

WEBVTT

NOTE duration:"00:51:56.9280000" language:en-us

NOTE Confidence: 0.870561599731445

00:00:01.530 --> 00:00:21.540 Welcome everyone to grand rounds. This is certainly a unique venue for us to do this. But it's it's very professorial here. You know it's been mentioned the patient right down here and you're I'd probably feel more comfortable with that, having a patient down here, but it's really an honor to start the screen.

NOTE Confidence: 0.852122724056244

00:00:22.330 --> 00:00:42.340 The full hour to have Pat LoRusso, he doesn't need any introduction to this crowd. Certainly the director of our early drug development group and the premier drug developer that I know currently and she's going to talk to us a little bit about some of her work, she's the associate director.

NOTE Confidence: 0.829012930393219

00:00:43.130 --> 00:01:03.140 Kid X and just talk about NCI 10020 allapaur alone or a combination within 10 solution map in patients with her 2 BRCA mutated breast cancer and it's going to be translation. And it's very best from the bank for the dead center backs up at. Thank you so thank you. All for coming. I've never given a talk with my entire audio.

NOTE Confidence: 0.898797869682312

00:01:03.930 --> 00:01:23.940 And I am so this is this is a first for Maine. Let me I didn't realize it was set up for right handed people, giving this talk, for a couple reasons, so first of all is part of the acd team at the Cancer Center. Charlie's been making a push towards trying to integrate probe.

NOTE Confidence: 0.940538227558136

00:01:45.540 --> 00:02:05.550 And essentially doing it, I think wouldn't you agree Joseph since the last 4 years and so I'm just going to show you a little bit about that and I'm going to use 10020, which is a trial that I'm currently overseeing which is a multi institutional national North American trial as an example of that.

NOTE Confidence: 0.935334026813507

00:02:06.340 --> 00:02:26.350 So the other reason is a little bit selfish. We're getting some really interesting results with NCI 10020. We're going to be getting into that in the next few minutes and it's a real exciting drug combination. That's extremely translation. TLE and I think has the potential to answer a lot of very important question.

NOTE Confidence: 0.920244634151459

00:02:27.140 --> 00:02:47.150 DNA repair in immunotherapy because it's so heavily biomarker, driven with multiple serial biopsy's and yet, all of the patients that have been recruited in the United States are outside of Yale. Yale has not found. One Bracken Mutant patient to put on this trial and it's been open.

NOTE Confidence: 0.926200091838837

00:03:08.740 --> 00:03:28.750 And the care centers that happened to be listening to grand rounds today. See one of these patients will consider this trial. I know it's heavily burdened for the patient. But I think we need to start answering these kind of questions that we're going to make a huge impact in the treatment of Bracken mutant breast cancer with an emphasis on triple neck.

NOTE Confidence: 0.907799661159515

00:03:29.540 --> 00:03:49.550 But it also recruits receptor positive patients my disclosures. So just to give those that don't know a little bit of background. This trial is being funded off of a UN one that I brought with me. When I came to Yale and it's fortunately or Unfortunately up for re competition. I'm in the active writing mode.

NOTE Confidence: 0.926666021347046

00:04:11.140 --> 00:04:31.150 Over North America for all of our trials and that's why the UN one is considered a really good mechanism for multi institutional trials because it has so many sites. There's about. I think 70 sites now total that are involved in the UN one mechanism, so you can folk.

NOTE Confidence: 0.899503648281097

00:04:52.740 --> 00:05:12.750 2 trials are run through this mechanism, so this is our little consortium. Yale is the mother ship for the consortium. We have 5 sites that we fund off of RUM one. Currently we have UCSF UCSD Karmanos, Vanderbilt and Yale.

NOTE Confidence: 0.901235580444336

00:05:13.540 --> 00:05:33.550 We chose Vanderbilt because of their funding mechanism through the NIH. This is a good mechanism to take concepts that are being funded off that have been developed through our one spores peo ones, and enter them into the clinic. It helps fund those clinical trials and then you either get supplements or apply for 20 ones or are.

NOTE Confidence: 0.916851401329041

00:05:34.490 --> 00:05:54.500 For the biomarkers UCSD we chose because of its Hispanic population. You See and because it had phenomenal science. Phenomenal science with an emphasis in hematology and UCSF. We chose not only for its population, but also because it was significantly funded peer review fun.

NOTE Confidence: 0.934240937232971

00:05:55.290 --> 00:06:15.300 We felt that we would get a lot of concepts through UCSF as well. However, we've been somewhat disappointed. We're not going back in with UCSF. We will remain with UCSD they've been a very good recruiting site for us and what we decided to do was bring onboard University of Oklahoma so we're going in with University of Oklahoma.

NOTE Confidence: 0.902893364429474

00:06:16.090 --> 00:06:36.100 Maybe one of the few grants funded through the NCI that is a clinical grant that services. A large Native American, and rural American population. University of Oklahoma is the number one recruiter to the lab scratch with the NC. TN mechanism as well as to GMG dochterman tell the Cancer Center director there.

NOTE Confidence: 0.925835967063904

00:06:36.890 --> 00:06:56.900 Kids Angie OG but 20% of their recruits 20 to 30%, depending on the year are Native. Americans we feel that we can learn a lot not only at Yale. But through our consortium because they have a phenomenal navigation system. That's funded through the federal government through supplemental funds in tired on their CC SG.

NOTE Confidence: 0.918791532516479

00:06:57.690 --> 00:07:17.700 To help navigate to bring in the rural Americans and the Native Americans to their site to their clinical trials. They also have a stellar bio bank and it there. They pretty much are associated with the bio bank right down the street. If you lookout their window you can see it and base.

