Daddy, thank you so much for joining us today. So for today’s grand rounds, I am thrilled to present our speaker to Steve Hardy from the Dana Farber Cancer Institute. Runs the Melanoma program and he also runs the immuno Oncology program up at the Farber. He’s a professor of medicine and has an endowed chair. He’s the Sharon Crowley market. Share in Melanoma. I’ve known Steve for many years. He’s been on the faculty...
00:00:30.675 --> 00:00:32.600 at Dana Farber since 1995.

00:00:32.600 --> 00:00:33.755 After finishing his medical school at Cornell.

00:00:33.755 --> 00:00:35.295 Great in his graduate education between the University of Pennsylvania and the Farber.

00:00:35.300 --> 00:00:37.335 Steve has made major contributions to the Melanoma field.

00:00:37.335 --> 00:00:40.298 He’s lead author or first author on multiple publications in major journals such as the New England Journal of Medicine, Lancet, Lancet, and the like.

00:00:40.300 --> 00:00:43.765 He’s made some similar breakthroughs in clinical.

00:00:43.770 --> 00:00:46.465 To the Melanoma field.

00:00:46.465 --> 00:00:48.440 Multiple publications in major journals such as the New England Journal of Medicine, Lancet, Lancet, and the like.

00:00:48.440 --> 00:00:51.464 Such as the New England Journal of Medicine, Lancet, Lancet, and the like.
And care as well as in Preclinical Research.

He’s pioneered two approaches that I recall that have really changed the landscape of what we’re studying and doing in Melanoma.

One is combination of angiogenic therapies and immunotherapy, and the other one is combinations of GM CSF with immunotherapy, and I believe you’ll be talking about at least about the letter.

He has a few other very novel gene therapy approaches that he’s using, which I think he will be talking about as well, so we actually originally wanted
Steve to come down last June.

Marcus and I invited him as part of the skins for.

Administrative core, but unfortunately wasn’t able to come last June.

Glad to have him here today and we look forward to seeing him in person sometime in the near future.

So without further ado, I’d like Steve to take the screen over and take it away.

And if you have any questions for Steve, please put them in the chat box.

But thank you very much, Harry,
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 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
is also fairly challenging, so in the world we’re living in the checkpoint world that we’re living in. Why do anti tumor responses are not happen in order to clear cancer, so they’ve either never developed? The immune cells are too few in number or there are exhausted, and this obviously the exhaustion is very important within the PD one we’re living in, they could physically be excluded from the tumor or the antigen. Presenting machinery is somehow disrupted with engine loss or the machine itself,
such as MSE loss, which we're going to try to address. Most of these over the next hour or so. So in the beginning there was appealing map antisocial foreign just to use Melanoma as as the paradigm example. Traditionally Melanoma would have about 11 months median survival for brain Mets, now we have with hippie the 22% of patients now having a long term survival with over 10 years of follow up and notice on the survival curves that there’s an inflection point or on the two and after three year point.
and then the flattening of the curve.

But we also interesting we see with no volume app anti PD one this is the.

Going to combine data, little bit of mixing apples and oranges in terms of dose and schedule.

All previously treated patients then now those patients, about 35% are living long term with no volume AB monotherapy and then moving on to the most recent update of the Checkmate 067 trial in Melanoma, which was a phase three trial that combine Knievel plus it be and compared it to Epyx alone Evo. Plus it be compared to niveau.
It was not designed.

The caveat here not designed to compare Niveau.

Happy to Nivo but now with six years of follow-up you again see this inflection point around 2:00 and after three years flattening of the curves with needle plus Tippy, now 56 percent,

57% of patients to living a long term with the disease.

So so the question is, with this kind of as the the new baseline, how can we improve upon these results? And we look at very important biomarker data, so the the importance of CD
8 and the invasive margin.

So it’s the tumor stromal interface and the proximity.

The closeness to the PD one PD interaction is highly predictive of responses to anti PD one therapy again in Melanoma and also that PDL one is a mark biomarker in now with the numerous diseases that PD one is looked at.

The back seat when expression on immune infiltrating cells.

So the new cells themselves, mostly macrophages, are also predicted responses to hear anti PDL one because it was a mad
in patients with lung cancer and now

other countries with kidney cancer.

So to briefly summarize other aspects

that could be applied to improving upon

those results quite a few years ago now,

Glenn Dranoff, my longtime mentor and friend,

and I did some anti slip or anybody trials

looking specifically in patients who had.

Received a prior GMC based vaccine,

but notice pathologically when they received.

If you limit map that

there was this in panel,

a area central necrosis with the

room available to around the outside,
and that room available tumor was heavily infiltrated with CD4CD8 CD 20s. But we notice throughout the tumor that there was an immune attack of the vascular vessels feeding the deposits depicted in panel F, and that these lymphocytes were attacking the blood vessels when the product will be in the center and probably leading to this TNF like effect that we virtualized in pathology. And so it raises the question of the combination as he was alluding to of combining anti angiogenesis and immune checkpoint in the importance of hypoxemia.
If 1A making veg F that not only involved into Genesis but Veg F being a very potent suppression of dentrix cell maturation. Another important myeloid as important suppressor cells that you might like. My Lloyd Wright suppressor cells also make important engineering factors such as Veg F that lead to also this suppressive feature and whether there was a role for. Andrew Genesis, in terms of not just being blocked for for blood vessel formation but also its role in immune activation.
and immune suppression.

