

WEBVTT

NOTE duration:"00:52:10.6900000"

NOTE language:en-us

NOTE Confidence: 0.889256834983826

00:00:00.030 --> 00:00:30.160 Open to grand rounds today. Today's a special grand rounds cause. We've invited a speaker from outside from Johns Hopkins Sidney Kimmel Cancer Center Doctor Miller Farahzad Doctor resides associate professor of oncology in a member of the gastrointestinal oncology program at Sidney Kimmel. She completed a fellowship in ecology at the NC. I became a member of the faculty there in 2008 since joining the faculty is sitting Kimmel at Johns Hopkins.

NOTE Confidence: 0.8573237657547

00:00:30.160 --> 00:00:52.670 Doctors odd is the P of numerous early phase clinical trials in solid tumors and gastrointestinal tumors that so many of us know her through collaborations. Doctors out as a clinically active medical Oncologist and is the color of the NCI funded U M1 Developmental Therapeutics. Clinical research program at the SKCCC. We have one of those here petruse unfortunate in Washington today, but she sends her best.

NOTE Confidence: 0.880227088928223

00:00:53.360 --> 00:01:24.210 She's a member of both the epigenetics and colon cancer stand up to cancer dream teams serving as a principle on the latter is a member of the NCI colon cancer task force the Advisory Board an abiding cancer initiative and the Executive Board on the cholangiocarcinoma foundation among others, she is a laboratory dedicated to Translational research and drug development that she uses to inform her clinical trials research as well here. But today is focused on epigenetic alterations in cancer cells changes in gene expression data potentially reversible modifications of DNA.

NOTE Confidence: 0.881050407886505

00:01:24.210 --> 00:01:39.040 And I'll let her tell us more about that. But it's really a wonderful to have no far here. So it really takes cancer therapy from the bank to the bedside and back and we're so grateful that you've taken time to visit us and look forward to your talk thank you.

NOTE Confidence: 0.926663875579834

00:01:45.830 --> 00:02:16.500 Oh, thank you. Roy for that kind introduction, and thank you for the invitation to be here. Today it's a real honor for me to be here today to talk about this work that we've been working on in our group for the last 10 years or so which is how can we move epigenetic therapy forward in patients with solid tumors, especially with GI cancers? It's particularly special for me because you're knew relatively new chairman of surgery need a huge a is

really the person responsible for bringing me into this field, a decade ago when I was a junior.

NOTE Confidence: 0.901827991008759

00:02:16.500 --> 00:02:34.610 Faculty member I had just started at Hopkins Anita was already a world renowned epigeneticist and wanted to have a clue operator in medical oncology and so she reached out to me and was really mentored me over these last many years, so it's very special for me to be able to present the work that our group has been working on for all these years.

NOTE Confidence: 0.935616791248322

00:02:35.220 --> 00:02:45.890 There's a lot of reason for us to be enthusia stick those of us in the epigenetics community about the possibility of using epigenetic modulators in cancer therapy.

NOTE Confidence: 0.939731359481812

00:02:46.420 --> 00:03:17.410 Because over the last 20 years if you think of what we have learned about cancer underlying cancer biology and abnormalities. We've understood and been able to profile a litany of genetic mutations. Infusions abnormalities and we now for most common cancers and even uncommon cancers can describe in detail the genetic abnormalities that are there, but we can't correct any of these abnormalities so we've got targeted therapies that deal with the ramifications of a given genetic abnormality.

NOTE Confidence: 0.938267707824707

00:03:17.410 --> 00:03:47.820 But when it comes to correcting the underlying lesion. We really can't change that underlying lesion and that is completely in opposition to what we can do with epigenetic abnormalities. We also have profiled and found that a given cancer generally has hundreds of epigenetic abnormalities as well. But those are abnormalities that with epigenetic modulators. We really can reverse and it gives us the potential of possibly changing the underlying biology of a cancer to maybe make it more.

NOTE Confidence: 0.930232644081116

00:03:47.820 --> 00:03:53.030 I mean, a sensitive or more chemo sensitive and that's really the area that we're going to talk about today.

NOTE Confidence: 0.932881355285645

00:03:53.770 --> 00:04:18.930 When it when we talk about the 2 different groups of epigenetic modulators. Today, that I'm going to discuss we're really going to focus on drugs that focus on post. Translational modifications of histones, especially histone acetylation, which makes it a major difference in how chromatin is configured and then DNA methylation, which can happen, both in normal cells and abnormal cells as we know to silence gene expression.

NOTE Confidence: 0.918501317501068

00:04:19.780 --> 00:04:52.760 And this is a very simplified cartoon of why histone acetylation in DNA. Methylations matters when it comes to gene expression so if you take an area of the genome, especially if you're looking at gene promoter regions and you've got areas of the gene promoter region that are methylated, which is represented by the red circles here or you've got a new set of acetylated histones. You're going to have a more tightly packed down chromatin configuration. That's going to impede transcription and the DNA methyl groups on those promoter regions are also going to impede the binding of transcription.

NOTE Confidence: 0.713039577007294

00:04:52.760 --> 00:04:53.330 Factors.

NOTE Confidence: 0.918599367141724

00:04:54.490 --> 00:05:18.270 The opposite is true when you have areas of chromatin that are open that are with histones that are associated with DNA that is deacetylated in these gene promoter regions. Now there's much complexity to epigenetic modulation. I'm narrowing it down to these 2 components because that's where we've had the most information and the most preclinical and clinical data, when it comes to using these kind of drugs.

NOTE Confidence: 0.912657380104065

00:05:19.080 --> 00:05:51.070 So DNA methyltransferase inhibitors as we all know are FDA approved in Myeloid Dysplasia, an AML precursor being in a society in our both approved in that setting these have very short half lives, though, so when it comes to solid tumors. There's a real challenge in terms of being able to have a pharmacodynamic effect at the tumor level when you've got a drug that is so quickly broken down in the circulation and that's why in the solid tumor community. I just met with Steve Gore earlier. Today, who said that he thought that God decided being was crap.

NOTE Confidence: 0.892899632453918

00:05:51.070 --> 00:06:14.820 'Cause he said, but aside to be in which has a more prolonged half-life in solid tumors may be more important because we really need time to have these drugs get to the tumor and Gladys Aida Binasa decided being pro drug and we have now many different trials where we have had tumor biopsies in these patients and shown that we actually can get good demethylation with these New Generation, DNA methylating agents.

