What you know it’s 1202 or why don’t we get started? And I know there are folks still logging on, so for those of us who are here, thank you for joining cancer grand rounds. I hope all of you had a restful and enjoyable Thanksgiving and. Obviously, I know we’re all looking forward to year’s end and hopefully celebrating a better 2021, but we’re really very fortunate to have two exceptional speakers today and I’ll start by introducing our first speaker, who frankly needs no introduction.
Dr. Barbara Burtness is a professor of Medicine Co, leader of the Developmental Therapeutics research program, and leader of the head and neck cancer program. She is internationally known for her leadership in clinical development and research and understanding the biology of heading cancer among her many accolades. We can add now only in the past month is the principal investigator of the head and Explorer of which we are just so proud of both Barbara and the entire team being awarded.
00:01:14.880 --> 00:01:17.428 this really coveted an elite grant.
NOTE Confidence: 0.859560012817383
00:01:17.430 --> 00:01:19.544 Of which I think will be from
NOTE Confidence: 0.859560012817383
00:01:19.544 --> 00:01:21.689 not correct if I’m not mistaken,
NOTE Confidence: 0.859560012817383
00:01:21.690 --> 00:01:23.658 there only two head neck spores
NOTE Confidence: 0.859560012817383
00:01:23.660 --> 00:01:25.963 now in the United States are the
NOTE Confidence: 0.859560012817383
00:01:25.963 --> 00:01:27.599 leader of one of them,
NOTE Confidence: 0.859560012817383
00:01:27.600 --> 00:01:29.742 which is an extraordinary distinction for
NOTE Confidence: 0.859560012817383
00:01:29.742 --> 00:01:32.516 the people who work in this space at Yale.
NOTE Confidence: 0.859560012817383
00:01:32.520 --> 00:01:34.326 So Barbara was kind enough to
NOTE Confidence: 0.859560012817383
00:01:34.326 --> 00:01:36.650 share with us the work she’s doing
NOTE Confidence: 0.859560012817383
00:01:36.650 --> 00:01:38.744 on head neck cancer and forever.
NOTE Confidence: 0.859560012817383
00:01:38.750 --> 00:01:40.058 Thank you for joining
NOTE Confidence: 0.823722958564758
00:01:40.060 --> 00:01:41.245 us today. Well,
NOTE Confidence: 0.823722958564758
00:01:41.245 --> 00:01:44.010 thank you for the invitation and for.
NOTE Confidence: 0.823722958564758
00:01:44.010 --> 00:01:46.946 All the support that’s gotten us this far.
NOTE Confidence: 0.823722958564758
00:01:46.950 --> 00:01:49.454 So what I wanted to do was talk
about P53 mutated head neck cancer, which is something I have a longstanding interest in. And obviously, P53 is a very critical tumor suppressor gene. It’s meant to be the cell’s way of reacting to cellular stress signals, and ideally in response to these P. So hypoxemia, DNA damage, replicative stress, and ideally in response to these P, 53 is activated and promotes the transcription of target genes and domains of cell cycle arrest DNA.
00:02:26.804 --> 00:02:29.319 repair a pop ptosis and others.
NOTE Confidence: 0.823722958564758
00:02:29.320 --> 00:02:29.824 However,
NOTE Confidence: 0.823722958564758
00:02:29.824 --> 00:02:33.352 in head neck cancer were aware that
NOTE Confidence: 0.823722958564758
00:02:33.352 --> 00:02:35.963 P53 functionally disrupted in the
NOTE Confidence: 0.823722958564758
00:02:35.963 --> 00:02:39.491 majority in HPV associated head neck cancer.
NOTE Confidence: 0.823722958564758
00:02:39.500 --> 00:02:42.769 P53 is wild type, but its degradation
NOTE Confidence: 0.823722958564758
00:02:42.769 --> 00:02:45.610 is fostered by viral proteins,
NOTE Confidence: 0.823722958564758
00:02:45.610 --> 00:02:49.768 an in HPV, negative head neck cancer.
NOTE Confidence: 0.823722958564758
00:02:49.770 --> 00:02:52.885 Over 85% have genomic disruption of P53,
NOTE Confidence: 0.823722958564758
00:02:52.890 --> 00:02:54.674 including in frame mutations,
NOTE Confidence: 0.823722958564758
00:02:54.674 --> 00:02:59.974 truncating mutations and missense mutations,
NOTE Confidence: 0.823722958564758
00:02:59.974 --> 00:03:02:59.974 and you can see here that many of
NOTE Confidence: 0.823722958564758
00:02:59.974 --> 00:03:03:150 these are clustered in the DNA binding
NOTE Confidence: 0.823722958564758
00:03:03:150 --> 00:03:06.506 domain and we know that this type
NOTE Confidence: 0.823722958564758
00:03:06.506 --> 00:03:09.810 of mutation is Villa terius for the
NOTE Confidence: 0.823722958564758
00:03:09.810 --> 00:03:12.520 Natural History of head neck cancer.
So this figure comes from a large trial that the legacy Kog Cooperative Group ran over 500 respected head neck cancers. All respected to margin, negativity, and all offered appropriate risk based animal therapy is with standard at the time and then P 50 three was sequenced and you can see here that long term outcome. Was worse for those patients who had P53 mutation, and if you classified the mutations as disruptive or nondisruptive, it was worse for those with disruption.
disruptive mutation and the definition

That was used in this paper.

That was for disruptive was a

mutation that was either truncating

or in the DNA binding domain.

So on the basis of these outcome data,

we were interested in the cognitive

Akron Head Neck Committee,

which I chair in studying intensification

of therapy for these poor prognosis

patients with disruptive P53 mutation.

But the first thing we wanted to

do was examined how we really

should be calling the P53 mutation.