So we looked into this further summarizing some work from a few years ago of combining simplified paid with entry into Genesis based on the vasculopathy that we saw. I thought the pathologically the role of Veg F and decrease in the Newcastle maturation work by George Lucas and others.

Also had shown that blocking Veg F and proved himself trafficking across Endothelia and we worked with Jed Walchak memorial looking at pre treatment levels of Veg F which were
associated with the higher the bowls with poor outcomes. Both less responses and less reliable. Again guilt by discussed by association. Then Jeff may play a role with the new checkpoint blockade. So this is just kind of some summary of that. Here’s a pet scan of a patient on the top. The CAT scan portion shows his liver metastasis and then that is lit up by pet and after just a few months of treatment delivery tasks hasn’t changed in size, but it has become metabolically cold and this trial would it be alone had a response rate of about 35% and 50% of.
patients doing well with controlled disease for six months or more. So this is a background. I think the correlatives give you the basis for this combination, and that we look at the pre and on treatment on the left and comparing to patients who received it alone on treatment on the right and some control samples and the patients received Bevis is a map. Anti Veg F had changes in the endothelium as depicted by CD 31, where they morphologically look plumper, columnar and biochemically were 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 --> 00:09:01.303 Here you can see that some red cells
NOTE Confidence: 0.7596663
00:09:01.303 --> 00:09:03.513 in the center of the endothelium and
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 --> 00:09:11.630 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

18
molecules such as the Cam and I Cam that you can see highlighted and Ethereum here. That also suggests that by blocking Veg F you can improve, potentially improve the trafficking of lymphocytes into the to my crime and in this approaching one of the concerns we had at the beginning of the talk, which was whether the lymphocytes immune cells can actually make it into my environment, or if they were excluded. So based on this they did something very smart. They gave a single dose of bevacizumab
00:09:51.320 --> 00:09:52.980 before combining with checkpoint.
00:09:52.980 --> 00:09:55.500 Did biopsies before and after above
00:09:55.500 --> 00:09:57.584 and fortunately showed that the
00:09:57.584 --> 00:09:59.908 Bev the Veg FA blockade by itself
00:09:59.908 --> 00:10:01.929 had changes in the endothelium.
00:10:01.930 --> 00:10:03.482 Ann had improved lymphocyte
00:10:03.482 --> 00:10:04.258 trafficking cross.
00:10:10.350 --> 00:10:12.934 Is your one and also the fact that
00:10:12.934 --> 00:10:15.600 the Arnie seek in the tumors that
00:10:15.600 --> 00:10:18.356 had a myeloid signature seems to do
00:10:18.356 --> 00:10:20.558 better when they receive this map.
00:10:20.560 --> 00:10:23.008 Again, tying in that myeloid suppressor
00:10:23.008 --> 00:10:26.341 function in the veg F function with the
00:10:26.341 --> 00:10:28.789 suppressive aspect of the immune system
00:10:28.858 --> 00:10:31.616 and that those patients who had those
00:10:31.616 --> 00:10:34.308...
those myeloid cells there and receive Bev

had a market improvement in their outcome.

So this concept has very rapidly progressed

and obviously in important issues such

as kidney cancer that is driven by hip

1A and in Genesis here is anti PDL,

one to value map plus.

XD Neb better far,

123 inhibitor TKI showing that

combination improvement

over soon to be alone.

Another day to Pember Lism AB

plus extended so anti PD 1 + 54.

One 2-3 and innovation versus

ended up having improvement in both

progression free and overall survival.
And this kind of concept has expanded very quickly to non small cell lung cancer with some data showing improvement with angiogenesis combinations and either will or has probably checkpoint plus anti Andrew Genesis be approvals in hepatocellular carcinoma, anamitra carcinoma and with other many combinations being being developed. So one of the questions we had is what is the role of the immune system in this anti into Genesis in terms of the role of anti genesis and it distract effect on on immunity and so in some of our patients we have a banking.
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 at before and after treatment with.
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
00:12:21.666 --> 00:12:24.221 functional that and so we were interested
00:12:24.221 --> 00:12:26.333 in trying to isolate what those
00:12:26.399 --> 00:12:28.949 targets are because they were seeing
00:12:28.949 --> 00:12:31.088 someone else somewhere seen actually
00:12:31.088 --> 00:12:33.278 on the endothelial cells themselves.
00:12:33.280 --> 00:12:34.705 Calls other medical mental illnesses
00:12:34.705 --> 00:12:36.517 and it comes stem cells within
00:12:36.517 --> 00:12:37.849 the tumor micro environment.
00:12:37.850 --> 00:12:39.796 So one of the factors that were
00:12:39.796 --> 00:12:42.602 found in in doing our kind of
00:12:42.602 --> 00:12:44.126 Sidney expression library screening
00:12:44.126 --> 00:12:46.584 of endothelial cells with this other
00:12:46.584 --> 00:12:48.923 energetic factor in your put into
00:12:48.923 --> 00:12:51.587 an so it kind of shows that patients
00:12:51.587 --> 00:12:54.661 can at least make any bodies against
NOTE Confidence: 0.74153435
another engine factory here at age 2
and age 2 is involved with in Genesis
through spreading and edit this on migration.
It’s involved with actually anchoring
the ilium to parasites and kind of
a scaffold of the deathly.
It’s also been shown to be involved with resistance to bed.
This is a map, so in many trials mostly chemotherapy.
Those pieces who developed resistance had higher levels of Angel
Queen too, as a kind of a resistant I
now to tie in the Ender Genesis back
with the potential for immune regulation
and repeating 2 not only signals by that I receptor found on endothelium, but also tide to accept it, which can be found. Onto your training monocytes and macrophages. So again, the myeloid component here being tide in as well as the link between angiogenesis, macrophage biology and immune suppression. So there could be a dual role for entropy into both in terms of the androgenic component as well as immune regulation, so we were further interest in just kind of taking a look at this and found for number of combinations that
Angel Queen 2 levels were associated with outcomes to treatment so so patients who had higher levels.