NOTE Confidence: 0.927014112472534

00:07:18.490 --> 00:07:38.500 Is the entire state of Oklahoma and it brings in bio specimens from patients that are not only recruited to clinical trials. But there are also diagnosed with cancer, not only at the University of Oklahoma. But throughout the entire state. And when I went there. I actually like I liked it. Tulsa is a pretty cool city so anyway.

NOTE Confidence: 0.916412711143494

00:07:39.290 --> 00:07:59.300 Just to talk a little bit more about what we as a consortium are 5 site consortium have done for the early Therapeutics. Clinical trials grant what we have done is primarily non solicited letters of intent. So what we mean by that is, we come up with an idea on our own not something that the NCI is so.

NOTE Confidence: 0.920742630958557

00:08:20.890 --> 00:08:40.900 To Toots clinical trials evaluation program in hopes that they will help support it. The the reason we use. Setapp is because they have a huge pharmacopia of drugs. So it gives us access to drugs that we might not necessarily have access to number one, but also most of what we do our.

NOTE Confidence: 0.937820255756378

00:08:41.690 --> 00:09:01.700 Chance and it's somewhat difficult to get 2 or 3 different drug companies to give us each independently a drug to do an art studies. But through the NCI. It's much easier to combine multiple different drugs for multiple pharmaceutical companies. So this is just showing you where we have been for letters of intent.

NOTE Confidence: 0.919192910194397

00:09:02.490 --> 00:09:22.500 Move the grant here in 2014 and that's actually when the UN one started and as you can see in total. We've submitted 35 letters of intent to the NCI based on concepts that we wanted to bring into the clinic. And if you see here. The majority of them are dark there blue they?

NOTE Confidence: 0.93419075012207

00:09:23.290 --> 00:09:43.300 Most of the letters of intent that have come from our consortium have come from Yale University. But more importantly than that and I think this is an important slide of those letters 35 letters of intent that we've submitted 17 of them have been approved to advance forward into clinical trials and if you look.

NOTE Confidence: 0.925021171569824

00:09:44.090 --> 00:10:04.100 The ones that were 35 that were submitted 17 that were approved 13 that were approved from Yale. So yeah, it is about a 90% track record and getting concepts approved through the NCI and as will be looking in the next several minutes. The reason why a couple of them were not approved was not because the NCI.

NOTE Confidence: 0.925597608089447

00:10:04.120 --> 00:10:24.130 I didn't like our concepts, so the average 'cause I'm writing the grants and I got these statistics yesterday. The average number of non solicited allies that are approved is 14%. So we're about 90%. So we're well above were well above the national average of letters of intent that are approved and I believe.

NOTE Confidence: 0.931394338607788

00:10:24.920 --> 00:10:44.930 The science and the teamwork that we bring on board and I'm going to show you example of that with NCI 10020. This is the first of 2 slides busy slide. I don't expect you to read it. But I think it shows us that what we're focusing on with our letters of intent is promoting growth of junior faculty.

NOTE Confidence: 0.927382409572601

00:10:45.720 --> 00:11:05.730 Make them develop into clinical researchers Joseph Kim and I have taken the road through this journey. I think Anne I'm very proud to say that the auditors that come from the NCI are extremely impressed. Now,

with Joseph Kim and they even indicated to me that they feel that he's 1 of the most solid clinical investigators.

NOTE Confidence: 0.928146123886108

00:11:06.520 --> 00:11:26.530 Have throughout the entire network. Not that I had anything to do with it. But I'm proud that he's had 3 protocols in 3. Los Joseph keep up the good work. But what we do is we try to mentor through this mechanism, so the senior investigators typically do not submit the yellow eyes and that's also extremely diff.

NOTE Confidence: 0.947767555713654

00:11:27.320 --> 00:11:47.330 The national average, we're about 98% junior faculty driven the average is about 12 to 15%. Junior faculty driven so we're really trying to educate our junior faculty and teach them how to do clinical research understand Translational research and work with basic science.

NOTE Confidence: 0.90646231174469

00:11:48.120 --> 00:12:08.130 Steps forward I point out these 2 because you saw Yale got 13 of the 17 allies that were approved and 2 of the yellow eyes that we got that were disapproved were not disapprove because they didn't like our concepts. They were initially approved by the NCI but Unfortunately, Astra Zeneca could not give us.

NOTE Confidence: 0.907150566577911

00:12:08.920 --> 00:12:28.930 Twitter remove that concept forward and by the way they decided to develop that concept in house and then the second. One was a trial from on our side and and we could not get the Atisa Loser map through Genetec because I believe that they were moving that concept in house as well.

NOTE Confidence: 0.920752644538879

00:12:29.720 --> 00:12:49.730 Sometimes our concepts are great and they're so good that companies want to move them internally, so that they can actually control. The data and move it through at a much faster pace and this is our cruel and I think our accruals really good so last year, we put on about 108 patients on the UN one trials.

NOTE Confidence: 0.914197325706482

00:12:50.520 --> 00:13:10.530 And I talked to the NCI last year last year, the end, the entire network. All 70 plus sites put out 700 patients. So we're 2nd probably I think Dana Farber. May I put on a couple more patience than we did. But we're actually doing quite well and as you can see for for the most part, Yale has.

NOTE Confidence: 0.922544956207275

00:13:11.320 --> 00:13:31.330 Instrumental in recruiting most of those patients to these trials could also be because we have invested interest. 'cause most of the ideas that have been driven from our consortium have come out of Yale University. So now I'm going to focus the rest of my talk on NCI 10020, which is the protocol number for the clinical trial.

NOTE Confidence: 0.900263905525208

00:13:32.120 --> 00:13:52.130 I did with the solicitation application so shortly after I got here at the NC I was looking for concepts to lose a map, which was one of the immune checkpoint inhibitors from Jinan Tech and I'd always wanted to look at an immune checkpoint inhibitor in combination with apartment had better be.

