:00.100 --> 00:23:01.900 Another group of 25 patients.

NOTE Confidence: 0.76873326

00:23:01.900 --> 00:23:03.085 At Microsoft stable,

NOTE Confidence: 0.76873326

00:23:03.085 --> 00:23:05.850 colorectal cancer that that core is just

NOTE Confidence: 0.76873326

00:23:05.915 --> 00:23:08.165 about finished enrolling right now and

NOTE Confidence: 0.76873326

00:23:08.165 --> 00:23:11.028 hope to get further analysis coming out.

NOTE Confidence: 0.76873326

00:23:11.030 --> 00:23:13.403 So I think in general the role

NOTE Confidence: 0.76873326

00:23:13.403 --> 00:23:15.013 of angiogenesis and combinations

NOTE Confidence: 0.76873326

00:23:15.013 --> 00:23:16.588 is very important.

NOTE Confidence: 0.76873326

00:23:16.590 --> 00:23:18.570 It has the immune activation

NOTE Confidence: 0.76873326

00:23:18.570 --> 00:23:20.154 seen by Vjet blockade.

NOTE Confidence: 0.76873326

00:23:20.160 --> 00:23:21.748 The benefits and efficacy

NOTE Confidence: 0.76873326

00:23:21.748 --> 00:23:22.939 across multiple cancers,

NOTE Confidence: 0.76873326

00:23:22.940 --> 00:23:24.592 except taxes are manageable,

NOTE Confidence: 0.76873326

00:23:24.592 --> 00:23:26.657 but also to further consider

NOTE Confidence: 0.76873326

00:23:26.657 --> 00:23:28.692 other targets an Angel into

NOTE Confidence: 0.76873326

00:23:28.692 --> 00:23:30.627 being the next potential target

NOTE Confidence: 0.76873326

00:23:30.627 --> 00:23:32.529 serum age 2 levels increase.

NOTE Confidence: 0.76873326

00:23:32.530 --> 00:23:34.098 Increase their social worse

NOTE Confidence: 0.76873326

00:23:34.098 --> 00:23:36.058 outcomes that veg appliqued me

NOTE Confidence: 0.76873326

00:23:36.058 --> 00:23:37.578 temporarily decrease into expression

NOTE Confidence: 0.76873326

00:23:37.578 --> 00:23:39.708 in effect things into my Chrome.

NOTE Confidence: 0.76873326

00:23:39.710 --> 00:23:42.966 It needs to be a mechanism for resistance

NOTE Confidence: 0.76873326

00:23:42.966 --> 00:23:45.598 to checkpoint blockade that that I

NOTE Confidence: 0.76873326

00:23:45.598 --> 00:23:48.214 think is deserving of further studies.

NOTE Confidence: 0.76873326

00:23:48.220 --> 00:23:51.286 So one of the questions and that

NOTE Confidence: 0.76873326

00:23:51.286 --> 00:23:54.482 Harry was alluding to is how can

NOTE Confidence: 0.76873326

00:23:54.482 --> 00:23:56.722 we improve the therapeutic index?

NOTE Confidence: 0.76873326

00:23:56.730 --> 00:23:59.523 So one of the aspects is bringing

NOTE Confidence: 0.76873326

00:23:59.523 --> 00:24:02.560 bring back the concept of cytokinin.

NOTE Confidence: 0.76873326

00:24:02.560 --> 00:24:05.185 So if you think about the original

NOTE Confidence: 0.76873326

00:24:05.185 --> 00:24:07.305 reports for SQL Blockchain frequent

NOTE Confidence: 0.76873326

00:24:07.305 --> 00:24:10.053 battles by Jim Allison that the

NOTE Confidence: 0.76873326

00:24:10.053 --> 00:24:13.024 effect of C2 for blockade wasn't

NOTE Confidence: 0.76873326

00:24:13.024 --> 00:24:15.499 really well understood or appreciated

NOTE Confidence: 0.76873326

00:24:15.499 --> 00:24:18.455 until it was combined with GMCS

NOTE Confidence: 0.76873326

00:24:18.455 --> 00:24:20.419 screening tumor cell vaccines.

NOTE Confidence: 0.76873326

00:24:20.420 --> 00:24:22.990 That the really demonstrated the

NOTE Confidence: 0.76873326

00:24:22.990 --> 00:24:25.046 synergetic simplistic potential in

NOTE Confidence: 0.76873326

00:24:25.046 --> 00:24:26.981 preclinical animal models and that

NOTE Confidence: 0.76873326

00:24:26.981 --> 00:24:29.340 work that Glenn Dranoff and I did.

NOTE Confidence: 0.76873326

00:24:29.340 --> 00:24:31.260 Together with James accept subpoena to

NOTE Confidence: 0.76873326

00:24:31.260 --> 00:24:33.000 missile vaccines with checkpoint blockade.

NOTE Confidence: 0.76873326

00:24:33.000 --> 00:24:34.670 Suggested a potential synergistic effect,

NOTE Confidence: 0.76873326

00:24:34.670 --> 00:24:36.560 but work by Craig Sling off and

NOTE Confidence: 0.76873326

00:24:36.560 --> 00:24:38.535 others and many others have had

NOTE Confidence: 0.76873326

00:24:38.535 --> 00:24:40.375 concerned that GM may induce

NOTE Confidence: 0.76873326

00:24:40.375 --> 00:24:42.227 negative regulatory aspects of the

NOTE Confidence: 0.76873326

00:24:42.227 --> 00:24:43.987 immune response by promoting Mayo.

NOTE Confidence: 0.76873326

00:24:43.990 --> 00:24:46.042 It's impression cells or T regs

NOTE Confidence: 0.76873326

00:24:46.042 --> 00:24:48.424 that are in specific in a number

NOTE Confidence: 0.76873326

00:24:48.424 --> 00:24:49.989 of studies have been done,

NOTE Confidence: 0.76873326

00:24:49.990 --> 00:24:52.321 so that was kind of the concern

NOTE Confidence: 0.76873326

00:24:52.321 --> 00:24:53.986 going into this. So originally.

NOTE Confidence: 0.76873326

00:24:53.986 --> 00:24:56.650 Again, going back to just things in Melanoma,

NOTE Confidence: 0.76873326

00:24:56.650 --> 00:24:58.310 as a proof of principle,

NOTE Confidence: 0.76873326

00:24:58.310 --> 00:25:01.640 and if he is the first proof of principle.

NOTE Confidence: 0.76873326

00:25:01.640 --> 00:25:04.370 We did this randomized study that.

NOTE Confidence: 0.76873326

00:25:04.370 --> 00:25:04.803 Combined,

NOTE Confidence: 0.76873326

00:25:04.803 --> 00:25:08.267 hippie noted to be here 10 mix working

NOTE Confidence: 0.76873326

00:25:08.267 --> 00:25:11.382 which is higher than the approved dose

NOTE Confidence: 0.76873326

00:25:11.382 --> 00:25:14.329 and had a maintenance portion to it

NOTE Confidence: 0.76873326

00:25:14.329 --> 00:25:17.390 with systemic GM CSF versus it be alone.

NOTE Confidence: 0.76873326

00:25:17.390 --> 00:25:19.490 An date is been published.

NOTE Confidence: 0.76873326

00:25:19.490 --> 00:25:21.170 Progression free survival between

NOTE Confidence: 0.76873326

00:25:21.170 --> 00:25:23.690 the two arms was not significant,

NOTE Confidence: 0.76873326

00:25:23.690 --> 00:25:25.642 but interestingly overall survival

NOTE Confidence: 0.76873326

00:25:25.642 --> 00:25:28.570 was significant for the GM's arm

NOTE Confidence: 0.76873326

00:25:28.651 --> 00:25:30.898 with the one year rate of survival

NOTE Confidence: 0.76873326

00:25:30.898 --> 00:25:33.719 for it be alone being 52.9 versus

NOTE Confidence: 0.76873326

00:25:33.719 --> 00:25:35.503 16.9 for the combination.

NOTE Confidence: 0.76873326

00:25:35.510 --> 00:25:37.234 Sargramostim or GM CSF.

NOTE Confidence: 0.76873326

00:25:37.234 --> 00:25:40.601 What will talk about this potential in just

NOTE Confidence: 0.76873326

00:25:40.601 --> 00:25:43.409 a moment when we looked at side effects.

NOTE Confidence: 0.76873326

00:25:43.410 --> 00:25:46.014 Usually when you combine things you

NOTE Confidence: 0.76873326

00:25:46.014 --> 00:25:48.558 have control over more side effects

NOTE Confidence: 0.76873326

00:25:48.558 --> 00:25:51.486 but we looked at the GMR mscramms to

NOTE Confidence: 0.76278245

00:25:51.568 --> 00:25:53.288 arm versus it be alone.

NOTE Confidence: 0.76278245

00:25:53.290 --> 00:25:55.285 The patients in the combination

NOTE Confidence: 0.76278245

00:25:55.285 --> 00:25:57.280 had fewer high grade adverse

NOTE Confidence: 0.76278245

00:25:57.348 --> 00:25:59.208 events compared to be alone,

NOTE Confidence: 0.76278245

00:25:59.210 --> 00:26:01.280 and specifically when we looked

NOTE Confidence: 0.76278245

00:26:01.280 --> 00:26:04.204 at the toxicity types there was a

NOTE Confidence: 0.76278245

00:26:04.204 --> 00:26:06.159 profound decrease in GI toxicity.

NOTE Confidence: 0.76278245

00:26:06.160 --> 00:26:08.060 Diarrhea colitis in Poly toxicity

NOTE Confidence: 0.76278245

00:26:08.060 --> 00:26:10.392 so colitis diarrhea is the biggest

NOTE Confidence: 0.76278245

00:26:10.392 --> 00:26:12.237 concern for Epyx itself in.

NOTE Confidence: 0.76278245

00:26:12.240 --> 00:26:13.760 In pneumonitis, lung inflammation

NOTE Confidence: 0.76278245

00:26:13.760 --> 00:26:16.040 being a primary concern for NTP,

NOTE Confidence: 0.76278245

00:26:16.040 --> 00:26:17.940 one based therapy so found

NOTE Confidence: 0.76278245

00:26:17.940 --> 00:26:19.840 that these two target organs,

NOTE Confidence: 0.76278245

00:26:19.840 --> 00:26:21.740 having improved benefits with the

NOTE Confidence: 0.76278245

00:26:21.740 --> 00:26:22.836 combination, fairly intriguing.

NOTE Confidence: 0.76278245

00:26:22.836 --> 00:26:24.984 So what is the potential mechanisms

NOTE Confidence: 0.76278245

00:26:24.984 --> 00:26:27.347 that GM improves survival but does

NOTE Confidence: 0.76278245

00:26:27.347 --> 00:26:29.332 not improve pressure free survival?

NOTE Confidence: 0.76278245

00:26:29.340 --> 00:26:31.240 So GM recruits todrick cells,

NOTE Confidence: 0.76278245

00:26:31.240 --> 00:26:32.404 macrophages, and presentation,

NOTE Confidence: 0.76278245

00:26:32.404 --> 00:26:34.732 and when you combine this with

NOTE Confidence: 0.76278245

00:26:34.732 --> 00:26:35.902 counteracting introductory elements

NOTE Confidence: 0.76278245

00:26:35.902 --> 00:26:38.074 such as would simply for blockade,

NOTE Confidence: 0.76278245

00:26:38.080 --> 00:26:41.048 you could see if surgery happening there.

NOTE Confidence: 0.76278245

00:26:41.050 --> 00:26:43.235 Maybe Jim improves depletion of

NOTE Confidence: 0.76278245

00:26:43.235 --> 00:26:45.920 of of regulatory cells that could

NOTE Confidence: 0.76278245

00:26:45.920 --> 00:26:48.452 be that there would be important

NOTE Confidence: 0.76278245

00:26:48.452 --> 00:26:51.019 when the President GM that's that

NOTE Confidence: 0.76278245

00:26:51.019 --> 00:26:53.054 was suggested by Alan Korman.

