

WEBVTT

NOTE duration:"00:40:32.8890000"

NOTE language:en-us

NOTE Confidence: 0.875900328159332

00:00:00.020 --> 00:00:34.950 So our next speaker is one of the Oh geez of immunotherapy. DSN OG means original gangster. It's like a rapper and old school rapper. It's oldtimer Mario Snow, who is professor of Medicine and medical oncology in the president of the Society for immunotherapy of cancer and he's going to be our anchor. Thank you. Mario it's good question for leaping now before I start still here. Still, here sleeping. I want to know for critical and non redundant pathways. Would you expect a phenotype in a mouse model?

NOTE Confidence: 0.844376027584076

00:00:34.950 --> 00:00:51.240 Like for example, you know with anti PD one even it doesn't have much of a phenotype if there are more prone to autoimmunity is he still a four. They dive lymph obliteration, so for a critical pathway. Lifecycle of 15 does it have a phenotype like if you induce autoimmune are they more prone to autoimmunity in the animal models.

NOTE Confidence: 0.836714267730713

00:00:51.950 --> 00:01:08.020 Although he was still study engineering is quite surprised and then I have now I cannot tell you now. I mean, listen very confusing data right now come out in terms autoimmunity by in terms of analysis of the different passwords. I think is.

NOTE Confidence: 0.860536873340607

00:01:08.800 --> 00:01:23.720 In a mouse model is I actually less trust mouse model in terms of the Hirogen 80 because mouse model tended to be much less hero. Genic now is a human human can be for example, human can be multi.

NOTE Confidence: 0.167852371931076

00:01:24.310 --> 00:01:24.610 All.

NOTE Confidence: 0.790028750896454

00:01:25.180 --> 00:01:39.280 Mechanism or possibly displayed simultaneously or comma, one by one by Mauser model usually do much more homogeneous means one state, but they'll chooses until now we still don't have.

NOTE Confidence: 0.789879560470581

00:01:40.100 --> 00:01:54.610 Any mouse model, which actually nature lior spontaneously expressible fit for example, in humans allowed infinite amounts. We don't really see them. So you can see that kind of awkward situation.

NOTE Confidence: 0.758887231349945

00:01:55.360 --> 00:01:59.490 Thank you to my question thanks.

NOTE Confidence: 0.884208381175995

00:02:00.760 --> 00:02:31.560 So thanks to the organizers for the invitation. I stand between you and the weekend, the when I was asked to give this talk, for 5 or 6 months ago. I thought Oh by then I would have something new to present but the answer is not really, and that goes to show to some degree. Maybe that the field is moving a little bit slowly. At least in terms of clinical application. So I'm just going to try and address just show that.

NOTE Confidence: 0.898209750652313

00:02:31.960 --> 00:03:00.300 Questions are very hard and the big question for me now is who does and who does respond to anti PD one? What are the mechanisms for non response? Is there anything that we can do about that and can we identify those patients in which we can do something about the mechanisms of non response. I'm going to try and indicate how difficult I think this is over the next few slides so.

NOTE Confidence: 0.880975306034088

00:03:00.950 --> 00:03:23.400 By now by the end of the day. You've already seen all my slides one piece of advice for any clinical. Investigators always be the first one to talk in a meeting because at least by then, none of no one is showing your slides at that point. But this is the data for the 5 year follow-up for NTPD one for the second trial of anti PD one in the clinic.

NOTE Confidence: 0.90895414352417

00:03:23.990 --> 00:03:56.890 We dose of 1st patient here in November of 2008, there's 10 year follow-up. Suzanne to Palian did most of the heavy lifting on this 5 year or actually less follow-up, which has at least 5 years of follow-up in all patients and it shows that the five year survival rate in Melanoma is 34%. I just want to point out how important that is that the prior to the air of the checkpoint inhibitors that 5 year survival rate would have been around 5% and even with anti CTA for the 5 year survival rate is only in the 15 to 20% so.

NOTE Confidence: 0.915127336978912

00:03:56.890 --> 00:04:29.920 NTPD one at least doubles and maybe triples, the survival rate for Melanoma at 5 years. But if it was only in Melanoma. None of us would be here because Melanoma so rare disease and nobody would really care and we really got people interested in the field is really the fact that the survival curve in non small cell lung cancer, which is unprecedented also because lung cancer is a big market. People became interested in this field and again. That's actually at least for the time and unprecedented survival curve. I think in non small cell lung cancer by the way. Scott guettinger here and I'm going to be a little yell centric in the talk.

NOTE Confidence: 0.880892336368561

00:04:29.920 --> 00:04:37.690 Accrued most probably the largest number of lung cancer patients in that trial.

NOTE Confidence: 0.890821039676666

00:04:38.790 --> 00:05:08.800 So drew showed a slide like this earlier this is my version of it showing that from that very first trial of anti. PD one number of other anti. PD one in an TPO on agents were developed and the list on the left, which I have to change almost with every talk that I give or the number of tumors for which anti PD one or Auntie P 01 has been approved either alone or a combination. It's really remarkable. There's a number of other tumors witchers clear activity, but just hasn't been approved yet.

