

WEBVTT

NOTE duration:"00:55:39.6480000"

NOTE language:en-us

NOTE Confidence: 0.859560012817383

00:00:00.000 --> 00:00:02.370 What you know it's 1202 or

NOTE Confidence: 0.859560012817383

00:00:02.370 --> 00:00:04.780 why don't we get started?

NOTE Confidence: 0.859560012817383

00:00:04.780 --> 00:00:08.416 And I know there are folks still logging on,

NOTE Confidence: 0.859560012817383

00:00:08.420 --> 00:00:11.644 so for those of us who are here,

NOTE Confidence: 0.859560012817383

00:00:11.650 --> 00:00:14.478 thank you for joining cancer grand rounds.

NOTE Confidence: 0.859560012817383

00:00:14.480 --> 00:00:17.592 I hope all of you had a restful

NOTE Confidence: 0.859560012817383

00:00:17.592 --> 00:00:19.929 and enjoyable Thanksgiving and.

NOTE Confidence: 0.859560012817383

00:00:19.930 --> 00:00:22.120 Obviously, I know we're all

NOTE Confidence: 0.859560012817383

00:00:22.120 --> 00:00:24.905 looking forward to year's end and

NOTE Confidence: 0.859560012817383

00:00:24.905 --> 00:00:27.470 hopefully celebrating a better 2021,

NOTE Confidence: 0.859560012817383

00:00:27.470 --> 00:00:30.837 but we're really very fortunate to have

NOTE Confidence: 0.859560012817383

00:00:30.837 --> 00:00:33.712 two exceptional speakers today and I'll

NOTE Confidence: 0.859560012817383

00:00:33.712 --> 00:00:36.418 start by introducing our first speaker,

NOTE Confidence: 0.859560012817383

00:00:36.420 --> 00:00:39.320 who frankly needs no introduction.

NOTE Confidence: 0.859560012817383

00:00:39.320 --> 00:00:41.052 Doctor Barbara Burtness is

NOTE Confidence: 0.859560012817383

00:00:41.052 --> 00:00:42.784 professor of Medicine Co,

NOTE Confidence: 0.859560012817383

00:00:42.790 --> 00:00:44.898 leader of the Developmental

NOTE Confidence: 0.859560012817383

00:00:44.898 --> 00:00:46.479 Therapeutics research program.

NOTE Confidence: 0.859560012817383

00:00:46.480 --> 00:00:49.104 And leader of the head neck cancer program

NOTE Confidence: 0.859560012817383

00:00:49.104 --> 00:00:51.270 and Yell Barbara is internationally

NOTE Confidence: 0.859560012817383

00:00:51.270 --> 00:00:54.162 known for her leadership in clinical

NOTE Confidence: 0.859560012817383

00:00:54.162 --> 00:00:56.001 development and research and

NOTE Confidence: 0.859560012817383

00:00:56.001 --> 00:00:58.151 understanding the biology of heading

NOTE Confidence: 0.859560012817383

00:00:58.151 --> 00:01:00.612 that canceran among her many accolades.

NOTE Confidence: 0.859560012817383

00:01:00.612 --> 00:01:04.019 We can add now only in the past

NOTE Confidence: 0.859560012817383

00:01:04.019 --> 00:01:06.344 month is the principle investigator

NOTE Confidence: 0.859560012817383

00:01:06.344 --> 00:01:09.688 of the head and Explorer of which we

NOTE Confidence: 0.859560012817383

00:01:09.688 --> 00:01:12.390 are just so proud of both Barbara

NOTE Confidence: 0.859560012817383

00:01:12.390 --> 00:01:14.880 and the entire team being awarded

NOTE Confidence: 0.859560012817383

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

NOTE Confidence: 0.823722958564758

00:01:49.454 --> 00:01:52.078 about P53 mutated head neck cancer,

NOTE Confidence: 0.823722958564758

00:01:52.080 --> 00:01:54.288 which is something I have a

NOTE Confidence: 0.823722958564758

00:01:54.288 --> 00:01:55.392 longstanding interest in.

NOTE Confidence: 0.823722958564758

00:01:55.400 --> 00:01:59.992 And. Obviously, P 53 is a very

NOTE Confidence: 0.823722958564758

00:01:59.992 --> 00:02:02.670 critical tumor suppressor gene.

NOTE Confidence: 0.823722958564758

00:02:02.670 --> 00:02:05.486 It's meant to be the cells way of

NOTE Confidence: 0.823722958564758

00:02:05.486 --> 00:02:08.159 reacting to cellular stress signals,

NOTE Confidence: 0.823722958564758

00:02:08.160 --> 00:02:11.496 and among these are many that we know

NOTE Confidence: 0.823722958564758

00:02:11.496 --> 00:02:14.057 are important in head neck cancer.