NOTE Confidence: 0.928630173206329

00:13:52.920 --> 00:14:12.930 Outback then even before we really had a lot of in depth science that DNA DNA repair was going to be pivotal and was going to be an important component in terms of response and possibly even potentiation or synergy in combination with immune checkpoint inhibitors so at that time, I had a young young junior.

NOTE Confidence: 0.918556988239288

00:14:13.720 --> 00:14:33.730 By the name of Joe McLaughlin, he was an instructor at the time and Mario who is one of the world's best immunologists. I mean, we're very lucky to have Mario here as a medical Oncologist, whose focus is immunology. Kurt Shelper, who was a young coming starred this was before the Translational Research Lab.

NOTE Confidence: 0.892388582229614

00:14:34.660 --> 00:14:54.670 Telab was developed I believe he was still under doctor rims direction. At that time in his lab Joanne Sweezy, who I had met and I knew was interested in DNA repair and then you share who was the bio statistician that was the umbrella biostatistician for RUM, one because the?

NOTE Confidence: 0.907867848873138

00:15:16.260 --> 00:15:36.270 So that we could ensure safety of the drugs. Watt Translational Biomarkers. We were going to need how many biopsy's we would need in order to be able to really, truly answer. What are the effects of apartment Heavener on the immune micro environment and the tumor and the tumor and does this have any in.

NOTE Confidence: 0.918276190757751

00:15:37.060 --> 00:15:57.070 On an immune checkpoint inhibitors benefit in these patients an also finally does do the 2 drugs in combination impact positively or negatively and can, we identify whether or not. There are biomarkers of response or resistance with this 2 drug combination. We went in with the Lipper.

NOTE Confidence: 0.90688568353653

00:15:57.860 --> 00:16:17.870 That was the only part inhibitor at the time that the well actually we went in with the biomarin compound, which is now owned by I think I don't know who its own by now. I think Pfizer but that compound was purchased by the drug company shortly after we submitted this. The company pulled the drug out of the pool.

NOTE Confidence: 0.877051770687103

00:16:18.660 --> 00:16:38.670 They had the Lipper ever abt 888 at the time and that was the only part inhibitor that the NC I had, and I didn't know how I could manipulate to get a lap rib. So we went with Phillip are because that's what the NCI told us we had to do the questions. We were trying to ask when we submitted that LOL. I was what is the spec?

NOTE Confidence: 0.868364989757538

00:16:39.460 --> 00:16:59.470 Micro environment in these Brad commuting tumors, nobody really understood the true profile. At that time do these tumors do these Bracken mutant breast tumors have a unique environment. Immune my immune micro environment relative to non braka mutant tumors? What is the mutational burden of these brat?

NOTE Confidence: 0.883458018302917

00:17:00.260 --> 00:17:20.270 Do parp inhibitors increase the tumor mutational burden possible. Neo Anna and potential neoantigens and as a result could they impact positively on the treatment response? What changes do occur to the immune infiltrate after we give apart inhibitor and does the combination of apartment hitter and an anti?

NOTE Confidence: 0.900637328624725

00:17:21.060 --> 00:17:41.070 Better improve the overall response rate, and duration of response over either. Parp alone or the immune checkpoint inhibitor alone. Our hypothesis for 3 that purp inhibitor in patients with triple negative disease in HDR deficiencies will increase the mutational load and Neo Antigen.

NOTE Confidence: 0.903600931167603

00:17:41.860 --> 00:18:01.870 Presentation that purp inhibition will increase the immune infiltrates and T cell activation in the tumor by increasing the mutational load or neo antigens. And then finally that the immune checkpoint inhibitor will be upregulated or PD. L one that target will be upregulated in response to the immune infiltrates.

NOTE Confidence: 0.932742953300476

00:18:02.660 --> 00:18:22.670 Page one interferon gamma signals caused by the Parp inhibitor, thereby increasing tumor. Neo epitopes and then potentially increasing the response rate or at least maybe potentially increasing the duration

of response of the 2 drugs in combination. So we went in with a little bit of background first of all.

NOTE Confidence: 0.927706301212311

00:18:23.460 --> 00:18:43.470 Triple negative breast cancer and we have subsequently changed it because the patient population was challenging and to begin to get more patients were just taking braka mutants. Triple negative or receptor positive patients with the amendment, but ironically, most all the patients that have been recruited or triple negative. We knew, at the time.

NOTE Confidence: 0.925869584083557

00:18:44.260 --> 00:19:04.270 Breast cancer accounted for about 2025 percent of all breast cancer about 20% that it was a poorly differentiated tumor an at the time that we brought this concept forward there really no standard therapy in the meta static setting for triple negative breast cancer. I don't think that's changed, too much. But what we also knew was said if you looked.

NOTE Confidence: 0.872876822948456

00:19:05.060 --> 00:19:17.250 Cancer patients and you looked at you sub sub-segmental subtype them. Interes poops sorry about that? How do I just suck I'm going the wrong way?

NOTE Confidence: 0.946461737155914

00:19:18.170 --> 00:19:19.820 It's a very sensitive.

NOTE Confidence: 0.917950391769409

00:19:21.580 --> 00:19:41.590 I don't think I'm yeah, right here and you looked at the subtypes. You looked at ER positive her 2 positive and triple negative what you identified, was that there was an increased number of tumor. Infiltrating lymphocytes in both the stroma as well as in the tumor relative to the in triple negative disease relative to the other so.

NOTE Confidence: 0.924309432506561

00:19:42.380 --> 00:20:02.390 Ask answer when we knew that Tills for increased but the question was what type of T cells are these and this was one of the things we felt it was important to know if we were going to better understand what we were doing with this drug combination. Kurtz lab had shown that triple negative disease or triple negative breast cancer.