NOTE Confidence: 0.900853276252747

00:05:08.940 --> 00:05:41.310 And in fact, we now talk about tumors. Unlike the old days where we talked about tumors where the immunotherapy was active there. One or 2 tumors. Now we talk about the one or 2 tumors where it's not active, but the problem is, is that despite being active in all these diseases. It's only active in a substantive heard before what's critical is trying to identify who is and who isn't a responder and why they don't respond so you've heard already about biomarkers Here clinically really there's only three that we use P DL1. We don't use the other ones we don't use.

NOTE Confidence: 0.889930546283722

00:05:41.310 --> 00:06:11.390 Interferon gamma gene signature, although it's probably could be useful. You would think that assessment of T cells in the tumor marker environment. It would be the best biomarker right you shouldn't respond less you have T cells in the micro environment and the other one which is a surrogate for having an antigen specific T cell response would be high tumor. Mutation burden in the circuit for that would be DNA mismatch repair and those are really the main biomarkers that have gained traction since the initiation of these trials just to drill down on the T cell.

NOTE Confidence: 0.871525824069977

00:06:11.640 --> 00:06:44.870 Response it does seem to associate with with activity for anti. PD one, but there's a number of things that have been looked at in it. Nothing is really sort of stuck right at this point, so you can look at the number of CD8T cells at the tumor invasive margin. You could look at the number of stromal. CDA tells you can look at the clone ality of the T cells. All those associate people have looked at subsets of T cells within the to Morocco environment ideal doubt is looked at CTL A4PD1A double positive cells and more recently, especially with a single cell RNA seq sequences.

NOTE Confidence: 0.906733930110931

00:06:44.870 --> 00:07:17.720 Become clear that perhaps maybe some subset of T cells are the ones that correlate so not all the CDA T cells are important only a subset, perhaps contribute to the anti tumor response and David and

others here started to look at the functionality of those T cells and that can also to some degree correlate with response to anti. PD one, but it gets really complicated. I just want to point out and I can't say that I understand any of these papers or at least 4 papers out there now on single cell sequencing of T cells in the micro environment, either before or before and after.

NOTE Confidence: 0.886038899421692

00:07:17.720 --> 00:07:24.900 Anti PD one and I think what the main message for this is that there's clearly a subset of cells.

NOTE Confidence: 0.904093503952026

00:07:25.760 --> 00:07:56.050 Probably early memory or stem cell memory like cells, it probably contribute the most to the response. You can identify those by markers and I think this will create an opportunity for start looking for different signals. It might really activate different subsets of T cells, which really sort of scary is the last paper seem to suggest that you needed T cells come from outside the tumor marker environment in order to get the response that some of those clones that are there after treatment weren't there before they probably come from the lymph node or some other place and if that's the case, then maybe all the information actually isn't within.

NOTE Confidence: 0.890734910964966

00:07:56.050 --> 00:07:58.070 The tumor marker environment itself.

NOTE Confidence: 0.656353652477264

00:07:58.730 --> 00:08:00.520 But.

NOTE Confidence: 0.895408153533936

00:08:01.560 --> 00:08:31.950 You can't start using this sort of information. All this information. At least the simple information to start trying to identify who would and who wouldn't respond at least you can reach to some degree who would respond to anti. PD one or anti. PD L1 and you can do that by maybe combining 2 biomarkers at the same time, and people, especially market started to look at this and look at for example, TMB on one axis and P. DL1 expression on the other or interferon gamma expression expression on one axis and.

NOTE Confidence: 0.907205104827881

00:08:32.040 --> 00:09:07.050 And TMB on the other axis and you can divide it up into quadrants and it seems to suggest that if you have both markers positive high TMB High P. DL1 or high interfering damaging signature. You tend to have the highest chance of response if you have one or the other positive you have some chance of responding if you have neither you have a very low chance for response. So this is important because it starts to tell us who is and who isn't likely to respond to anti PD one even if you can identify all the responders and non responders with these assays. But what it gets you in the point that

I'm going to ultimately make is that it doesn't really tell you what you need to do for the nonresponders in order to move the fee.

NOTE Confidence: 0.909275829792023

00:09:07.050 --> 00:09:37.100 Look forward it just tells you who might or might not respond to this one drug but not what you need to add or give to the nonresponders in order to get a clinical effect, so one way to sort of start to think about. That is to look at what the actual mechanisms are non response and you sort of heard this from limping. This is a different way of looking at this, you can imagine that there's a group of patients for which are no T cells in the micro environment that would be leaping's double negative. Groupon there more than one reason why that might be the case so it could be.

NOTE Confidence: 0.890213787555695

00:09:37.100 --> 00:09:49.140 No priming or it could be signals that exclude T cells from the micro environment. But even then, there's a deeper layer, which is what are the mechanisms that drive that there's probably a group of patients for which?