So we started with what we called

the poeta rule,
so those were the rules from the paper I just showed you and we compared them to 14 other cloud 13 other classifiers that are out there, many of which are based on in silico predictions of disruption, some of which are based on experimental evidence actually of the decrease in OIF 1 activation for every specific mutation and then we also examine Dar poeta rules augmented with information about the splice site mutations. And you can see that this very simple definition of truncating or DNA binding domain actually outperformed
in terms of clinical prognosis. All of the other indicators, and so in our clinical trial. We moved forward with this poets rules plus splice site mutations and the trial that we’re now about halfway through is a randomized phase. Two trial of. Post operative therapy for patients who meet the criteria for radiation but have negative margins, don’t meet the criteria for chemotherapy, and then we want to ask in those patients with disruptive mutation, do we see an advantage for the addition of platinum that we
00:05:36.558 --> 00:05:38.538 don’t see in other patients?

00:05:38.540 --> 00:05:40.500 This is supported by.

00:05:40.500 --> 00:05:47.382 Is Bisquick grant that takes care of all of the sequencing and we have two investigators who are doing the mutation calling in real time.

00:05:47.382 --> 00:05:49.864 So continue to support this trial and see this is kind of an important resource in terms of all the sequencing information that we’re going to have on top of the clinical outcome.

00:05:49.864 --> 00:06:02.716 We also have support for a clinical trials planning meeting at the NCI which is going to happen in January.

00:06:02.716 --> 00:06:06.628 The goal of this is to write trials.
both for locally advanced and recurrent metastatic disease, identifying promising therapies for P53 mutated cancer. We also want to develop a national infrastructure. For the sequencing and mutation, calling with the consensus approach that all of the groups within the NCT and will accept the breakout groups for this have been meeting for about five months now. I can tell you that the focus is very strong and immunotherapy and synthetic lethal strategies and I’ll mention both of those in in
the remaining minutes of this talk.

So head neck cancer is one of the cancers where it appears that increase tumor mutation burden is predictive of response to immunotherapy. And we know that this is a cancer with a higher number of nonsynonymous mutations, particularly in the HPV negative cancers. In the platinum refractory setting, both for Pember Lizum app in this early single ARM trial and for development in a randomized phase three trial. In the also in the platinum refractory setting, in both cases we see that as
tumor mutation burden rises, the likelihood of benefit from immunotherapy increases. So working with my long term collaborator at Fox Chase Circle, we wanted to examine whether or not mutations in not only P. 53, which is the most commonly mutated tumor suppressor and head neck cancer, but also CDK into a which is mutated in slightly over half of HPV negative cancers as well. See how these related to DNA damage.
as reflected in tumor mutation burden with the idea of establishing whether or not P53 mutated cancers. Would be particularly susceptible or appropriate for study with immunotherapy. We had access to a data set of 1010 HPV negative cancers that have been profiled at Caris Life Sciences. Their gene panel is about a 600 gene panel. They exclude HPV associated cancers with standard methods and then the mutations that we saw were almost invariably truncations or deletions. So we included all of those, but for P53 we were interested once.
again in what’s the best way of calling?

Meaningful mutations,

so we started with the American College of Medical Genetics variants calling this included essentially all the P53 mutations that we SPA.

We then looked for consensus between the ACM G and two other variant calling algorithms, interference linker.

We use the International Agency for Research on Cancer guidelines for what was dominant, negative or loss of function.

We then looked at the variance is defined by the poeta rules that I just alluded to, and then we called out those patients who seem to have gain of function mutations,
most of which are defined experimentally across a range of publications, and TMB was. Measured just by counting all nonsynonymous missense mutations across the about 1.4 mega bases that are included in this panel. This shows you the the patient characteristics so predominantly oral cavity in order. Pharynx cancers as we see in the clinic. Males outnumbering females, and as you see at the bottom, the number of patients who had P53 the karris was higher than if we looked at the consensus
calls or the disruptive call gain of P53, and indeed it turned out that either P53 or CDK into a mutation. 

Here we looked for threshold of 15 per per megabases as being likely predictive of response to immunotherapy. And you can see that across the board having both genes mutated was associated with higher TMB than having one or the other, and The only exception here was that those patients with gain of function mutations in P53 did not have an increase in tumor mutation burden.
So you know, we concluded that mutation of P53 or CDK in two ways associated with increased tumor mutation burden. This is highest when they’re damaging mutations in both jeans and so just to kind of segue to the next part of the talk, where I’m going to talk a little bit more about synthetic lethal strategies. P53 mutated head neck cancer, I think, remains a really important subject for study, because it’s common. It has a poor prognosis. We still don’t, after many decades of people examining this,
have agents which directly target mutated P.

And so the increasing evidence that synthetic lethal strategies might have promise in these patients is has kind of attracted our attention in in the lab. And so one of the things that we know about disruptive P53 mutation is that you lose the cell, loses the ability to perform cell cycle arrest at the G1 S transition, and as a result it becomes much more dependent on transition at G2 M and so we I mean obviously many people have been interested in this across many cancers, but we were interested in
examining some of the.

Potential targets that regulate G2

We know that auroras increasing.

I'll show you a little bit about this.

We know that Aurora expression is increased in head neck

is increased in head neck

cancer and. Aurora content

will go up at the end of G2.

Its activity is required to localize

CDK one to the to the centromere to to.

will go up at the end of G2.

Foster mitotic entry Aurora also,

in addition to its roles

in centrosome maturation.

It also has the property of.

Activating the city.
See 25 phosphatase, which removes an inhibitory phosphorylation from CDK one and on the other hand, inhibitory phosphorylation is placed by the mitotic checkpoint kinase we want and so both we won an Auror recognized is up regulated and head neck cancer. Both of them are potential. Points of synthetic lethality in P53 mutated cancers, but they appear to have kind of contradictory or opposing roles, and so that the data that I’m going to show you now.
the case that by co-treating these cancers with an Aurora inhibitor, which will lead to Abnormal spindle formation. Defective cytokinesis, but by inhibiting the rural will lose the ability to remove the inhibitory phosphorylation from CDK one and that will result in cell cycle arrest that we can counter that by inhibition of we won so that phosphorylation isn’t placed and accelerate these cells into mitosis where given the spindle disruption that’s been
00:14:13.347 --> 00:14:16.107 caused by the Aurora inhibition.