NOTE Confidence: 0.823722958564758

00:02:14.060 --> 00:02:15.752 So hypoxemia, DNA damage,

NOTE Confidence: 0.823722958564758

00:02:15.752 --> 00:02:16.598 replicative stress,

NOTE Confidence: 0.823722958564758

00:02:16.600 --> 00:02:19.547 and ideally in response to these P.

NOTE Confidence: 0.823722958564758

00:02:19.550 --> 00:02:22.322 53 is activated and promotes the

NOTE Confidence: 0.823722958564758

00:02:22.322 --> 00:02:24.614 transcription of target genes and

NOTE Confidence: 0.823722958564758

00:02:24.614 --> 00:02:26.804 domains of cell cycle arrest DNA

NOTE Confidence: 0.823722958564758

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 --> 00:02:56.904 truncating mutations and missense mutations,
NOTE Confidence: 0.823722958564758

00:02:56.910 --> 00:02:59.974 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.

NOTE Confidence: 0.823722958564758

00:03:12.520 --> 00:03:15.544 So this figure comes from a large trial

NOTE Confidence: 0.823722958564758

00:03:15.544 --> 00:03:18.310 that the legacy Kog Cooperative Group

NOTE Confidence: 0.823722958564758

00:03:18.310 --> 00:03:21.910 ran over 500 respected head neck cancers.

NOTE Confidence: 0.823722958564758

00:03:21.910 --> 00:03:23.438 All respected to margin,

NOTE Confidence: 0.823722958564758

00:03:23.438 --> 00:03:23.820 negativity,

NOTE Confidence: 0.823722958564758

00:03:23.820 --> 00:03:26.095 and all offered appropriate risk

NOTE Confidence: 0.823722958564758

00:03:26.095 --> 00:03:28.370 based animal therapy is with

NOTE Confidence: 0.823722958564758

00:03:28.453 --> 00:03:31.077 standard at the time and then P 50

NOTE Confidence: 0.823722958564758

00:03:31.077 --> 00:03:33.427 three was sequenced and you can

NOTE Confidence: 0.823722958564758

00:03:33.427 --> 00:03:35.845 see here that long term outcome.

NOTE Confidence: 0.823722958564758

00:03:35.850 --> 00:03:37.875 Was worse for those patients

NOTE Confidence: 0.823722958564758

00:03:37.875 --> 00:03:39.495 who had P53 mutation,

NOTE Confidence: 0.823722958564758

00:03:39.500 --> 00:03:41.936 and if you classified the mutations

NOTE Confidence: 0.823722958564758

00:03:41.936 --> 00:03:43.560 as disruptive or nondisruptive,

NOTE Confidence: 0.823722958564758

00:03:43.560 --> 00:03:46.188 it was worse for those with

NOTE Confidence: 0.823722958564758

00:03:46.188 --> 00:03:48.472 disruptive mutation and the definition
NOTE Confidence: 0.823722958564758

00:03:48.472 --> 00:03:51.136 that was used in this paper.
NOTE Confidence: 0.823722958564758

00:03:51.140 --> 00:03:53.654 That was for disruptive was a
NOTE Confidence: 0.823722958564758

00:03:53.654 --> 00:03:55.856 mutation that was either truncating
NOTE Confidence: 0.823722958564758

00:03:55.856 --> 00:03:58.514 or in the DNA binding domain.
NOTE Confidence: 0.823722958564758

00:03:58.520 --> 00:04:01.984 So on the basis of these outcome data,
NOTE Confidence: 0.823722958564758

00:04:01.990 --> 00:04:04.594 we were interested in the cognitive
NOTE Confidence: 0.823722958564758

00:04:04.594 --> 00:04:06.330 Akron Head Neck Committee,
NOTE Confidence: 0.823722958564758

00:04:06.330 --> 00:04:08.694 which I chair in studying intensification
NOTE Confidence: 0.823722958564758

00:04:08.694 --> 00:04:11.300 of therapy for these poor prognosis
NOTE Confidence: 0.823722958564758

00:04:11.300 --> 00:04:13.705 patients with disruptive P53 mutation.
NOTE Confidence: 0.823722958564758

00:04:13.710 --> 00:04:16.538 But the first thing we wanted to
NOTE Confidence: 0.823722958564758

00:04:16.538 --> 00:04:19.214 do was examined how we really
NOTE Confidence: 0.823722958564758