NOTE Confidence: 0.910969078540802

00:09:49.880 --> 00:10:21.210 There's a lack of agony signals of T cells are there, but they don't have enough agonist signals or perhaps there are other inhibitory signals for example, the signal 15 and then there's probably a group of patients for which there not responsive to T cells at all because they've lost class one or beta 2, Microglobulin If you've heard from Katie earlier and as I've looked through the literature. You can find all these mechanisms as you look through these mechanisms carefully you see that possibly some can be addressed. But maybe some cannot and that's a real problem? What's even harder is whether you can actually.

NOTE Confidence: 0.884696006774902

00:10:21.270 --> 00:10:51.530 Sort of assess these before you treat a patient figure out what the right mechanism is and then give them the right drug with or without anti. PD one in order to get activity. So what that's led to is this huge number of clinical trials. All based on really decent animal models. All of which show some positive effect and that you can divide them up into 2 kinds of trials. Those leaping sort of pointed this out. Also, those that provide some sort of agonist signal. They either give you either give cytokines or you give till cells or you give.

NOTE Confidence: 0.915635764598846

00:10:51.530 --> 00:11:23.420 Try and induce an immune response or you give Co stimulatory signals and then there's the other sort of way of looking at it, which is to try and block negative regulatory elements within the tomb rocker environment and there's a bunch of them and the real question is, are some of these dominant? How do you identify which ones are dominant but that hasn't

stopped the development of multiple clinical trials and you can imagine that if you go into a clinical trial of 100 patients in a disease and maybe multiple mechanisms are responsible for assistance.

NOTE Confidence: 0.915841281414032

00:11:23.430 --> 00:11:53.900 And you're only doing one combination. You may only identify response in a small number of patients at that signal may not be enough to drive development of that combination forwarder that agent forward so this creates a real clinical problem in that having that biomarker to tell you, which agent to add a which agent to give when the mechanism. That's relevant is only present in a small subset of patients is really critical for development. So I'm going to spend a little bit of time on just one combination actually 3 combinations.

NOTE Confidence: 0.908947587013245

00:11:54.010 --> 00:12:25.780 To sort of show you what the clinical conundrum is how difficult this is so back in 2009. We actually treated the first patient here with blue map in Devola Mab and it really made sense to give that combination not only did it make biological sense, but it would they? Were the only two agents that were available at the time so we didn't have to think hard about trying to combine those 2 agents and we were surprised not only at the level of activity, but at the level of toxicity of those, 2 drugs. And when I'm showing you here is the 5 year follow-up. This was a Phase 1 trial in Melanoma.

NOTE Confidence: 0.882909893989563

00:12:25.820 --> 00:12:57.130 And the five year survival now for Melanoma using a blue map. Nevada map combinations is in the range of 50%. This is our Phase 1 trial data, which was 94. Patients who just really remarkable and it's probably better than anti PD one. Although I'll show you in a minute in randomized trials. It wasn't that straightforward and might have to dab koernke vetoed app car who were here at the time took samples that we collected in those trials and they did all sorts of studies and really anti seated for an anti PD one did what you wanted to do it.

NOTE Confidence: 0.855296432971954

00:12:57.130 --> 00:13:09.490 It if you looked at gene expression in T cells and monocytes in the peripheral blood. You got ahold net subset of Genesys is shown here, both in the 1st I guess I need a?

NOTE Confidence: 0.878964364528656

00:13:10.370 --> 00:13:40.380 I point well doesn't matter the be the first set of slides there really shows it in T cells. You get a whole set of jeans that are up regulated by the combination that you don't see with either agent alone. That's also true in Maná sides and if you look at cytokines that are inducing the peripheral blood for the ones that were looked at these are the ones where you saw major effect. You saw an increase in CXL 10 theoretically downstream

Interferon Gamma. You saw an increase in soluble. I'll 2 receptor, which means you got more T cell activation. You got IO 1A, which not sure exactly where that came from.

NOTE Confidence: 0.922071695327759

00:13:40.380 --> 00:13:53.380 But in any event, you got clear immune activation you got more toxicity. And so you would have thought this would have been an ideal combination. We should have seen great activity. A lot more response and you would have expected with just niveau alone.

NOTE Confidence: 0.855657875537872

00:13:54.230 --> 00:14:09.080 So this is now the five year follow-up for the randomized trial of it bill imaginable. A map versus nevala map versus it dilemma. Mab in Melanoma and there are some striking results here.

NOTE Confidence: 0.903804659843445

00:14:09.980 --> 00:14:41.320 52% five year survival free balloon amount of all the map very similar to what we got in our Phase 1 trial, the 36% progression free survival rate for it. Blumenthal map at 5 years is amazing 'cause that probably a correlate of a complete response, which means that 1/3 of patients almost 1/3 of patients are probably cured of their cancer with this combination. But the key point that I want to make. Here's despite this all of the biological activity that we saw at pharmacodynamic activity, the improvement over anti PD one alone was only.

NOTE Confidence: 0.911004543304443

00:14:41.320 --> 00:15:11.910 A very small amount as you can see and in fact, the survival differences here. We're not statistically significant progression free survival was so you have to ask a question then well. You know which groups of patients are responding to the anti. CTA 4 because we're adding a lot of toxicity. And when you look at the forest plot and look at all. The variables for what was looked at really nothing comes through that's clearly sickly significant. There's some indication well if you live in Europe. You're going to do worse there must be some biology to that.