NOTE Confidence: 0.894850313663483

00:20:03.180 --> 00:20:23.190 Lymphocyte infiltration and if you look here. This is breast cancer with low tells and as you can see here. This is breast cancer with significantly high Tills. It had an increase in panties cell marker CD 3, but also of the side attack succeed Cytotoxic T cells CD.

NOTE Confidence: 0.891288220882416



00:20:23.230 --> 00:20:43.240 8. So when you saw here relative to Herman Receptor positive disease with both C 3 as well as a set of toxic T cells. CD 8 using QF statistically significant. Those P values are huge. There was a greater amount of both CD 3 and CD 8 cells in.

NOTE Confidence: 0.905255198478699

00:20:44.030 --> 00:21:04.040 Breast cancer, we also had data from lawyers manuscript from JC oh that showed that tumor infiltrating lymphocytes were actually prognostic in patients would triple negative breast cancer, so if you look down here in the in the in this patient population in terms of overall surv.

NOTE Confidence: 0.91573041677475

00:21:04.850 --> 00:21:24.860 Those those patients whose breast tumors had lymphocyte predominant breast cancer had an overall survival advantage over those patients tumors over those patients whose tumors did not have lymphocyte predominant breast cancer and it was a predictive biomarker essentially of survival.

NOTE Confidence: 0.916674554347992

00:21:25.650 --> 00:21:45.660 Hey at Allen David rims lab had shown around the same time or shortly around the time that we were putting this together that there was an Association with PD one expression. It was associated with trip. Both triple negative breast cancer and in elevation and tumor infiltrating lymphocytes using 3 independent antibodies and.

NOTE Confidence: 0.931165456771851

00:21:46.450 --> 00:22:06.460 Cohorts of patient tumor samples they were able to demonstrate a statistically significant increase, and PDL one expression in those triple negative breast cancer samples that had elevated levels of pills and then finally again in that paper. She also showed that.

NOTE Confidence: 0.889699637889862

00:22:07.250 --> 00:22:27.260 PDL one protein as well as RNA were higher in those tumors that had lymphocyte predominant. In those tumors that were lymphocyte predominant versus those that were not lymphocyte predominant as you can see here looking at both the the tumor itself using Acqua's.

NOTE Confidence: 0.910234272480011

00:22:28.050 --> 00:22:48.060 The stromal the stromal population of cells and Kurt with a large boost. I went on to show that in those triple negative breast cancer samples bracket deficiency was was a real positive marker of those patients that were going to.

NOTE Confidence: 0.889261841773987

00:22:48.850 --> 00:23:08.860 An increase in Neo Anagen load in an increase in inflammation and they actually did this by using various RNA signatures

and as a result, basically what this showed is of those triple negative tumors and patients that had triple negative disease. Those that had Bracken Mutant tumors the.

NOTE Confidence: 0.899161517620087

00:23:09.650 --> 00:23:29.660 Demonstrated in increased adaptive immune response over the triple negatives that were non braka mutants. Around that time, we started getting some of the preliminary early phase data from the atisa, losing mab. OSCE story and what it showed in this is just looking at breast cancer patients that were.

NOTE Confidence: 0.924717903137207

00:23:30.450 --> 00:23:50.460 Treated with the Teso in the early phase study, there was an unconfirmed response rate in monotherapy of about 24% with 3 partial responses and 2 complete responses with the duration that was up to about 42 or so weeks and the progression free survival at 24 weeks in these patients was about 33.

NOTE Confidence: 0.914209961891174

00:23:51.290 --> 00:24:11.300 So there were several patients there were some patients that responded. Unfortunately, there were a lot of patients that didn't respond and there were no biopsies taken and we didn't really know exactly what these tumors look like or whether or not any of these tumors had anything that would be a potential predictive biomarker of monotherapy response and.

NOTE Confidence: 0.921038925647736

00:24:12.090 --> 00:24:32.100 Information around the same time or shortly before that there was in a preliminary Phase 2 trial that was published in Lancet, a few years before we put this through and it showed that Illapa Rib demonstrated an improved benefit and patients that had braka mutant breast cancer. This was a preliminary.

NOTE Confidence: 0.932092487812042

00:24:32.890 --> 00:24:52.900 The trial, it looked at 2 different sources. The higher dose. Obviously had a better progression. Free survival than the lower dose. But even with this. The overall response was not earth, shattering and exciting, but it was better than anything. We had for these patients and so while we were submitting our protocol the phase 3.

NOTE Confidence: 0.895014762878418

00:24:53.690 --> 00:25:13.700 Was moving forward looking at Elappara versus standard of care in this bracket. Mutant patient population. So we submitted the proposal and it was looking at Philip Arrub and atisa loosen map. We started with Joe McLaughlin. And Unfortunately, he moved on, and I inherited the I inherited the protocol. So we

NOTE Confidence: 0.916809320449829

00:25:14.490 --> 00:25:34.500 Forward and there's something that I'd always been interested in I've been interested in breast cancer ever since. I started on Cology and spent a lot of time developing cancer drugs that move forward and move forward to the FDA in this arena. So we initially started with a 3 armed trial. We wanted to know what did the Model Therapy Department.

NOTE Confidence: 0.903286218643188

00:25:35.290 --> 00:25:55.300 What did the monotherapy pedia one inhibitor? Do and what did the combination do and the only way we could look at this was initially treat with monotherapy and 2 arms in a combination and then subsequently any of these patients in the monotherapy arm. Add progression could be crossed over before we treated these patients.