NOTE Confidence: 0.76278245

00:26:53.060 --> 00:26:55.588 The importance of of C play 4 in

NOTE Confidence: 0.76278245

00:26:55.588 --> 00:26:57.670 terms of depleting regulatory cells

NOTE Confidence: 0.76278245

00:26:57.670 --> 00:27:01.470 could be amplified by GM in this UN

NOTE Confidence: 0.76278245

00:27:01.470 --> 00:27:04.644 coupling of overall survival and progression,

NOTE Confidence: 0.76278245

00:27:04.650 --> 00:27:06.385 free survival has been previously

NOTE Confidence: 0.76278245

00:27:06.385 --> 00:27:08.120 described for other GMC based

NOTE Confidence: 0.76278245

00:27:08.180 --> 00:27:10.220 immunological therapeutic approaches,

NOTE Confidence: 0.76278245

00:27:10.220 --> 00:27:10.960 specifically supercell.

NOTE Confidence: 0.76278245

00:27:10.960 --> 00:27:12.440 Tea and prostate cancer

NOTE Confidence: 0.76278245

00:27:12.440 --> 00:27:13.920 dendritic cell vaccine has,

NOTE Confidence: 0.76278245

00:27:13.920 --> 00:27:16.170 as part of its component GM put into it

NOTE Confidence: 0.76278245

00:27:16.170 --> 00:27:18.777 and there was a also a disconnection

NOTE Confidence: 0.76278245

00:27:18.777 --> 00:27:20.773 between progression free survival and

NOTE Confidence: 0.76278245

00:27:20.773 --> 00:27:22.758 overall survival with an improvement.

NOTE Confidence: 0.76278245

00:27:22.760 --> 00:27:24.460 Overall survival in those studies

NOTE Confidence: 0.76278245

00:27:24.460 --> 00:27:25.820 that included super Salty,

NOTE Confidence: 0.76278245

00:27:25.820 --> 00:27:27.520 so it's teen prostate cancer.

NOTE Confidence: 0.76278245

00:27:27.520 --> 00:27:29.220 So there's another basis for

NOTE Confidence: 0.76278245

00:27:29.220 --> 00:27:30.920 this observation in the past.

NOTE Confidence: 0.76278245

00:27:30.920 --> 00:27:33.300 But when we look at the possible

NOTE Confidence: 0.76278245

00:27:33.300 --> 00:27:35.000 mechanisms of improved Palmer TX,

NOTE Confidence: 0.76278245

00:27:35.000 --> 00:27:37.272 is Glenn Dranoff had had done the GM

NOTE Confidence: 0.76278245

00:27:37.272 --> 00:27:39.876 knockout mouse and and those gym mice

NOTE Confidence: 0.76278245

00:27:39.876 --> 00:27:41.460 develop significant lymphoid hyperplasia.

NOTE Confidence: 0.76278245

00:27:41.460 --> 00:27:42.880 This around the Airways,

NOTE Confidence: 0.76278245

00:27:42.880 --> 00:27:44.300 in the lung vasculature.

NOTE Confidence: 0.76278245

00:27:44.300 --> 00:27:45.784 They're really clearly demonstrates

NOTE Confidence: 0.76278245

00:27:45.784 --> 00:27:48.819 the role of GM in Palmer home stasis,

NOTE Confidence: 0.76278245

00:27:48.820 --> 00:27:51.388 and you can see in panel A is

NOTE Confidence: 0.76278245

00:27:51.388 --> 00:27:53.816 a normal mouse lung and panel

NOTE Confidence: 0.76278245

00:27:53.816 --> 00:27:56.354 B being the GM knockout mice,

NOTE Confidence: 0.76278245

00:27:56.360 --> 00:27:57.868 showing the profound inflammation

NOTE Confidence: 0.76278245

00:27:57.868 --> 00:27:58.999 in the Airways.

NOTE Confidence: 0.76278245

00:27:59.000 --> 00:27:59.698 In addition,

NOTE Confidence: 0.76278245

00:27:59.698 --> 00:28:01.792 GM is a cytokinins involved in

NOTE Confidence: 0.76278245

00:28:01.792 --> 00:28:03.766 the coastal homeostasis in in

NOTE Confidence: 0.76278245

00:28:03.766 --> 00:28:05.786 really promotes GI equal healing.

NOTE Confidence: 0.76278245

00:28:05.790 --> 00:28:07.716 The knockout mice have colitis and

NOTE Confidence: 0.76278245

00:28:07.716 --> 00:28:09.981 this can be partially reversed with

NOTE Confidence: 0.76278245

00:28:09.981 --> 00:28:11.817 administering systemic James half.

NOTE Confidence: 0.76278245

00:28:11.820 --> 00:28:14.178 If you look at idiopathic bowel

NOTE Confidence: 0.76278245

00:28:14.178 --> 00:28:15.357 inflammatory bowel disease.

NOTE Confidence: 0.76278245

00:28:15.360 --> 00:28:17.346 Jim may have a role there,

NOTE Confidence: 0.76278245

00:28:17.350 --> 00:28:19.408 so there are trials of giving GM

NOTE Confidence: 0.76278245

00:28:19.408 --> 00:28:21.340 to patient with Crohn's disease.

NOTE Confidence: 0.76278245

00:28:21.340 --> 00:28:22.604 They have shown improvement,

NOTE Confidence: 0.76278245

00:28:22.604 --> 00:28:24.500 a subset of patients with Crohn's

NOTE Confidence: 0.76278245

00:28:24.555 --> 00:28:26.275 disease have high titer neutralizing

NOTE Confidence: 0.76278245

00:28:26.275 --> 00:28:27.307 antibodies to GM.

NOTE Confidence: 0.76278245

00:28:27.310 --> 00:28:29.284 They show a mechanism weijia may be

NOTE Confidence: 0.76278245

00:28:29.284 --> 00:28:31.630 important in some inflammatory bowel disease.

NOTE Confidence: 0.76278245

00:28:31.630 --> 00:28:32.954 Patients actually have decreased

NOTE Confidence: 0.76278245

00:28:32.954 --> 00:28:34.278 levels of GM receptors,

NOTE Confidence: 0.76278245

00:28:34.280 --> 00:28:35.648 again making this combination.

NOTE Confidence: 0.76278245

00:28:35.648 --> 00:28:38.453 So we moved on to doing a randomized

NOTE Confidence: 0.76278245

00:28:38.453 --> 00:28:40.505 phase two three trial of submission

NOTE Confidence: 0.76278245

00:28:40.505 --> 00:28:43.046 or GM CSF plus nivo it be versus

NOTE Confidence: 0.76278245

00:28:43.046 --> 00:28:44.238 Navy would be alone.

NOTE Confidence: 0.76278245

00:28:44.240 --> 00:28:45.900 The primary endpoints were overall

NOTE Confidence: 0.76278245

00:28:45.900 --> 00:28:47.520 survival relapse, free survival.

NOTE Confidence: 0.76278245

00:28:47.520 --> 00:28:49.420 In in potential reduction

NOTE Confidence: 0.76278245

00:28:49.420 --> 00:28:52.169 toxicities Anne's hair and I were

NOTE Confidence: 0.76278245

00:28:52.169 --> 00:28:53.725 talking right before this.

NOTE Confidence: 0.76278245

00:28:53.730 --> 00:28:56.460 The trial is ongoing in the

NOTE Confidence: 0.76278245

00:28:56.460 --> 00:28:58.280 midst of phase three,

NOTE Confidence: 0.76278245

00:28:58.280 --> 00:29:02.375 so I think the role of GM is interesting,

NOTE Confidence: 0.7772081

00:29:02.380 --> 00:29:04.416 possibly from exclamation point,

NOTE Confidence: 0.7772081

00:29:04.416 --> 00:29:06.961 but particularly from his possible

NOTE Confidence: 0.7772081

00:29:06.961 --> 00:29:08.868 reduction in in side effects

NOTE Confidence: 0.7772081

00:29:08.868 --> 00:29:10.854 in that cytokines may behave in

NOTE Confidence: 0.7772081

00:29:10.920 --> 00:29:12.840 different organs differently,

NOTE Confidence: 0.7772081

00:29:12.840 --> 00:29:15.120 so the lung and gut,

NOTE Confidence: 0.7772081

00:29:15.120 --> 00:29:17.946 which is the mainstay of protection.

NOTE Confidence: 0.7772081

00:29:17.950 --> 00:29:18.892 Against invading microorganisms,

NOTE Confidence: 0.7772081

00:29:18.892 --> 00:29:20.776 GM may play a very important

NOTE Confidence: 0.7772081

00:29:20.776 --> 00:29:21.610 homeostatic role there,

NOTE Confidence: 0.7772081

00:29:21.610 --> 00:29:23.548 and they play different roles systemically

NOTE Confidence: 0.7772081

00:29:23.548 --> 00:29:25.269 throughout the other parts of body,

NOTE Confidence: 0.7772081

00:29:25.270 --> 00:29:27.442 and this is other areas were

NOTE Confidence: 0.7772081

00:29:27.442 --> 00:29:28.890 interested in looking at.

NOTE Confidence: 0.7772081

00:29:28.890 --> 00:29:31.164 So what what drives response to

NOTE Confidence: 0.7772081

00:29:31.164 --> 00:29:33.328 checkpoint blockade is kind of next

NOTE Confidence: 0.7772081

00:29:33.328 --> 00:29:35.351 next question and we set up some

NOTE Confidence: 0.7772081

00:29:35.351 --> 00:29:37.415 site off panels looking at patients

NOTE Confidence: 0.7772081

00:29:37.415 --> 00:29:39.752 who had received it be alone and

NOTE Confidence: 0.7772081

00:29:39.752 --> 00:29:41.964 receive PD one alone and spent a

NOTE Confidence: 0.7772081

00:29:41.964 --> 00:29:44.239 long time saying these panels up.

NOTE Confidence: 0.7772081

00:29:44.240 --> 00:29:46.640 And would you find out with the site

NOTE Confidence: 0.7772081

00:29:46.640 --> 00:29:48.454 offers that doing the experiments

NOTE Confidence: 0.7772081

00:29:48.454 --> 00:29:50.369 may may become much easier,

NOTE Confidence: 0.7772081

00:29:50.370 --> 00:29:53.023 but the analysis of the data from

NOTE Confidence: 0.7772081

00:29:53.023 --> 00:29:54.160 computational biologist endpoint

NOTE Confidence: 0.7772081

00:29:54.218 --> 00:29:56.164 can be quite onerous and and such,

NOTE Confidence: 0.7772081

00:29:56.170 --> 00:29:59.419 but these are some of the Disney plots that.

NOTE Confidence: 0.7772081

00:29:59.420 --> 00:30:01.376 Be a established looking at the

NOTE Confidence: 0.7772081

00:30:01.376 --> 00:30:02.992 different subsets of cells that

NOTE Confidence: 0.7772081

00:30:02.992 --> 00:30:04.763 we could look at in the purple

NOTE Confidence: 0.7772081

00:30:04.763 --> 00:30:06.562 blood and again focused on patients

NOTE Confidence: 0.7772081

00:30:06.562 --> 00:30:08.416 who had received it be alone.

NOTE Confidence: 0.7772081

00:30:08.420 --> 00:30:10.760 Initially in Pembroke alone.

NOTE Confidence: 0.7772081

00:30:10.760 --> 00:30:13.644 And what we found is that patients

NOTE Confidence: 0.7772081

00:30:13.644 --> 00:30:16.309 who between those those two chords,

NOTE Confidence: 0.7772081

00:30:16.310 --> 00:30:18.346 lymphocytes and monocytes frequencies

NOTE Confidence: 0.7772081

00:30:18.346 --> 00:30:21.400 very much differ between responders and

NOTE Confidence: 0.7772081

00:30:21.468 --> 00:30:23.967 non responders where you can you see

NOTE Confidence: 0.7772081

00:30:23.967 --> 00:30:26.557 with patients who responded to Penn Bro,

NOTE Confidence: 0.7772081

00:30:26.560 --> 00:30:28.268 there's actually less lymphocytes

NOTE Confidence: 0.7772081

00:30:28.268 --> 00:30:29.976 in the purple blood.