NOTE Confidence: 0.896779358386993

00:15:11.910 --> 00:15:41.420 If you if your P DL1 negative. It looks like it blew map at something to the combination. But that's not statistically significant when you go across all variables, so really we don't know which subset of patients really benefit from the aunties each way forward. Despite all of the activity and later. I'm going to try and go back and tie this to the mechanism to show you again. How difficult this all is in trying to develop rational therapies. Let me spend a moment on lung cancer for a moment.

NOTE Confidence: 0.921532571315765

00:15:42.010 --> 00:16:13.910 So the other combination that seemed to show activity. There's 3 there's shown activity in Phase 3 trials is a combination of federalism. Abing chemotherapy and non small cell lung cancer and what I show you here is the data from the New England Journal of Medicine. Article showing you the activity for patients who are P. DL1 less than 1% which is the Top line 1 to 49%, which is the middle graph and then the last one. The one at the bottom on the left hand side is 50% or greater where Primrose as a map alone had already shown activity.

NOTE Confidence: 0.890993177890778

00:16:13.910 --> 00:16:46.780 An improvement in survival over chemotherapy So what these data suggested was that at least for the patients who were pedia one negative 1 to 49%, Pember Alism. Add really did add in combination with chemotherapy really did. Add something compared to chemotherapy alone in the patients were PD on high. It wasn't clear that adding Pember Lizum app to chemotherapy did much more than one Pember Alism app. Did did alone. This is all very early. Follow up in this trial. So this combination worked in one of the questions you could ask him will address in a minute is.

NOTE Confidence: 0.907664895057678

00:16:46.780 --> 00:16:57.530 How did chemotherapy actually improve this response? What it actually do that it added to the activity of of pember lism abra vice versa to improve overall survival.

NOTE Confidence: 0.898163497447968

00:16:58.050 --> 00:17:28.240 So at Ezmo in just a couple of weeks ago and just published in the New England Journal of Madison. BMS just published a very large trial of Nivola map it dilemma. Mab versus chemotherapy in non small cell lung cancer. And if you look here. The graph on the left is the overall Niveau Eppie versus chemotherapy which was statistically significant. The graph at the very Top this trial was a very complicated study so in the patients who were.

NOTE Confidence: 0.882325172424316

00:17:28.240 --> 00:17:58.250 P DL1 positive, which is the graph at the Top patients were randomized. Get niveau hippie versus Niveau alone versus chemotherapy. And if they were pedia one negative. They got randomized to niveau it be versus Niveau Chemo Therapy versus chemotherapy and what it suggests again is that niveau hippie is better than chemotherapy. Regardless of PD L1 expression. It didn't really beat Niveau in the PD. L1 positive group. It really looked very good in this sort of post talk analysis.

NOTE Confidence: 0.925139725208282

00:17:58.250 --> 00:18:20.810 In the PDA one negative group what's interesting here in something that I think we should think about is that the nivo chemotherapy. Arms should be identical to Pembroke chemotherapy and it does look a little bit better, but I don't think that was statistically significant like it was in

the other trial. But you can see that the survival curve seem to come together and it's part of my concern that combinations with chemotherapy may not be as effective in the long run.

NOTE Confidence: 0.925337493419647

00:18:21.540 --> 00:18:30.390 As combinations with immunotherapy because there might be some negative effect on long-term durable responses, but it gets even more complicated than that.

NOTE Confidence: 0.871207058429718

00:18:31.590 --> 00:19:02.020 This is just to show you that the curves for niveau are very similar to Pembroke trouble, we can actually skip. This life so it's just look at the hazard ratios for a moment So what was kind of interesting is that the nivo. Eppie effect was seen in patients who are P. DL1 negative and the ones who are pedia on greater than 50%. But if you look at the hazard ratio for the one to 49% it's .94 that's

NOTE Confidence: 0.890913665294647

00:19:02.020 --> 00:19:30.660 Also is also too, for Pembroke versus chemotherapy but was not too for Pembroke. Chemo therapy versus chemotherapy alone, so if you sort of put all these data together. You sort of have 3 groups of patients and how do you explain this in the PD L1 negative group Pembroke IMO Anevo April it beat both look better than chemotherapy niveau IP probably is better than Pembroke chemotherapy. But that's to be determined in the one to 49% group.

NOTE Confidence: 0.895893275737762

00:19:31.320 --> 00:20:02.680 It looks like neither pem bro. Nor Niveau Eppie really do much compared to chemotherapy. But Pembroke IMO is better than chemotherapy. So, in that group chemotherapy plus anti. PD one does look better than the immunotherapy's alone. And if your P. DL1 high again. Niveau IP Ian Pem bro. Probably are as good as Pembroke chemotherapy are compared to chemotherapy alone. So I present. All that data to show you how confusing this is and how do we develop biomarkers?