00:04:19.214 --> 00:04:21.962 should be calling the P53 mutation.
NOTE Confidence: 0.823722958564758

00:04:21.970 --> 00:04:24.483 So we started with what we called
NOTE Confidence: 0.823722958564758

00:04:24.483 --> 00:04:25.560 the poeta rule,

NOTE Confidence: 0.823722958564758
00:04:25.560 --> 00:04:27.800 so those were the rules from the
NOTE Confidence: 0.823722958564758
00:04:27.800 --> 00:04:30.234 paper I just showed you and we
NOTE Confidence: 0.823722958564758
00:04:30.234 --> 00:04:32.807 compared them to 14 other cloud 13
NOTE Confidence: 0.823722958564758
00:04:32.807 --> 00:04:35.249 other classifiers that are out there,
NOTE Confidence: 0.823722958564758
00:04:35.250 --> 00:04:37.483 many of which are based on in
NOTE Confidence: 0.823722958564758
00:04:37.483 --> 00:04:39.200 silico predictions of disruption,
NOTE Confidence: 0.823722958564758
00:04:39.200 --> 00:04:41.755 some of which are based on experimental
NOTE Confidence: 0.823722958564758
00:04:41.755 --> 00:04:44.007 evidence actually of the decrease in
NOTE Confidence: 0.823722958564758
00:04:44.007 --> 00:04:46.197 OIF 1 activation for every specific
NOTE Confidence: 0.823722958564758
00:04:46.197 --> 00:04:48.627 mutation and then we also examine Dar
NOTE Confidence: 0.823722958564758
00:04:48.627 --> 00:04:50.336 poeta rules augmented with information
NOTE Confidence: 0.823722958564758
00:04:50.336 --> 00:04:52.166 about the splice site mutations.
NOTE Confidence: 0.823722958564758
00:04:52.170 --> 00:04:54.810 And you can see that this very simple
NOTE Confidence: 0.823722958564758
00:04:54.810 --> 00:04:56.826 definition of truncating or DNA
NOTE Confidence: 0.823722958564758
00:04:56.826 --> 00:04:58.538 binding domain actually outperformed
NOTE Confidence: 0.823722958564758

00:04:58.538 --> 00:05:01.120 in terms of clinical prognosis.
NOTE Confidence: 0.823722958564758

00:05:01.120 --> 00:05:03.420 All of the other indicators,
NOTE Confidence: 0.823722958564758

00:05:03.420 --> 00:05:06.168 and so in our clinical trial.
NOTE Confidence: 0.823722958564758

00:05:06.170 --> 00:05:08.786 We moved forward with this poeta
NOTE Confidence: 0.823722958564758

00:05:08.786 --> 00:05:11.085 rules plus splice site mutations
NOTE Confidence: 0.823722958564758

00:05:11.085 --> 00:05:14.410 and the trial that we're now about
NOTE Confidence: 0.823722958564758

00:05:14.410 --> 00:05:15.360 halfway through
NOTE Confidence: 0.807921290397644

00:05:15.446 --> 00:05:18.336 is a randomized phase. Two trial of.
NOTE Confidence: 0.807921290397644

00:05:18.336 --> 00:05:20.246 Post operative therapy for patients
NOTE Confidence: 0.807921290397644

00:05:20.246 --> 00:05:22.831 who meet the criteria for radiation
NOTE Confidence: 0.807921290397644

00:05:22.831 --> 00:05:24.579 but have negative margins,
NOTE Confidence: 0.807921290397644

00:05:24.580 --> 00:05:26.968 don't meet the criteria for chemotherapy,
NOTE Confidence: 0.807921290397644

00:05:26.970 --> 00:05:29.594 and then we want to ask in those
NOTE Confidence: 0.807921290397644

00:05:29.594 --> 00:05:31.760 patients with disruptive mutation,
NOTE Confidence: 0.807921290397644

00:05:31.760 --> 00:05:34.504 do we see an advantage for the
NOTE Confidence: 0.807921290397644

00:05:34.504 --> 00:05:36.558 addition of platinum that we

NOTE Confidence: 0.807921290397644

00:05:36.558 --> 00:05:38.538 don't see in other patients?

NOTE Confidence: 0.807921290397644

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

NOTE Confidence: 0.807921290397644

00:05:40.500 --> 00:05:44.015 Is Bisquick grant that takes care of

NOTE Confidence: 0.807921290397644

00:05:44.015 --> 00:05:47.382 all of the sequencing and we have

NOTE Confidence: 0.807921290397644

00:05:47.382 --> 00:05:49.864 two investigators who are doing

NOTE Confidence: 0.807921290397644

00:05:49.864 --> 00:05:52.714 the mutation calling in real time.