NOTE Confidence: 0.916540443897247

00:06:16.130 --> 00:06:40.690 Now, histone deacetylase inhibitors have been in the clinic for 20 years. There is some fair skepticism, I would say about the ability to use a DNA methyltransferase inhibitors in solid tumors. They are FDA approved in cutaneous T cell lymphoma's but I'm going to show you I hope a wealth of data that has been generated, especially in the last 5 years that indicate that we might have ways. We can really use these drugs and solid tumor patients, as well.

NOTE Confidence: 0.916565775871277

00:06:41.810 --> 00:07:03.610 But I will say from the outset that multiple clinical trials looking at epigenetic agents alone have been negative in every solid tumor that they've been tested in and I'm specifically talking about DNA methyltransferase inhibitors in H Doc Inhibitors, but we've looked at them alone and we've looked at them together with each other and that effort looking at.

NOTE Confidence: 0.911425769329071

00:07:04.120 --> 00:07:35.750 H tack plus DNA methyltransferase inhibitors alone was really led by the initial stand Up To Cancer Dream Team, Steve Balan and Peter Jones were the head of that. That's when I came into the epigenetics community. We were running three clinical trials in colon breast and lung cancer and all three of those trials were negative and so the use of these agents is single agents in solid tumors is not appropriate and doesn't work. But there are some small subsets of patients that are genomically defined where epigenetic modulators might be effective.

NOTE Confidence: 0.900261521339417

00:07:35.750 --> 00:08:06.280 So Bromo Domain Inhibitors have been shown to have activity and nut midline tumors, which have a BRD 4 Mutation and then I put a question mark here in terms of ID H1 mutated cancers because I DH one mutated cholangio carcinoma. We are seeing some benefit with ID H1 inhibition, but it's a little bit controversial whether I DH one is really considered an epigenetic modulator or not I DH one is as you all know an important gene and protein that's involved in aerobic glycolysis.

NOTE Confidence: 0.91352641582489

00:08:06.830 --> 00:08:40.260 In the setting of having a mutation of IDH 1:00 and 2:00. We have a build up of two HG and this leads to widespread epigenetic dysregulation and so even though I DH one inhibition is not necessarily a pure epigenetic modulator. It has dramatic epigenetic impact, which has been shown in many preclinical studies. This is intra paddock. Cholangio Carcinoma because it's a GI cancer and that this is an area where this, actually is functional. An clinically beneficial. I did just want to highlight it with a couple of slides.

NOTE Confidence: 0.918652653694153

00:08:40.260 --> 00:09:04.390 25% of Intra Paddock Cholangio Carcinoma has a mutation and ID. H1 RID H2 predominantly. I DH one and the initial Phase 1 study of which we were apart did show that even though there were very few resist criteria responses in these studies that a majority of patients at least had stable disease with 40% of those patients having continued stable disease, even at 6 months.

NOTE Confidence: 0.918418943881989

00:09:05.090 --> 00:09:30.700 We've just had this paper accepted to Lancet

Gastro Enterology, which expands on that with 73 patients that were treated with Intra Paddick. Cholangio carcinoma, showing again a small response rate of 5%, but a broad number of patients having stable disease and you can see here on the swimmers plot again around 40%. Even in the expanded cohort have 6 months or greater progression free survival.

NOTE Confidence: 0.937128067016602

00:09:31.920 --> 00:09:55.770 But that's really it when it comes to solid tumors and single agent activity of these kinds of drugs and where the money really feels like it is, is in combination therapies, especially to change chemo sensitivity and immune sensitivity and I'll talk about chemo sensitivity first I just want to highlight the initial dream team that I was talking about because this is really been a collaborative effort across.

NOTE Confidence: 0.937782168388367

00:09:56.280 --> 00:10:04.520 Different groups of basic science, investigators and laboratory investigators to get this field to where it is now.

NOTE Confidence: 0.923771500587463

00:10:05.410 --> 00:10:27.860 So go back to this trials that I mentioned a few moments ago. We did 3 clinical trials in heavily pretreated lung cancer colon cancer breast cancer. All three of those trials used the same doses of a society in an antenna stat that had been previously defined. Another clinical trials. Many of those trials that Steve Gore was actually involved in when they were run as Phase 1.

NOTE Confidence: 0.923608005046844

00:10:28.360 --> 00:11:02.140 And all three were negative. But Luckily John Wrangle, who is a fellow at that time at Hopkins decided to do a posthoc analysis to look at what happened to the lung cancer patients when they went on to their subsequent therapy and this is the analysis that John did and what he found was in this heavily pretreated group of lung cancer patient so these are 4 or more prior therapies as a median 30% of those patients went on to have a resist criteria response and another 30% or more of patients went on to have stable disease.

NOTE Confidence: 0.939074397087097

00:11:02.140 --> 00:11:13.420 So this is really not what you would expect for heavily pretreated lung cancer and it just began. The question about whether or not. We were seeing some sort of a priming effect or whether this was just happenstance.

NOTE Confidence: 0.878592431545258

00:11:14.160 --> 00:11:40.530 So other groups had looked at this in GI cancers. I said only really been explored in a couple of studies. One pre clinical and one clinical with Axali Platten showing maybe some priming with Oxalic Platten

in vitro based studies as well as Xena graph studies. But when this study was performed at MD. Anderson looking in patients across GI tumors at trial was completely negative.

NOTE Confidence: 0.90381646156311

00:11:41.160 --> 00:12:03.230 But in breast cancer the use of H Doc Inhibitors was looking Anne is looking more compelling and even though today, we're talking about GI cancers. I do want to highlight a few places where we really might have some opportunity to use these agents in solid tumors in breast cancer with re sensitizing to hormonal therapy and then in ovarian cancer looking to re sensitized to platinum therapy.

NOTE Confidence: 0.884439289569855

00:12:03.750 --> 00:12:33.860 So this is the breast cancer preclinical data initially looking at antenna stat in an animal model system and showing what happens as this tumor. Initially is controlled by excusing by let Rizal and then in tennis. Stat is added and we get benefit when antenna status added. Even if you can continue left result or if you switch to XMS stain when none of these have any benefit if their continued as a single agent.