NOTE Confidence: 0.904731690883636

00:20:02.680 --> 00:20:22.770 And how do we explain these results right 'cause? I spent all weekend trying to figure out? What these results. Benan I could not figure out what the biology was and I want to point out that it's not because so is the epy data real and so they in this lung cancer study. They gave like a whiff of it bloom in Mabin milligram per kilogram every 6 weeks together with TI vo.

NOTE Confidence: 0.91045755147934

00:20:23.400 --> 00:20:50.140 And you would have expected that would have been very toxic. But in fact, the rate of Grey, 34 toxicity was around 30 to

35% somewhere in that range, which is not dissimilar from we give that that same dose of EPI every 3 weeks with Devo. So it clearly the hippie was doing something biological in this study, so let me just spend a minute on mechanisms of action. So can, we explain any of this with by the mechanisms of action of CTA 4 if you.

NOTE Confidence: 0.845852553844452

00:20:50.970 --> 00:21:22.080 If you look at what's ETA 4 does it, you know clearly it may have some intrinsic mechanism of action inhibiting T cells. It clearly has a role in tier eggs when when you give auntie CTA for you probably expose CDA. Dion CD 86 Co stimulatory molecules, which may be necessary. CTA for can cause upregulation of ID Oh by dendritic cells crosslinking CTA 4 on T Rex can upregulate TGF beta and IL 10.

NOTE Confidence: 0.887643933296204

00:21:22.210 --> 00:21:52.220 Sitella 4 effects of mobility of T cells. He tell you for does a lot of things in CTF or maybe working in the lymph node in the tumor brain left the tertiary lymphoid structures that could be working directly in the tumor microenvironment. It could be something happening on T regs or effector cells. It could be related to new engine presentation or activation of memory cells and it could be modifying hyphenated or low finity cells and the question is for all of these effects, which ones are the ones that are important in any individual patient and we really don't know.

NOTE Confidence: 0.891437113285065

00:21:52.220 --> 00:22:23.190 And so we see that each LA 4 works in some small subset of patients. We can't even tell which of these are facts are the ones that are important so if we can't figure that out? How are we going to be developed biomarkers that would actually tell us who needs the Chile foreign who who won't I just showed this slide because this is data from an animal model that you can obviously get the results. You want from any animal model. But this is time. Guess he's showing that using FTY 720, which blocks egress of T cells.

NOTE Confidence: 0.895692944526672

00:22:23.390 --> 00:22:53.580 From lymph nodes showing that and if you look at just the last two and establish tumor in a mouse model if you give FTY 720. You don't affect the anti tumor activity. Avanti CTA for an anti PD. One very much which at least in this animal model suggests that most of the action is occurring within the tumor microenvironment itself and that you don't need any T cells coming in from outside the tumor in order to get your anti tumor activity, which is actually directly contradicts recent data that was resulted from.

NOTE Confidence: 0.897601723670959

00:22:53.580 --> 00:23:25.570 Single cell sequencing from human tumor, squamous cell carcinoma. There were treated with anti PD one. The recently published data so again. It becomes very confusing. This is the last these 2 sides,

which I'll skip over 'cause. It's like really just goes to show that at least in the animal models. It's very important to eliminate T regs. That's what's ETA 4 seems to be doing and if you don't eliminate T regs. You lose a lot of the anti tumor activity. Avantis ETA 4, so this is a long way of saying that C T4 does a lot of things it's clearly an active it's not as active as we would expect.

NOTE Confidence: 0.9123175740242

00:23:25.570 --> 00:23:59.100 And it's just even though it's a very simple combination. We still can't actually figure out what it's doing and when you start thinking about chemotherapy and trying to sort of trying to terminate lease. Rationally, who's going to respond and who's not in what sort of biology. You're addressing when you add chemotherapy to anti PD one. There's a whole bunch of things that chemotherapy could be doing and I've listed them all here. And Unfortunately, it's going to be very hard for us to know in any individual patient. Which of these effects are really critical? Are we just reducing tumor burden or we?

NOTE Confidence: 0.875772714614868

00:23:59.100 --> 00:24:23.740 Getting rid of T rags are we getting rid of MDS ease or we activating staying are increasing antigen presentation. We just don't don't know the only other combination here is the veggie for scepter combination with anti PD one in renal cancer here again. We don't know the mechanism. Although we can tie this more directly to some of the pre clinical studies so.

NOTE Confidence: 0.900642037391663

00:24:24.440 --> 00:24:55.470 I'm just going to take a moment and just say that what this tells us is that really we don't really have good biomarkers for addressing the mechanisms of response are non resistance in patients who don't respond to anti PD one. We're left with in the clinic is really developing these agents in patients who either we predict to have a low response to NTPD one based on the biomarkers that we have or taking resistant patients and that means that what we're doing in the clinic is very empiric and we can make mistakes this is.

NOTE Confidence: 0.88115668296814

00:24:56.270 --> 00:25:13.900 Try Love Pember Lism map plus or minus an IDO inhibitor in Melanoma based on very good face to data when it went to Phase 3. You couldn't put a piece of paper between those curves and we still don't really understand why this trial failed so.