NOTE Confidence: 0.819094598293304

00:14:16.110 --> 00:14:19.078 They will be unable to complete a normal

NOTE Confidence: 0.819094598293304

00:14:19.078 --> 00:14:21.552 mitosis and instead will apoptose

NOTE Confidence: 0.819094598293304

00:14:21.552 --> 00:14:23.756 are undergo mitotic catastrophe.

NOTE Confidence: 0.819094598293304

00:14:23.760 --> 00:14:24.227 So,

NOTE Confidence: 0.819094598293304

00:14:24.227 --> 00:14:24.694 um,

NOTE Confidence: 0.819094598293304

00:14:24.694 --> 00:14:27.496 it's been recognized that Aurora content

NOTE Confidence: 0.819094598293304

00:14:27.496 --> 00:14:30.397 is increased in the face of loss of

NOTE Confidence: 0.819094598293304

00:14:30.397 --> 00:14:32.959 P53 and their host of publications,

NOTE Confidence: 0.819094598293304

00:14:32.960 --> 00:14:34.945 which demonstrate that increased Aurora

NOTE Confidence: 0.819094598293304

00:14:34.945 --> 00:14:37.550 levels are correlated with poor prognosis.

NOTE Confidence: 0.819094598293304

00:14:37.550 --> 00:14:40.546 I’ll show you some of our work.

NOTE Confidence: 0.819094598293304

00:14:40.550 --> 00:14:43.133 This is a panel of cell lines

NOTE Confidence: 0.819094598293304

00:14:43.133 --> 00:14:45.647 that that we use in the lab,

NOTE Confidence: 0.819094598293304

00:14:45.650 --> 00:14:47.470 all of which have either

NOTE Confidence: 0.819094598293304

00:14:47.470 --> 00:14:49.290 mutated or P53 null status,
and you can see that all of them increase the expression of arorae relative to either fibroblasts or normal epithelial tissue. When I was at Fox Chase, we worked on an Aqua essay and insight to fluorescence assay for Aurora that could be applied to tissue microarrays. So you see here that green is for carrot and defines where these head neck cancer nests are within the tissue core Blues for dampit. And so you see here that green is for carrot and defines where these head neck cancer nests are within the tissue core Blues for dampit. So that will be your nucleus and red is for Aurora and in this Aurora high cancer.
00:15:28.840 --> 00:15:31.167 is the high level of expression
NOTE Confidence: 0.819094598293304
00:15:31.167 --> 00:15:33.307 of Aurora within the nucleus.
NOTE Confidence: 0.819094598293304
00:15:33.310 --> 00:15:35.452 When we looked at nuclear Aurora
NOTE Confidence: 0.819094598293304
00:15:35.452 --> 00:15:37.285 in the tissue microarray first
NOTE Confidence: 0.819094598293304
00:15:37.285 --> 00:15:39.651 for all cases we saw that high
NOTE Confidence: 0.819094598293304
00:15:39.651 --> 00:15:41.273 Aurora expression was associated
NOTE Confidence: 0.819094598293304
00:15:41.273 --> 00:15:42.590 with worse survival.
NOTE Confidence: 0.819094598293304
00:15:42.590 --> 00:15:43.902 This is also true,
NOTE Confidence: 0.819094598293304
00:15:43.902 --> 00:15:45.870 just is a reflection of Natural
NOTE Confidence: 0.819094598293304
00:15:45.943 --> 00:15:48.109 History in those patients who had
NOTE Confidence: 0.819094598293304
00:15:48.109 --> 00:15:50.072 had no post operative treatments
NOTE Confidence: 0.819094598293304
00:15:50.072 --> 00:15:51.860 and never been exposed.
NOTE Confidence: 0.819094598293304
00:15:51.860 --> 00:15:54.184 Any DNA damaging agents and we were
NOTE Confidence: 0.819094598293304
00:15:54.184 --> 00:15:56.866 able to show that this was entirely
NOTE Confidence: 0.819094598293304
00:15:56.866 --> 00:15:59.278 driven by the HPV negative cancers.
NOTE Confidence: 0.819094598293304
00:15:59.280 --> 00:16:01.576 So on the basis of this these
data we went to Millennium.

And argued that.

Aurora could potentially be a good target in head and neck cancer.

They were doing a trial of Al assertive, which is an inhibitor.

which is in Aurora a inhibitor.

Val asserted monotherapy across a bunch of solid tumors,

a bunch of solid tumors,

and we were able to convince them to add a head neck cohort,

but this was crushingly disappointing because the response rate for Aurora turned out to be about 9% and given the increasing experimental
evidence that are or inhibition may always be intrinsically limited. Limited by this kind of compensatory cell cycle arrest. We were then interested in what would be. The rational combination with Arorae inhibition that could. Optimize the targeting of what we continued to think was likely to be an important target in this disease, and so any Mendez and colleagues at the University of Washington together with Dell Yarbrough are former colleague here had undertaken a functional kind, ohmic screen. In P53,
00:17:14.480 --> 00:17:16.880 mutated head and neck cancer and

00:17:16.956 --> 00:17:19.917 actually Aurora came out of that screen.

00:17:19.920 --> 00:17:22.302 But another thing that came out

00:17:22.302 --> 00:17:24.296 was this mitotic checkpoint kinase

00:17:24.296 --> 00:17:25.976 that I just alluded to.

00:17:25.980 --> 00:17:27.078 We want and.

00:17:27.078 --> 00:17:28.908 People have been interested in

00:17:28.908 --> 00:17:31.403 the idea that inhibitors of G1

00:17:31.403 --> 00:17:33.513 will abrogate the G2 checkpoint.

00:17:33.520 --> 00:17:34.258 You have.