Andrew Queen 2.

Or changes in between 2 levels did worse and that patients who developed antibodies to interpret into did better, showing both for patients with it be on the bottom here.

And for patients who received it be plus businesses map on the top right hand corner, which is the ratio of antibodies.

Change two afterwards to pre levels. There are a couple of patients who had high titer antibodies and whether entropy to go up there.
They had the highest danger point to any bodies that were present, so the one of the questions is whether the humoral immunity being developed is actually functional and we have some data that the patients who are making any bias to interpret into some of those antibodies can actually block Type 2 signaling both on endothelium and in macrophages, so so the immune system may be very smart in terms of actually making functional antibodies against an engineering factor here, such as interpreting 2.
So here is some of the data showing that as a function of treatment, patients get higher levels of agent into anybody's he both with patients received hippy dippy Bev. We have data showing anti PD one patients also developed any bias to injure Queen 2 as a function of treatment. So one of the questions again, maybe goodbye Sociation is the expression of a gene two, which seems to be suppressed by Veja blockade at times associated with these myeloid cells in the tumor microman people find M1 macrophages as more tumor.
Sidell M2 is more suppressive in humans. It’s a bit more challenging to define M1 versus 2 and it’s really more functional characteristics, but he wanted to look at. Patients received if he alone would be Bev. So we had these samples to look at Angel Queen two expression before and after treatment and what we found is that with businesses amab, if you look both in the tumor and acylium that you get decrease in entropy into expression as a function of the decade, But with hippie alone endocrine.
two seems to increase in both the tumor cells and in the endothelium.

We then correlated the level of Andrew Queen two that we could find in the ilium, to see 163 cells in the tumor marker firemint, CDC. Once we can be a marker for my Lord suppressor cells, or dendritic cells, and what we found in the dozen or so cases that there was a seems to be a correlation with age 2 expression in CD163 cells. So the higher the age 2, the more CD wants 3 cells that were noted. The tumor marker aren’t these city wants 3 cells would be the cells that 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 get the interpreting to blockade. NOTE Confidence: 0.7170105
00:17:41.327 --> 00:17:43.469 Black entropy and one would maybe potentially do a slightly different effect, NOTE Confidence: 0.7170105
00:17:43.470 --> 00:17:45.432 but we know that both veg F in this cartoon here as well as age 2 have some overlapping functions into distinct functions both on their veg F and H2 effects. NOTE Confidence: 0.7170105
00:17:45.432 --> 00:17:47.749 On myeloid suppressor cells, making important factors of style 10 and such the potential role for PDL 1 onto associated macrophages in the role that the entropy do in twin two increases that expression on tumor social macrophages went back
00:18:13.276 --> 00:18:14.820 to one day regional.

00:18:14.820 --> 00:18:16.540 Slide showing how PD one immune cells into my crime.

00:18:16.540 --> 00:18:18.260 It was predictive of a Tesla smab responses to in lung cancer and other myeloid cells such as neutrophils and that are becoming more highlighted in terms of their role in immune suppression.

00:18:20.374 --> 00:18:22.806 It was predictive of a Tesla smab responses to in lung cancer and other myeloid cells such as neutrophils and that are becoming more highlighted in terms of their role in immune suppression.

00:18:25.058 --> 00:18:27.170 that are becoming more highlighted in terms of their role in immune suppression.

00:18:27.170 --> 00:18:29.486 So we’re going to show you the first group of patients that were rolled in this study were 17 microsatellite stable patients with clinical cancer.

00:18:29.486 --> 00:18:31.964 So we’re going to show you the first group of patients that were rolled in this study were 17 microsatellite stable patients with clinical cancer.

00:18:31.964 --> 00:18:33.806 group of patients that were rolled in this study were 17 microsatellite stable patients with clinical cancer.

00:18:33.806 --> 00:18:36.072 in this study were 17 microsatellite stable patients with clinical cancer.

00:18:36.072 --> 00:18:38.207 in this study were 17 microsatellite stable patients with clinical cancer.

00:18:38.210 --> 00:18:40.166 All had been heavily pretreated meeting time of 2.6 years since her diagnosis.

00:18:40.166 --> 00:18:42.680 All had been heavily pretreated meeting time of 2.6 years since her diagnosis.