NOTE Confidence: 0.908126294612885

00:25:14.610 --> 00:25:37.230 Again, going back here, the really sort of major block in clinical development of these agents is that we're getting better at Biomarkers. It can tell us who will and won't respond to anti PD one. But we really don't have that second biomarker for what you need to add to the nonresponders in order to improve the survival curves.

NOTE Confidence: 0.900753259658813

00:25:37.890 --> 00:26:06.730 I wanted to say one thing about developing agents in PD one nonresponders. Not all Nonresponders Orchulli Nonresponders. Their patients who have pseudo progression. And so when you look at the data from those trials. If you have a very low signal of activity. Some of that may or may not be related to the drug that you're adding to anti PD one so if you've had a short duration of Anti. PD one therapy. If you've been on anti PD one for a very short period of time.

NOTE Confidence: 0.899078667163849

00:26:07.770 --> 00:26:38.340 Those patients who then go onto another dog might have responded to PD one late for patients who have been on anti. PD one and responded and then go off drug a lot of those patients, especially in Melanoma. If you wait long enough can respond again to anti. PD one when they relapse so if you're including those patients in your trials and you're claiming activity of your agent that might not be a signal from the agent that you're giving and not all progression is the same in the clinic so if you have multiple non nodal sites of disease that are growing that's probably true progression.

NOTE Confidence: 0.895307242870331

00:26:38.350 --> 00:26:58.530 But if you have oligoclonal progression that doesn't really mean that the patient is resistant. They may be resistant in those sites. But you can take care of those individual growing lesions with surgery radiation and may still get a very good outcome and so, if you're looking at survival. In that setting your drug may not really be affecting survival and if you only have nodal only progression.

NOTE Confidence: 0.879233837127686

00:26:59.110 --> 00:27:26.560 We see that all the time in the clinic and that's not true progression. That's just inflammatory response so the SITC is trying to develop a paper so to traditional guidelines more uniform guidelines for entry of patients into the PD1 non responder trial so that at least if you do see a response in a signal you're pretty sure that it suited the drug, and not just to alight effective anti. PD one orrori response to anti PD one and just to show you that.

NOTE Confidence: 0.875947535037994

00:27:27.260 --> 00:27:57.270 Oligoclonal progression can be misleading. This is data from Clemens here at Yale. He's a surgeon. He went back and looked at all of our data and Melanoma over the last 10 years with either anti PD one. Anti C 24 of the combination and he basically looked at the patients who had all eagle clonal progression that we then sent to surgery. So these are patients. We either had a single progressing site or a single residual side of disease.

NOTE Confidence: 0.910624861717224

00:27:57.270 --> 00:28:28.020 Or patients were only one side of disease was progressing in the rest of disease was stable and if you look on the right hand side of this curve. You can see that for the patients that did go on to surgery. They had outstanding outcomes. Many of them were progression free for quite a period of time after the surgery and if you look at the survival of these patients who would have been considered progressors that outstanding survival. So if those patients were to go onto a PD one resistance trial and you were going to look at survival. You'd be fooled because those patients would have done well regardless of any.

NOTE Confidence: 0.675458371639252

00:28:28.020 --> 00:28:29.860 Of treatment.

NOTE Confidence: 0.912570476531982

00:28:30.500 --> 00:29:00.510 So I'm going to spend the last minute, just going through just a few strategies. This is if I were to guess what was going to work in the clinic. This is would be my Top four choices. I think there's probably going to be something in reactivating exhausted or dysfunctional pools and there may be ways of doing that. Not all the T cells are trash, but they may not all, be responsive to anti. PD one and maybe sighted kinds like errands. I'll 18DR or, maybe combinations of other checkpoints might reactivate those cells.

NOTE Confidence: 0.892569541931152

00:29:00.620 --> 00:29:31.910 It may be necessary in some patients to give them new T cells. New Antigen specific T CRS and you may be able to do that either by immunization, plus or minus ETA 4. Steve Rosenberg is actually taking TCR some T Rex, which are not the same as the TCR is in effect. Yourselves put him back into naive T cells and giving those back and there are people who are basically taking modified TC, Rs against shared antigens and giving those back and seeing responses. There are novel checkpoints like leaping Sigler 15 and then the other thing that I think might be very.

NOTE Confidence: 0.895892322063446

00:29:31.910 --> 00:29:51.590 Fruitful in the clinic would be things that are non T cell dependent so things at Target into tumoral macrophages. You saw from data that was presented earlier for Marcus and many of the cells within the human microbiome or macrophages. And I'll show you a little bit of data with CD 40 just one or 2 anecdotes to suggest that that might be a productive strategy.

NOTE Confidence: 0.860415160655975

00:29:52.260 --> 00:30:25.970 So CD 40s very interesting, it's a TNF light receptor on dendritic cells monocytes back pages and B cells. Some years ago, Bob Vonderheide did a trial of anti CD 40 and actually showed signal agent activity and in Melanoma. There were 4 responders out of 15. There was a second trial was given. Too often, and not active. It was basically dropped and

then Marcus and Sue started looking at at CD. 40 here and showed activity in first in Marcoussis model and then in combination with CSF 1 R.