NOTE Confidence: 0.7772081

00:30:29.980 --> 00:30:30.358 Well,

NOTE Confidence: 0.7772081

00:30:30.358 --> 00:30:33.382 if that's not the case and that there

NOTE Confidence: 0.7772081

00:30:33.382 --> 00:30:36.171 also are higher monocytes in patients

NOTE Confidence: 0.7772081

00:30:36.171 --> 00:30:39.369 responding in the blood to Japan bro.

NOTE Confidence: 0.7772081

00:30:39.370 --> 00:30:40.128 And then.

NOTE Confidence: 0.7772081

00:30:40.128 --> 00:30:43.490 Sanders and that is not the case with 50.

NOTE Confidence: 0.7772081

00:30:43.490 --> 00:30:45.303 One of the things that kind of

NOTE Confidence: 0.7772081

00:30:45.303 --> 00:30:47.751 fell out in the data set is that

NOTE Confidence: 0.7772081

00:30:47.751 --> 00:30:49.722 patients who failed response to anti

NOTE Confidence: 0.7772081

00:30:49.722 --> 00:30:51.829 PD one had lower expression of CD.

NOTE Confidence: 0.7772081

00:30:51.830 --> 00:30:54.142 69 would be in case also kind of

NOTE Confidence: 0.7772081

00:30:54.142 --> 00:30:55.404 activated circulating NK cells

NOTE Confidence: 0.7772081

00:30:55.404 --> 00:30:57.294 in the peripheral blood an we've

NOTE Confidence: 0.7772081

00:30:57.294 --> 00:30:59.098 subsequently have a couple of other

NOTE Confidence: 0.7772081

00:30:59.098 --> 00:31:00.766 other datasets working on the kind

NOTE Confidence: 0.7772081

00:31:00.770 --> 00:31:02.260 of has confirmed these observations.

NOTE Confidence: 0.7772081

00:31:02.260 --> 00:31:04.262 It really brings out the question of

NOTE Confidence: 0.7772081

00:31:04.262 --> 00:31:06.440 what the role of innate immunity is.

NOTE Confidence: 0.7772081

00:31:06.440 --> 00:31:08.414 Here we know that in case cells

NOTE Confidence: 0.7772081

00:31:08.414 --> 00:31:10.310 have PD one in the surface,

NOTE Confidence: 0.7772081

00:31:10.310 --> 00:31:12.098 but when you the most profound

NOTE Confidence: 0.7772081

00:31:12.098 --> 00:31:13.700 effects have been on these.

NOTE Confidence: 0.7772081

00:31:13.700 --> 00:31:15.552 Circulating activated CD-69 that

NOTE Confidence: 0.7772081

00:31:15.552 --> 00:31:18.844 would be positive NK cells in the

NOTE Confidence: 0.7772081

00:31:18.844 --> 00:31:21.442 peripheral blood that seems to be

NOTE Confidence: 0.7772081

00:31:21.442 --> 00:31:23.439 associated most with pembrolizumab

NOTE Confidence: 0.7772081

00:31:23.439 --> 00:31:25.290 efficacy in normal.

NOTE Confidence: 0.7772081

00:31:25.290 --> 00:31:27.858 So with that as a basis,

NOTE Confidence: 0.7772081

00:31:27.860 --> 00:31:30.756 we wanted to say what other aspects of

NOTE Confidence: 0.7772081

00:31:30.756 --> 00:31:33.870 the tool micro vironment contribute to.

NOTE Confidence: 0.7772081

00:31:33.870 --> 00:31:35.940 Maybe Check Point resistance or

NOTE Confidence: 0.7772081

00:31:35.940 --> 00:31:38.957 efficacy and there we could have many

NOTE Confidence: 0.7772081

00:31:38.957 --> 00:31:41.585 lectures on all the areas investigation.

NOTE Confidence: 0.7772081

00:31:41.590 --> 00:31:43.990 We've seen that ACR Anasco recently

NOTE Confidence: 0.7772081

00:31:43.990 --> 00:31:47.021 of areas are looking at quote unquote

NOTE Confidence: 0.7772081

00:31:47.021 --> 00:31:49.733 resistant mechanisms to PD one blockade,

NOTE Confidence: 0.7772081

00:31:49.740 --> 00:31:52.449 so we talked the importance of having

NOTE Confidence: 0.7772081

00:31:52.449 --> 00:31:55.379 seen infiltrate the importance of interferon.

NOTE Confidence: 0.7772081

00:31:55.380 --> 00:31:57.432 In the two microenvironment and then

NOTE Confidence: 0.7772081

00:31:57.432 --> 00:31:59.491 things such as beta two mutations

NOTE Confidence: 0.7772081

00:31:59.491 --> 00:32:01.987 that may be part of the APC machinery

NOTE Confidence: 0.7772081

00:32:02.049 --> 00:32:03.150 or Jack mutations.

NOTE Confidence: 0.7772081

00:32:03.150 --> 00:32:05.034 Part of interferon signaling that they

NOTE Confidence: 0.7772081

00:32:05.034 --> 00:32:06.870 may be important resistant mechanisms,

NOTE Confidence: 0.7772081

00:32:06.870 --> 00:32:08.555 but we were further interested

NOTE Confidence: 0.7772081

00:32:08.555 --> 00:32:09.903 in looking into that.

NOTE Confidence: 0.7773844

00:32:09.910 --> 00:32:12.199 My work with Scott Rodick was simply

NOTE Confidence: 0.7773844

00:32:12.199 --> 00:32:14.648 want to look at the protein level.

NOTE Confidence: 0.7773844

00:32:14.650 --> 00:32:16.706 What class one and Class 2 as part

NOTE Confidence: 0.7773844

00:32:16.706 --> 00:32:18.646 of the APC mechanisms are doing

NOTE Confidence: 0.7773844

00:32:18.646 --> 00:32:20.680 as part of this resistance in

NOTE Confidence: 0.7773844

00:32:20.748 --> 00:32:22.760 relative to checkpoint blockade.

NOTE Confidence: 0.7773844

00:32:22.760 --> 00:32:25.119 So we took advantage of this study.

NOTE Confidence: 0.7773844

00:32:25.120 --> 00:32:26.875 The so called Checkmate 064

NOTE Confidence: 0.7773844

00:32:26.875 --> 00:32:27.928 Study investigation study.

NOTE Confidence: 0.7773844

00:32:27.930 --> 00:32:29.794 That randomized patients untreated

NOTE Confidence: 0.7773844

00:32:29.794 --> 00:32:32.124 patients mellema to either receive

NOTE Confidence: 0.7773844

00:32:32.124 --> 00:32:34.172 first niveau induction followed by

NOTE Confidence: 0.7773844

00:32:34.172 --> 00:32:36.446 a four switch to Epyx induction,

NOTE Confidence: 0.7773844

00:32:36.450 --> 00:32:38.694 or the other half of patients

NOTE Confidence: 0.7773844

00:32:38.694 --> 00:32:41.103 received it be first induction for

NOTE Confidence: 0.7773844

00:32:41.103 --> 00:32:43.617 12 weeks followed by NIVEAU and

NOTE Confidence: 0.7773844

00:32:43.617 --> 00:32:46.248 then after both induction periods,

NOTE Confidence: 0.7773844

00:32:46.250 --> 00:32:48.800 all the patients got needle maintenance

NOTE Confidence: 0.7773844

00:32:48.800 --> 00:32:51.360 and everyone got biopsies before hand.

NOTE Confidence: 0.7773844

00:32:51.360 --> 00:32:53.490 In between the two inductions

NOTE Confidence: 0.7773844

00:32:53.490 --> 00:32:54.768 in falling induction,

NOTE Confidence: 0.7773844

00:32:54.770 --> 00:32:57.866 two as well as a collection

NOTE Confidence: 0.7773844

00:32:57.866 --> 00:32:59.930 of peripheral blood samples.

NOTE Confidence: 0.7773844

00:32:59.930 --> 00:33:01.754 And we want to look specifically

NOTE Confidence: 0.7773844

00:33:01.754 --> 00:33:02.970 at the protein level,

NOTE Confidence: 0.7773844

00:33:02.970 --> 00:33:05.162 so this is work and penalty by Scott

NOTE Confidence: 0.7773844

00:33:05.162 --> 00:33:07.058 Rodick and looking at class one

NOTE Confidence: 0.7773844

00:33:07.058 --> 00:33:09.350 expression in the left hand column in

NOTE Confidence: 0.7773844

00:33:09.350 --> 00:33:11.790 Class 2 expression in the right hand column.

NOTE Confidence: 0.7773844

00:33:11.790 --> 00:33:14.830 And there's a little bit of our part to this,

NOTE Confidence: 0.7773844

00:33:14.830 --> 00:33:16.972 so if you look in a room normal 1/3

NOTE Confidence: 0.7773844

00:33:16.972 --> 00:33:19.294 and five you have high levels of

NOTE Confidence: 0.7773844

00:33:19.294 --> 00:33:21.369 class one expression which you should

NOTE Confidence: 0.7773844

00:33:21.369 --> 00:33:23.334 see in all nucleated cells, right?

NOTE Confidence: 0.7773844

00:33:23.334 --> 00:33:25.158 All nucleus should have high class.

NOTE Confidence: 0.7773844

00:33:25.160 --> 00:33:27.134 My expression three is decrease and

NOTE Confidence: 0.7773844

00:33:27.134 --> 00:33:29.419 five is almost absence of of class one.

NOTE Confidence: 0.7773844

00:33:29.420 --> 00:33:31.000 But interesting in this tumor.

NOTE Confidence: 0.7773844

00:33:31.000 --> 00:33:32.776 You have your control cells there.

NOTE Confidence: 0.7773844

00:33:32.780 --> 00:33:34.550 You have immune cells there that

NOTE Confidence: 0.7773844

00:33:34.550 --> 00:33:35.435 have class one.

NOTE Confidence: 0.7773844

00:33:35.440 --> 00:33:36.920 That kind of show you,

NOTE Confidence: 0.7773844

00:33:36.920 --> 00:33:37.574 I think,

NOTE Confidence: 0.7773844

00:33:37.574 --> 00:33:39.209 fairly profoundly that the tumor

NOTE Confidence: 0.7773844

00:33:39.209 --> 00:33:41.346 itself is last class one and then

NOTE Confidence: 0.7773844

00:33:41.346 --> 00:33:43.328 on the right hand column for 246

NOTE Confidence: 0.7773844

00:33:43.328 --> 00:33:44.972 you have Class 2 expression of

NOTE Confidence: 0.7773844

00:33:44.972 --> 00:33:46.079 high Class 2 expression,

NOTE Confidence: 0.7773844

00:33:46.079 --> 00:33:47.474 which is typically not all

NOTE Confidence: 0.7773844

00:33:47.474 --> 00:33:49.060 that common in cancer Melanoma.

NOTE Confidence: 0.7773844

00:33:49.060 --> 00:33:51.517 You have medium and then you have no Class

NOTE Confidence: 0.7773844

00:33:51.517 --> 00:33:54.087 2 expression in panel 6 on the bottom.

NOTE Confidence: 0.7773844

00:33:54.090 --> 00:33:55.734 Figure what we've done is we've

NOTE Confidence: 0.7773844

00:33:55.734 --> 00:33:58.026 color coded on the top the the level

NOTE Confidence: 0.7773844

00:33:58.026 --> 00:33:59.736 of class one expression across all

NOTE Confidence: 0.7773844

00:33:59.791 --> 00:34:01.486 the tumors that were evaluated.

NOTE Confidence: 0.7773844

00:34:01.490 --> 00:34:03.902 So the darker has the highest

NOTE Confidence: 0.7773844

00:34:03.902 --> 00:34:05.108 class my expression.

NOTE Confidence: 0.7773844

00:34:05.110 --> 00:34:07.120 Approaching level all the way down

NOTE Confidence: 0.7773844

00:34:07.120 --> 00:34:09.507 to kind of complete loss of classics

NOTE Confidence: 0.7773844

00:34:09.507 --> 00:34:11.803 pressure on the right and then right

NOTE Confidence: 0.7773844

00:34:11.874 --> 00:34:14.475 below that is by HC is Class 2 expression.