00:18:42.680 --> 00:18:45.432 In this trial there are no DLT’s in
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,
A number of cancers were treated, including colorectal cancer, ovarian renal cell, showing that there were a couple of partial responses include rectal cancer and some stable disease, and the writer the spaghetti plots for spider plots showing the clinical activity in patients with colorectal cancer who received. This combination in the color took or hurt the meantime. Depression was 2.8 months that the meaning of survival of nine months. We’re going to go through a little just now with this.
So we applied site off which is looking at staining immune cells in the from the purple blood using any bodies that have heavy metal conjugation which, as opposed to doing flow cytometry, are permitted to do markers at a time, and this is looking at patients with the 1st 12 weeks of cycles of therapy in specifically focusing on the colorectal cohort and in splitting up patients who received clinical benefit as defined as either response or stable disease, lasting six months or more. What we found is that there were certainly higher CC-3 positive cells
in patients with clinical benefit following their first mission therapy. Both C4G8 cells decrease in patients that did not have clinical benefit. CD 8 effector cell, specifically, the memory phenotypes decrease the patients that do not have clinical benefit in both the CD four and 8603 cells decreased in patients who had no clinical benefit. In particular, was noted in patients who had rapid progressive disease that these cells were. Were quite were quite low in decreased,
almost non-detectable.

We're looking at other phenotypes in terms of an NK cell analysis.

Those and we're going to think further discussed the potential role for innate immunity here.

So this is going to be the first kind of hinted that there are trends that increases in the city.

Fix ceases, Dim CD, 60 negative cells in patients with no clinical benefit, 16 positive cells were higher in patients with clinical benefit, which goes along with the potential
Indeed aspects.

There are no differences in the CD fix excels.

According to the cycle or clinical benefits, it didn’t seem that it was had to do with timing over treatment and the CD 56 positive cells were higher in patients clinical benefit as well as the NK marker Pete 3056 positive cells were higher in patients received clinical benefit. This was consistent across really all of the patients with the significance look in my Lloyd cells, which you would assume that the Pepto
body might be affecting my self.

That Mila cells increased in patients with no clinical benefit, but the myeloid derived suppressor cell phenotypes seems to increase in patients with no clinical benefit in the classical monocytes. Also, The M2 like macrophages, which the markers again are not as well defined in humans, trended to be higher inpatient clinical benefit but did not reach statistical significance. So the activity of anti PD one
plus the end

two pepta body probando combination

may be hindered by increasing the

price of my life cells leading to

decrease in memory and effector

T cell populations interesting.

There was an association between

baseline NK cell activity,

an expansion of the cytolytic NK

cells and think that the role of

the of checkpoint and other things

on a native beauty needs to be

fully explored will talk about

it a bit and we’re currently in

the midst of another enrolling.
Another group of 25 patients.

At Microsoft stable, colorectal cancer that that core is just about finished enrolling right now and hope to get further analysis coming out.

So I think in general the role of angiogenesis and combinations is very important. It has the immune activation seen by Vjet blockade. The benefits and efficacy across multiple cancers, except taxes are manageable, but also to further consider other targets an Angel into being the next potential target.
serum age 2 levels increase.
Increase their social worse outcomes that veg appliqued me temporarily decrease into expression in effect things into my Chrome. It needs to be a mechanism for resistance to checkpoint blockade that that I think is deserving of further studies. So one of the questions and that Harry was alluding to is how can we improve the therapeutic index? So one of the aspects is bringing back the concept of cytokinin. So if you think about the original reports for SQL Blockchain frequent
battles by Jim Allison that the effect of C2 for blockade wasn’t really well understood or appreciated until it was combined with GMCS screening tumor cell vaccines. That the really demonstrated the synergetic simplistic potential in preclinical animal models and that work that Glenn Dranoff and I did. Suggested a potential synergistic effect, but work by Craig Sling off and others and many others have had concerned that GM may induce negative regulatory aspects of the
immune response by promoting Mayo.

It's impression cells or T regs that are in specific in a number of studies have been done, so that was kind of the concern going into this. So originally.

Again, going back to just things in Melanoma, as a proof of principle, and if he is the first proof of principle. We did this randomized study that.