NOTE Confidence: 0.902850031852722

00:12:33.860 --> 00:13:05.290 So on court, 301 was a clinical trial that reported on a randomized Phase 2 trial of this combination looking at XMS stain. An antenna stat versus XA. Mustang alone, so these are all in patients that have previously progressed on an aromat ACE inhibitor and the P value that they were looking for a one sided significance level was .1. So this is a double blind placebo controlled study and they did meet their one sided P value of .05 with a 2 month improvement in progression free survival.

NOTE Confidence: 0.907033324241638

00:13:05.290 --> 00:13:25.890 But what was surprising was that the overall survival benefit was substantially greater so there was an 8 month statistically significant survival in an overall survival for the antenna stat. XA Mustang treated patients, suggesting that potentially antenna stat had better effects. Even after the patients progressed on the XA Mustang therapy.

NOTE Confidence: 0.913825452327728

00:13:26.500 --> 00:13:58.350 And this has led to a large cooperative group study that is presently completing enrollment. This is a trial again looking at patients who had previously been treated with an aromat ACE inhibitor an randomizing these patients to XMS stain plus antenna stout versus placebo. The sample sizes increase for an overall survival endpoint and this is a trial that's being run by my recent former colleague rushing Connelly, who's just left. Hopkins to move back to Ireland. But we hope to see these results sometime soon. And this is the best chance that we have in terms of a phase 3 trial.

NOTE Confidence: 0.892469763755798

00:13:58.350 --> 00:14:02.730 To potentially result in having a Jack inhibitor approved in a solid tumor.

NOTE Confidence: 0.89081197977066

00:14:03.540 --> 00:14:31.100 I mentioned chemo sensitisation as well in ovarian cancer that data has gone the furthest. This is pre. Clinical work looking at SGI when 10 or guada cited being the next generation. D methylating drug. I mentioned and showing here that in ovarian cancer animal models. Platinum resistant disease became more sensitive significantly more sensitive when the D methylating agent was added even though there was almost no activity of the D methylating agent alone.

NOTE Confidence: 0.909524202346802

00:14:31.700 --> 00:15:03.050 The initial clinical trials that they did was using decided being a VE decided being showing some responses in platinum resistant disease with the progression free survival in these patients of 8 months. But this was a non. Randomized trial and so the group in this all of this work has really been led by Danielle Imita and Ken nephews out of Indiana. Daniela now being at Northwestern. But there when Randomized Phase 2 study of 100 patients and found that there was a progression free survival benefit.

NOTE Confidence: 0.902753174304962

00:15:03.050 --> 00:15:15.780 For the gotta cited being plus platinum treated patients 16 weeks versus 9 weeks with the PFS at 6 months. That was also improved and somewhat improved overall survival that did not meet statistical significance in this trial.

NOTE Confidence: 0.90937352180481

00:15:17.230 --> 00:15:50.660 So need A and I were interested in exploring whether this was happening in our colon cancer patients after they came off of our epigenetics trial as well. But Unfortunately this was back in 2013, 2014 and at that time. Our patients really didn't have a subsequent therapy to go onto all of our patients had been prior treated with XLE platinum. Renati can't by the few and so most of our patients actually moved on to comfort care after they came off of the study. Sonita and her lab and this is work that was led by Anoop Sharma, who is now here at Yale.

NOTE Confidence: 0.909848153591156

00:15:50.660 --> 00:16:21.170 Move forward and looking at this in the laboratory so Anoop's work first tried to define a dose of a D methylating agent that would not be cytotoxic to in order to really focus on the demethylation component of the D methylating agent rather than a cytotoxic effect and defining this lower dose of Asus Idine. They were able to show here that they were able to decrease

DNA methyltransferase. One and down here in panel E what you'll see is across a panel of cell lines.

NOTE Confidence: 0.897676765918732

00:16:21.170 --> 00:16:30.630 They were able to show global demethylation that was significantly greater with a society. Dean then they saw for mock.

NOTE Confidence: 0.905772387981415

00:16:32.100 --> 00:17:02.250 Anoop then profiled these same cell lines treated with Asus siding against a screen of multiple chemotherapy drugs and found that out of those chemotherapy drugs or renati. Ken was the one where there was the best chance of having a sensitisation effect and move forward looking at first, and in vitro assays and showing that in cell lines like H CT116, which is extraordinarily sensitive to rent A tick in there was really no additional benefit of adding a low dose of a society Dean but in resistant cell lines.

NOTE Confidence: 0.884844183921814

00:17:02.250 --> 00:17:34.480 There was a benefit to adding these low doses of Asus. I didn't similar in clonogenic assays and then here in in vivo assays again. If a cell line was already sensitive to Ridenti Ken. There was no additional benefit. This is the pink line that is a renati can alone versus the blue line. That's the combination. No benefit to adding AA aside, it into those animals on the other hand in a very resistant cell line as you can see both Asus ID Nanda. Renati can having no effect. But when you combine the agents you get complete.

NOTE Confidence: 0.864446401596069

00:17:34.480 --> 00:17:35.960 Aggregation of tumor growth.

NOTE Confidence: 0.903618633747101

00:17:36.680 --> 00:18:07.710 So that was exciting and we thought that that was worth moving forward into clinical trials and so we did. We move this forward into a clinical study combining guada cited being with their innotek in in patients that had metastatic colon cancer and this clinical trial was a study that was designed as a Phase 1 study, so at a standard 3 + 3 design. But every patient had to have prior exposure to Eren Attican before they were allowed to go on. This study and we incorporated paired tumor biopsy's so that we could in later after the trial was completed.

NOTE Confidence: 0.903328061103821

00:18:07.710 --> 00:18:15.350 Do some correlative work to see if we were really seeing demethylation or not, and if there was something productive in the biopsies that would be helpful.

NOTE Confidence: 0.928758680820465



00:18:16.170 --> 00:18:47.010 So we started our trial and immediately found that even at doses that were substantially lower than what was given in the MDS trials. We had significant toxicity in terms of neutropenia and neutropenic complications. And so we ended up having to Deescalate and add growth factor support and with the addition of growth factors support. We were able to re escalate and get back up to a dose level that we were interested in being at where we knew that there had previously been signs of demethylation in other clinical trials.