NOTE Confidence: 0.90870988368988

00:25:56.090 --> 00:26:16.100 They had a baseline biopsy subsequent to that they were randomized, we didn't randomize it first 'cause. We were worried about fallout. We treated them at 6 weeks. We did another biopsy and then if they progress. They could go on to crossover if they didn't progress. They maintained and if they're on the combination. They maintained and then we continue them.

NOTE Confidence: 0.919857263565063

00:26:16.890 --> 00:26:36.900 Synonym progression we did another biopsy, thereby allowing us to understand the various components in terms of biologic benefit that hopefully would predict for therapeutic benefit in the future but at the same time, we really didn't know what pelipper of did or the Parp Inhibitors and there wasn't a lot of data in the literature and so.

NOTE Confidence: 0.903093993663788

00:26:37.690 --> 00:26:57.700 Dance weezy came in so we were developmental therapeutics or the experimental Therapeutics program. Joanne Sweezy was the radio biology and radiation therapy program courage. Shopper was the immunology program so we brought 3 different programs together with the dart the phase one dart to move this forward.

NOTE Confidence: 0.884584426879883

00:26:58.490 --> 00:27:18.500 My neck but we had to go back to the bench 'cause. We wanted to understand what was it that these parts. Inhibitors really did, and that's where Joanne came in. It was unknown. What part than hitters did to neo antigen load that was a question, we wanted to ask it was unknown what they did immunologically to the micro environment in the tumor. It was unknown what the?

NOTE Confidence: 0.911630690097809

00:27:19.290 --> 00:27:39.300 Benefits of the combination would be and if it all, there would be a therapeutic benefit benefit of the combination could we determine why so she went back into the bench and the first thing we had to do is figure out where we could sell lines to study this well. There aren't a lot of complementary braking, mutant cracker wildtype cell lines.

NOTE Confidence: 0.895453274250031

00:27:40.090 --> 00:27:59.620 HCC 1937 and what which is Abraka Mutant cell line and what she had to do was complemented so that there was an assimilation of Abraka wildtype versus Abraka Mutant cell line and as you can see her lab did a really good job of complementing this cell line to make it bracket complemented or.

NOTE Confidence: 0.908148348331451

00:28:00.630 --> 00:28:20.640 OK, well, somebody slab did this thank God so then what she wanted to do was try to you know separate out. These cells so that she could try to understand exactly what was going on so she took the bulk tumor. I might be saying this wrong, so thank God she's in the audience, she single cell cloned these cells.

NOTE Confidence: 0.887246251106262

00:28:21.430 --> 00:28:41.440 Wendy's single cell clones for 3 weeks with Philip Arrub went back and single cell clone them again. And then after she single cell clone them. She took each of these independent clones and looked at DNA sequencing. RNA sequencing looked at mutational load mutational signatures in Neo Ann.

NOTE Confidence: 0.880029737949371

00:28:42.230 --> 00:29:02.240 Channel so bracket complemented Braka Mutants cell lines what she identified here in this in this experiment was that deliberate could induce mutations. They actually in the bracket complemented cells. If you look at the Braka Mutant. They already have a significant mutational load.

NOTE Confidence: 0.880904793739319

00:29:03.030 --> 00:29:23.040 Flip a rib really didn't change it that much. The bracket complemented had a much lower mutational loaded baseline, exposing them develop a rib increase that mutational load increase that mutational load somewhat but still not nearly as high as the mutational load of the inherent brachium.

NOTE Confidence: 0.904929220676422

00:29:44.630 --> 00:30:04.640 Free as you would expect relative to the Braka Mutant cell line, which had no molecular signature 5, but was predominantly molecular signature 3, then which she did is she exposed both of these cell lines to Velip, a rib and developed a new molecular signature 12 in these cell lines, but

NOTE Confidence: 0.900154650211334

00:30:05.430 --> 00:30:25.440 Your signature 3 in the bracket mutant cell lines was pretty persistent. Despite being treated with the Parp Inhibitor and as you can see here. The main changes were in the development of a new molecular signature that was induced by the Perp Inhibitor Velip, a rib. She then went on to look.

NOTE Confidence: 0.893652141094208

00:30:25.480 --> 00:30:45.490 That whether or not there were any change in any inflammatory or immunological changes and what she identified, was that there was up regulation of both Interferon Alpha, an interferon gamma in the braka complemented blip retreated cell lines, which was interesting indicating.

NOTE Confidence: 0.897713363170624

00:30:46.280 --> 00:31:06.290 Response but she also sought at least as well in the braking mutant cell line. She saw up regulation of both Interferon Gamma and interferon. Alpha both in the complemented as well as in the braking, mute cell lines, but she also saw was up regulation of pathways.

NOTE Confidence: 0.87101149559021

00:31:07.080 --> 00:31:27.090 Pacific to the Braca one mutation that were specific to the the bracket. Mutant cell lines. She saw a hallmark inflammatory response. She also saw enrichment of aisle 6. Jack stat 3, signaling which demonstrates a poor clinic or which.

NOTE Confidence: 0.891126811504364

00:31:27.880 --> 00:31:47.890 Is 2 a poor clinical response? Which we see in these patients if we don't treat them with purp inhibitors and she's seeing this in the bracket. Mutant cell lines and she also saw a TNF Alpha signaling response, which is indicative of key self suppression and she also saw greater up regulation.

NOTE Confidence: 0.891873121261597

00:31:48.680 --> 00:32:08.690 Amatory pathways in the Braka Mutant cells, so these are the bracket complemented cells of the bracket. Wild type and you do see with the Lipper abuse easum up regulation of the inflammatory pathways. But if you take the Braka Mutant cells, you see significant increase in the 3 and.

NOTE Confidence: 0.860306143760681

00:32:09.480 --> 00:32:15.090 Pathways CCL 5 RFIRF one as well as CD 74.