Combined, hippie noted to be here 10 mix working which is higher than the approved dose and had a maintenance portion to it with systemic GM CSF versus it be alone.
An date is been published. Progression free survival between the two arms was not significant, but interestingly overall survival was significant for the GM’s arm with the one year rate of survival for it be alone being 52.9 versus 16.9 for the combination. Sargramostim or GM CSF. Usually when you combine things you have control over more side effects but we looked at the GMR msramms to arm versus it be alone. The patients in the combination
had fewer high grade adverse events compared to being alone, and specifically when we looked at the toxicity types there was a profound decrease in GI toxicity. Diarrhea colitis in Poly toxicity so colitis diarrhea is the biggest concern for Epyx itself in. Pneumonitis, lung inflammation being a primary concern for NTP, one based therapy so found that these two target organs, having improved benefits with the combination, fairly intriguing. So what is the potential mechanisms?
00:26:24.984 --> 00:26:27.347 that GM improves survival but does not improve pressure free survival?
NOTE Confidence: 0.76278245
00:26:27.347 --> 00:26:29.332 So GM recruits tdrick cells,
NOTE Confidence: 0.76278245
00:26:29.340 --> 00:26:31.240 macrophages, and presentation,
NOTE Confidence: 0.76278245
00:26:31.240 --> 00:26:32.404 and when you combine this with counteracting introductory elements such as would simply for blockade,
NOTE Confidence: 0.76278245
00:26:32.404 --> 00:26:34.732 you could see if surgery happening there.
NOTE Confidence: 0.76278245
00:26:34.732 --> 00:26:35.902 Maybe Jim improves depletion of regulatory cells that could be that there would be important when the President GM that’s that was suggested by Alan Korman.
NOTE Confidence: 0.76278245
00:26:35.920 --> 00:26:38.074 The importance of depleting regulatory cells could be amplified by GM in this UN...
coupling of overall survival and progression, free survival has been previously described for other GMC based immunological therapeutic approaches, specifically supercell. Tea and prostate cancer dendritic cell vaccine has, as part of its component GM put into it and there was a also a disconnection between progression free survival and overall survival with an improvement. Overall survival in those studies that included super Salty, so it’s teen prostate cancer. So there’s another basis for
this observation in the past. But when we look at the possible mechanisms of improved Palmer TX, is Glenn Dranoff had had done the GM knockout mouse and and those gym mice develop significant lymphoid hyperplasia. This around the Airways, in the lung vasculature. They’re really clearly demonstrates the role of GM in Palmer home stasis, and you can see in panel A is a normal mouse lung and panel B being the GM knockout mice, showing the profound inflammation in the Airways. In addition,
00:27:59.698 --> 00:28:01.792 GM is a cytokinins involved in
the coastal homeostasis in in
NOTE Confidence: 0.76278245
00:28:01.792 --> 00:28:03.766 really promotes GI equal healing.
NOTE Confidence: 0.76278245
00:28:03.766 --> 00:28:05.786 The knockout mice have colitis and
this can be partially reversed with
NOTE Confidence: 0.76278245
00:28:05.790 --> 00:28:07.716 administering systemic James half.
NOTE Confidence: 0.76278245
00:28:07.716 --> 00:28:09.981 If you look at idiopathic bowel
inflammatory bowel disease.
NOTE Confidence: 0.76278245
00:28:11.820 --> 00:28:14.178 Jim may have a role there,
NOTE Confidence: 0.76278245
00:28:14.178 --> 00:28:15.357 a subset of patients with Crohn’s disease.
NOTE Confidence: 0.76278245
00:28:17.350 --> 00:28:19.408 They have shown improvement,
NOTE Confidence: 0.76278245
00:28:21.340 --> 00:28:24.500 a subset of patients with Crohn’s
disease have high titer neutralizing
NOTE Confidence: 0.76278245
00:28:22.604 --> 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 important in some inflammatory bowel disease.

NOTE Confidence: 0.76278245

00:28:29.284 --> 00:28:31.630 Patients actually have decreased levels of GM receptors,

NOTE Confidence: 0.76278245

00:28:31.630 --> 00:28:34.278 again making this combination.

NOTE Confidence: 0.76278245

00:28:34.278 --> 00:28:35.648 So we moved on to doing a randomized phase two three trial of submission or GM CSF plus nivo it be versus Navy would be alone.

NOTE Confidence: 0.76278245

00:28:43.046 --> 00:28:45.900 The primary endpoints were overall survival relapse, free survival.

NOTE Confidence: 0.76278245

00:28:45.900 --> 00:28:52.169 toxicities Anne’s hair and I were talking right before this.

NOTE Confidence: 0.76278245

00:28:52.169 --> 00:28:56.460 The trial is ongoing in the midst of phase three,
so I think the role of GM is interesting, possibly from exclamation point, but particularly from his possible reduction in side effects in that cytokines may behave in different organs differently, so the lung and gut, which is the mainstay of protection. Against invading microorganisms, GM may play a very important homeostatic role there, and they play different roles systemically throughout the other parts of body, and this is other areas were interested in looking at.
So what drives response to checkpoint blockade is kind of next question and we set up some site off panels looking at patients who had received it alone and received PD one alone and spent a long time saying these panels up. And would you find out with the site offers that doing the experiments may become much easier, but the analysis of the data from computational biologist endpoint can be quite onerous and such, but these are some of the Disney plots that. Be established looking at the different subsets of cells that
00:30:02.992 --> 00:30:04.763 we could look at in the purple blood and again focused on patients who had received it be alone.

00:30:08.420 --> 00:30:10.760 Initially in Pembroke alone.

00:30:13.644 --> 00:30:16.309 And what we found is that patients between those two chords, lymphocytes and monocytes frequencies very much differ between responders and non responders where you can see with patients who responded to Penn Bro, there’s actually less lymphocytes in the purple blood.

00:30:28.268 --> 00:30:29.976 in the purple blood.

00:30:29.980 --> 00:30:30.358 Well, if that’s not the case and that there also are higher monocytes in patients
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 --> 00:30:54.410 activated circulating NK cells
NOTE Confidence: 0.7772081
00:30:54.410 --> 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
have PD one in the surface, but when you the most profound effects have been on these. Circulating activated CD-69 that would be positive NK cells in the peripheral blood that seems to be associated most with pembrolizumab efficacy in normal. So with that as a basis, we wanted to say what other aspects of the tool micro vironment contribute to. Maybe Check Point resistance or efficacy and there we could have many lectures on all the areas investigation. We’ve seen that ACR Anasco recently
areas are looking at quote unquote resistant mechanisms to PD one blockade,
so we talked the importance of having seen infiltrate the importance of interferon.
In the two microenvironment and then things such as beta two mutations that may be part of the APC machinery may be important resistant mechanisms,
but we were further interested in looking into that.
My work with Scott Rodick was simply Part of interferon signaling that they may be important resistant mechanisms,
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as part of this resistance in relative to checkpoint blockade. So we took advantage of this study. The so called Checkmate 064 Study investigation study. That randomized patients untreated patients mellem to either receive first niveau induction followed by a four switch to Epyx induction, or the other half of patients received it be first induction for 12 weeks followed by NIVEAU and then after both induction periods, all the patients got needle maintenance and everyone got biopsies before hand.
In between the two inductions
NOTE Confidence: 0.7773844