NOTE Confidence: 0.7773844

00:34:14.480 --> 00:34:16.190 Then we looked at both Arnie

NOTE Confidence: 0.7773844

00:34:16.190 --> 00:34:18.030 seek and whole exome sequencing.

NOTE Confidence: 0.7773844

00:34:18.030 --> 00:34:20.179 For these samples and so the middle

NOTE Confidence: 0.7773844

00:34:20.179 --> 00:34:22.078 panel shows you Barney seek class

NOTE Confidence: 0.7773844

00:34:22.078 --> 00:34:23.914 one expression HLA B&C and on

NOTE Confidence: 0.7773844

00:34:23.914 --> 00:34:26.004 the bottom shows you where there

NOTE Confidence: 0.7773844

00:34:26.004 --> 00:34:28.042 are mutations and the things that

NOTE Confidence: 0.7773844

00:34:28.042 --> 00:34:29.974 you would be most interested in,

NOTE Confidence: 0.7773844

00:34:29.980 --> 00:34:32.234 such as beta two and Jack Stack.

NOTE Confidence: 0.7773844

00:34:32.240 --> 00:34:34.676 So of note there were very few.

NOTE Confidence: 0.7773844

00:34:34.680 --> 00:34:36.606 Mutations and beta to attract Staten.

NOTE Confidence: 0.7773844

00:34:36.610 --> 00:34:38.530 Actually one of the major mutations.

NOTE Confidence: 0.7773844

00:34:38.530 --> 00:34:40.802 If you look at the left hand portion

NOTE Confidence: 0.7773844

00:34:40.802 --> 00:34:43.222 and purple where there was a detective

NOTE Confidence: 0.7773844

00:34:43.222 --> 00:34:45.007 beta mutation actually had very

NOTE Confidence: 0.7773844

00:34:45.071 --> 00:34:46.611 high level of classification by

NOTE Confidence: 0.7773844

00:34:46.611 --> 00:34:49.123 Etsy and we when we look into there

NOTE Confidence: 0.7773844

00:34:49.123 --> 00:34:50.728 that that that actually patients

NOTE Confidence: 0.7773844

00:34:50.728 --> 00:34:52.669 tumor had about was estimated about

NOTE Confidence: 0.7773844

00:34:52.669 --> 00:34:54.580 7% of reeds had abated mutation,

NOTE Confidence: 0.7773844

00:34:54.580 --> 00:34:56.506 so most of them did not,

NOTE Confidence: 0.7773844

00:34:56.510 --> 00:34:58.646 but it was probably a minor

NOTE Confidence: 0.7773844

00:34:58.646 --> 00:35:00.070 population and maybe suggest

NOTE Confidence: 0.7429117

00:35:00.141 --> 00:35:01.428 mechanisms of acquired

NOTE Confidence: 0.7429117

00:35:01.428 --> 00:35:03.573 resistance going down the road.

NOTE Confidence: 0.7429117

00:35:03.580 --> 00:35:06.205 So we looked at the initial response

NOTE Confidence: 0.7429117

00:35:06.205 --> 00:35:08.845 to patients who either on the top

NOTE Confidence: 0.7429117

00:35:08.845 --> 00:35:11.005 here received hippie first or so

NOTE Confidence: 0.7429117

00:35:11.086 --> 00:35:13.540 simply for blockade on the bottom,

NOTE Confidence: 0.7429117

00:35:13.540 --> 00:35:16.088 received niveau or anti PD one and

NOTE Confidence: 0.7429117

00:35:16.088 --> 00:35:18.813 what we found is that the patients

NOTE Confidence: 0.7429117

00:35:18.813 --> 00:35:21.135 who had reduction in class one

NOTE Confidence: 0.7429117

00:35:21.219 --> 00:35:23.886 which was determined to be 50% or

NOTE Confidence: 0.7429117

00:35:23.886 --> 00:35:26.202 more reduction class one did really

NOTE Confidence: 0.7429117

00:35:26.202 --> 00:35:28.820 poorly to CFO blockade tippy while

NOTE Confidence: 0.7429117

00:35:28.820 --> 00:35:31.120 patients with reduction class one

NOTE Confidence: 0.7429117

00:35:31.120 --> 00:35:34.238 did not seem to affect the response

NOTE Confidence: 0.7429117

00:35:34.238 --> 00:35:36.353 rates for outcomes to Geneva.

NOTE Confidence: 0.7429117

00:35:36.360 --> 00:35:36.793 Interestingly,

NOTE Confidence: 0.7429117

00:35:36.793 --> 00:35:39.824 patients who had any Class 2 expression

NOTE Confidence: 0.7429117

00:35:39.824 --> 00:35:42.646 as defined by 1% did really well to

NOTE Confidence: 0.7429117

00:35:42.646 --> 00:35:45.420 Nivo had improvement in outcome to Nivo,

NOTE Confidence: 0.7429117

00:35:45.420 --> 00:35:48.528 but do not seem to affect all

NOTE Confidence: 0.7429117

00:35:48.528 --> 00:35:50.405 their clinical outcomes to

NOTE Confidence: 0.7429117

00:35:50.405 --> 00:35:52.705 see full blockade with hippie.

NOTE Confidence: 0.7429117

00:35:52.710 --> 00:35:54.310 So these are the Catman.

NOTE Confidence: 0.7429117

00:35:54.310 --> 00:35:55.658 Alesis and Gray are.

NOTE Confidence: 0.7429117

00:35:55.658 --> 00:35:57.680 Some patients were not a valuable

NOTE Confidence: 0.7429117

00:35:57.749 --> 00:35:59.744 few patients an an here we have,

NOTE Confidence: 0.7429117

00:35:59.750 --> 00:36:01.350 the blue being patients who

NOTE Confidence: 0.7429117

00:36:01.350 --> 00:36:02.630 had intact class one.

NOTE Confidence: 0.7429117

00:36:02.630 --> 00:36:05.208 So if greater than 50% or intact class

NOTE Confidence: 0.7429117

00:36:05.208 --> 00:36:08.149 one in the red being patients who had a

NOTE Confidence: 0.7429117

00:36:08.149 --> 00:36:10.950 reduction of 50% or or loss of Class 1.

NOTE Confidence: 0.7429117

00:36:10.950 --> 00:36:12.515 The patients who received it

NOTE Confidence: 0.7429117

00:36:12.515 --> 00:36:14.470 be first and went to Nivo.

NOTE Confidence: 0.7429117

00:36:14.470 --> 00:36:17.030 You can see here did much much better.

NOTE Confidence: 0.7429117

00:36:17.030 --> 00:36:19.130 Who if they had class one intact

NOTE Confidence: 0.7429117

00:36:19.130 --> 00:36:20.826 if they had reduction class

NOTE Confidence: 0.7429117

00:36:20.826 --> 00:36:22.980 we did very poorly in red.

NOTE Confidence: 0.7429117

00:36:22.980 --> 00:36:24.968 And actually took us a little while

NOTE Confidence: 0.7429117

00:36:24.968 --> 00:36:27.151 to figure this out because there were

NOTE Confidence: 0.7429117

00:36:27.151 --> 00:36:29.059 a number of patients who received

NOTE Confidence: 0.7429117

00:36:29.119 --> 00:36:30.869 it be first who are quote unquote

NOTE Confidence: 0.7429117

00:36:30.869 --> 00:36:32.950 in not not valuable at 1st and the

NOTE Confidence: 0.7429117

00:36:32.950 --> 00:36:34.653 reason is because some of those

NOTE Confidence: 0.7429117

00:36:34.653 --> 00:36:36.519 patients who had the lowest class,

NOTE Confidence: 0.7429117

00:36:36.520 --> 00:36:38.548 one expression or complete loss of

NOTE Confidence: 0.7429117

00:36:38.548 --> 00:36:39.900 classic session unfortunately never

NOTE Confidence: 0.7429117

00:36:39.957 --> 00:36:41.982 made it to the first set of staging scans.

NOTE Confidence: 0.7429117

00:36:41.990 --> 00:36:43.355 They either progress very rapidly

NOTE Confidence: 0.7429117

00:36:43.355 --> 00:36:45.395 or passed away early on in their

NOTE Confidence: 0.7429117

00:36:45.395 --> 00:36:46.017 treatment course.

NOTE Confidence: 0.7429117

00:36:46.020 --> 00:36:47.988 This is compared to a panel on the

NOTE Confidence: 0.7429117

00:36:47.988 --> 00:36:49.793 right who received niveau 1st and

NOTE Confidence: 0.7429117

00:36:49.793 --> 00:36:52.070 there was no difference on their class.

NOTE Confidence: 0.7429117

00:36:52.070 --> 00:36:54.908 One expression on outcomes to Nevo.

NOTE Confidence: 0.7429117

00:36:54.910 --> 00:36:56.260 Here's Class 2 expression again

NOTE Confidence: 0.7429117

00:36:56.260 --> 00:36:57.340 on the left patient,

NOTE Confidence: 0.7429117

00:36:57.340 --> 00:36:59.500 receiving it be first in the right place.

NOTE Confidence: 0.7429117

00:36:59.500 --> 00:37:00.850 For seeing you go first,

NOTE Confidence: 0.7429117

00:37:00.850 --> 00:37:03.010 there was a slight trend, but not squeeze.

NOTE Confidence: 0.7429117

00:37:03.010 --> 00:37:04.630 Some big difference for me first,

NOTE Confidence: 0.7429117

00:37:04.630 --> 00:37:06.877 but the patients who had any Class

NOTE Confidence: 0.7429117

00:37:06.877 --> 00:37:08.855 2 expression did really well to

NOTE Confidence: 0.7429117

00:37:08.855 --> 00:37:10.745 niveau as depicted by the blue

NOTE Confidence: 0.7429117

00:37:10.745 --> 00:37:12.636 line on the right hand panel.

NOTE Confidence: 0.7429117

00:37:12.640 --> 00:37:13.200 So we.

NOTE Confidence: 0.7429117

00:37:13.200 --> 00:37:15.160 Had the Arnie seek data and we

NOTE Confidence: 0.7429117

00:37:15.160 --> 00:37:17.446 want to further kind of investigate

NOTE Confidence: 0.7429117

00:37:17.446 --> 00:37:19.761 what genes could be related with

NOTE Confidence: 0.7429117

00:37:19.761 --> 00:37:21.316 a focus on the patient.

NOTE Confidence: 0.7429117

00:37:21.320 --> 00:37:23.364 Received Niveau 1st and these are the

NOTE Confidence: 0.7429117

00:37:23.364 --> 00:37:25.513 top top jeans that were so sheated

NOTE Confidence: 0.7429117

00:37:25.513 --> 00:37:27.688 with with with good outcomes but had

NOTE Confidence: 0.7429117

00:37:27.688 --> 00:37:29.440 low class one expressions and many

NOTE Confidence: 0.7429117

00:37:29.440 --> 00:37:32.120 of these are in a fair and target genes.

NOTE Confidence: 0.7429117

00:37:32.120 --> 00:37:34.304 As you can see as you would expect

NOTE Confidence: 0.7429117

00:37:34.304 --> 00:37:36.756 and of no down near the bottom is

NOTE Confidence: 0.7429117

00:37:36.756 --> 00:37:39.277 I'll 15 which would be a target in

NOTE Confidence: 0.7429117

00:37:39.277 --> 00:37:41.572 case it was also significant in that.

NOTE Confidence: 0.7429117

00:37:41.572 --> 00:37:44.284 So we looked at the interferon.

NOTE Confidence: 0.7429117

00:37:44.290 --> 00:37:46.080 Genes are associated with outcomes

NOTE Confidence: 0.7429117

00:37:46.080 --> 00:37:47.870 in the patients receive needle

NOTE Confidence: 0.7566492

00:37:47.929 --> 00:37:50.095 first. We also had the interference

NOTE Confidence: 0.7566492

00:37:50.095 --> 00:37:51.563 publishing secure from from

NOTE Confidence: 0.7566492

00:37:51.563 --> 00:37:52.951 mercantile we visited, looked,

NOTE Confidence: 0.7566492

00:37:52.951 --> 00:37:55.117 would they looked at Penn Bro.