NOTE Confidence: 0.922222435474396

00:18:47.830 --> 00:19:20.230 This is our table one which just shows that this was a very standard colon cancer patient population. It's a small study because of Phase 1 of 22 patients, but all the patients had prior exposure to the agents that you would expect in a in a Phase 1 study, focusing on colon cancer and these patients had good performance status and this just shows the dose limiting toxicities that we saw in these patients really all focused on neutropenic fever and neutropenic complications, but really decreasing substantially once we added.

NOTE Confidence: 0.907178401947021

00:19:20.630 --> 00:19:35.850 After support we can also see here in terms of the number of cycles that we had many patients that even with prior exposure to renati can and were able to remain on this treatment and tolerably remain on this treatment for significant period of time.

NOTE Confidence: 0.9075026512146

00:19:36.900 --> 00:19:54.730 Our overall toxicity profile was what we expected when we combine these agents so significant issues with leukopenia and neutropenia. But overall otherwise. We were seeing. The toxicities that we would expect with the renati can predominantly low grade GI toxicities as well as some anorexia as well.

NOTE Confidence: 0.93073970079422

00:19:55.920 --> 00:20:12.630 But again what we found interesting was that in a subset of these patients about half of the patients. We were seeing durable benefit in terms of at least stable disease in these patients and biochemically. We were seeing similar effects in terms of our tumor markers as well.

NOTE Confidence: 0.904109299182892

00:20:13.600 --> 00:20:43.990 And I always like to highlight this particular patient. She was a patient of Nidaan Mine. We shared her needed performed all of her surgeries and I took care of her in medical oncology. But this is it case that's really illustrative of how epigenetic therapy may really be changing. Patients underlying biology, so this patient Tryna came to us as a 42 year old who had really high risk Stage 3 disease, she underwent agimat chemotherapy with full Fox in the first time that she got re staged.

NOTE Confidence: 0.896812856197357

00:20:43.990 --> 00:20:52.650 One month after she completed adjuvant therapy, she already had required so anyone who takes care of colon cancer can tell you that that is a harbinger of badness for a patient.

NOTE Confidence: 0.904107809066772

00:20:53.310 --> 00:21:09.590 She then got chemo radiation to that area that record, and immediately next scan. She progress is and has progressive disease with peritoneal metastasis. We give her full therapy she goes to surgery. She comes off of full therapy and immediately progress is again.

NOTE Confidence: 0.880708575248718

00:21:10.150 --> 00:21:41.020 She was enrolled in a clinical trial of amok 5 inhibitor because she had Mch five staining. This was a study that was running through our Phase 1 program immediately progressed on that study as well. So every therapy that she had she either progressed on or she progressed as soon as that therapy ended if it was in the adjuvant setting until she came on this trial of God aside of being Anaren Attican and was able to stay on this study for almost 2 years and did very well on it, and this is her scans. You can see this very thick rind of tumor.

NOTE Confidence: 0.91415399312973

00:21:41.020 --> 00:22:02.290 That was present that basically disappeared within a few months on therapy and this stayed that way for her as well as her changes in CEA for all of the time that she was on study. In fact when she came off of study, she came off the study because of a single liver lesion. That was elsewhere that had come up as a new lesion, which met resist criteria for progressive disease.

NOTE Confidence: 0.91490113735199

00:22:03.450 --> 00:22:36.450 So we're clinical results of this study showed that our patients were able to be on study for about 4, 1/2 months in that historical control to that is red graph and observe Argo, Orlon surf where the median progression free survival is 1.9 months or 2 months. This is a much smaller study and run at only one institution, so that's just a historical control. But we thought that it was interesting enough to follow up on we did see benefit of both the 30 and 45 milligram cohorts and then we decided that we wanted to use our correlated specimens.

NOTE Confidence: 0.906328797340393

00:22:36.450 --> 00:23:06.990 To help define whether we should be aiming for a higher or lower dose level between these 2 doses and so we as I mentioned had timed are coral. It's to try to make it as perfect, as possible to only look at the effects of Goddess Sita being on the tumor without any compelling contributing

factor of a renati can so we added a biopsy after only 8 days on therapy and this is how the perfect can really get in the way of what is good because?

NOTE Confidence: 0.895797312259674

00:23:06.990 --> 00:23:38.010 Only 8 days of therapy with a D methylating agent was in hindsight, a mistake and what we did was assessed this using line. One so line. One is an ass. A That is used as a surrogate for global demethylation. It looks at certain areas of line elements in tumor DNA about 17% of our genome is made up of line elements and these are highly meth lated areas. So it's a circuit of global demethylation. But it was also the acid that was used in the initial studies of Guada side of being.

NOTE Confidence: 0.90586256980896

00:23:38.510 --> 00:24:09.020 In MDSML and what this curve here shows from that figure from jumpy Reese's work is that when you got to 60 milligrams per meter squared there was really no increase in terms of demethylation and even at 45 milligrams or 36 milligrams per meter squared. We were seeing significant demethylation in MDS so we really thought that this was kind of the sweet spot that we wanted to be in and we looked at initially our tumor. Biopsy's and what we found in this is that there was very variable so when you.

NOTE Confidence: 0.904741823673248

00:24:09.020 --> 00:24:29.790 Look at these tumor samples at Day 8, the demethylation was really all over the place. But when we went and looked at our cerium cereal blood samples both looking at WB CS as well as looking in circulating tumor DNA by cycle. Two we were seeing consistent demethylation across the samples and.

NOTE Confidence: 0.914678394794464

00:24:30.370 --> 00:24:50.450 That we were seeing demethylation at both the 30 and the 45 milligram per meter squared dose, though there did seem to be more depth to that demethylation at the 45 milligram dose and so that is what supported us moving forward with that dose level, but feeling comfortable about a dose reduction for the patients that needed it down to 30 as well.

NOTE Confidence: 0.917378902435303

00:24:51.020 --> 00:25:22.810 And that's how our Phase 2 study was designed with a 45 milligram dose level based on correlate of work and I just say this because we often get pushed back in Phase 1 studies to incorporate endpoints and correlative endpoints. Unless we can demonstrate at the beginning what we are absolutely going to do with it, but being able to have those specimens really helps inform future clinical trials, even though that wasn't the initial intention of those biopsies. So this was a randomized Phase 2 study looking at Renati Kinango outta sight of the inverses.