in falling induction,
NOTE Confidence: 0.7773844

two as well as a collection
NOTE Confidence: 0.7773844

of peripheral blood samples.
NOTE Confidence: 0.7773844

And we want to look specifically
NOTE Confidence: 0.7773844

at the protein level,
NOTE Confidence: 0.7773844

so this is work and penalty by Scott
NOTE Confidence: 0.7773844

Rodick and looking at class one
NOTE Confidence: 0.7773844

expression in the left hand column in
NOTE Confidence: 0.7773844

Class 2 expression in the right hand column.
NOTE Confidence: 0.7773844

And there’s a little bit of our part to this,
NOTE Confidence: 0.7773844

so if you look in a room normal 1/3
NOTE Confidence: 0.7773844

and five you have high levels of
NOTE Confidence: 0.7773844

class one expression which you should
NOTE Confidence: 0.7773844

see in all nucleated cells, right?
NOTE Confidence: 0.7773844

All nucleus should have high class.
00:33:25.160 --> 00:33:27.134 My expression three is decrease and
00:33:27.134 --> 00:33:29.419 five is almost absence of of class one.
00:33:29.420 --> 00:33:31.000 But interesting in this tumor.
00:33:31.000 --> 00:33:32.776 You have your control cells there.
00:33:32.780 --> 00:33:34.550 You have immune cells there that
00:33:34.550 --> 00:33:35.435 have class one.
00:33:35.440 --> 00:33:36.920 That kind of show you,
00:33:36.920 --> 00:33:37.574 I think,
00:33:37.574 --> 00:33:39.209 fairly profoundly that the tumor
00:33:39.209 --> 00:33:41.346 itself is last class one and then
00:33:41.346 --> 00:33:43.328 on the right hand column for 246
00:33:43.328 --> 00:33:44.972 you have Class 2 expression of
00:33:44.972 --> 00:33:46.079 high Class 2 expression,
00:33:46.079 --> 00:33:47.474 which is typically not all
00:33:47.474 --> 00:33:49.060 that common in cancer Melanoma.

NOTE Confidence: 0.7773844
You have medium and then you have no Class expression in panel 6 on the bottom. Figure what we’ve done is we’ve color coded on the top the level of class one expression across all the tumors that were evaluated. So the darker has the highest pressure on the right and then right below that is by HC is Class 2 expression. Then we looked at both Arnie seek and whole exome sequencing. For these samples and so the middle panel shows you Barney seek class 63.
one expression HLA B&C and on the bottom shows you where there are mutations and the things that you would be most interested in, such as beta two and Jack Stack. So of note there were very few. Mutations and beta to attract Staten. Actually one of the major mutations. If you look at the left hand portion and purple where there was a detective beta mutation actually had very high level of classification by Etsy and we when we look into there that that actually patients tumor had about was estimated about.
7% of reeds had abated mutation, so most of them did not, but it was probably a minor population and maybe suggest mechanisms of acquired resistance going down the road. So we looked at the initial response to patients who either on the top here received hippie first or so simply for blockade on the bottom, received niveau or anti PD one and what we found is that the patients who had reduction in class one poorly to CFO blockade tippy while which was determined to be 50% or more reduction class one did really poorly to CFO blockade tippy while
patients with reduction class one did not seem to affect the response rates for outcomes to Geneva. Interestingly, patients who had any Class 2 expression as defined by 1% did really well to Nivo had improvement in outcome to Nivo, but do not seem to affect all their clinical outcomes to see full blockade with hippie. So these are the Catman. Some patients were not a valuable few patients an an here we have, the blue being patients who
had intact class one.

So if greater than 50% or intact class one in the red being patients who had a reduction of 50% or or loss of Class 1.

The patients who received it be first and went to Nivo. You can see here did much much better.

Who if they had class one intact if they had reduction class we did very poorly in red.

And actually took us a little while to figure this out because there were a number of patients who received it be first who are quote unquote not valuable at 1st and the reason is because some of those
patients who had the lowest class, one expression or complete loss of classic session unfortunately never made it to the first set of staging scans. They either progress very rapidly or passed away early on in their treatment course. This is compared to a panel on the right who received niveau 1st and there was no difference on their class. One expression on outcomes to Nevo. Here’s Class 2 expression again on the left patient, receiving it be first in the right place. For seeing you go first,
there was a slight trend, but not squeeze.

Some big difference for me first, but the patients who had any Class 2 expression did really well to niveau as depicted by the blue line on the right hand panel. So we. Had the Arnie seek data and we want to further kind of investigate what genes could be related with a focus on the patient. Received Niveau 1st and these are the top top jeans that were so sheated with with good outcomes but had low class one expressions and many of these are in a fair and target genes.
As you can see as you would expect and of no down near the bottom is I’ll 15 which would be a target in case it was also significant in that.