NOTE Confidence: 0.902198791503906

00:32:16.210 --> 00:32:36.220 And would also was very interesting. 'cause see gas sting was becoming very important at the time she looked to determine whether or not, she could see a differential in C gas sting and whether or not.

It was upregulated with Philip Arrub, so in this experiment what she did is she expose these cells to deliberate for a few weeks.

NOTE Confidence: 0.885627329349518

00:32:37.010 --> 00:32:57.020 And then she removed the Velip Arrub from the cell culture from the medium. She noticed as soon as she removed it. There was an upregulation in you know, see gas sting in the bracket complemented cell lines, but it really didn't change after 24 hours of being void of the velip aerobics.

NOTE Confidence: 0.909590482711792

00:32:57.890 --> 00:33:17.900 But in the mutant cell lines what she saw is when she removed the bullet bourbon after 3 weeks of exposure. There wasn't up regulation. But after 24 hours. The C gas sting response really escalated in this in vitro cell line experiment demonstrating that this was significantly.

NOTE Confidence: 0.8705775141716

00:33:18.690 --> 00:33:38.700 Mission in the mutant cell lines relative to in the complemented or wild type cell lines. Finally, she looked at up expression of chemo attractants or cytokines. So basically what she did, she exposed these lines to PBM season, it conditioned medium and then which she did.

NOTE Confidence: 0.873897254467011

00:33:39.490 --> 00:33:59.500 That the Pbo Count and the amount of cytokines are chemo attractants and she really didn't see much of anything so kind of increase in the braka complemented cell lines, but what she did see a significant increase in cytokine expression in those braka, mute this cell line.

NOTE Confidence: 0.905297100543976

00:34:00.290 --> 00:34:20.300 Or exposed to Pelipper Herb and this just showed that this part, trapping also seem to correlate with the induction of both cytokines as well as T cell migration and as you can see here. This was statistically significant for the majority of the cytokines that she that she investigated.

NOTE Confidence: 0.902075052261353

00:34:21.090 --> 00:34:41.100 Out around that time, we were she was doing all these beautiful experiments and we had this flipper of 3 arm study that wasn't doing much in terms of recruitment nationally. There were some patients that were going on. But if we were going to and at that time, we needed like 130 patients 'cause of the 3 arms study and if we were going to wait to complete the trial with.

NOTE Confidence: 0.885972082614899

00:34:41.890 --> 00:35:01.900 Probably all going to be dead or at least I was going to be by the time. It got completed and I really wanted to see what the results were, and the reason we weren't recruiting this 'cause of the Elappara

Parp Inhibitor. The elaborate data had been presented and it did come out and we knew as effect that Illapa Rib was probably at that time and prob.

NOTE Confidence: 0.910271406173706

00:35:02.690 --> 00:35:22.700 As the primary power pin hitter the most relevant parp inhibitor in the treatment of these women with germline Bracken Mutation. In these men and women that have germline braking mutations and breast cancer and so we not only. This data showed that there was an increase in progression free survival.

NOTE Confidence: 0.935472249984741

00:35:23.490 --> 00:35:43.500 Huge but there was an increase, but the thing that there wasn't was there was no overall survival advantage, So what we said was let's go back to the table. This is very common with clinical research. We need to go back and figure out how can we make this trials such that it will be attractive to patients attractive to the?

NOTE Confidence: 0.93279492855072

00:35:44.290 --> 00:36:04.300 We have to put them on the trial 'cause. It's a challenging trial requiring 3 biopsies and at the same time, you know, we can get the information that we need, and we said. We got a great response here in terms of progression free survival. But the overall survival in this patient population left a lot to be left.

NOTE Confidence: 0.890879988670349

00:36:05.090 --> 00:36:25.100 Improvement and so we also around the time had the media. Ola data, which was the combination of Elappara in combination with their value mad and what you saw here was set. The duration of response was 9 months with the combination versus 6 months for monotherapy elappara as was defined in the olympiad try.

NOTE Confidence: 0.915906012058258

00:36:25.890 --> 00:36:45.900 Progression free survival is you can see was about 8 months versus 7 months again. The combination was better than monotherapy. But we still needed to understand why although biopsies were optional in the medial a trial. We have Astra Zeneca with us here. Today I don't think they got too many.

NOTE Confidence: 0.925265848636627

00:36:46.690 --> 00:37:06.700 Cerebral biopsies in those patients so it's great to be first to the finish line in terms of recruiting your patients. But if the data is equivocal or just somewhat better and you've got all these all come are patients that you haven't defined what they really mean it's much more important to understand the tumor at this point than just the germline mutation.

NOTE Confidence: 0.906202614307404

00:37:07.490 --> 00:37:27.500 Go and look at the tumor because that's going to really help you identify so we went back to the NCI. This was a high priority trial. By then by the time this happened. The NCI had already given Kurt about one and a half million dollars to do his biomarkers so we needed to get tissue and we went back and we redefined the trial.

NOTE Confidence: 0.890419363975525

00:37:28.290 --> 00:37:48.300 And all those patients number 2. We knew that the monotherapy data for PD L one was not earth, shattering and we were worried that patients were not going to be wanting to go on. This study because that model therapy at TI. So we also knew at the time that deliberate data had been read out and it was equivalent, not superior to standard of care and.

NOTE Confidence: 0.915314733982086

00:38:09.890 --> 00:38:29.900 Between a lapper of monotherapy and the combination and we did allow because it wasn't survival. It was just progression free survival. We allowed the patients with monotherapy again to crossover to the combination of progression alot of secondary objectives. And that's where that issue comes in. We wanted to compare the progress.