NOTE Confidence: 0.90857207775116

00:25:22.810 --> 00:25:50.230 Red graph numbers to Barga as our control arm. It's a 2 to one randomization and all of these patients have to be a renati can resistant and using these data. We also moved the biopsy's for these patients into cycle 2, so that hopefully will have more information from this clinical trial. This study is completely accrued and is presently undergoing analysis and I'm hoping that we will have these data to present to you all by Asko in January ask OG I.

NOTE Confidence: 0.926292717456818

00:25:52.210 --> 00:26:22.900 So the next major area that we've been interested in moving epigenetic therapy forward is in strategies that look at me to modular. Tori combinations and again. I'm going to take you back to this figure that I showed you a few moments ago, where this analysis was done this post. Hawk analysis of the lung cancer patients. What was interesting is it was completely accidental. But it turned out that Julie Braymer was running the very first studies of the metarex drug that we now know is nuvola mab.

NOTE Confidence: 0.905782163143158

00:26:22.900 --> 00:26:53.790 That drug was in phase one at Hopkins and so a few patients from the epigenetic trial progressed on their epigenetic therapy and happened to go on to their next trial, which was the PD one inhibitor and everyone of those patients. It was six patients, but everyone of those patients did well and three of those patients had very deep durable responses to therapy. That's these patients here. Even the patients that didn't have a resist criteria response were on study for over 6 months without progression and so it's difficult.

NOTE Confidence: 0.926903963088989

00:26:53.790 --> 00:27:27.320 In a setting where you've got a drug that you know now is active in lung cancer to know whether this was just the fact that some patients were going to do well on the PD one inhibitor and this had nothing to do with the fact that the patient had epigenetic therapy first or whether this was really a priming effect from the epigenetic agents. But what I will posit to you is that if you look at what a cancer cell has to do in order to survive the immune system. It makes an inordinate amount of sense that you might want to combine it with an epigenetic agent.

NOTE Confidence: 0.932691216468811

00:27:27.320 --> 00:27:58.030 I still think this is a fantastic figure from the science paper from Schreiber, looking at and trying to detail what happens with a tumor that is able to be eradicated by the immune system versus one that's able to be that one that's able to escape the immune system and if you look at the things that you might want in a tumor microenvironment in order to have a good immune response if you want to lower the number of immunosuppressive cells in that tumor microenvironment or increase the number of cytotoxic cells if you want to increase.

NOTE Confidence: 0.925894021987915

00:27:58.030 --> 00:28:18.310 Immune checkpoint expression on tumors or an immune cells all of these things we've got data that support immunity epigenetic therapy can do. These things can increase MHC class expression and in the next few minutes that we have together. I'm going to try to talk you through some of the data that exists, but these are just representative papers and studies.

NOTE Confidence: 0.91996431350708

00:28:18.850 --> 00:28:51.220 That have been done that have shown this, but there have been many reports in the last 5 years that have really focused on the immunomodulatory effect of epigenetic therapy. So this is hopefully going to give you a flavor of those data so if we first want to look at tumor. Associated antigens expression. There's a running hypothesis that tumor associated antigens or neo. Antigen expression may be responsible for responses to immunotherapy. These are tumor. Associated antigens on the left, you see this in prostate cancer on the right.

NOTE Confidence: 0.910558760166168

00:28:51.220 --> 00:29:17.830 Mike Topper cell paper and lung cancer and they've used a heat mat format to show increases in gene expression across these tumor. Associated antigens with D methylating agents H Doc Inhibitors or the combination and this is also been demonstrated by need's group and colon cancer. It's been demonstrated by other groups and breast cancer. Ovarian cancer so this is a perpetual theme. That's been shown by many groups that we can increase antigen expression.

NOTE Confidence: 0.905743539333344

00:29:19.390 --> 00:29:50.520 When we look at cost stimulatory molecule expression that's necessary for an immune response necessary, but not necessarily sufficient. We do have increases that have been shown in MHC class molecules and C40C. DATHLA's increasing with exposure on the left here to H Doc. In addition, on the right to both H Jack inhibition and D methylating agents is here in Melanoma. These are some of the earlier studies, but there have been other studies that have come since here, too.

NOTE Confidence: 0.908318758010864

00:29:50.520 --> 00:30:19.830 And I also think interesting Lee if you look at the side. A kind profile that happens after exposure to epigenetic modulators. There's also a shift in vitro and in vivo in the site of kind profiles to a more pro inflammatory cytokine profile with increases and I'll to an interferon gamma decreases in aisle 10 and in the heme literature patients that have been treated with Asus ID and this is also been demonstrated in patient samples as well in terms of this shift inside a kind profile as well.

NOTE Confidence: 0.91624242067337

00:30:20.630 --> 00:30:51.280 And then in just the last 2 years. There have been multiple papers that have also looked at immune checkpoint expression with epigenetic modulators here. I'm in Pam. Monsters work looking at various epigenetic modulators and breast cancer and showing increase PD. One expression across breast cancer cell lines. She's also showed this in primary xenographs. In another paper here on the right in ovarian cancer models looking at ox 40 and four one BBL expression increasing.

NOTE Confidence: 0.854148805141449

00:30:51.280 --> 00:30:57.210 Both with pharmacological as well as SI RNA based inhibition of H Doc as well as DNA methyltransferase.

NOTE Confidence: 0.909197330474854

00:30:58.170 --> 00:31:28.860 John Wrangle, who was the fellow I had mentioned previously is now a faculty member in South Carolina had also shown P. DL1 expression increases in lung cancer cell lines, but John also then did an analysis looking at gene sets that N pathways that were up regulated when cell lines were exposed to Asus Ida Dean and showed that across the majority of lung cancer cell lines. There was significant increase in immune related pathways. Mike Topper has taken that work forward.

NOTE Confidence: 0.921662390232086

00:31:28.860 --> 00:31:59.330 And look and tried to refine it, even further looking at and again showing that there are many important gene sets involved in the inflammasome an immune pathways that are up regulated but also showing that a given cell has unique pathways that are up regulated compared to another given cell line and that there are some there is some commonality. But there's also pathways that are unique to each individual cell line and likely to each individual tumor as well.