So we looked at the interferon. Genes are associated with outcomes in the patients receive needle first. We also had the interference publishing secure from from mercantile we visited, looked, mercantile we visited, looked, we had our top 25 jeans and of course We had our top 25 jeans and of course any good computational group would want to have their own their own signature. So they develop their own infernal legions.
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.
There were some gammadelta cells that were associated with outcomes as well as an in case signature as depicted on the left, and those signatures were not influential for patient received it be first in terms of outcomes, we were able to in those patients who had low class one expression and who had low class one expression and good outcomes were able to identify in the two mark apartment by C. Both Gamma, Delta and in case files. There were few, but they were detectable in those patients by HC. Anne’s kind of hinted before I’ll
specifically in the patients who had low class and expression or single first was associ with better outcomes in on the left. Here an we’re not influencing the outcomes to page received it first on the right. So we were interested trying to confirm in some way another group of samples that were well clinically annotated for outcomes and went to the Checkmate 069 study, which was a study that had got the proof on evil Epion Melanoma, and so there was one Group A source evil it be an another group that received it, be alone and had samples available
While we were able to show is that the patients got it be alone who are downregulation of class one basically had 100% negative predicted value for both response and an for poor clinical outcomes. So if they had loss of class one again they did very very poorly for the patient seen evil. Plus it be there were there were trends but there was nothing stuff. Obviously this is not ideal that it was combination that is hard to dissect out.
There was a trend toward the Class 2 being beneficial, but it does not reach. Here are the major analysis for patients with class one expression, again high versus low class profession with iffy on the left and evil clip in the right and you can see the difference received it be with low class expression doing very poorly. It was no difference for patient received new needle plus it being. Nearest Class 2 expression that again reached had a trend but did not reach significance.
So it appears that secretly for blockade, responses are dependent on MHC class one expression while PD one blockade is not entirely dependent class but is improved with Class 2 expression and with also previously described interference signatures, they really show the importance of interfering there. I think this raises a lot of questions and on what other aspects interest to do. We are interested in looking at other other cancers in the Class 2 component which has been also reported by other groups importantly.
Suggest that maybe CD four cells
NOTE Confidence: 0.7055627

making game in assure on could be
NOTE Confidence: 0.7055627

very important for for PD one
NOTE Confidence: 0.7055627

blockade dependence on class one.
NOTE Confidence: 0.7055627

For 64 we’ve always been interested in using.
NOTE Confidence: 0.7055627

This is a predictive marker.
NOTE Confidence: 0.7055627

Prognostic studies and are looking at
NOTE Confidence: 0.7055627

other groups of patients both needle,
NOTE Confidence: 0.7055627

plus if it in order to try to really
NOTE Confidence: 0.7055627

say if patient has downregulation
NOTE Confidence: 0.7055627

class one which should it be considered
NOTE Confidence: 0.7055627

or not as part of the regiment?
NOTE Confidence: 0.7055627

So we’re really now applying newer
NOTE Confidence: 0.7055627

technologies to understand the spatial
NOTE Confidence: 0.7055627

relationships with immune cells,
NOTE Confidence: 0.7055627

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
looking the difference between needle versus AP or simply for speedy one or the control for NK cells.

Even with checkpoint blockade, important role of cytokines, both the efficacy as well as some examples of possible reduction in in toxicities combination.

Drink factors and really using data for rational combinations of checkpoint blockade based therapies in the future.

So many of the things I’ve discussed with you today were investigating initiated and it’s always very hard to do investigation studies. And this is just a list of the many
00:43:05.196 --> 00:43:07.715 folks that were involved with these studies in the approaches that the result for them and I just want to pay thanks to them. And these are my disclosures too.

Thank you.

Thank you Steve.

I’m going to ask folks to please enter questions into the chat box, but while folks do that I will start with one or two.

That’s OK with you.

So first question was the dose delivery better when you gave the AP and the GM CSF versus APLON?
In other words, were you able to get more cycles in?

Now that’s a very good question. So when we looked at that and in response to some of the reviewers comments, is there was good question there done not seem to be a significant difference in number of cycles there were between the two arms, so if you reduce the we know that super blockade, we know going from 3 to 10 you have more toxicity and more responses, and so the question is great.
question is whether you could just get more Dragon and. Watching at least between the storms, do not seem to be a significant difference between that, but that’s a great question and something we need to continue to look into as we move on to the needle at the study. Let’s not thank you. Expression is So what directions are you planning on taking for class one? Deficient melanomas. Yeah, we number one have been interested in looking at whether the
class one observation is important.

Other cancers Sony would be is now a lung cancer and kidney cancer and we've been trying to gain access to some of them just to see you know, does class one influence that? So that's the first thing. The other thing is we were kind of interested to look at a just biomarker driven trial for classroom expression to say, should patients who have low work session. Getting it be, or if there's an efficacy change, we just haven't been able to
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
if they received bags.

Do you have any ideas as to why that could be?

Yeah so. One of the questions that could be confusing is whether the PEO expressions on the tumor on the mileage component so in brain tumors you gonna have the myeloid like cells or run that probably have a lot of people and expression, and so one of the hints from the Genentech trial is that the immune cells express PD L1. The myeloid cells also for both markers. For predicting this to improve outcomes to budget blockade and so depending upon you know sometimes maybe more myeloid dependent on my Lord Rich and others.
Include by blocking veg F for engineering factors you actually having a greater effect on that myeloid suppressor compartment that my suppressor effect then then actually on the tumor itself. So that would mean without having a definitive answer, that would be one of the hypotheses is that you’re when you’re blocking with Bev that you that you may be affecting both your immune cells that are pretty one positive as well as as well as the myeloid component that affects, and so if the tumor is is more dependent on myeloid cells or in such that you.
Milo suppressive cells. You may be having a benefit by blocking benchev there. That's again something that needs to be more definitively determine in patients, but I think a reasonable hypothesis. Now then, maybe Antonio can respond to the question of whether it's actually primarily expressed in the my load or in the glioma cells themselves. 'cause I've seen some really strongly positive gliomas tumor cells. It is interesting, then why folks into other questions. I'm going to ask you a question about your early date on the vasculopathy with the CTA.
Four at that pic. That figure that your shoulder is actually quite stunning. Do you think that that’s organ dependent? More likely. See it in the liver or whatever. Or do you think and maybe you’ve had a chance to look at that now, had a chance to look at that now, so we’ve so, at least in that very early stage. Way back when they do not seem to be organized and we had, we saw the best drop, the many different, many different organs that were biopsied. And. In so we’ve also as many are looking
at tertiary lymphoid's liquid structures.