NOTE Confidence: 0.903486490249634

00:30:26.220 --> 00:30:56.540 And then Harriet and cougar and Sara Weiss here had the opportunity to participate in the trial of Anti. CD 40 and nuvola mab in patients who were non responsive to anti. PD one alone or at progressed on anti. PD one and our initial experience with this is really quite interesting because we've treated about 12 patients and now we have already. I think almost 4 we have 4 responders. I don't know what the entire databases. But this is a real drug and this is one of my patients that had.

NOTE Confidence: 0.897717475891113

00:30:56.540 --> 00:31:27.070 Mucosal Melanoma had it been evos had maybe a little bit of response. When an anti PD one and after several months had progression multiple sites of disease, she might have responded to it. Beanie Boo again. But it's unlikely. We gave our anti CD 40 an anti PD one and within 8 weeks. You had an amazing response had responses in the liver. This is one of the liver responses. This mesenteric mass are you see over here. I'd have to point. The pointer, but it's over on the right side of the abdomen completely disappeared and she's.

NOTE Confidence: 0.907150268554688

00:31:27.070 --> 00:31:39.310 Progression free now at a year and this is I said 1 of 3 or 4 responders that we have now not everybody responds. But this is a real drug there's a responder in lung cancer and.

NOTE Confidence: 0.878167748451233

00:31:40.020 --> 00:32:12.750 Based in part on this work and some of the work that was done with the combination of Anti. CD 40 in CSF one R by Marcus and Sue Harriet and Sarah started a Phase 1 trial of the triple combination of an anti CD 40 agonist. Kabira, which is an antibody against CSF one R and Niveau. We've gone through the Phase 1. It has significant toxicity and started the Phase 2 and in Melanoma, but Harriet just told me that we had a responder recently. And so we don't really know how much is CSF one R adds to this, but again?

NOTE Confidence: 0.897792935371399

00:32:12.830 --> 00:32:46.270 It's an approach that I think might be interesting what's interesting about this is that some of the activity of this combination, which is specifically targeting macrophages is non T cell dependent in the mouse models. There are other strategies that are very interesting reason why I showed this slide is the scientists. Valerie older guard actually did her. pH D in amino biology here at Yale developed an antibody with a small molecule. TLR 8 as a payload on this antibody when you give this and it binds to macrophages in the tumor microenvironment has to bind to its antigen then.

NOTE Confidence: 0.90533983707428

00:32:46.330 --> 00:33:16.880 Gets internalized into the macrophages through NFC dependent mechanism carries a TLR 8 agonist into the tumor basically induces substantial activation of those macrophages. And in early animal models. She seen amazing activity. That's both T cell dependent an independent so this is a strategy that I think would be very interesting. If you have a fairly specific tumor target for the antibody and then the last thing that I just want to talk about are.

NOTE Confidence: 0.827422678470612

00:33:16.880 --> 00:33:19.380 This adoptive immunotherapy.

NOTE Confidence: 0.868367195129395

00:33:20.040 --> 00:33:51.810 This is another way of getting T cells into the tumor marker environment Steve Rosenberg is shown activity of till some years ago in a small company developed a methodology for making these in a commercially viable way. This is the data that they presented on one of the cohorts. We've participated in this trial. This is better data than we've seen in our own hands. But these patients and is significant size cohort almost all had had an TC TI-4 all had to head anti PD one.

NOTE Confidence: 0.909448087215424

00:33:51.810 --> 00:34:23.960 The objective response rate was 38%. Now, maybe they're the same patients it might respond to CD 40 Anevo in Vivo. I don't know, but the response rate with till therapy is very significant and it may be that adopted amino therapy may be necessary. In a subset. Obviously, they would have to have antigen specific T cells in the tumor microenvironment. But, perhaps you need to take them out of the body and reactivate them and give them back in order to see activity and it is Moe. This is also quite interesting because this is an A fitting modified TCR against.

NOTE Confidence: 0.891990780830383

00:34:24.130 --> 00:34:43.690 May J4 it's transfected into peripheral blood lymphocytes and given back and in synovial sarcoma fairly large percentage of the patients actually had activity so this may be another way of maybe delivering new TC argents. The tumor marker environment plus or minus anti. PD one in order to get anti tumor effects.

NOTE Confidence: 0.872891545295715

00:34:44.260 --> 00:34:47.300 So, In summary.

NOTE Confidence: 0.917306661605835

00:34:47.900 --> 00:35:19.610 I think that that clinical development is really quite complicated because we just don't have good biomarkers for what that second agent should be together with anti PD one and what makes it even more

complicated is that the agents that we give have multiple mechanism of action so actually trying to identify the mechanism that you're needing that you need to address in vivo is complicated. And it's even more complicated. When you realize that not all the T cells in the tumor micro environment or doing the same thing or would be functional.