NOTE Confidence: 0.807921290397644

00:05:52.720 --> 00:05:54.910 So continue to support this trial

NOTE Confidence: 0.807921290397644

00:05:54.910 --> 00:05:57.906 and see this is kind of an important

NOTE Confidence: 0.807921290397644

00:05:57.906 --> 00:06:00.596 resource in terms of all the sequencing

NOTE Confidence: 0.807921290397644

00:06:00.596 --> 00:06:02.716 information that we're going to

NOTE Confidence: 0.807921290397644

00:06:02.716 --> 00:06:06.628 have on top of the clinical outcome.

NOTE Confidence: 0.807921290397644

00:06:06.630 --> 00:06:09.563 We also have support for a clinical

NOTE Confidence: 0.807921290397644

00:06:09.563 --> 00:06:11.891 trials planning meeting at the NCI

NOTE Confidence: 0.807921290397644

00:06:11.891 --> 00:06:14.222 which is going to happen in January.

NOTE Confidence: 0.807921290397644

00:06:14.230 --> 00:06:16.478 The goal of this is to write trials

NOTE Confidence: 0.807921290397644

00:06:16.478 --> 00:06:18.709 both for locally advanced and
NOTE Confidence: 0.807921290397644

00:06:18.709 --> 00:06:20.308 recurrent metastatic disease,
NOTE Confidence: 0.807921290397644

00:06:20.310 --> 00:06:21.450 identifying promising therapies
NOTE Confidence: 0.807921290397644

00:06:21.450 --> 00:06:22.970 for P53 mutated cancer.
NOTE Confidence: 0.807921290397644

00:06:22.970 --> 00:06:25.760 We also want to develop a
NOTE Confidence: 0.807921290397644

00:06:25.760 --> 00:06:26.690 national infrastructure.
NOTE Confidence: 0.807921290397644

00:06:26.690 --> 00:06:28.550 For the sequencing and mutation,
NOTE Confidence: 0.807921290397644

00:06:28.550 --> 00:06:30.460 calling with the consensus approach
NOTE Confidence: 0.807921290397644

00:06:30.460 --> 00:06:33.153 that all of the groups within the
NOTE Confidence: 0.807921290397644

00:06:33.153 --> 00:06:35.289 NCT and will accept the breakout
NOTE Confidence: 0.807921290397644

00:06:35.289 --> 00:06:37.504 groups for this have been meeting
NOTE Confidence: 0.807921290397644

00:06:37.504 --> 00:06:39.299 for about five months now.
NOTE Confidence: 0.807921290397644

00:06:39.300 --> 00:06:41.556 I can tell you that the focus is
NOTE Confidence: 0.807921290397644

00:06:41.556 --> 00:06:43.609 very strong and immunotherapy and
NOTE Confidence: 0.807921290397644

00:06:43.609 --> 00:06:45.974 synthetic lethal strategies and I'll.
NOTE Confidence: 0.807921290397644

00:06:45.980 --> 00:06:49.039 I'll mention both of those in in

NOTE Confidence: 0.807921290397644
00:06:49.039 --> 00:06:51.490 the remaining minutes of this talk.
NOTE Confidence: 0.807921290397644
00:06:51.490 --> 00:06:54.090 So head neck cancer is one of the
NOTE Confidence: 0.807921290397644
00:06:54.090 --> 00:06:56.556 cancers where it appears that increase
NOTE Confidence: 0.807921290397644
00:06:56.556 --> 00:06:58.736 tumor mutation burden is predictive
NOTE Confidence: 0.807921290397644
00:06:58.736 --> 00:07:01.038 of response to immunotherapy.
NOTE Confidence: 0.807921290397644
00:07:01.040 --> 00:07:03.506 And we know that this is a cancer with
NOTE Confidence: 0.807921290397644
00:07:03.506 --> 00:07:06.670 a higher number of nonsynonymous mutations,
NOTE Confidence: 0.807921290397644
00:07:06.670 --> 00:07:09.538 particularly in the HPV negative cancers.
NOTE Confidence: 0.807921290397644
00:07:09.540 --> 00:07:12.096 And in the platinum refractory setting,
NOTE Confidence: 0.807921290397644
00:07:12.100 --> 00:07:15.468 both for Pember Lizum app in this early
NOTE Confidence: 0.807921290397644
00:07:15.468 --> 00:07:18.421 single ARM trial and for development
NOTE Confidence: 0.807921290397644
00:07:18.421 --> 00:07:21.451 in a randomized phase three trial.
NOTE Confidence: 0.807921290397644
00:07:21.460 --> 00:07:24.202 In the also in the platinum
NOTE Confidence: 0.807921290397644
00:07:24.202 --> 00:07:25.116 refractory setting,
NOTE Confidence: 0.807921290397644
00:07:25.120 --> 00:07:28.214 in both cases we see that as
NOTE Confidence: 0.807921290397644