00:17:34.258 --> 00:17:36.103 The G1 checkpoint is already

00:17:36.103 --> 00:17:38.567 advocated by P53 mutation and that

00:17:38.567 --> 00:17:40.707 this might accelerate cell death,

00:17:40.710 --> 00:17:42.978 particularly in the presence of DNA

00:17:42.978 --> 00:17:45.866 damage such as you might generate with

00:17:45.875 --> 00:17:47.880
cisplatin and they showed in animal models that we one inhibitor MK 1775, which is now known as the data sorted, was synergistic with platinum in P53 mutated head neck cancer models. Eddie Mendez then took this forward as a window trial and head neck cancer, so a small number of patients treated with a DAB assertive together with low dose weekly chemotherapy. And you can see here that the majority of patients had some diminution in tumor size and a number of them had rather major pathologic responses, and most intriguingly, you can see that there was evidence that there was evidence
00:18:24.443 --> 00:18:25.799 of target engagement,
00:18:25.800 --> 00:18:28.188 and so among those patients who
00:18:28.188 --> 00:18:28.984 had responses,
00:18:28.990 --> 00:18:31.425 there was a decrease in
00:18:31.425 --> 00:18:32.886 phosphorylation of CDK.
00:18:32.890 --> 00:18:35.900 There was a decrease in
00:18:35.900 --> 00:18:38.910 fast focus Stone Age 3.
00:18:38.910 --> 00:18:41.640 And potentially you could see
00:18:41.640 --> 00:18:44.954 some increase in gamma, H2, ax.
00:18:44.954 --> 00:18:48.326 They also were able to correlate
00:18:48.326 --> 00:18:50.715 both pathologic and clinical
00:18:50.715 --> 00:18:54.207 response with the presence of P53
00:18:54.207 --> 00:18:57.781 mutation in the HPV negative cancers
00:18:57.781 --> 00:19:00.089 and across the board.
00:19:00.090 --> 00:19:02.722 These P53 mutations are
00:19:02.722 --> 00:19:04.696 disruptive or deletions.

00:19:04.700 --> 00:19:07.166 So we’ve been exploring whether or

00:19:07.166 --> 00:19:10.530 not you can combine Aurora A and we

00:19:10.530 --> 00:19:12.585 want inhibition and observe synergy

00:19:12.585 --> 00:19:15.278 in P53 mutated head neck cancer,

00:19:15.280 --> 00:19:19.078 and you see here a picture of John Wooley,

00:19:19.080 --> 00:19:21.200 my colleague in the lamp,

00:19:21.200 --> 00:19:24.154 who has done the majority of these

00:19:24.154 --> 00:19:26.698 experiments and so you’ll see MLN,

00:19:26.700 --> 00:19:28.500 that’s the Aurora inhibitor,

00:19:28.500 --> 00:19:31.200 Azd 1775 that’s the wee one

00:19:31.280 --> 00:19:33.610 inhibitor and we see synergy.

00:19:33.610 --> 00:19:36.130 In terms of cell viability,

00:19:36.130 --> 00:19:38.565 soft auger oncosphere formation and

00:19:38.565 --> 00:19:41.569 this was present in two separate

00:19:41.569 --> 00:19:44.491 HPV negative head neck cancer cell
lines that bear P53 mutations. Trying to figure out whether or not our guests about the mechanism was correct. You can see here that when you give the Aurora inhibitor there’s a dramatic increase in phosphorylation of CDK one. This happens in a slightly different timeline in the two South and the two different cell lines, but seems to be a reproducible phenomenon, and that’s abrogated by the addition of the wee one inhibitor and completely abolished when you give it together. This results in an increase in the number
of mitotic figures that’s abnormal to the.

The Presence of really only single digit normal mitotic figures in the presence of the combination.

So if you just walk through here, these are the normal mitotic figures. When you give the wee one inhibitor, you get some dis aggregation of chromatin reflected here in the fast food Stone Age 3 stain. When you give the Aurora inhibitor, you get the formation of these multipolar spindles three to four spindles, and when you give the Purcell, and when you give the two together you get a, uh. Abnormal catastrophic mitotic figure.
We also showed in using Annexin 5 flow and looking for cleaved PARP that there's an increase in a pop ptosis. And we wanted to compare this to Aurora B inhibition, which completely cuts off mitotic entry by aggregating the phosphorylation of histone H3 and there was no synergy between these two agents and you can see there. The lack of fastball, histone H3, an increase in DNA damage. Taking this into xenograft models here at either of two doses of the wee one inhibitor, the standard dose of the Aurora
inhibitor tumors continued to grow not too differently from vehicle, but when we gave the two together, there was control of tumor growth and actually statistically significant improvement in survival for the animals. Looking at the tumors under the microscope when we gave the two agents together, there was a decrease in proliferation reflected in decreased Ki 67, there was increased cleaved caspase and there was a decrease in fast for CDK, one within tissue and if we did Aquaphor phospho CDK one and counted the amount of phosphorus, IDK one signal in the tumor leading edge.
You can see this was dramatically decreased. Ellisor to has been a difficult drug to work within the clinic. It’s associated with Mila suppression, and there’s been a negative phase three monotherapy trial, and so we were concerned that the development of that agent might not go forward. However, there’s been a number of 2nd generation or inhibitors that have come forward and we’ve had access to a compound from Taiho called task 119 recently been acquired by Bit Track.
And it’s gonna be called Vic 1911

moving forward and once again across a range of P53 mutated cell lines we see dramatic synergy for the two agents. Once again, we see synergy in xenograft models. This is confocal microscopy that again shows you the multipolar spindle formation with the use of task 119 is the Aurora inhibitor. But with the cells really arresting in that or becoming quiet sent in that multipolar spindle state an as they then attempt to enter mitosis in the presence of both the wee one.
inhibitor and the Aurora inhibitor, developing these very catastrophic mitotic phenotypes, an notice that I’m sort of running out of time here, so I won’t March you through this, but the mechanism looks to be identical here, as what we saw with assertive. I’m working with our Columbus is Lambert at Fox Chase. We undertook a high throughput screen to see if we could find additional partners that would be. Both hindering and an fostering mitotic entry again with the attempt to exploit these multiple regulators of G2,
M and another hit that appeared

very strong was the check one

inhibitor Prexasertib agent.