NOTE Confidence: 0.911434888839722

00:32:00.030 --> 00:32:30.960 Anita will recognize this paper that also what really focused on gene set pathway analysis with Cindy Zano. Their work really focused on trying to identify those commonly upregulated gene set pathways and so this was in a large panel of breast ovarian and colon cancer cell lines that were treated with low doses of Asus. I didn't and then the common pathways that were up and down regulated were assessed and it and they found that immune related pathways were a common subset of pathways that were.

NOTE Confidence: 0.903807878494263

00:32:30.960 --> 00:33:01.770 Up regulated using these pathways, they derived a signature of Asus. I didn't exposure that leads to immune related activation and went to the TCG A and found that if you looked at TCG, a primary tumor samples so these are all untreated with epigenetic therapy right so primary tumor samples can still segregate and cluster based on this immune gene signature and

those of us who did colon cancer, particularly found it interesting that in colon cancer.

NOTE Confidence: 0.893275022506714

00:33:01.770 --> 00:33:20.700 The patients that had the high immune gene cell signature from a decided Dean but they had it Dinovo where the microsatellite unstable cancers, which we now know are highly sensitive to immunotherapy and so that was biologically a satisfying output when these samples were assessed.

NOTE Confidence: 0.905797123908997

00:33:22.360 --> 00:33:53.610 Now there are other groups have really tried to focus on what happens in the tumor microenvironment in terms of which cell types are upregulated or increased or decreased with treatment with epigenetic modulators. So this is a work looking at Saha or vorinostat, which is an H Doc Inhibitor in a peritoneal mesothelioma model first staining for CD 8 positive cells and showing that in this animal model. CD8 positive cells increased with exposure to H Doc In addition, while regulatory T cells.

NOTE Confidence: 0.932689130306244

00:33:53.610 --> 00:33:59.970 Such as shown here decreased so both going in the direction that you would want for an improved immune response.

NOTE Confidence: 0.892160594463348

00:34:01.140 --> 00:34:31.450 Roberto pily I'm has really focused on this extensively in terms of his interest looking at the impact of each dark inhibitors in renal cell cancer and so Roberto first showing in the Ronco to model that the known compensable. Tori increase, and regulatory T cells that happens with I'll 2 therapy is able to be abated with the use of antenna stat. This does also potentially result in improved benefit when these agents is decided. I'm a antenna stat in particular.

NOTE Confidence: 0.913442254066467

00:34:31.450 --> 00:34:34.090 Is combined with PD one therapy?

NOTE Confidence: 0.923651337623596

00:34:34.930 --> 00:35:04.650 Roberto is taken this into the clinic and so this is his report of his Phase 1 study looking at antenna stat in combination with I'll two and showing so this is an untreated patients with renal cell cancer, but had an almost 40% response rate with I'll two and a medium progression free survival of 13.8 months, so again only 40 patients in this study, but a compelling compared to historical controls and he is presently in rolling a randomized Phase 2 study of this combination.

NOTE Confidence: 0.914298593997955

00:35:05.520 --> 00:35:39.630 This idea of combining these agents with immune checkpoint inhibitors has been looked at by many groups in the laboratory

here on the left. We see a combination of most attendance dad. Another H Doc Inhibitor with PD one or P. DL1 antibodies in a lung cancer model and showing that the only places where tumor regression was seen were seen in patients that got combination therapy and the change in polarity as well as the change in cell number when it came to the tumor. Microenvironment was exactly in the direction that you would want with decreasing regulatory T cells.

NOTE Confidence: 0.888386487960815

00:35:39.630 --> 00:36:04.510 With Mosa tennis dot weather given alone or in combination with P. DL1 and increases and CD 8 positive cells as well. And then here on the left again. Pan monsters work looking and breast cancer combination immunotherapy with CTLA for an PD. One was given with antenna stat and here you see very nice benefit in this animal model system when that triplet was given.

NOTE Confidence: 0.905203402042389

00:36:05.190 --> 00:36:35.560 That validated work that had come out of Shippons Owls Lab, a few years earlier looking at combination. See TLA foreign PD. One therapy with combination epigenetic therapy in CT 26 and 41. So a highly aggressive breast cancer model and colon cancer model where you can see nice regression of these tumors. In fact, these animals majority of the animals were cured in combination therapy and you see the metastasis had also decreased down in here in this figure.

NOTE Confidence: 0.91087019443512

00:36:35.560 --> 00:37:06.350 No shippons group attempt it gave a relatively high dose of antenna stat and we were unsure whether that dose was a dose that was going to be tolerable. But in their hands when they were looking at what happened at the tumor microenvironment level. the CD 8 positive cells really didn't shift. But what they did. See was a decrease a small decrease in regulatory T cells. But a substantial decrease in MDS ease in this initial cursory profiling that they had done in their paper to look for mechanism.

NOTE Confidence: 0.9231276512146

00:37:06.350 --> 00:37:36.520 So based on those data Liz Jaffe, an I move forward in a collaboration interested in exploring this in pancreatic cancer as well. And this is Brian Christmas, who is a graduate student in the lab. This is his thesis work, which he had funded by a less garden, Grant and so we were lucky to be able to try to elucidate. This a little bit better in pancreatic cancer as well, and we initially saw a very discrepant results than what had been previously demonstrated.

NOTE Confidence: 0.878160297870636

00:37:36.520 --> 00:37:47.960 By Shippons hours group we didn't see increases or decreases in MDS ease. We instead saw increases in MDS ease when these animals were treated with antenna stat.



NOTE Confidence: 0.902291834354401

00:37:48.490 --> 00:38:20.980 Further profiling of these my Lloyd drive suppressor cells did show that there was a potential decrease in the MMDSE compartment, which arguably maybe the more immunosuppressive cells. But the substantial number of cells that were MDSE's were far greater in terms of the number of GM DSC's that were present compared to MMDS ease but then Brian moved on to try to assess their functional status. And that's where it got more interesting because when he did Coculture assays with CD 8 positive cells.

NOTE Confidence: 0.900627434253693

00:38:20.980 --> 00:38:44.240 Antenna stat treated cells in these animals were able to survive an CD 8 positive cells were able to propagate where they were completely suppressed in any arm that didn't contain antenna stat and arginase activity, which is also a circuit of functional. MDS ease also decreased substantially both in the G and the MMDSE compartment.