00:07:28.214 --> 00:07:30.160 tumor mutation burden rises,
NOTE Confidence: 0.807921290397644

00:07:30.160 --> 00:07:32.404 the likelihood of benefit
NOTE Confidence: 0.807921290397644

00:07:32.404 --> 00:07:34.087 from immunotherapy increases.
NOTE Confidence: 0.807921290397644

00:07:34.090 --> 00:07:36.436 So working with my long term
NOTE Confidence: 0.807921290397644

00:07:36.436 --> 00:07:38.590 collaborator at Fox Chase Circle,
NOTE Confidence: 0.807921290397644

00:07:38.590 --> 00:07:39.030 Columbus,
NOTE Confidence: 0.807921290397644

00:07:39.030 --> 00:07:41.670 we wanted to examine whether or
NOTE Confidence: 0.807921290397644

00:07:41.670 --> 00:07:43.908 not mutations in not only P.
NOTE Confidence: 0.807921290397644

00:07:43.910 --> 00:07:44.295 53,
NOTE Confidence: 0.807921290397644

00:07:44.295 --> 00:07:46.605 which is the most common most
NOTE Confidence: 0.807921290397644

00:07:46.605 --> 00:07:48.276 commonly mutated tumor suppressor
NOTE Confidence: 0.807921290397644

00:07:48.276 --> 00:07:50.036 and head neck cancer,
NOTE Confidence: 0.807921290397644

00:07:50.040 --> 00:07:52.756 but also CDK into a which is
NOTE Confidence: 0.807921290397644

00:07:52.756 --> 00:07:54.851 mutated in slightly over half
NOTE Confidence: 0.807921290397644

00:07:54.851 --> 00:07:57.395 of HPV negative cancers as well.
NOTE Confidence: 0.807921290397644

00:07:57.400 --> 00:07:59.927 See how these related to DNA damage

NOTE Confidence: 0.807921290397644
00:07:59.927 --> 00:08:01.967 as reflected in tumor mutation
NOTE Confidence: 0.807921290397644
00:08:01.967 --> 00:08:04.601 burden with the idea of establishing
NOTE Confidence: 0.807921290397644
00:08:04.601 --> 00:08:07.258 whether or not P53 mutated cancers.
NOTE Confidence: 0.807921290397644
00:08:07.260 --> 00:08:10.225 Would be particularly susceptible or
NOTE Confidence: 0.807921290397644
00:08:10.225 --> 00:08:13.190 appropriate for study with immunotherapy.
NOTE Confidence: 0.807921290397644
00:08:13.190 --> 00:08:15.899 We had access to a data set of 1010
NOTE Confidence: 0.807921290397644
00:08:15.899 --> 00:08:18.752 HPV negative cancers that have been
NOTE Confidence: 0.807921290397644
00:08:18.752 --> 00:08:21.222 profiled at Caris Life Sciences.
NOTE Confidence: 0.807921290397644
00:08:21.230 --> 00:08:24.848 There gene panel is about a 600 gene panel.
NOTE Confidence: 0.807921290397644
00:08:24.850 --> 00:08:26.945 They exclude HPV associated cancers
NOTE Confidence: 0.807921290397644
00:08:26.945 --> 00:08:29.408 with standard methods and then the
NOTE Confidence: 0.807921290397644
00:08:29.408 --> 00:08:31.840 CDK into a mutations that we saw were
NOTE Confidence: 0.807921290397644
00:08:31.840 --> 00:08:34.498 almost invariably truncations or deletions.
NOTE Confidence: 0.807921290397644
00:08:34.500 --> 00:08:36.906 So we included all of those,
NOTE Confidence: 0.807921290397644
00:08:36.910 --> 00:08:40.046 but for P53 we were interested once
NOTE Confidence: 0.807921290397644

00:08:40.046 --> 00:08:43.597 again in what's the best way of calling?
NOTE Confidence: 0.807921290397644

00:08:43.600 --> 00:08:44.466 Meaningful mutations,
NOTE Confidence: 0.807921290397644

00:08:44.466 --> 00:08:47.930 so we started with the American College of
NOTE Confidence: 0.806212067604065