It’s not really moving forward in

the clinic because of its toxicity,

but I wanted to show this just

because with very low dose Ng and

a single dose we saw a profound.

Energetic survival effects that make us

hopeful that with a number of these pairs,

we might be able to go to very

low doses in the clinic.

So test 119 has completed

two clinical trials.

There’s a recommended phase two dose.

The toxicity seems to be very manageable
00:25:03.290 --> 00:25:05.750 with diarrhea and eye disorders.

00:25:05.750 --> 00:25:07.598 Probably the prominent most

00:25:07.598 --> 00:25:08.984 prominent side effects,

00:25:08.990 --> 00:25:11.834 and so we are moving forward

00:25:11.834 --> 00:25:14.530 with a window trial in HPV,

00:25:14.530 --> 00:25:17.080 negative head neck cancer that will

00:25:17.080 --> 00:25:20.070 have both an initial dose escalation.

00:25:20.070 --> 00:25:22.054 Looking at the combination

00:25:22.054 --> 00:25:24.534 of Vic and DAB assertive.

00:25:24.540 --> 00:25:26.948 And followed by a dose expansion and

00:25:26.948 --> 00:25:29.485 that will be part of Project two of

00:25:29.485 --> 00:25:32.459 our head next 4 so I wanted to leave

00:25:32.459 --> 00:25:34.649 a couple of minutes for questions,

00:25:34.650 --> 00:25:36.785 but I didn’t want to end without

00:25:36.785 --> 00:25:39.291 first of all calling out all of

NOTE Confidence: 0.815518438816071

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the fabulous colleagues who were part of the team that they put the head and explore in and then acknowledging all the people whose work I’ve just talked about, particularly John Wooley Jannike Parameshwar on in Teresa Sandoval Schaefer in the lamp. So thank you very much. Barbara, thank you. That’s fabulous work. Congratulations on all of it and and folks can submit questions on the on the chat box of the zoom, but I wanted to ask, you know, with regard as you look through.
the combination of an Aurora kinase and we want inhibitors, do you have a sense of 1st what might emerge? I'm even when you're getting response because of the complexity of those pathways. What might emerges mechanism? Resistance that will occur when you have dual inhibition of any and then the second question I have is what do you anticipate will be the toxicity profile or the therapeutic window for the combination clinically. So the we want inhibitors been quite tolerable 'cause I'm going to take the second question
'cause I've already wrestled with X and a lot that we want. Inhibitors been quite tolerable in the clinic but when it was combined with PARP inhibition, diarrhea really became the dose limiting. Side effect, and so this second generation Aurora inhibitor did have about a 25% rate of high grade diarrhea at the recommended phase two dose. So the two things that were sort of hoping is 1. That will get away with lower doses as we have in the animal models and second of all, the diarrhea as it dose limiting toxicity is one of the easier ones to
manage and so that if we’re on top of this with an Imodium regimen early on, hopefully that will be helpful in terms of resistance mechanisms with this is not something that we’ve really gone into with the combination yet, but is well studied for both of the agents independently and one of the. Resistance mechanisms to the Aurora agents has been a kind of conformational dependence on the inhibitor, so inhibitor binds to the activated form of Aurora A and if you get a an adaptive process where the cell just generates more inactive Aurora,
the current generation of inhibitors may not work as well and there is a group. Kevan Shokat lab has been developing novel Aurora inhibitors that maybe. More able to bind the inactive confirmation as well. And in terms of we want inhibitors there there is. Suggestions that? The the. Do you need damage effects of? That we want inhibitors may have an S phase. Could actually upregulate some checkpoints that are earlier in the cell cycle. But it’s a good question. Probably something we should devote more effort to. Yeah, well, I’m sure it’ll
it’ll definitely emerge. Emerge as you get samples from your trial. So it’s really exciting. And congratulations so I know we’re at 12:31. Wherever so why don’t we will turn out to people? Can submit questions to Barbara Online, but will turn now to our second speaker and very fortunate to have another valued member of our faculty speaking. Doctor Elizabeth Klaus is a professor of Biostatistics and neurosurgery. Focused not only on brain tumors but also the Epidemiology, most notably the genetic
Epidemiology of these malignancies. She received her MD and PhD from Yale and completed her surgery here in their surgery and through her work she really has been an international leader in the investigation of the Epidemiology of CNS Malignancy’s, most notably serving as the leader of the Meningioma consortium, that meningioma Genome Wide Association study. Also, a leader of the AL Acoustic neuroma study, and we again were so pleased to have talented people who bridge the gap of Epidemiology in biology of cancer
and Elizabeth thank you so much for sharing your work with us today.

Thanks very much.

Can you see my slides?