NOTE Confidence: 0.7566492

00:37:55.120 --> 00:37:57.640 We had our top 25 jeans and of course

NOTE Confidence: 0.7566492

00:37:57.640 --> 00:38:00.010 any good computational group would want

NOTE Confidence: 0.7566492

00:38:00.010 --> 00:38:03.060 to have their own their own signature.

NOTE Confidence: 0.7566492

00:38:03.060 --> 00:38:05.587 So they develop their own infernal legions.

NOTE Confidence: 0.7566492

00:38:05.590 --> 00:38:07.958 Was had some overlap so that on the

NOTE Confidence: 0.7566492

00:38:07.958 --> 00:38:10.270 left or patient received needle first

NOTE Confidence: 0.7566492

00:38:10.270 --> 00:38:13.230 on the writer page received it first.

NOTE Confidence: 0.7566492

00:38:13.230 --> 00:38:15.312 In the patients who had these

NOTE Confidence: 0.7566492

00:38:15.312 --> 00:38:17.170 signatures and had low class,

NOTE Confidence: 0.7566492

00:38:17.170 --> 00:38:20.026 one expression still did very well to niveau,

NOTE Confidence: 0.7566492

00:38:20.030 --> 00:38:22.514 but the expression of these genes

NOTE Confidence: 0.7566492

00:38:22.514 --> 00:38:24.592 most of interferon target genes

NOTE Confidence: 0.7566492

00:38:24.592 --> 00:38:26.656 do not affect their outcomes to

NOTE Confidence: 0.7566492

00:38:26.656 --> 00:38:29.659 Epyx and so this would is what you

NOTE Confidence: 0.7566492

00:38:29.659 --> 00:38:31.554 would have would have accepted.

NOTE Confidence: 0.7566492

00:38:31.560 --> 00:38:34.128 When we looked at the patients receive me,

NOTE Confidence: 0.7566492

00:38:34.130 --> 00:38:36.167 go first and had low class one

NOTE Confidence: 0.7566492

00:38:36.167 --> 00:38:38.488 expression and looked at what other gene

NOTE Confidence: 0.7566492

00:38:38.488 --> 00:38:40.228 signatures were associated with that.

NOTE Confidence: 0.7566492

00:38:40.230 --> 00:38:42.470 The patients again who got needle first.

NOTE Confidence: 0.7566492

00:38:42.470 --> 00:38:45.144 There were some gammadelta cells that were

NOTE Confidence: 0.7566492

00:38:45.144 --> 00:38:47.657 associated with outcomes as well as an in

NOTE Confidence: 0.7566492

00:38:47.657 --> 00:38:49.539 case signature as depicted on the left,

NOTE Confidence: 0.7566492

00:38:49.540 --> 00:38:51.275 and those signatures were not

NOTE Confidence: 0.7566492

00:38:51.275 --> 00:38:52.663 influential for patient received

NOTE Confidence: 0.7566492

00:38:52.663 --> 00:38:54.669 it be first in terms of outcomes,

NOTE Confidence: 0.7566492

00:38:54.670 --> 00:38:56.672 we were able to in those patients

NOTE Confidence: 0.7566492

00:38:56.672 --> 00:38:59.117 who had low class one expression and

NOTE Confidence: 0.7566492

00:38:59.117 --> 00:39:01.403 good outcomes were able to identify

NOTE Confidence: 0.7566492

00:39:01.470 --> 00:39:03.437 in the two mark apartment by C.

NOTE Confidence: 0.7566492

00:39:03.440 --> 00:39:05.120 Both Gamma, Delta and in case files.

NOTE Confidence: 0.7566492

00:39:05.120 --> 00:39:06.089 There were few,

NOTE Confidence: 0.7566492

00:39:06.089 --> 00:39:08.027 but they were detectable in those

NOTE Confidence: 0.7566492

00:39:08.027 --> 00:39:09.719 in those patients by HC.

NOTE Confidence: 0.7566492

00:39:09.720 --> 00:39:11.736 Anne's kind of hinted before I'll

NOTE Confidence: 0.7566492

00:39:11.736 --> 00:39:13.482 15 specifically in the patients

NOTE Confidence: 0.7566492

00:39:13.482 --> 00:39:15.534 who had low class and expression

NOTE Confidence: 0.7566492

00:39:15.534 --> 00:39:17.559 or single first was associ with

NOTE Confidence: 0.7566492

00:39:17.559 --> 00:39:19.437 better outcomes in on the left.

NOTE Confidence: 0.7566492

00:39:19.440 --> 00:39:22.618 Here an we're not influencing the outcomes

NOTE Confidence: 0.7566492

00:39:22.618 --> 00:39:25.759 to page received it first on the right.

NOTE Confidence: 0.7566492

00:39:25.760 --> 00:39:27.482 So we were interested trying to

NOTE Confidence: 0.7566492

00:39:27.482 --> 00:39:29.411 confirm in some way another group

NOTE Confidence: 0.7566492

00:39:29.411 --> 00:39:31.571 of samples that were well clinically

NOTE Confidence: 0.7566492

00:39:31.571 --> 00:39:33.305 annotated for outcomes and went

NOTE Confidence: 0.7566492

00:39:33.305 --> 00:39:34.890 to the Checkmate 069 study,

NOTE Confidence: 0.7566492

00:39:34.890 --> 00:39:36.878 which was a study that had got

NOTE Confidence: 0.7566492

00:39:36.878 --> 00:39:39.128 the proof on evil Epion Melanoma,

NOTE Confidence: 0.7566492

00:39:39.130 --> 00:39:41.776 and so there was one Group A source evil

NOTE Confidence: 0.7566492

00:39:41.776 --> 00:39:44.666 it be an another group that received it,

NOTE Confidence: 0.7566492

00:39:44.670 --> 00:39:47.082 be alone and had samples available

NOTE Confidence: 0.7566492

00:39:47.082 --> 00:39:47.886 for analysis.

NOTE Confidence: 0.7566492

00:39:47.890 --> 00:39:50.114 While we were able to show is that

NOTE Confidence: 0.7566492

00:39:50.114 --> 00:39:52.243 the patients got it be alone who

NOTE Confidence: 0.7566492

00:39:52.243 --> 00:39:53.753 are downregulation of class one

NOTE Confidence: 0.7566492

00:39:53.814 --> 00:39:55.436 basically had 100% negative predicted

NOTE Confidence: 0.7566492

00:39:55.436 --> 00:39:57.104 value for for both response and

NOTE Confidence: 0.7566492

00:39:57.104 --> 00:39:58.830 an for poor clinical outcomes.

NOTE Confidence: 0.7566492

00:39:58.830 --> 00:40:01.014 So if they had loss of class one

NOTE Confidence: 0.7566492

00:40:01.014 --> 00:40:02.949 again they did very very poorly

NOTE Confidence: 0.7566492

00:40:02.949 --> 00:40:04.604 for the patient seen evil.

NOTE Confidence: 0.7566492

00:40:04.610 --> 00:40:06.598 Plus it be there were there were

NOTE Confidence: 0.7566492

00:40:06.598 --> 00:40:08.558 trends but there was nothing stuff.

NOTE Confidence: 0.7566492

00:40:08.560 --> 00:40:08.884 Again.

NOTE Confidence: 0.7566492

00:40:08.884 --> 00:40:11.476 Obviously this is not ideal that it was

NOTE Confidence: 0.7566492

00:40:11.476 --> 00:40:13.429 combination that is hard to dissect out.

NOTE Confidence: 0.7566492

00:40:13.430 --> 00:40:15.254 There was a trend toward the

NOTE Confidence: 0.7566492

00:40:15.254 --> 00:40:16.470 Class 2 being beneficial,

NOTE Confidence: 0.7566492

00:40:16.470 --> 00:40:18.300 but it does not reach.

NOTE Confidence: 0.7566492

00:40:18.300 --> 00:40:19.108 Sickle significance.

NOTE Confidence: 0.7566492

00:40:19.108 --> 00:40:21.936 Here are the the mayor analysis for

NOTE Confidence: 0.7566492

00:40:21.936 --> 00:40:24.019 patients with class one expression,

NOTE Confidence: 0.7566492

00:40:24.020 --> 00:40:25.982 again high versus low class profession

NOTE Confidence: 0.7566492

00:40:25.982 --> 00:40:28.383 with iffy on the left and evil clip

NOTE Confidence: 0.7566492

00:40:28.383 --> 00:40:30.672 in the right and you can see the

NOTE Confidence: 0.7566492

00:40:30.672 --> 00:40:32.742 difference received it be with low

NOTE Confidence: 0.7566492

00:40:32.742 --> 00:40:34.613 class xpression doing very poorly.

NOTE Confidence: 0.7566492

00:40:34.613 --> 00:40:37.350 It was no difference for patient received

NOTE Confidence: 0.7055627

00:40:37.419 --> 00:40:39.049 new needle plus it being.

NOTE Confidence: 0.7055627

00:40:39.050 --> 00:40:41.855 Nearest Class 2 expression that

NOTE Confidence: 0.7055627

00:40:41.855 --> 00:40:45.369 again reached had a trend but

NOTE Confidence: 0.7055627

00:40:45.369 --> 00:40:47.809 did not reach significance.

NOTE Confidence: 0.7055627

00:40:47.810 --> 00:40:50.365 So it appears that secretly for blockade,

NOTE Confidence: 0.7055627

00:40:50.370 --> 00:40:52.512 responses are dependent on MHC class

NOTE Confidence: 0.7055627

00:40:52.512 --> 00:40:54.654 one expression while PD one blockade

NOTE Confidence: 0.7055627

00:40:54.654 --> 00:40:56.289 is not entirely dependent class

NOTE Confidence: 0.7055627

00:40:56.289 --> 00:40:58.925 one but is improved with Class 2

NOTE Confidence: 0.7055627

00:40:58.925 --> 00:41:00.915 expression and with also previously

NOTE Confidence: 0.7055627

00:41:00.915 --> 00:41:02.050 described interference signatures,

NOTE Confidence: 0.7055627

00:41:02.050 --> 00:41:03.875 they really show the importance

NOTE Confidence: 0.7055627

00:41:03.875 --> 00:41:04.970 of interfering there.

NOTE Confidence: 0.7055627

00:41:04.970 --> 00:41:07.594 I think this raises a lot of questions

NOTE Confidence: 0.7055627

00:41:07.594 --> 00:41:10.806 and on what other aspects interest to do.

NOTE Confidence: 0.7055627

00:41:10.810 --> 00:41:12.934 We are interested in looking at

NOTE Confidence: 0.7055627

00:41:12.934 --> 00:41:15.112 other other cancers in the Class

NOTE Confidence: 0.7055627

00:41:15.112 --> 00:41:17.194 2 component which has been also

NOTE Confidence: 0.7055627

00:41:17.194 --> 00:41:19.598 reported by other groups importantly.

NOTE Confidence: 0.7055627

00:41:19.600 --> 00:41:21.676 Suggest that maybe CD four cells

NOTE Confidence: 0.7055627

00:41:21.676 --> 00:41:23.994 making game in assure on could be

NOTE Confidence: 0.7055627

00:41:23.994 --> 00:41:26.010 very important for for for PD one

NOTE Confidence: 0.7055627

00:41:26.082 --> 00:41:28.197 blockade dependence on class one.

NOTE Confidence: 0.7055627

00:41:28.200 --> 00:41:30.944 For 64 we've always been interested in using.

NOTE Confidence: 0.7055627

00:41:30.950 --> 00:41:32.670 This is a predictive marker.

NOTE Confidence: 0.7055627

00:41:32.670 --> 00:41:34.716 Prognostic studies and are looking at

NOTE Confidence: 0.7055627

00:41:34.716 --> 00:41:36.799 other groups of patients both needle,

NOTE Confidence: 0.7055627

00:41:36.800 --> 00:41:39.770 plus if it in order to to try to really

NOTE Confidence: 0.7055627

00:41:39.851 --> 00:41:42.101 say if patient has downregulation

NOTE Confidence: 0.7055627

00:41:42.101 --> 00:41:45.190 class one which should it be considered

NOTE Confidence: 0.7055627

00:41:45.190 --> 00:41:47.857 or not as part of the regiment?