00:08:47.999 --> 00:08:49.919 Medical Genetics variants calling
NOTE Confidence: 0.806212067604065

00:08:49.919 --> 00:08:52.319 this included essentially all the
NOTE Confidence: 0.806212067604065

00:08:52.319 --> 00:08:54.698 P53 mutations that that we SPA.
NOTE Confidence: 0.806212067604065

00:08:54.700 --> 00:08:56.968 We then looked for consensus between
NOTE Confidence: 0.806212067604065

00:08:56.968 --> 00:09:00.800 the ACM G and two other variant calling
NOTE Confidence: 0.806212067604065

00:09:00.800 --> 00:09:02.244 algorithms, interference linver.
NOTE Confidence: 0.806212067604065

00:09:02.244 --> 00:09:05.338 We use the International Agency for Research
NOTE Confidence: 0.806212067604065

00:09:05.338 --> 00:09:08.458 on Cancer guidelines for what was dominant,
NOTE Confidence: 0.806212067604065

00:09:08.460 --> 00:09:11.380 negative or loss of function.
NOTE Confidence: 0.806212067604065

00:09:11.380 --> 00:09:14.396 We then looked at the variance is defined
NOTE Confidence: 0.806212067604065

00:09:14.396 --> 00:09:17.974 by the poeta rules that I just alluded to,
NOTE Confidence: 0.806212067604065

00:09:17.980 --> 00:09:20.756 and then we called out those patients who
NOTE Confidence: 0.806212067604065

00:09:20.756 --> 00:09:23.799 seem to have gain of function mutations,

NOTE Confidence: 0.806212067604065

00:09:23.800 --> 00:09:25.858 most of which are defined experimentally

NOTE Confidence: 0.806212067604065

00:09:25.858 --> 00:09:28.060 across a range of publications,

NOTE Confidence: 0.806212067604065

00:09:28.060 --> 00:09:29.461 and TMB was.

NOTE Confidence: 0.806212067604065

00:09:29.461 --> 00:09:32.263 Measured just by counting all nonsynonymous

NOTE Confidence: 0.806212067604065

00:09:32.263 --> 00:09:34.927 missense mutations across the about 1.4

NOTE Confidence: 0.806212067604065

00:09:34.927 --> 00:09:38.128 mega bases that are included in this panel.

NOTE Confidence: 0.806212067604065

00:09:38.130 --> 00:09:40.764 This shows you the the patient

NOTE Confidence: 0.806212067604065

00:09:40.764 --> 00:09:42.081 characteristics so predominantly

NOTE Confidence: 0.806212067604065

00:09:42.081 --> 00:09:43.619 oral cavity in order.

NOTE Confidence: 0.806212067604065

00:09:43.620 --> 00:09:47.004 Pharynx cancers as we see in the clinic.

NOTE Confidence: 0.806212067604065

00:09:47.010 --> 00:09:48.366 Males outnumbering females,

NOTE Confidence: 0.806212067604065

00:09:48.366 --> 00:09:51.530 and as you see at the bottom,

NOTE Confidence: 0.806212067604065

00:09:51.530 --> 00:09:54.533 the number of patients who had P53

NOTE Confidence: 0.806212067604065

00:09:54.533 --> 00:09:57.245 mutation by the karris was higher

NOTE Confidence: 0.806212067604065

00:09:57.245 --> 00:10:00.367 than if we looked at the consensus

NOTE Confidence: 0.806212067604065

00:10:00.456 --> 00:10:03.697 calls or the disruptive call gain of
NOTE Confidence: 0.806212067604065

00:10:03.697 --> 00:10:07.485 function was less than 10% of all of
NOTE Confidence: 0.806212067604065

00:10:07.485 --> 00:10:10.968 the mutations that we saw in be 53,
NOTE Confidence: 0.806212067604065

00:10:10.970 --> 00:10:14.578 and indeed it turned out that either P.
NOTE Confidence: 0.806212067604065

00:10:14.580 --> 00:10:17.340 53 or CDK into a mutation.
NOTE Confidence: 0.806212067604065

00:10:17.340 --> 00:10:20.175 Was associated with an increase in TMB.
NOTE Confidence: 0.806212067604065

00:10:20.180 --> 00:10:22.371 Here we looked for threshold of 15
NOTE Confidence: 0.806212067604065

00:10:22.371 --> 00:10:25.374 per per per megabases as being likely
NOTE Confidence: 0.806212067604065

00:10:25.374 --> 00:10:27.869 predictive of response to immunotherapy.
NOTE Confidence: 0.806212067604065