OK,

So I’m going to talk a little bit about something we’ve been working on and I do want to note that this is work done in collaboration with Jeff Townsend’s Group and Vincent Kenna Tarot as well as Steven Gaffney. So despite all the things
that we’ve attempted to do, we still don’t know much about risk factors for glioma. And we wanted to take a look and see if they were different methods that we could use. To see if we could tease out both environmental and then also another hot topic is sex specific signatures of glioma causation. So you all know that gliomas are the most common type of malignant brain tumor, accounting for about 1/3 of all brain tumors, and the majority of malignant tumors. But they proved to be very heterogeneous and we have not done a
great job identifying risk factors, be they genetic or environmental for glioma. And so we were interested in doing that, particularly in light of the poor outcomes that we see with this group of patients. So we do know that there are sex specific differences in glioma risk and outcome and the plots I have here are for all gliomas, an then glioblastoma or sort of an IDH positive. Excuse me, IDH negative tumor and then lower grade gliomas. The males being the blue, the females being the red.
And it’s interesting in that we see this sex specific difference across the entire age range, so it’s a little bit different than we see with, for example, meningiomas where we see the women having greater risk, but the risk difference decreasing once women passed through the menopause. Whereas here we see the sex differences for glioma across the age spectrum and across all subtypes, and so that obviously suggests that other mechanisms in addition to a good sex hormones must be.
Are behind the difference men are at greater risk of being diagnosed with the disease. And again, that’s across pretty much all the subtypes and they also have lower survival in general then for females across all subtypes. So we’ve looked at this a little bit and I’ve been lucky enough to collaborate with a group of individuals called the glioma. International Case Controls Consortium, that’s led by Melissa Bondy, initially at MD Anderson, then it Baylor.
Now she heads up the Epidemiology section at Stanford, but we were able to gather over 10,000 cases and 10,000 controls, and so these are essentially looking at constitutional or germline risk alleles by sex. So if I can draw your attention to the table over here, these are the variants that we found to be significantly different at the germline level, males versus females. Males being the blue, and females being the red.
but we were also interested in looking at things at the tumor or their cinematic level.

Sex is a biologic variables I mentioned. This is a very hot topic. Now we obviously know there are biologic differences between males and females. There’s also some thought as to whether there’s variation in the prevalence of risk factors, and then also whether there’s a difference in sort of a gene by environmental interaction. So, for example, and this has long been postulated,
but it’s really been pretty difficult to prove that males in particular are more likely to be exposed to work like toxins that might be associated with risk, and so that was one of the things we wanted to look at as well. And in part, why we divided our analysis. So there’s two goals and what we wanted to look at the relative contribution and this is based on some of the work that I know you’ve already appreciated with Jeff Townsend, but we’re applying it specifically now to glioma.
but looking at the relative contribution of cancer cell lineages, proliferation and survival of single nucleotide mutations, and we divided our study subjects up by IDH mutation. And, as most of you know, IDH mutation is one of the key dividers into the. The higher in the lower grade tumors, certainly a prognostic factor, as well as a factor in response to treatment. We also wanted to quantify, and this is something that is a little bit new to Epidemiology.
in terms of how we’ve tried to identify risk exposures. Typically we’ve done things like large case control studies where we look at large numbers of people that have the disease, compare them to large numbers of people without the disease, and look at things like questionnaire or work pic. Exposure and see if we can figure out differences between the cases and controls. So what we’re doing now, this is sort of an emerging field in cancer Epidemiology, is to look at the cosmic cancer
mutational signatures in tumors and see if we can then backtrack match it to possible risk exposures, and one of the things we’re hoping to do in the future is to go back to our cohorts and studies for which we collected good occupational data and see if we can match it up to. Mutational signatures So the methods I’ll talk a little bit about. I am highlighting here. Jeff’s paper that he had in J&CI two years ago, and I think you’ve seen some of these sorts of methods applied,
in particular to actually head and neck cancer. So the Cancer Genome Atlas, and others, including the glioma Longitudinal Analysis Consortium, or Glass, which is led by roll. Their Hokage, Jackson Labs and which I'm also a member of. So these groups have identified the most common genetic changes in primary glioma tumors including TP 53, IDH, EGFR with the relative importance of these mutations and how they relate to tumorigenesis. Is not well known,
so one of the things that we’ve been working on, and Jeff has been a leader in is defining this cancer affect size. So this metric of the relative overabundance of variance due to their contributions to survival, indvision versus what you’re actually seeing in the tumor. So we’re quantifying the cancer affect size. We’re using single nucleotide mutations, and then we basically do a scaled selection coefficient for the for the different variants we look at.
By sex and by IDH subtype.

And so we're trying to get a feel for whether this would help us explain any differences in the glioma, risk and outcome that we see by sex.

And then we're going to move on to the cosmic mutations so I won't go into the gory statistical detail.

This is drawn from Jeffs paper, but basically you're comparing expected to observed so expected number of synonymous mutations, and then we're looking at the rate at which the mutations actually occur.

The data that we're using here,
our whole exome sequencing data from a pretty good size data set in terms of glioma, so about 1100 and these are all adult patients. There’s no pediatric patients in here and we drew it from the Cancer Genome Atlas study. And as I mentioned, I know some of you may be aware of what glasses, so it’s an effort. As I mentioned led by role Verhaag, but which yell is also a member of looking at not only the initial tumors, but the humours overtime. So how do they change?
In terms of their genetic makeup, when we do nothing to them when we do chemotherapy or we do radiation, or a combination of all the above and what changes do we see and what do we learn from that in terms of what we should or should not be doing? And then we also used a lot of data. All of this is readily available off the Internet, but we use tissue specific mutational covariance and this helped. Just figure out what sort of mutation rate calculations we should use. Gave us a little bit of information about replication timing.
And some of the other datasets that are listed here. So here's some of the results. Just to take you through it a little bit. So I have a divided by tumor type and it's by seksan by mutation. So the wild type tumors who would be considered the higher grade are primarily the glioblastoma tumors are in the first 2 rows and the IDH mutant, which would more typically be the lower grade tumors. And then I have males versus females, males versus females, and then there's sort of a
cancer affect size here.

The blue is non coding region.

And the red is coding so you can see the patterns are quite different for what might be called the low and the high grade, the IDH mutant tumors had few unique recurrent substitutions. All of them were in coding regions, whereas the wild type tumors, and obviously this is in part what makes them so hard to manage is they exhibited many substitutions, but they were primarily in non coding regions. So here’s another picture.
A little busy but divided once again, the IDH mutant or the lower grade tumors are presented first. The wild types are second, and there's female male, female, male, and So what we're looking at here is that. Items that top the list are the most important. The size of the circle that is attached to them measures the prevalence so there can be kind of this. Disconnect as to what is important and how frequently it occurs so we can see that in the low grades it's pretty much as expected.
Previously reported mutations in IDH one and two TP 53. Some of the other classics were confirmed, but what's interesting is if we go here to the IDH. Wild type tumors the most important with respect to cancer affect. Is this B R A F V 600 E so we know that it's important. It turns out that it looks like it's the most important, but obviously it doesn’t occur.
What drives some of these gliomas here?