NOTE Confidence: 0.7055627

00:41:47.860 --> 00:41:50.734 So we're really now applying newer

NOTE Confidence: 0.7055627

00:41:50.734 --> 00:41:53.319 technologies to understand the spatial

NOTE Confidence: 0.7055627

00:41:53.319 --> 00:41:55.679 relationships with immune cells,

NOTE Confidence: 0.7055627

00:41:55.680 --> 00:41:56.654 tumor environment,

NOTE Confidence: 0.7055627

00:41:56.654 --> 00:41:59.576 doing both MIDI and other other

NOTE Confidence: 0.7055627

00:41:59.576 --> 00:42:01.410 important imaging techniques,

NOTE Confidence: 0.7055627

00:42:01.410 --> 00:42:04.512 sisyphe and others to understand the

NOTE Confidence: 0.7055627

00:42:04.512 --> 00:42:07.140 interactions of these immune cells.

NOTE Confidence: 0.7055627

00:42:07.140 --> 00:42:09.224 Myeloid cells CD4 CD,

NOTE Confidence: 0.7055627

00:42:09.224 --> 00:42:11.308 eight other other aspects,

NOTE Confidence: 0.7055627

00:42:11.310 --> 00:42:14.070 as well as the APC machinery

NOTE Confidence: 0.7055627

00:42:14.070 --> 00:42:16.686 nearest neighbors to understand the

NOTE Confidence: 0.7055627

00:42:16.686 --> 00:42:18.759 interaction between requirement.

NOTE Confidence: 0.7055627

00:42:18.760 --> 00:42:21.336 We think it's important to better define

NOTE Confidence: 0.7055627

00:42:21.336 --> 00:42:24.460 the role of Class 2 and CD4 cells as

NOTE Confidence: 0.7055627

00:42:24.460 --> 00:42:27.108 well as the potential for Nate immunity.

NOTE Confidence: 0.7055627

00:42:27.110 --> 00:42:28.920 We have some hints there,

NOTE Confidence: 0.7055627

00:42:28.920 --> 00:42:31.153 both from their early site off as

NOTE Confidence: 0.7055627

00:42:31.153 --> 00:42:33.928 well as some of the aspects and

NOTE Confidence: 0.7055627

00:42:33.928 --> 00:42:36.113 looking the difference between needle

NOTE Confidence: 0.7055627

00:42:36.113 --> 00:42:38.214 versus AP or simply for speedy

NOTE Confidence: 0.7055627

00:42:38.214 --> 00:42:40.536 one or the control for NK cells.

NOTE Confidence: 0.7055627

00:42:40.536 --> 00:42:41.988 Even with checkpoint blockade,

NOTE Confidence: 0.7055627

00:42:41.990 --> 00:42:43.290 important role of cytokines,

NOTE Confidence: 0.7055627

00:42:43.290 --> 00:42:45.717 both the efficacy as well as some

NOTE Confidence: 0.7055627

00:42:45.717 --> 00:42:47.365 examples of possible reduction

NOTE Confidence: 0.7055627

00:42:47.365 --> 00:42:49.013 in in toxicities combination.

NOTE Confidence: 0.7055627

00:42:49.020 --> 00:42:51.316 Drink factors and really using data for

NOTE Confidence: 0.7055627

00:42:51.316 --> 00:42:52.721 rational combinations of checkpoint

NOTE Confidence: 0.7055627

00:42:52.721 --> 00:42:54.917 blockade based therapies in the future.

NOTE Confidence: 0.7055627

00:42:54.920 --> 00:42:56.936 So many of the things I've discussed

NOTE Confidence: 0.7055627

00:42:56.936 --> 00:42:58.537 with you today were investigating

NOTE Confidence: 0.7055627

00:42:58.537 --> 00:43:00.232 initiated and it's always very

NOTE Confidence: 0.7055627

00:43:00.232 --> 00:43:02.549 hard to do investigation studies.

NOTE Confidence: 0.7055627

00:43:02.550 --> 00:43:05.196 And this is just a list of the many

NOTE Confidence: 0.7055627

00:43:05.196 --> 00:43:07.715 folks that were involved with these

NOTE Confidence: 0.7055627

00:43:07.715 --> 00:43:10.246 studies in the approaches that the

NOTE Confidence: 0.7055627

00:43:10.246 --> 00:43:12.353 result for them and I just want

NOTE Confidence: 0.7055627

00:43:12.353 --> 00:43:14.964 to pay pay thanks to them.

NOTE Confidence: 0.7055627

00:43:14.964 --> 00:43:17.970 And these are my disclosures too.

NOTE Confidence: 0.9041823

00:43:22.570 --> 00:43:23.290 Thank you.

NOTE Confidence: 0.85573786

00:43:25.710 --> 00:43:26.601 Thank you Steve.

NOTE Confidence: 0.85573786

00:43:26.601 --> 00:43:28.680 I'm going to ask folks to please

NOTE Confidence: 0.85573786

00:43:28.746 --> 00:43:30.810 enter questions into the chat box,

NOTE Confidence: 0.85573786

00:43:30.810 --> 00:43:33.085 but while folks do that I will

NOTE Confidence: 0.85573786

00:43:33.085 --> 00:43:34.640 start with one or two.

NOTE Confidence: 0.85573786

00:43:34.640 --> 00:43:37.728 That's OK with you.

NOTE Confidence: 0.85573786

00:43:37.730 --> 00:43:39.596 So first question was the dose

NOTE Confidence: 0.85573786

00:43:39.596 --> 00:43:41.399 delivery better when you gave the

NOTE Confidence: 0.85573786

00:43:41.399 --> 00:43:43.156 AP and the GM CSF versus APLON?

NOTE Confidence: 0.85573786

00:43:43.160 --> 00:43:44.030 In other words,

NOTE Confidence: 0.85573786

00:43:44.030 --> 00:43:46.310 were you able to get more cycles in?

NOTE Confidence: 0.7635931

00:43:47.310 --> 00:43:49.710 Now that's a very it's very good question.

NOTE Confidence: 0.7635931

00:43:49.710 --> 00:43:52.170 So when and when we looked at that and in

NOTE Confidence: 0.7635931

00:43:52.230 --> 00:43:54.806 response to some of the reviewers comments,

NOTE Confidence: 0.7635931

00:43:54.810 --> 00:43:56.436 is there was good question there

NOTE Confidence: 0.7635931

00:43:56.436 --> 00:43:58.542 done not seem to be a significant

NOTE Confidence: 0.7635931

00:43:58.542 --> 00:44:00.147 difference in number of cycles

NOTE Confidence: 0.7635931

00:44:00.147 --> 00:44:02.007 there were between the two arms,

NOTE Confidence: 0.7635931

00:44:02.010 --> 00:44:03.810 so so that's a great question.

NOTE Confidence: 0.7635931

00:44:03.810 --> 00:44:05.610 So if you reduce the we

NOTE Confidence: 0.7635931

00:44:05.610 --> 00:44:06.810 know that super blockade,

NOTE Confidence: 0.7635931

00:44:06.810 --> 00:44:09.458 we know that if he is dose dependent, right?

NOTE Confidence: 0.7635931

00:44:09.458 --> 00:44:11.690 We know going from 3 to 10 you have

NOTE Confidence: 0.7635931

00:44:11.756 --> 00:44:13.706 more toxicity and more responses,

NOTE Confidence: 0.7635931

00:44:13.710 --> 00:44:15.648 and so the question is great

NOTE Confidence: 0.7635931

00:44:15.648 --> 00:44:17.322 question is whether you could

NOTE Confidence: 0.7635931

00:44:17.322 --> 00:44:19.236 just get more more Dragon and.

NOTE Confidence: 0.7635931

00:44:19.240 --> 00:44:20.638 Watching at least between the storms,

NOTE Confidence: 0.7635931

00:44:20.640 --> 00:44:22.271 do not seem to be a significant

NOTE Confidence: 0.7635931

00:44:22.271 --> 00:44:23.220 difference between between that,

NOTE Confidence: 0.7635931

00:44:23.220 --> 00:44:24.977 but that's a great question and something

NOTE Confidence: 0.7635931

00:44:24.977 --> 00:44:26.798 we need to continue to look into as

NOTE Confidence: 0.7635931

00:44:26.798 --> 00:44:28.827 we move on to the needle at the study.

NOTE Confidence: 0.842177

00:44:29.650 --> 00:44:32.110 Let's not thank you.

NOTE Confidence: 0.842177

00:44:32.110 --> 00:44:33.558 Expression is So what

NOTE Confidence: 0.842177

00:44:33.558 --> 00:44:35.006 directions are you planning

NOTE Confidence: 0.842177

00:44:35.006 --> 00:44:36.660 on taking for class one?

NOTE Confidence: 0.842177

00:44:36.660 --> 00:44:37.360 Deficient melanomas.

NOTE Confidence: 0.796128

00:44:38.600 --> 00:44:40.749 Yeah, we we number one have been

NOTE Confidence: 0.796128

00:44:40.749 --> 00:44:42.800 interested in looking at whether the

NOTE Confidence: 0.796128

00:44:42.800 --> 00:44:44.580 class one observation is important.

NOTE Confidence: 0.796128

00:44:44.580 --> 00:44:46.869 Other cancers Sony would be is now

NOTE Confidence: 0.796128

00:44:46.869 --> 00:44:49.395 a lung cancer and kidney cancer and

NOTE Confidence: 0.796128

00:44:49.395 --> 00:44:51.956 we've been trying to gain access to

NOTE Confidence: 0.796128

00:44:51.956 --> 00:44:54.196 some of them just to see you know,

NOTE Confidence: 0.796128

00:44:54.200 --> 00:44:56.198 does does class one influence that?

NOTE Confidence: 0.796128

00:44:56.200 --> 00:44:57.860 So that's the first thing.

NOTE Confidence: 0.796128

00:44:57.860 --> 00:44:59.981 The other thing is we were kind

NOTE Confidence: 0.796128

00:44:59.981 --> 00:45:02.168 of interested to look at a just

NOTE Confidence: 0.796128

00:45:02.168 --> 00:45:03.683 even a biomarker driven trial

NOTE Confidence: 0.796128

00:45:03.683 --> 00:45:05.819 for classroom expression to say,

NOTE Confidence: 0.796128

00:45:05.820 --> 00:45:07.580 should patients who have low

NOTE Confidence: 0.796128

00:45:07.580 --> 00:45:08.636 class work session.

NOTE Confidence: 0.796128

00:45:08.640 --> 00:45:09.522 Getting it be,

NOTE Confidence: 0.796128

00:45:09.522 --> 00:45:11.286 or if there's an efficacy change,

NOTE Confidence: 0.796128

00:45:11.290 --> 00:45:12.916 we just haven't been able to

NOTE Confidence: 0.796128

00:45:12.916 --> 00:45:14.942 get traction to do such trials

NOTE Confidence: 0.796128

00:45:14.942 --> 00:45:16.259 and logistical standpoint.

NOTE Confidence: 0.796128

00:45:16.260 --> 00:45:16.540 Yeah,

NOTE Confidence: 0.8072471

00:45:16.540 --> 00:45:17.910 it's very complicated and you

NOTE Confidence: 0.8072471

00:45:17.910 --> 00:45:19.870 got a lot of them going on,

NOTE Confidence: 0.8072471

00:45:19.870 --> 00:45:21.538 so there's a question from the

NOTE Confidence: 0.8072471

00:45:21.538 --> 00:45:22.650 audience from Antonio Muro.

NOTE Confidence: 0.8072471

00:45:22.650 --> 00:45:24.040 Thank you for your presentation.

NOTE Confidence: 0.8072471

00:45:24.040 --> 00:45:25.708 By the way, thank you for

NOTE Confidence: 0.8072471

00:45:25.708 --> 00:45:26.820 the presentation is awesome.