NOTE Confidence: 0.7719938

That anti interests may also be influenced in.

NOTE Confidence: 0.7719938

So we actually saw a large I didn’t think into this into much detail.

NOTE Confidence: 0.7719938

A number of tertiary lymphoid structures associated with that,

NOTE Confidence: 0.7719938

and you think that maybe those are making any bodies and those mission

NOTE Confidence: 0.7719938

with good outcomes, but that,

NOTE Confidence: 0.7719938

but as we’re looking at for these traditional infrastructures,

NOTE Confidence: 0.7719938

we also saw these vast properties in many different organs,

NOTE Confidence: 0.7719938

so there’s different degrees of it,

NOTE Confidence: 0.7719938

but but it does not seem to be working.
Interesting, and then if you followed up on your studies of the angio, followed up on your studies of the angio,

the edge two expression in the Tigers

two expression in the Tigers

in patients who got deep in Eva.

No, there’s blood studies that your

blood studies that your

shirt yeah yeah yeah, yeah.

shirt yeah yeah yeah, yeah.

So we so with evil if he also and we

So we so with evil if he also and we

do have some data that we’re putting

do have some data that we’re putting

together that while the antibody titers

together that while the antibody titers

are not as the increase in anybody,

are not as the increase in anybody,

are not as high.

are not as high.

If the patient had received which.

If the patient had received which.

Maybe again suggest maybe there’s

Maybe again suggest maybe there’s

some humanity effects to anti

some humanity effects to anti
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,
so that’s been one of the challenges, but there are. There are some companies that are looking at dual veg F. 

H2 inhibition in cancer, and I think that those studies will probably shed further light, so when you block veg F, Ange two goes down temporarily and then H2 comes up is kind of resistant mechanism and so the question is whether you would also be beneficial with veg F and likelihood. It probably would be in terms of if these hypotheses are right, but effect PFS because you’ll be
blocking into an once resistance comes out, so those some of those trials are being done early on. H2 inhibitors that were studied were many of the companies have shelved that as a target because the inhibitors, when combined with chemo, didn’t seem to do any better than blocking VEGF, combining chemo, and so there was, I think, less enthusiasm. At that point, hopefully some of the mechanism questions and combining with checkpoint blockade may give a little bit of impetus to look at this further in cancer therapeutics
by combining with checkpoint and and the complexities of indigenous actors, so hopefully there will be some reinitiation of that. What happens to entry point into levels when you give of edge of receptor inhibitor? As opposed to especially the Dirty inhibitors, yeah, we went yeah yeah but I think yeah we went yeah yeah but I think yeah the the kidney cancer and the all those, all those states.
could look at the issue levels.

I have not been able to look at that, but that’s a very good question.

Maybe even the Lebanon studies have been coming out in Melanoma and others are also very interesting in Aladdin.

Bullhead veg F receptors, also FGF in those studies.

Some of them just recently presented at ASCO are also kind of indicative of this combination, so then looking at other its effects, another energetic factors age 2 I think would be an opportunity.

So Steve is a final question for you. What do you think the next big
00:51:40.232 --> 00:51:41.919 hit is going to be in Melanoma?
00:51:41.920 --> 00:51:43.516 Let’s put aside the leg 3 because we already know about that one.
00:51:46.580 --> 00:51:49.199 Yeah, I, I think that the live Adam data also looks very interesting, right?
00:51:49.199 --> 00:51:51.396 In terms of combinations where that fits into the portfolio of options for patients in terms of line and such,
00:51:51.396 --> 00:51:53.472 it will need to be kind of further detailed.
00:51:55.904 --> 00:52:01.367 I do think that as a field for me in therapy in general, making hints to it that we have to understand the role of an aide,
00:52:01.370 --> 00:52:03.379 immunity and that so some of the targets for NK cells and targeting my light
00:52:03.379 --> 00:52:05.838 it will need to be kind of further detailed.
00:52:05.840 --> 00:52:08.696 making hints to it that we have to understand the role of an aide,
00:52:08.696 --> 00:52:10.660 immunity and that so some of the targets for NK cells and targeting my light
96
cells I think are interesting very.

Early in development, but will Melanoma and other cancers have?
P1 is a base will be an opportunity to test those aspects with innate immunity.

It's not a matter of getting the innate immunity started, but I think more of how durable those interactions are.

So in case else, or may be interesting, but how do you propagate them long term so I would say like 3 looks good.

We'll see what GM does, but that the future interest in other excitement.
In addition to the checkpoints would probably be how we manipulate innate immunity to help patients with cancer in the future. Steve, I think that there are no other questions.