The other thing we looked at is do males and females show the same pattern of what significantly overburdened, and there were a lot of similarities the way that we have this broken up here is each panel is a gene. The mutants come first in each panel and then within each panel we’ve got the females in the mails.

So we did see some differences, although overall most the things the males and females showed were similar, but we did see differences in the P3K
00:41:24.400 --> 00:41:27.405 pathway, so an IDH mutant, tumors the PK.
NOTE Confidence: 0.850281715393066
00:41:27.410 --> 00:41:29.552 Three CA mutations were located in
NOTE Confidence: 0.850281715393066
00:41:29.552 --> 00:41:31.550 the helical domain for females,
NOTE Confidence: 0.850281715393066
00:41:31.550 --> 00:41:34.175 and the kinase domain for the males,
NOTE Confidence: 0.850281715393066
00:41:34.180 --> 00:41:36.120 and so that’s appear.
NOTE Confidence: 0.850281715393066
00:41:36.120 --> 00:41:37.575 This panel here.
NOTE Confidence: 0.850281715393066
00:41:37.580 --> 00:41:37.926 OK,
NOTE Confidence: 0.850281715393066
00:41:37.926 --> 00:41:40.348 so it’s the mutant and non mutant
NOTE Confidence: 0.850281715393066
00:41:40.348 --> 00:41:42.715 and then the variance of import
NOTE Confidence: 0.850281715393066
00:41:42.715 --> 00:41:45.109 also differed by sex for PK3R1
NOTE Confidence: 0.850281715393066
00:41:45.184 --> 00:41:47.620 and so that’s interesting in part
NOTE Confidence: 0.850281715393066
00:41:47.620 --> 00:41:50.234 because we know that the way in
NOTE Confidence: 0.850281715393066
00:41:50.234 --> 00:41:52.202 which these areas are targeted by
NOTE Confidence: 0.850281715393066
00:41:52.202 --> 00:41:54.309 various chemotherapies does differ.
NOTE Confidence: 0.850281715393066
00:41:54.310 --> 00:41:56.718 We looked in the literature an we
NOTE Confidence: 0.850281715393066
00:41:56.718 --> 00:41:59.359 don’t see too much reported honest.
We did find a paper by Dan Cahill at all at mass general and although they didn’t report it as such, they found something similar where the females tended to have. Variations in the he local domain and the males had them in the kinase domain, and so as I said, although both domains are involved with glioma Genesis, there is differential amounts of potentiated by these two regions. And obviously there’s different sensitivity to various treatment types depending upon domain.
So back to environmental exposure. We have searched and not just our group of many groups have searched long and hard for environmental and genetic risk factors for glioma. In terms of genetic risk factors, we have found small numbers of families with high risk but typically that does not relate to the general population and so no genetic risk factors really explain a large proportion of inherited risk and other than high dose radiation to which not many people. Thankfully are exposed. We really haven’t found much of an Association between environmental
00:43:12.653 --> 00:43:15.188 risk factors in glioma risk.

00:43:15.190 --> 00:43:17.830 There has been reported a fairly consistent but low effect,

00:43:17.830 --> 00:43:19.590 an inverse Association with history of allergy.

00:43:19.590 --> 00:43:21.698 So the question comes, why haven’t we found anything?

00:43:21.698 --> 00:43:23.279 Is it that there is no Association?

00:43:23.280 --> 00:43:24.736 Or is it basically statistical power

00:43:24.736 --> 00:43:26.556 that there’s so few cases of glioma relative to other things we’ve looked at?

00:43:26.560 --> 00:43:29.094 For example, I started my work with breast cancer and even just using the state of Connecticut as a base,
you would have enough cases

That is not true and also likely a lot of the exposures that we think are causing risk are themselves rare.

So one of the things that people have been thinking about doing, is there another way to do this now?

So now that we have these mutational signatures that are listed in the Catalogue of Somatic mutations and cancer or cosmic can use that as a way to match up to exposure, particularly if you have previously obtained environmental or other exposure history in the patients.
So we did that here with the 1100 cases that we mentioned, we group Jack Sonic. SNV and tried to match him up to what is in cosmic, and so you know that the cosmic catalog is rapidly changing. New things are always being added, but we looked at what existed at this point, and obviously they have previously found a match up over environmental exposure to signatures not only in head and neck cancer, but smoking and lung cancer, UV exposure, and so we looked at that for glioma.
And so again, here's our slide again, broken into IDH Mutant, which is the top row IDH, Wildtype bottom row and then females. 