NOTE Confidence: 0.8072471

00:45:26.820 --> 00:45:28.766 It's going to end up with that,

NOTE Confidence: 0.8072471

00:45:28.770 --> 00:45:30.160 but in the GBM trial,

NOTE Confidence: 0.8072471

00:45:30.160 --> 00:45:30.994 comparing neighbor versus

NOTE Confidence: 0.8072471

00:45:30.994 --> 00:45:32.106 Beth patients with PD,

NOTE Confidence: 0.8072471

00:45:32.110 --> 00:45:33.218 L1 expression survived longer

NOTE Confidence: 0.8072471

00:45:33.218 --> 00:45:34.326 if they received bags.

NOTE Confidence: 0.8072471

00:45:34.330 --> 00:45:36.004 Do you have any ideas as

NOTE Confidence: 0.8072471

00:45:36.004 --> 00:45:37.390 to why that could be?

NOTE Confidence: 0.93798274

00:45:38.660 --> 00:45:43.000 Yeah so. One of the questions that could

NOTE Confidence: 0.93798274

00:45:43.000 --> 00:45:45.380 be confusing is whether the PEO expressions

NOTE Confidence: 0.93798274

00:45:45.380 --> 00:45:47.739 on the tumor on the mileage component

NOTE Confidence: 0.93798274

00:45:47.806 --> 00:45:50.362 so in in brain tumors you gonna have the

NOTE Confidence: 0.93798274

00:45:50.362 --> 00:45:52.300 myeloid like cells or run that probably

NOTE Confidence: 0.93798274

00:45:52.300 --> 00:45:54.808 have a lot of people and expression,

NOTE Confidence: 0.93798274

00:45:54.810 --> 00:45:57.636 and so one of the hints from the Genentech

NOTE Confidence: 0.93798274

00:45:57.636 --> 00:46:00.569 trial is that the immune cells express PD L1.

NOTE Confidence: 0.93798274

00:46:00.570 --> 00:46:02.810 The myeloid cells also for both markers.

NOTE Confidence: 0.93798274

00:46:02.810 --> 00:46:04.844 For predicting this to improve outcomes

NOTE Confidence: 0.93798274

00:46:04.844 --> 00:46:07.329 to budget blockade and so depending upon

NOTE Confidence: 0.93798274

00:46:07.329 --> 00:46:09.465 you know sometimes maybe more myeloid

NOTE Confidence: 0.93798274

00:46:09.465 --> 00:46:11.515 dependent on my my Lord Rich and others.

NOTE Confidence: 0.93798274

00:46:11.520 --> 00:46:13.578 Include by blocking veg F for engineering

NOTE Confidence: 0.93798274

00:46:13.578 --> 00:46:15.459 factors you actually having a greater

NOTE Confidence: 0.93798274

00:46:15.459 --> 00:46:17.044 effect on that myeloid suppressor

NOTE Confidence: 0.93798274

00:46:17.044 --> 00:46:18.586 compartment that my suppressor effect

NOTE Confidence: 0.93798274

00:46:18.586 --> 00:46:20.574 then then actually on the tumor itself.

NOTE Confidence: 0.93798274

00:46:20.580 --> 00:46:22.392 So that would mean without having

NOTE Confidence: 0.93798274

00:46:22.392 --> 00:46:23.298 a definitive answer,

NOTE Confidence: 0.93798274

00:46:23.300 --> 00:46:25.484 that that would be one of the hypotheses

NOTE Confidence: 0.93798274

00:46:25.484 --> 00:46:27.627 is that you're when you're blocking with

NOTE Confidence: 0.93798274

00:46:27.627 --> 00:46:30.165 Bev that you that you may be affecting

NOTE Confidence: 0.93798274

00:46:30.165 --> 00:46:32.356 both your immune cells that are pretty

NOTE Confidence: 0.93798274

00:46:32.360 --> 00:46:34.416 one positive as well as as well as

NOTE Confidence: 0.93798274

00:46:34.416 --> 00:46:36.279 the myeloid component that affects,

NOTE Confidence: 0.93798274

00:46:36.280 --> 00:46:39.300 and so if the tumor is is is more dependent

NOTE Confidence: 0.93798274

00:46:39.371 --> 00:46:41.963 on myeloid cells or in such that you.

NOTE Confidence: 0.93798274

00:46:41.970 --> 00:46:42.897 Milo suppressive cells.

NOTE Confidence: 0.93798274

00:46:42.897 --> 00:46:44.751 You may be having a benefit

NOTE Confidence: 0.93798274

00:46:44.751 --> 00:46:46.439 by blocking benchev there.

NOTE Confidence: 0.93798274

00:46:46.440 --> 00:46:48.855 That's again something that needs to be

NOTE Confidence: 0.93798274

00:46:48.855 --> 00:46:50.569 more definitively determine in patients,

NOTE Confidence: 0.93798274

00:46:50.570 --> 00:46:52.628 but I think a reasonable hypothesis.

NOTE Confidence: 0.769605800000001

00:46:53.450 --> 00:46:55.417 Now then, maybe Antonio can respond to

NOTE Confidence: 0.769605800000001

00:46:55.417 --> 00:46:57.288 the question of whether it's actually

NOTE Confidence: 0.769605800000001

00:46:57.288 --> 00:46:59.226 primarily expressed in the my load

NOTE Confidence: 0.769605800000001

00:46:59.226 --> 00:47:01.376 cells or in the glioma cells themselves.

NOTE Confidence: 0.769605800000001

00:47:01.380 --> 00:47:04.272 'cause I've seen some really strongly

NOTE Confidence: 0.769605800000001

00:47:04.272 --> 00:47:06.200 positive gliomas tumor cells.

NOTE Confidence: 0.769605800000001

00:47:06.200 --> 00:47:07.082 It is interesting,

NOTE Confidence: 0.769605800000001

00:47:07.082 --> 00:47:08.846 then why folks into other questions.

NOTE Confidence: 0.769605800000001

00:47:08.850 --> 00:47:11.325 I'm going to ask you a question about your

NOTE Confidence: 0.769605800000001

00:47:11.325 --> 00:47:13.837 early date on the vasculopathy with the CTA.

NOTE Confidence: 0.769605800000001

00:47:13.840 --> 00:47:14.868 Four at that pic.

NOTE Confidence: 0.769605800000001

00:47:14.868 --> 00:47:16.153 That figure that your shoulder

NOTE Confidence: 0.769605800000001

00:47:16.153 --> 00:47:17.670 is actually quite stunning.

NOTE Confidence: 0.769605800000001

00:47:17.670 --> 00:47:19.714 Do you think that that's organ dependent?

NOTE Confidence: 0.769605800000001

00:47:19.720 --> 00:47:20.308 More likely.

NOTE Confidence: 0.769605800000001

00:47:20.308 --> 00:47:22.366 See it in the liver or whatever.

NOTE Confidence: 0.769605800000001

00:47:22.370 --> 00:47:24.470 Or do you think and maybe you've

NOTE Confidence: 0.769605800000001

00:47:24.470 --> 00:47:26.779 had a chance to look at that now,

NOTE Confidence: 0.7719938

00:47:26.780 --> 00:47:28.544 so we've so, at least in

NOTE Confidence: 0.7719938

00:47:28.544 --> 00:47:29.720 that very early stage.

NOTE Confidence: 0.7719938

00:47:29.720 --> 00:47:31.841 Way back when they do not seem

NOTE Confidence: 0.7719938

00:47:31.841 --> 00:47:33.539 to be organized and we had,

NOTE Confidence: 0.7719938

00:47:33.540 --> 00:47:36.018 we saw the best drop, the many different,

NOTE Confidence: 0.7719938

00:47:36.018 --> 00:47:38.034 many different organs that were biopsied.

NOTE Confidence: 0.7719938

00:47:38.040 --> 00:47:42.600 And. In so we've also as many are looking

NOTE Confidence: 0.7719938

00:47:42.600 --> 00:47:44.679 at tertiary lyford's liquid structures.

NOTE Confidence: 0.7719938

00:47:44.680 --> 00:47:45.968 That anti interests may

NOTE Confidence: 0.7719938

00:47:45.968 --> 00:47:47.256 also be influenced in.

NOTE Confidence: 0.7719938

00:47:47.260 --> 00:47:49.676 So we actually saw a large I didn't

NOTE Confidence: 0.7719938

00:47:49.676 --> 00:47:51.790 think into this into much detail.

NOTE Confidence: 0.7719938

00:47:51.790 --> 00:47:53.400 A number of tertiary lymphoid

NOTE Confidence: 0.7719938

00:47:53.400 --> 00:47:54.688 structures associated with that,

NOTE Confidence: 0.7719938

00:47:54.690 --> 00:47:56.776 and you think that maybe those are

NOTE Confidence: 0.7719938

00:47:56.776 --> 00:47:58.797 making any bodies and those mission

NOTE Confidence: 0.7719938

00:47:58.797 --> 00:48:00.402 with good outcomes, but that,

NOTE Confidence: 0.7719938

00:48:00.402 --> 00:48:02.299 but as we're looking at for these

NOTE Confidence: 0.7719938

00:48:02.299 --> 00:48:03.410 traditional infrastructures,

NOTE Confidence: 0.7719938

00:48:03.410 --> 00:48:05.348 we also saw these vast properties

NOTE Confidence: 0.7719938

00:48:05.348 --> 00:48:06.640 in many different organs,

NOTE Confidence: 0.7719938

00:48:06.640 --> 00:48:08.578 so there's different degrees of it,

NOTE Confidence: 0.7719938

00:48:08.580 --> 00:48:11.990 but but but it does not seem to be working.

NOTE Confidence: 0.7719938

00:48:11.990 --> 00:48:12.190 It.

NOTE Confidence: 0.7564188

00:48:13.280 --> 00:48:15.518 Interesting, and then if you followed

NOTE Confidence: 0.7564188

00:48:15.518 --> 00:48:18.448 followed up on your studies of the angio,

NOTE Confidence: 0.7564188

00:48:18.450 --> 00:48:21.180 the edge two expression in the Tigers

NOTE Confidence: 0.7564188

00:48:21.180 --> 00:48:23.607 in patients who got deep in Eva.

NOTE Confidence: 0.7564188

00:48:23.610 --> 00:48:25.830 No, there's blood studies that your

NOTE Confidence: 0.7564188

00:48:25.830 --> 00:48:27.670 shirt yeah yeah yeah, yeah.

NOTE Confidence: 0.7564188

00:48:27.670 --> 00:48:30.340 So we so with evil if he also and we

NOTE Confidence: 0.7564188

00:48:30.419 --> 00:48:33.331 do have some data that we're putting

NOTE Confidence: 0.7564188

00:48:33.331 --> 00:48:35.878 together that while the antibody titers

NOTE Confidence: 0.7564188

00:48:35.878 --> 00:48:38.734 are not as the increase in anybody,

NOTE Confidence: 0.7564188

00:48:38.740 --> 00:48:40.590 titers are not as high.

NOTE Confidence: 0.7564188

00:48:40.590 --> 00:48:42.870 If the patient had received which.

NOTE Confidence: 0.7564188

00:48:42.870 --> 00:48:44.660 Maybe again suggest maybe there's

NOTE Confidence: 0.7564188

00:48:44.660 --> 00:48:46.450 some humanity effects to anti

NOTE Confidence: 0.7564188

00:48:46.516 --> 00:48:48.281 Backdraft patients who did develop

NOTE Confidence: 0.7564188

00:48:48.281 --> 00:48:50.390 antibodies to enter into an evil.

NOTE Confidence: 0.7564188

00:48:50.390 --> 00:48:52.889 If he did seem to do better

NOTE Confidence: 0.7564188

00:48:52.889 --> 00:48:54.680 than patients who did not,

NOTE Confidence: 0.7564188

00:48:54.680 --> 00:48:56.828 but the waiting to do our

NOTE Confidence: 0.7564188

00:48:56.828 --> 00:48:58.260 confirmatory cord right now.