00:10:27.870 --> 00:10:30.814 And you can see that across the board
NOTE Confidence: 0.806212067604065

00:10:30.814 --> 00:10:33.432 having both genes mutated was associated
NOTE Confidence: 0.806212067604065

00:10:33.432 --> 00:10:37.188 with higher TMB than having one or the other,
NOTE Confidence: 0.806212067604065

00:10:37.190 --> 00:10:40.011 and The only exception here was that
NOTE Confidence: 0.806212067604065

00:10:40.011 --> 00:10:42.356 those patients with gain of function
NOTE Confidence: 0.806212067604065

00:10:42.356 --> 00:10:44.827 mutations in P53 did not have an
NOTE Confidence: 0.806212067604065

00:10:44.900 --> 00:10:47.350 increase in tumor mutation burden.

NOTE Confidence: 0.806212067604065
00:10:47.350 --> 00:10:48.322 So you know,
NOTE Confidence: 0.806212067604065
00:10:48.322 --> 00:10:50.266 we concluded that mutation of P53
NOTE Confidence: 0.806212067604065
00:10:50.266 --> 00:10:53.210 or CDK in two ways associated with
NOTE Confidence: 0.806212067604065
00:10:53.210 --> 00:10:54.906 increased tumor mutation burden.
NOTE Confidence: 0.806212067604065
00:10:54.910 --> 00:10:57.676 This is highest when they're damaging
NOTE Confidence: 0.806212067604065
00:10:57.676 --> 00:11:00.804 mutations in both jeans and so just to
NOTE Confidence: 0.806212067604065
00:11:00.804 --> 00:11:03.979 kind of segue to the next part of the talk,
NOTE Confidence: 0.806212067604065
00:11:03.980 --> 00:11:06.412 where I'm going to talk a little bit
NOTE Confidence: 0.806212067604065
00:11:06.412 --> 00:11:08.899 more about synthetic lethal strategies.
NOTE Confidence: 0.806212067604065
00:11:08.900 --> 00:11:11.544 P53 mutated head neck cancer, I think,
NOTE Confidence: 0.806212067604065
00:11:11.544 --> 00:11:14.183 remains a really important subject for study,
NOTE Confidence: 0.806212067604065
00:11:14.190 --> 00:11:15.555 because it's common.
NOTE Confidence: 0.806212067604065
00:11:15.555 --> 00:11:17.830 It has a poor prognosis.
NOTE Confidence: 0.806212067604065
00:11:17.830 --> 00:11:19.087 We still don't,
NOTE Confidence: 0.806212067604065
00:11:19.087 --> 00:11:22.020 after many decades of people examining this,
NOTE Confidence: 0.806212067604065

00:11:22.020 --> 00:11:24.946 have agents which directly target mutated P.
NOTE Confidence: 0.806212067604065

00:11:24.950 --> 00:11:25.479 53.
NOTE Confidence: 0.806212067604065

00:11:25.479 --> 00:11:28.653 And so the increasing evidence that
NOTE Confidence: 0.806212067604065

00:11:28.653 --> 00:11:31.131 synthetic lethal strategies might have
NOTE Confidence: 0.806212067604065

00:11:31.131 --> 00:11:33.952 promise in these patients is has kind
NOTE Confidence: 0.806212067604065

00:11:33.952 --> 00:11:37.439 of attracted our attention in in the lab.
NOTE Confidence: 0.806212067604065

00:11:37.440 --> 00:11:40.536 And so one of the things that we
NOTE Confidence: 0.806212067604065

00:11:40.536 --> 00:11:42.900 know about disruptive P53 mutation
NOTE Confidence: 0.806212067604065

00:11:42.900 --> 00:11:45.900 is that you lose the cell,
NOTE Confidence: 0.806212067604065

00:11:45.900 --> 00:11:48.522 loses the ability to perform cell
NOTE Confidence: 0.806212067604065

00:11:48.522 --> 00:11:51.679 cycle arrest at the G1 S transition,
NOTE Confidence: 0.806212067604065

00:11:51.680 --> 00:11:55.008 and as a result it becomes much more
NOTE Confidence: 0.806212067604065

00:11:55.008 --> 00:11:58.224 dependent on transition at G2 M and so
NOTE Confidence: 0.806212067604065

00:11:58.224 --> 00:12:01.397 we I mean obviously many people have
NOTE Confidence: 0.806212067604065

00:12:01.397 --> 00:12:05.023 been interested in this across many cancers,
NOTE Confidence: 0.806212067604065

00:12:05.030 --> 00:12:07.270 but we were interested in

NOTE Confidence: 0.806212067604065

00:12:07.270 --> 00:12:09.062 examining some of the.