NOTE Confidence: 0.921420216560364

00:38:45.130 --> 00:39:16.020 The functional studies of this combination in the animals also showed an improved statistically significant improvement in survival for these animals and based on these data. We have moved forward on a clinical trial in pancreatic cancer. There also is a cholangio carcinoma cohort to this as well because our Phase 1 study actually had a cholangio response, but we've been very interested in the pancreatic model based on what was shown by Brians work. This study has a leading period of 2 weeks of intense dad alone.

NOTE Confidence: 0.900062739849091

00:39:16.020 --> 00:39:38.560 With biopsies that are done a baseline and only after in tennis dot therapy for us to try to isolate if we can. We don't know if that biopsy is a little too early. But we didn't think in pancreatic cancer. We could get away with longer than 2 weeks have just antenna stout therapy. So 2 weeks of antenna stat with paired biopsy's before and after and then a third biopsy done a month later after the patients are started on nuvola mab.

NOTE Confidence: 0.930196940898895

00:39:39.590 --> 00:39:54.300 This is unpublished data but is the early results of our study 22 evaluable patients have been enrolled in this study, and we had had 3 patients who have had partial responses to this combination and none of those patients were microsatellite unstable.

NOTE Confidence: 0.919274628162384

00:39:55.030 --> 00:40:27.200 All three of those patients have had durable responses to therapy. We still have a patient who is presently on it over a year and a half on study and this patient who was our first responder had you can see here as her lung lesion disappeared. She had an almost complete response to

therapy with normalization of her CA 19, nine and we actually lost this patient. She passed away, not because your cancer progress. But a year after she came off of therapy and was just hanging out 'cause you don't want to come into Hopkins anymore.

NOTE Confidence: 0.91659551858902

00:40:27.200 --> 00:40:53.210 Get treated, she decided to get surgery to repair a hernia and ended up having a septic complication of her hernia surgery and so, but all three of the patients had relatively durable responses that we've been excited about. That's still only a 14% response rate, and so trying to identify what about those patients made them be the patients that responded is really our next challenge and we're hoping that are biopsies will will help with that.

NOTE Confidence: 0.907303094863892

00:40:54.150 --> 00:41:27.360 And we're not the only People that are seeing responses with this H doc plus PD. One combination strategy so this is Ryan Sullivans, an abstract that was presented at it as an oral plenary session at ACR just a couple of months ago, he presented data looking at pretreated Melanoma, so these were patients that had previously been exposed to PD. One therapy and progressed on PD. One therapy that then went on to get combination therapy within tennis. Dot P D1 and their response rate. You can see here in the waterfall plot. They had multiple patients that did very well with resist criteria responses.

NOTE Confidence: 0.931659281253815

00:41:27.360 --> 00:41:37.240 The response rate of about 20% and the spider plot shows. The duration and durability. Of those responses to with the median duration of response in those patients being 13 months.

NOTE Confidence: 0.922642529010773

00:41:38.170 --> 00:42:08.120 They have been trying to identify biomarkers as have. We we've actually been working in concert with them looking at our samples and their samples. They looked at circulating CD 8 positive and MMDS season found that there did seem to be a decrease in MMDS ease in the periphery for patients that were responders. But there is nothing productive at baseline in this patient population so far. That was able to predict the 20% that did well and the added 20% that had stable disease.

NOTE Confidence: 0.931185007095337

00:42:08.700 --> 00:42:36.540 And in lung cancer presented earlier this year, same combination in lung cancer that had previously progressed on PD. One therapy again. We see multiple patients that had durable responses to treatment with combination therapy. But a response rate of only 10%, though 50% of patients had stable disease, so again another place we're trying to identify who these People are and how we find them is going to be key, as we try to move these therapies forward.

NOTE Confidence: 0.918175876140594

00:42:37.280 --> 00:43:02.680 They had peripheral blood on these patients and looked at baseline monocyte levels. There did seem to be a trend towards high minus site levels at baseline with those patients potentially having a target present to decrease and being on trial longer with enhanced durability. But that was not statistically significant and you can see, there were plenty of patients that had high monocyte levels that didn't do well on the trial as well.

NOTE Confidence: 0.909522294998169

00:43:03.300 --> 00:43:35.150 And then the last working hypothesis that we're working on presently is the idea that it may be a component of M1K modulation. That is important in tennin that is known to affect M1K decrease. M1K expression and M1K expression has been associated with resistance to PD. One therapy and so looking at for paired biopsy. So it wasn't very many biopsies is very hard to make anything out of it, but doing an unsupervised analysis of the for responders what they found was in those patients.

NOTE Confidence: 0.91476845741272

00:43:35.150 --> 00:43:46.300 There was decreased in M1K when we did a n1n super or they did an unsupervised analysis. And so that's just one working hypothesis. But I'm clearly there's a lot of complexity to that as well.

NOTE Confidence: 0.891573369503021

00:43:47.750 --> 00:44:19.340 And before I end I don't want to forget about the D methylating agents. There is a lot more clinical data. That's present with each doc inhibitor combinations. But we remain interested in the idea of looking at D methylating agents as well, and Anthony Alqueria. Nyarko running a clinical trial looking at quite a sight of being in combination with devala mab in patients with pancreas had a cellular or cholangio carcinoma that trailers presently accruing and we anticipate that it will finish accruing in the next year.

NOTE Confidence: 0.921647310256958

00:44:19.340 --> 00:44:49.430 But we hope that we'll see some benefit in that patient population or one of those patient populations as well. And we're about to report out on this clinical trial, as well. That was designed with n1ta to look at whether we need an H dot component? Do we need a D methylating agent or is it. The combination that might be most beneficial? When we try to do immune modulation so this was a clinical trial that was actually designed as a phase 0 study, so each one of these arms only has 5:00 to 8:00 patients in it.

NOTE Confidence: 0.923763036727905

00:44:49.430 --> 00:45:07.960 And is designed with the primary end point of looking at tumor, infiltrating lymphocytes to determine which of these combinations have the most impact on tumor infiltrating lymphocytes that then can

be moved forward into a properly powered Phase 2 study, and again we expect that study to report out by later this year.