NOTE Confidence: 0.7686038

00:48:59.550 --> 00:49:01.464 That's great, and then so you're

NOTE Confidence: 0.7686038

00:49:01.464 --> 00:49:03.427 planning on following up on those

NOTE Confidence: 0.7686038

00:49:03.427 --> 00:49:04.987 studies with the engine point,

NOTE Confidence: 0.7686038

00:49:04.990 --> 00:49:06.650 and we wanted to inhibitors

NOTE Confidence: 0.7686038

00:49:06.650 --> 00:49:08.674 in other cancers or with EPI

NOTE Confidence: 0.7686038

00:49:08.674 --> 00:49:10.426 Nevo as opposed to a dragon.

NOTE Confidence: 0.7686038

00:49:10.430 --> 00:49:12.990 Yeah, so I heard you're always my therapist.

NOTE Confidence: 0.7686038

00:49:12.990 --> 00:49:15.234 It's always been challenging to gain

NOTE Confidence: 0.7686038

00:49:15.234 --> 00:49:17.857 access to these drugs for grade to do

NOTE Confidence: 0.7686038

00:49:17.857 --> 00:49:20.029 some of the the stage you want to,

NOTE Confidence: 0.7686038

00:49:20.030 --> 00:49:22.270 so that's been one of the challenges,

NOTE Confidence: 0.7686038

00:49:22.270 --> 00:49:24.811 but there are. There are some companies

NOTE Confidence: 0.7686038

00:49:24.811 --> 00:49:27.067 that are looking at at dual veg F.

NOTE Confidence: 0.7686038

00:49:27.070 --> 00:49:28.334 H2 inhibition in cancer,

NOTE Confidence: 0.7686038

00:49:28.334 --> 00:49:31.100 and I think that those studies will probably.

NOTE Confidence: 0.7686038

00:49:31.100 --> 00:49:32.300 People shed further light,

NOTE Confidence: 0.7686038

00:49:32.300 --> 00:49:34.100 so when you block veg F,

NOTE Confidence: 0.7686038

00:49:34.100 --> 00:49:36.095 Ange two goes down temporarily and then

NOTE Confidence: 0.7686038

00:49:36.095 --> 00:49:38.487 H2 comes up is kind of resistant mechanism

NOTE Confidence: 0.7686038

00:49:38.487 --> 00:49:40.639 and so the question is whether you

NOTE Confidence: 0.7686038

00:49:40.639 --> 00:49:42.788 whether the blocking age 2 would would

NOTE Confidence: 0.7686038

00:49:42.788 --> 00:49:46.467 also be beneficial with veg F and likelihood.

NOTE Confidence: 0.7686038

00:49:46.470 --> 00:49:49.088 It probably would be in terms of

NOTE Confidence: 0.7686038

00:49:49.088 --> 00:49:51.009 if these hypotheses are right,

NOTE Confidence: 0.7686038

00:49:51.010 --> 00:49:53.523 but effect PFS because because you'll be

NOTE Confidence: 0.7686038

00:49:53.523 --> 00:49:56.299 blocking into an once resistance comes out,

NOTE Confidence: 0.7686038

00:49:56.300 --> 00:49:58.610 so those some of those trials

NOTE Confidence: 0.7686038

00:49:58.610 --> 00:50:00.460 are being done early on.

NOTE Confidence: 0.7686038

00:50:00.460 --> 00:50:02.686 H2 inhibitors that were studied were

NOTE Confidence: 0.7686038

00:50:02.686 --> 00:50:05.373 many of the companies have shelved that

NOTE Confidence: 0.7686038

00:50:05.373 --> 00:50:07.635 as a target because the inhibitors,

NOTE Confidence: 0.7686038

00:50:07.640 --> 00:50:09.788 when combined with chemo, didn't seem

NOTE Confidence: 0.7686038

00:50:09.788 --> 00:50:12.549 to do any better than blocking VEGF,

NOTE Confidence: 0.7686038

00:50:12.550 --> 00:50:14.818 combining chemo, and so there was,

NOTE Confidence: 0.7686038

00:50:14.820 --> 00:50:16.452 I think, less enthusiasm.

NOTE Confidence: 0.7686038

00:50:16.452 --> 00:50:17.676 At that point,

NOTE Confidence: 0.7686038

00:50:17.680 --> 00:50:20.362 hopefully some of the mechanism questions

NOTE Confidence: 0.7686038

00:50:20.362 --> 00:50:23.081 and the questions and combining with

NOTE Confidence: 0.7686038

00:50:23.081 --> 00:50:25.637 checkpoint blockade may may give a

NOTE Confidence: 0.7686038

00:50:25.637 --> 00:50:28.394 little bit of impetus to to look at

NOTE Confidence: 0.7686038

00:50:28.394 --> 00:50:30.416 this further in in cancer therapeutics

NOTE Confidence: 0.7686038

00:50:30.416 --> 00:50:32.804 by combining with checkpoint and and

NOTE Confidence: 0.7686038

00:50:32.804 --> 00:50:34.798 the complexities of indigenous actors,

NOTE Confidence: 0.7686038

00:50:34.800 --> 00:50:36.785 so hopefully there will be

NOTE Confidence: 0.7686038

00:50:36.785 --> 00:50:38.373 some reinitiation of that.

NOTE Confidence: 0.7686038

00:50:38.380 --> 00:50:39.568 So what happens

NOTE Confidence: 0.766523

00:50:39.570 --> 00:50:42.475 to entry point into levels when you

NOTE Confidence: 0.766523

00:50:42.475 --> 00:50:45.709 give of edge of receptor inhibitor?

NOTE Confidence: 0.766523

00:50:45.710 --> 00:50:47.166 As opposed to especially

NOTE Confidence: 0.766523

00:50:47.166 --> 00:50:48.610 The Dirty inhibitors, yeah,

NOTE Confidence: 0.79777086

00:50:48.610 --> 00:50:52.102 I don't. I don't think I haven't seen any

NOTE Confidence: 0.79777086

00:50:52.102 --> 00:50:55.356 data that specifically looked at that.

NOTE Confidence: 0.79777086

00:50:55.360 --> 00:50:58.506 We went yeah yeah but I think yeah

NOTE Confidence: 0.79777086

00:50:58.506 --> 00:51:02.044 yeah so I think that you know

NOTE Confidence: 0.79777086

00:51:02.044 --> 00:51:05.170 the the kidney cancer and and.

NOTE Confidence: 0.79777086

00:51:05.170 --> 00:51:06.430 The all those, all those states

NOTE Confidence: 0.79777086

00:51:06.430 --> 00:51:07.879 could look at the issue levels.

NOTE Confidence: 0.79777086

00:51:07.880 --> 00:51:09.914 I have not been able to look at that,

NOTE Confidence: 0.79777086

00:51:09.920 --> 00:51:13.040 but that's a very good question.

NOTE Confidence: 0.79777086

00:51:13.040 --> 00:51:15.164 Maybe even even the Lebanon studies have

NOTE Confidence: 0.79777086

00:51:15.164 --> 00:51:17.491 been coming out in Melanoma and others

NOTE Confidence: 0.79777086

00:51:17.491 --> 00:51:19.633 are also very interesting in Aladdin.

NOTE Confidence: 0.79777086

00:51:19.640 --> 00:51:20.960 Bullhead veg F receptors,

NOTE Confidence: 0.79777086

00:51:20.960 --> 00:51:22.610 also FGF in those studies.

NOTE Confidence: 0.79777086

00:51:22.610 --> 00:51:24.476 Some of them just recently presented

NOTE Confidence: 0.79777086

00:51:24.476 --> 00:51:26.821 at ASCO are also kind of indicative

NOTE Confidence: 0.79777086

00:51:26.821 --> 00:51:28.546 of this of this combination,

NOTE Confidence: 0.79777086

00:51:28.550 --> 00:51:30.860 so then looking at other its effects,

NOTE Confidence: 0.79777086

00:51:30.860 --> 00:51:32.305 another energetic factors age 2

NOTE Confidence: 0.79777086

00:51:32.305 --> 00:51:34.490 I think would be an opportunity.

NOTE Confidence: 0.85894936

00:51:36.790 --> 00:51:38.646 So Steve is a final question for you.

NOTE Confidence: 0.85894936

00:51:38.650 --> 00:51:40.232 What do you think the next big

NOTE Confidence: 0.85894936

00:51:40.232 --> 00:51:41.919 hit is going to be in Melanoma?

NOTE Confidence: 0.85894936

00:51:41.920 --> 00:51:43.516 Let's put aside the leg 3 because

NOTE Confidence: 0.85894936

00:51:43.516 --> 00:51:44.950 we already know about that one.

NOTE Confidence: 0.8150727

00:51:46.580 --> 00:51:49.199 Yeah, I, I think that the live Adam data

NOTE Confidence: 0.8150727

00:51:49.199 --> 00:51:51.396 also looks very interesting, right?

NOTE Confidence: 0.8150727

00:51:51.396 --> 00:51:53.472 In terms of combinations where that

NOTE Confidence: 0.8150727

00:51:53.472 --> 00:51:55.904 fits into the portfolio of options for

NOTE Confidence: 0.8150727

00:51:55.904 --> 00:51:58.280 patients in terms of line and such,

NOTE Confidence: 0.8150727

00:51:58.280 --> 00:52:01.367 it will need to be kind of further detailed.

NOTE Confidence: 0.8150727

00:52:01.370 --> 00:52:03.379 I do think that as a field

NOTE Confidence: 0.8150727

00:52:03.379 --> 00:52:05.838 for me in therapy in general,

NOTE Confidence: 0.8150727

00:52:05.840 --> 00:52:08.696 making hints to it that we have to

NOTE Confidence: 0.8150727

00:52:08.696 --> 00:52:10.660 understand the role of an aide,

NOTE Confidence: 0.8150727

00:52:10.660 --> 00:52:13.100 immunity and that so some of the targets

NOTE Confidence: 0.8150727

00:52:13.100 --> 00:52:15.669 for NK cells and targeting my light

NOTE Confidence: 0.8150727

00:52:15.669 --> 00:52:17.950 cells I think are interesting very.

NOTE Confidence: 0.8150727

00:52:17.950 --> 00:52:18.973 Early in development,

NOTE Confidence: 0.8150727

00:52:18.973 --> 00:52:21.360 but will Melanoma and other cancers have?

NOTE Confidence: 0.8150727

00:52:21.360 --> 00:52:23.862 P1 is a base will be an opportunity to

NOTE Confidence: 0.8150727

00:52:23.862 --> 00:52:26.477 test those aspects with innate immunity.

NOTE Confidence: 0.8150727

00:52:26.480 --> 00:52:28.526 It's not a matter of getting

NOTE Confidence: 0.8150727

00:52:28.526 --> 00:52:29.890 the innate immunity started,

NOTE Confidence: 0.8150727

00:52:29.890 --> 00:52:32.242 but I think more of how how durable

NOTE Confidence: 0.8150727

00:52:32.242 --> 00:52:33.980 that those interactions are.

NOTE Confidence: 0.8150727

00:52:33.980 --> 00:52:36.708 So in case else, or may be interesting,

NOTE Confidence: 0.8150727

00:52:36.710 --> 00:52:39.006 but how do you propagate them long

NOTE Confidence: 0.8150727

00:52:39.006 --> 00:52:42.158 term so I would say like 3 looks good.

NOTE Confidence: 0.8150727

00:52:42.160 --> 00:52:44.547 I will say in Genesis looks good.

NOTE Confidence: 0.8150727

00:52:44.550 --> 00:52:46.250 We'll see what GM does,

NOTE Confidence: 0.8150727

00:52:46.250 --> 00:52:48.040 but that the future interest

NOTE Confidence: 0.8150727

00:52:48.040 --> 00:52:49.114 in other excitement.

NOTE Confidence: 0.8150727

00:52:49.120 --> 00:52:50.380 In addition to the checkpoints

NOTE Confidence: 0.8150727

00:52:50.380 --> 00:52:51.969 would probably be how we manipulate

NOTE Confidence: 0.8150727

00:52:51.969 --> 00:52:53.643 innate immunity to to help patients

NOTE Confidence: 0.8150727

00:52:53.643 --> 00:52:55.039 with cancer in the future.

NOTE Confidence: 0.8208993

00:52:56.810 --> 00:52:58.105 Steve, I think that there

NOTE Confidence: 0.8208993

00:52:58.105 --> 00:52:59.141 are no other questions.