Each of these bar charts relates to is the proportion of our cases for whom the majority seem to be associated with a certain signature. And the overall news is a little bit depressing in the sense that the primary molecular signature identified was age related mutagenesis. Basically the older you get, the more at risk you are,
but we did find one thing that was quite interesting, particularly in light of their such positive risk factors identified for glioma and that was occupational exposure to something called Halo alkanes. Pretty much true across whether you are male or female. And whether you were IDH, mutant or not, we did find a little greater rate of the signature showing up in the males versus the females. But we certainly saw them in both and then we also saw which we
haven’t quite figured out how to explain yet. These UV light signatures are interesting because glioma has been associated in the number of instances with Melanoma and also with the B RAF. So we’re trying to sort out whether that has anything to do with why we’re just seeing some of those signatures? So hello, alkanes are basically used for many industrial and day-to-day purposes. Of interest there seen in refrigerants, fire extinguishers, flame retardants, and we thought this was very interesting because there’s always sort of been this theory that in some of these occupations including for firemen.
and that has been reported that there is an increased risk of glioma, and so, whether or not this ties things together or not is unclear, so the signature was basically developed by looking at cholangio carcinoma in a group of workers that were exposed, known, exposed to hello Alkins in Japan and so essentially they had 111 workers that were exposed. Would you all know to be a pretty rare? Cancer, so it was quite unusual that this number of individuals was diagnosed with it.
They all were working in printing companies and they all were known to have occupational exposure and so essentially what they did was they took the tumors from these individuals, looked at the molecular pattern and developed this signature. So that’s essentially how that signature was initially identified, and so that’s what we’re seeing. Basically in our data. So conclusions here that the majority of cancer causing mutations in these gliomas we’re seeing primarily as a consequence of endogenous, rather than actual, exogenous exposures.
We did think was interesting that different domains of jeans in the P3K pathway were different for males and females. For those of us that have searched long and hard for some of these risk factors for glioma, we are excited that at least potentially, there’s a new means to try and identify even if rare, these environmental risk factors and it’s sort of a whole new aspect of glioma that were looking at so some of our future directions. We’re looking now to partner with colleagues who have worked with us.
both in the meningioma consortia man,
And we also in our international low grade glioma registry.
So the San Francisco Bay Area Glioma study,
which is led by Margaret Wrench and John Winky,
they collected extremely detailed occupational history for their cohort,
and they have all the tumors.
So we’re going to try and go back and Genotype those tumors and see if
we can confirm these associations, which they found with firefighters. And glioma. And also they found it with painters as well. And so we are also collecting glioma patients with occupational histories and just sort of throwing it out to people. If you’re aware of any firefighters or similar occupied individuals with glioma would love to try and get a cohort together. The other thing that was just sort of luck this past semester. So I teach over at the school, public health and everything has been remote.
And so as I was meeting via zoom with one of my students for her final project, she revealed that she was actually the principle project director for the Firefighters Cancer Cohort study. So we’re also hoping to parano. NIH is a big directive to try and look further at environmental exposures and cancer, so we’re hoping that we can partner with some of these folks to look at individuals, either living or dead that may have undiagnosed glioma that we now have this exposure. With thank you all for your time. I wanted to also thank Jeff Townsend,
Vinston, Canna Terra, who was a postdoc in Jeff's lab but now as an assistant professor of biology up the road, a little bit of Emmanuel College and I have to thank him. He made all the beautiful pictures and Steven Gaffney, who also works in Jeff Slab. Thank the various.

Brain tumor associations, including the ABCA in the NBTS as well as Luglio Anna, a Dutch group called Stop Brain for their support and then also thank you for Doctor Rolled.
their hacking the Glass consortium
who allowed us access to the data.
So happy to take any questions.
Elizabeth, thank you.
That was a terrific summary of your
work and obviously will open it
up to questions on the chat line.
But let me ask.
I found it interesting the
observation I guess from Asia
about the Association of Halo
alkanes with cholangiocarcinoma.
As you may know,
there’s a biologic
difference between intrahepatic,
where extra panic actually gave IDH mutations but insured don’t wear the cases that they found in Asia with an extra paddock. You know, I don’t know the answer to that. I gave a similar talk at UCSF and they mentioned this as well, so we’re trying to gain access to some of that information, but I don’t know at present. And then. With regard to the finding of the potential differential in mutations within pick three CA by gender by sex, is there an understanding of
why those two domains would be different between men and women?
No, and you know, we started to look at that a little bit and we collaborate a bit with Dan Cahill. As I mentioned up at mass general so we don’t know yet, but he’s going to try to take a look into that he he presented the data but didn’t note the differences, so he’s going to try to take a look and see what that. Might entail.
And then my last question, and this is gonna show my naivete
and understanding brain tumors.

But instead of the natural history of the low grades. Is there an evolution of the semantic events such that they look more like high grades? So it depends. They generally remain quite different. The IDH mutation stays constant throughout and so that’s sort of been one of the issues is what you show up to the party with you tend to be what you stay within. That makes it a little bit different to manage them.
We didn’t find in some of the glass consortium work that we’ve looked at that really things changed that much whether you gave them treatment or whether you didn’t give them treatment. It’s a little bit disheartening, but we’re going to try to look a little bit further at that.

Judging by the way you describe for the presence of Halo alkanes, you could imagine they may be more ubiquitous in our environment than we might otherwise appreciate given.
all the things they are in absolutely and it doesn’t have to just relate to glioma. You know could relate to lots of different things so. Well, very interesting. You know we’re just about out of time. An really appreciate. Oh actually, JoJo contest hasn’t question, forgive me. So Joe’s question is high dose radiation therapy delivered to pediatric patients can lead to glioma? Have you found evidence that medical imaging and radiation exposure in
this setting is associated? So

there's actually, and you probably

even know of these two studies.

There's a big cohort from Australia as

well as a second cohort from England,

and they did find that even exposure to

head CT’s at an early age in children

was associated with the I mean.

It’s a very small increase in risk,

but a definite increase in risk

of both glioma and meningioma,

and then anything we looked at

we did find it was a fairly hotly

contested topic we did find.

And exposure to bite wings was associated

with an increased risk of meningioma,
but that's sort of exposure level in terms of dental X, Rays generally doesn't exist now.

But yeah, in terms of head CT's, anyone to do suggest that, although you know, the absolute numbers are small. And then Antonio Murray asks, is great talk. Have you looked at thyroid hormones, thyroid disease and differences between men and women?

So we haven’t but one thing that
is very interesting, and it relates a little bit more to meningioma. Is a gene that we found, and this is a constitutional gene on chromosome 10. We’ve found to be associated with meningioma, breast, ovarian and also now thyroid tumors. Interest. Elizabeth, thank you. We are at the top of the hour. Appreciate both your talk and Barbara’s really extending work. Thank you for sharing all of it with us and to everyone who joins us today. Thank you for taking the time to join grand rounds and we’ll
see you all again next week.

Have a good day.