NOTE Confidence: 0.916475176811218

00:45:09.980 --> 00:45:40.650 I didn't want to close without mentioning all the other epigenetic agents that are out there that we do not have as much data regarding and that the epigenetics community is just starting to work through there are drugs in the clinic. There are specific and nonspecific chromatin remodeling remodelers. There are epigenetic readers like Chromodomain, Inhibitors, where there are hints that there may be a mean a modular. Tori impact as well, but all very early pre clinical work.

NOTE Confidence: 0.936434864997864

00:45:40.650 --> 00:45:51.280 And so these are areas where in the next 5 or 10 years. I think we in the epigenetics world are really interested in trying out some of these new agents to see what their impact is as well.

NOTE Confidence: 0.942246735095978

00:45:52.530 --> 00:46:23.930 So In conclusion, I hope that I have both given you a flavor for what is happening in the epigenetics modulation world but also some enthusiasm for the fact that even though these drugs are so non specific and when it comes to an era of science, where we're trying to understand such detail about cancer biology drugs like epigenetic drugs can be really dissatisfying and we understand that because there's so broad in their effect. But maybe this breath is actually.

NOTE Confidence: 0.939738094806671

00:46:23.930 --> 00:46:55.900 What is beneficial when we are trying to work with complex systems like the immune system or chemo resistance and so these drugs. I still believe have significant potential if we figure out how to use them better and which patients we should use them in. But we need to make sure that our clinical trials are designed in such a way where we can really answer. Some of these questions with the one or 2 responders that happen on each of these studies. So we can learn better. What is actually happening when we combine these drugs and with that I'm just going to think?

NOTE Confidence: 0.933865666389465

00:46:55.900 --> 00:47:27.450 The many People over the last 10 years needa you came in a little late. But I already thanked you but I'm going to thank you again for being a fantastic mentor and bringing me into this field. We always have to think our patients when we talk about this kind of work, they have been through patients and their families through many negative clinical trials to just get to the point now where we might be able to benefit them and we've had a fantastic research team both at Hopkins and across the country and we've even had a couple of International.

NOTE Confidence: 0.915659129619598

00:47:27.450 --> 00:47:33.320 Collaborators that have been really, really helpful, so with that I will take any questions.

NOTE Confidence: 0.887442529201508

00:47:38.270 --> 00:47:43.280 Thanks a lot for a wonderful talk, we have time for a few questions or comments.

NOTE Confidence: 0.858624339103699

00:47:43.990 --> 00:48:06.380 I'll start clearly you know, there's activity to see activity in IO. Refractory patients is huge for the lung cancer. That group was here actually talk to us recently. And why would monocytes have an effect. I guess it's hard enough to know what the regular negative regulators are for the IO response to begin with, and, of course, what's the epic genetic therapy is modifying? Why wouldn't monocytes have a role.

NOTE Confidence: 0.925475299358368

00:48:06.890 --> 00:48:37.080 So the the interest in looking at the monocyte group was to try to subdivide with the MDOC story. That was coming to look in the periphery and to see whether there was a monocytic component to it, and from my conversations with them. It looked like they were looking at many different components and that was the one that hit when they were looking at that analysis, but I think that that's the challenges that we don't understand. Whether that's really the underlying story or not, and why.

NOTE Confidence: 0.917560636997223

00:48:37.080 --> 00:48:44.410 That would be the appropriate biomarker and more and more. I think People are are believing that what we need is as needed to find in her work.

NOTE Confidence: 0.901880323886871

00:48:44.960 --> 00:49:15.110 Biomarkers signatures that take into account multiple different aspects multiple different immune cell subsets or you'll get that familiar tissue pre and post studies. We will but we are, but the challenge. Of course, is in the pancreas study. We have 3 responders. Luckily, those 3 responders have 3 biopsies each but we have a few patients with stable disease. But when the numbers are small, even when you do these broad explore expirations. It's very hard to know how much of this is just accidental hits or not so pooling.

NOTE Confidence: 0.91543972492218

00:49:15.110 --> 00:49:46.640 I think the ability to pull the data. We have with the Melanoma people with a long People. That's going to be where we might get bigger numbers that would be more informative absolutely truly great talk in your last slide. You mention it. The ability that maybe even looking specifically at chromatin remodelling as a as a means to modify or enhance the

immune response about 25% of cancers actually have mutations in that in that particular region.

NOTE Confidence: 0.899276256561279

00:49:46.640 --> 00:50:21.650 You know those jeans is there any evidence that those mutations can drive response or resistance immune therapies so there have been a few studies that have looked at for example, Easy H2. Mutations and small cell lung cancer. There hasn't been a great correlation between the agents that we presently have to use and the mutations that occur in the solid tumor, setting to mutations where there has been some potential pre clinical work that looks at those tattoo mutations, but it's.

NOTE Confidence: 0.89408153295517

00:50:21.650 --> 00:50:38.540 It's like less than 1% of tumors that have that particular mutation so I think they end up causing such widespread dysregulation that once you've got that Mutation just reversing that one piece may not be enough.

NOTE Confidence: 0.90846836566925

00:50:44.590 --> 00:51:16.160 You will thanks so much for being here and really presenting all the work. You've done in this field, it has come a remarkable way. Let me ask your comments on differences between D methylating in each deck inhibited in the pre clinical work, they seemed to be almost comprable, yet clinically there seems to be a little bit of difference in signaling, especially in the MENA model. Tori behavior can you comment a little bit more on that so I'm I'm not sure I would agree with you? I don't think that the D methylating agents have been.

NOTE Confidence: 0.897013008594513

00:51:16.160 --> 00:51:46.270 Properly tested with the right drugs within combinations with immunomodulatory agents. Where is the H deck inhibitors have been and I think for a long time that was because of where those drugs were in their development, so these were more business strategies. A society and decided being were already off patent and so nobody was really interested in using those drugs so the Goddess. I did mean study that we're talking about that. We have in GI cancers. There's a similar ovarian cancer study that's going to report out I think those.

NOTE Confidence: 0.915591180324554

00:51:46.270 --> 00:52:00.120 Those data are still developing and we don't know if they're going to be as interesting or not 'cause again. The response rate. Even with each Jack Inhibitors looks to be in that 10 to 20% of refractory patients and so I think I just don't think we have the answer to that question yeah.

NOTE Confidence: 0.881166696548462

00:52:02.420 --> 00:52:09.030 Great any other questions, saying that Niall thank you for a wonderful talk and enjoy having you here. The rest of the day. Thank you.