NOTE Confidence: 0.906213879585266

00:38:30.690 --> 00:38:50.700 Go to any immune response that we had seen. We wanted to compare the time to treatment failure based on immune recist as well as normal recessed as well as look at overall survival and duration of response based on response rate by both immune resistant regular determine the changes in the extent of the mutational.

NOTE Confidence: 0.884853363037109

00:38:51.490 --> 00:39:11.500 In these tumors at baseline in progression evaluating characterize the changes in the extent of PD L one expression and tumor immune infiltrates and retrospectively evaluate tumors with limited immunity infiltrate which were non inflamed to determine it purp inhibitors could increase that immune infiltration and then finally to determine the.

NOTE Confidence: 0.910369217395782

00:39:12.290 --> 00:39:32.300 Best overall response of the combination and then we had our exploratory objectives. Obviously, you need to sequence to look at Neo. Antigen differences, so we were evaluating changes and candidate. Neoantigens profiles and immune inflammation signatures using DNA and RNA sequencing evaluating and characterizing circle.

NOTE Confidence: 0.888897836208344

00:39:33.090 --> 00:39:53.100 Being immune parameters by now we've even listed Abby Patel, the help us test the hypothesis that DNA repair status effects. Tumor immune interaction characterize the mechanism of action of the



Parp Inhibitor Illapa rib and explore the inclusion of patient reported outcomes because.

NOTE Confidence: 0.923947811126709

00:39:53.890 --> 00:40:13.900 Big thing in the FDA is starting to require that as we're moving forward in the FDA FDA approval of new drugs so this is essentially what our wish list of biomarkers looked like we were also initially collecting frozen tissue. But what we ran into was at sites.

NOTE Confidence: 0.867361903190613

00:40:14.690 --> 00:40:34.700 Didn't snap freeze their tissue and so that was limiting recruitment so we moved everything over into FFPE and we essentially had. We were looking at both tumor tissue as well as peripheral blood and PBM CS and we were as you can see here looking at PDL one by HC Tills by both HNNQF.

NOTE Confidence: 0.865003883838654

00:40:34.780 --> 00:40:54.790 Quiet even mute presence DNA mutations by whole exome sequencing. So we could look for mutational signature and Neo manages antigens and then RNA expression by RNA seq looking at transcript signature again in Neo Antigen expression. We prioritize these is the top 5 wish list.

NOTE Confidence: 0.86826628446579

00:40:55.580 --> 00:41:15.590 When you have tumor tissue you may not always have tumor in those cores. So we had to do a prioritization. List first and foremost. PDL one by HC Tills by HNA tells by QF whole exome sequencing. RNA sequencing and if we add extra tumor park commonality we?

NOTE Confidence: 0.882822275161743

00:41:16.380 --> 00:41:36.390 I'm glad for circulating tumor DNA and then if we had any extra tissue site off because curd at this time was developing a site off directed DNA DNA panel and we wanted to see what that looked like and potentially if there was any tumor left off left over we were going to ask the NCI the Fred.

NOTE Confidence: 0.895607471466064

00:41:37.180 --> 00:41:57.190 If they would do a comparative analysis between Kurt site off DNA repair panel and their multi. Plex DNA repair piano where they looked at Foss, one BS rad, 51 and Gamma H 2 X and as you can see here. This I think is extremely important, and the reason is because in 20.

NOTE Confidence: 0.923227429389954

00:41:57.980 --> 00:42:17.990 Intel working group defined how they were going to evaluate tumor infiltrating lymphocytes in breast cancer. It was by H&E. We knew that H&E was probably not the best way to do it. However, the

International Working Group had already defined how they were defining tills and so in order to do a comparative between what we

NOTE Confidence: 0.915757298469543

00:42:18.780 --> 00:42:38.790 Fine and what was out there. We felt that at minimum. We had to do the same type of evaluation that the International Working Group was doing and so this is just looking at the initial part of the trial where we did. The Lipper above only and that's what I'm going to focus on today in terms of the biomarkers, but what?

NOTE Confidence: 0.902135670185089

00:42:39.580 --> 00:42:59.590 But yes, we could collect cereal, biopsy's are on our patients. So those patients that went on trial had a minimum of 2 serial biopsy's some of them as you can see had 3 serial biopsy's? What current is doing is he's doing image digitalization analysis with every cord that we get before we start doing.

NOTE Confidence: 0.90981650352478

00:43:41.980 --> 00:44:01.990 Seeing an increase, and tumor infiltrating lymphocytes and it's primarily being seen after the park monotherapy or the perp combination. Biopsy is assessed and as you can see here, though he's also looking at it with more than a chini because H&E can't tell.

NOTE Confidence: 0.916711330413818

00:44:23.580 --> 00:44:43.590 In the T cell infiltration across multiple samples and T cells subsets. So it isn't a huge data set because this is only the first component of the trial where we were using the lipa rib. But what it does show you his number one. Yes, we can work together as a team, so program.

NOTE Confidence: 0.920086681842804

00:44:44.380 --> 00:45:04.390 Together, yes, you can bring ideas into the clinic. That's what we did here and it's working we can get cereal samples you can use the ETCTN to help you do your trials because they focus on biomarker driven investigator initiated trials and we can handle that issue.

NOTE Confidence: 0.91154009103775

00:45:05.180 --> 00:45:25.190 Results so finally I just want to show you these are a couple. These are some of the samples that we took in the initial 3 arm study where we looked at baseline biopsies and tumor at 6 weeks. So one thing that he looked at was individual T cell receptor.

NOTE Confidence: 0.924693644046783

00:45:25.980 --> 00:45:45.990 And as you can see here, he showed for the most part with Philip Arrub, and with the combination in an increase in the Alpha Gamma Beta and Delta components of the T cell receptors with very interesting

is this patient right here. 'cause when I show you the clinical data, although it's minimal.