NOTE Confidence: 0.894153833389282

00:35:20.960 --> 00:35:51.870 I think that there are rational approaches and T cell failure or rational purses and T cell. Ferrier require really a more comprehensive understanding of what the critical signals are for activation of those diversity cell subsets or we need to make new TC, Rs and probably although I don't think we've actually at the ceiling of things that would be that would work by T cell mechanisms. We really need to focus a lot more on non T cell dependent mechanisms. There's a bunch of tumors out there that just don't have antigens.

NOTE Confidence: 0.939401030540466

00:35:51.870 --> 00:36:09.690 Will lose MHC class one and I think that's where the real major opportunity is over the next several years, so I'll stop there. Thank you for your attention. I apologize for keeping you late on a on a Friday afternoon and happy to answer questions probably afterwards if if you have any.

NOTE Confidence: 0.854433536529541

00:36:15.890 --> 00:36:19.300 You got the President Sisi up here we can ask him a question or 2.

NOTE Confidence: 0.640193939208984

00:36:19.950 --> 00:36:21.250 Smart and sleeping.

NOTE Confidence: 0.366786420345306

00:36:22.710 --> 00:36:23.940 Mario the

NOTE Confidence: 0.880539655685425

00:36:24.690 --> 00:36:37.130 I actually get completely confused the after the so the question. What is the channel philosophy or the logic behind this combo or selection or combo?

NOTE Confidence: 0.864242196083069

00:36:37.670 --> 00:36:41.530 I mean, is the now I look the overall the feel is.

NOTE Confidence: 0.822013139724731

00:36:42.290 --> 00:36:45.660 Now you have a PD? Why would you worked and then plus?

NOTE Confidence: 0.858621537685394

00:36:46.390 --> 00:36:59.780 Plus anything today, so that's one way right. But the anything else, which is not even sure single agent activity. Most of them are not right right and then just keep a combo so then.

NOTE Confidence: 0.897323668003082

00:37:00.310 --> 00:37:10.870 But I agree which could be Michael environment or entire immune system is could be multi hit multi problems so combo makes sense in that way. But.

NOTE Confidence: 0.8879274725914

00:37:11.620 --> 00:37:44.410 How do you know which 22 Campbell I mean it's just you cannot just keep adding number right like like one like later will be triple or four, five different combos. I mean that's the point. I was making is that you don't know there's no way to know there's no way to know what signal you need to give so even if you have T cells in the micro environment. Let's say there are T cells. Air and you don't respond to PD one? How do you know whether you need to give another checkpoint inhibitor Acosta Matori molecule cytokine?

NOTE Confidence: 0.921236097812653

00:37:44.410 --> 00:38:14.800 How do you know what? What signal you need to drive that into some threshold for anti tumor response and maybe even some of those signals are redundant and non critical right so someday, maybe even the same pathway, so given the complexity of the micro environment there. At least at this point. I don't know how you would know which of those different approaches you would take in order to convert that into a responder but I saw was the I saw was the least you combine 2 agent.

NOTE Confidence: 0.855659544467926

00:38:14.800 --> 00:38:21.980 Or 3 agent, which the least work as a single agent. So then by that way you at least get edited effect.

NOTE Confidence: 0.902491390705109

00:38:22.630 --> 00:38:57.640 Or could cook it edit if it well, potentially maybe images and events, so that would be ideal. But at least everything repair because the different mechanism, maybe at least making work as $1 + 2$ equal equal to 3. So I agree. There's a couple of ways to thinking about doing this one is to say. I'm just going to combine active agents and that work by different mechanisms or the other way to do it would be to say to try and guess. What critical non redundant signals are necessary in the micro environment. You could say well, CD 40, is probably a really important signal right because.

NOTE Confidence: 0.865532994270325

00:38:57.640 --> 00:39:28.850 It activates DCS it activates macrophages. It upregulates class Wine Etapa regulate CD80 CD 86, you get up regulation of IO 12. You could say all of those things are really nifty and it should work and

I'm going to combine it with with anti. PD one, but you don't know up front, which patients need that or if any in Phase 2 trial. If the single agent don't work that well means the mechanism might not be significant in most the patient.

NOTE Confidence: 0.89452999830246

00:39:28.850 --> 00:39:58.940 That's a major argument in the field. If the single agent doesn't work. Would it still be worth combining so you can make that argument for So what if it if you needed T cells. There no T cells. You need it to prime well vaccine by itself, probably won't have any activity, but it may be that for the vaccine. You may need to give CTA 4 and maybe even anti. PD one in order to see optimal effects. But the vaccine itself wouldn't may not have any activity because.

NOTE Confidence: 0.898057997226715

00:39:58.940 --> 00:40:17.670 That's how many signals that you need downstream in order to make that work. Yeah, but that's bad, though, because that you have. No, you don't really know how to combine then I can see that they in the future. Are you looking for you, looking for combining 34578 point agent to be future.

NOTE Confidence: 0.897550642490387

00:40:18.770 --> 00:40:26.500 I mean that that is, I don't know that's the problem is that I don't know.

NOTE Confidence: 0.846735537052155

00:40:27.160 --> 00:40:32.890 Totally, brilliant, Mario so everybody join me in thanking him and I'm going to.