NOTE Confidence: 0.931305348873138

00:45:46.780 --> 00:46:06.790 So this is just you know this is just suggestion. We don't have a big enough data set. This patient is actually quite interesting. He also showed that there was a change in T cell sequencing or Clone, a type count again demonstrating that yes, we can do this on the samples and actually these are precious samples because they?

NOTE Confidence: 0.874744653701782

00:46:07.580 --> 00:46:27.590 Biopsies overtime they're not archival. We know we have the annotation down 100%. We know what the Bracken. Mutation is we know what the Neo Antigen. Load changes are the DNA and we have circulating tumor DNA to move this through to be able to map CT DNA with tumor DNA and all the RNA seq.

NOTE Confidence: 0.907534301280975

00:46:28.380 --> 00:46:48.390 Made and he also showed that there is a Max there's a maximum CDR 3 link that it's increasing so it's showing that it looks like, at least that we're putting pressure on T cells that are more likely to recognize the antigenic tumor peptides, so this was that first group of patients that we treated this.

NOTE Confidence: 0.870572924613953

00:46:49.180 --> 00:47:09.190 Science data and this is the patient that had that high T cell receptor load and the clonal sequencing in the clone ality and this patient progressed envelope road never responded and went on, and this is a PR almost CR this patient went on to have a really nice durable response.

NOTE Confidence: 0.892841458320618

00:47:09.980 --> 00:47:29.990 Added Atisa, losing map to the combination and this is the study that's aren't going right now, we actually just put the 24th patient on we need 68 patients to make a difference and I urge you to send your patients to us instead of just treating them with off label Elappara off study a lap robe, although it's FDA.

NOTE Confidence: 0.91379451751709

00:47:30.780 --> 00:47:50.790 Going to learn if we just treat and see response 'cause what we're trying to do is understand mechanisms of response and resistance. But what we're seeing with the combinations is we're seeing some nice responses and these are durable responses and a couple of these patients have come off opioids are doing really, really well finally.

NOTE Confidence: 0.925352990627289

00:47:51.580 --> 00:48:11.590 That all was great, but why are some of these patients progressing and are there is there anything that we can look at within the tumor especially the post progression progression biopsy to help us and so, Ryan Jensen and Megan. King had been working closely with us to look and see whether or not they can help us figure.

NOTE Confidence: 0.8782799243927

00:48:12.380 --> 00:48:32.390 Sharp inhibitory resistance mechanisms in the brackets settings, so the goals of this component are to identify more patients who may benefit from perp inhibitory therapy due to HDR deficiency and a rigorously test a pre version of wheels in that braka underlie parp inhibitory resist.

NOTE Confidence: 0.92290872335434

00:48:33.180 --> 00:48:53.190 In the functions that play a role and then finally to broadly understand resistance mechanisms so that we can rationally design combination therapies in the future. It not only give patients with Bracken mutations as an example elappara but maybe better understand which should be getting APDL one inhibitor as well. But.

NOTE Confidence: 0.923387408256531

00:48:53.980 --> 00:49:13.990 Personalized that combination further based on what type of resistance mechanisms. Or maybe baseline biomarkers that we see with those patients so their first question that they want to answer is how does bracket status at the time of treatment affect response and we're doing that by looking at Genomic sequencing to Detur.

NOTE Confidence: 0.89877724647522

00:49:14.780 --> 00:49:34.790 Status in the frequency and then secondly, we want to know whether not bracker reversion alleles are responsible for Parp inhibitory resistance and tumor relapse. Ryan has some beautiful cell based and biochemical functional assays and these novel and or anticipated functions.

NOTE Confidence: 0.900944828987122

00:49:35.580 --> 00:49:55.590 Zachary version alleles appear to be driving tumor progression, but he wants to understand that more and so he's really looking at the Bracco Reversions to see whether or not those truly equates with drug resistance, however.

NOTE Confidence: 0.914477407932281

00:49:56.380 --> 00:50:16.390 Shunts that's probably not going to help you understand that because not all patients end up with re versions. And so we've been very, very fortunate to team up with Astra Zeneca. They're giving us all of their solo 2 data. Although I'll be. It is an ovarian cancer and they didn't do tumor biopsies, but they did.

NOTE Confidence: 0.919903755187988

00:50:17.180 --> 00:50:37.190 Circulating tumor DNA on these patients and several of them have re versions and basically. I think this data set that Astra Zeneca is given us is the biggest single handed data set with 3 versions that we know of 2 date and so we're pretty excited to work with them, Ryan in May.

NOTE Confidence: 0.902539789676666

00:50:37.210 --> 00:50:57.220 I've already started working with them on these on this program. But the essential questions. Do these putative reversion alleles reconstitute bracket function are they responsible for Parp Inhibitor resistance inpatient relapse and finally are these reversions neomorphic tumor.

NOTE Confidence: 0.908789813518524

00:50:58.300 --> 00:51:18.310 I think the outstanding scientific question that we're all asking is what is the molecular basis for parp inhibitor mediated synthetic lethal killing and bracket deficient tumors and how does or how does Bracken wanted to an other HDR pathway changes successfully deal with park in?

NOTE Confidence: 0.900071144104004

00:51:19.490 --> 00:51:39.500 I think for future there is difficult, clinical questions that need to be answered. We need predictive biomarkers for HDR in park inhibitor patient stratification. It's not good enough to just give everybody the same drug can, we suppress inhibitor Department hitter resistance mechanisms what?

NOTE Confidence: 0.892569363117218

00:51:40.290 --> 00:51:56.900 Optimal combination therapy for Purp Inhibitors and will it be different depending on what that initial tumor looks like and will these combinations as I said need to be personalized. Thank you very much.