NOTE Confidence: 0.806212067604065

00:12:09.070 --> 00:12:10.690 Potential targets that regulate G2

NOTE Confidence: 0.806212067604065

00:12:10.690 --> 00:12:13.000 M We know that auroras increasing.

NOTE Confidence: 0.806212067604065

00:12:13.000 --> 00:12:15.848 I'll show you a little bit about this.

NOTE Confidence: 0.806212067604065

00:12:15.850 --> 00:12:17.990 We know that Aurora expression

NOTE Confidence: 0.806212067604065

00:12:17.990 --> 00:12:20.130 is increased in head neck

NOTE Confidence: 0.819094598293304

00:12:20.209 --> 00:12:22.414 cancer and. Aurora content

NOTE Confidence: 0.819094598293304

00:12:22.414 --> 00:12:27.870 will go up at the end of G2.

NOTE Confidence: 0.819094598293304

00:12:27.870 --> 00:12:32.238 Its activity is required to localize

NOTE Confidence: 0.819094598293304

00:12:32.238 --> 00:12:38.726 CDK one to the to the centromere to to.

NOTE Confidence: 0.819094598293304

00:12:38.730 --> 00:12:41.710 Foster mitotic entry Aurora also,

NOTE Confidence: 0.819094598293304

00:12:41.710 --> 00:12:44.685 in addition to its roles

NOTE Confidence: 0.819094598293304

00:12:44.685 --> 00:12:46.470 in centrosome maturation.

NOTE Confidence: 0.819094598293304

00:12:46.470 --> 00:12:50.856 It also has the property of.

NOTE Confidence: 0.819094598293304

00:12:50.860 --> 00:12:52.354 Activating the city.

NOTE Confidence: 0.819094598293304

00:12:52.354 --> 00:12:53.848 See 25 phosphatase,
NOTE Confidence: 0.819094598293304

00:12:53.850 --> 00:12:56.430 which removes an inhibitory phosphorylation
NOTE Confidence: 0.819094598293304

00:12:56.430 --> 00:13:00.319 from CDK one and on the other hand,
NOTE Confidence: 0.819094598293304

00:13:00.320 --> 00:13:03.872 it's important to know that that
NOTE Confidence: 0.819094598293304

00:13:03.872 --> 00:13:05.648 inhibitory phosphorylation is
NOTE Confidence: 0.819094598293304

00:13:05.648 --> 00:13:08.114 placed by the mitotic checkpoint
NOTE Confidence: 0.819094598293304

00:13:08.114 --> 00:13:11.318 kinase we want and so both we
NOTE Confidence: 0.819094598293304

00:13:11.318 --> 00:13:13.940 won an Auror recognized is up
NOTE Confidence: 0.819094598293304

00:13:13.940 --> 00:13:16.428 regulated and head neck cancer.
NOTE Confidence: 0.819094598293304

00:13:16.428 --> 00:13:19.348 Both of them are potential.
NOTE Confidence: 0.819094598293304

00:13:19.350 --> 00:13:21.230 Points of synthetic lethality
NOTE Confidence: 0.819094598293304

00:13:21.230 --> 00:13:23.110 in P53 mutated cancers,
NOTE Confidence: 0.819094598293304

00:13:23.110 --> 00:13:26.330 but they appear to have kind of
NOTE Confidence: 0.819094598293304

00:13:26.330 --> 00:13:28.280 contradictory or opposing roles,
NOTE Confidence: 0.819094598293304

00:13:28.280 --> 00:13:31.584 and so that the data that I'm going
NOTE Confidence: 0.819094598293304

00:13:31.584 --> 00:13:34.865 to show you now will try to make

NOTE Confidence: 0.819094598293304

00:13:34.865 --> 00:13:38.377 the case that by Co treating these

NOTE Confidence: 0.819094598293304

00:13:38.377 --> 00:13:41.437 cancers with an Aurora inhibitor,

NOTE Confidence: 0.819094598293304

00:13:41.440 --> 00:13:43.416 which will lead to.

NOTE Confidence: 0.819094598293304

00:13:43.416 --> 00:13:44.898 Abnormal spindle formation.

NOTE Confidence: 0.819094598293304

00:13:44.900 --> 00:13:45.988 Defective cytokinesis,

NOTE Confidence: 0.819094598293304

00:13:45.988 --> 00:13:49.252 but by inhibiting the rural will

NOTE Confidence: 0.819094598293304

00:13:49.252 --> 00:13:52.633 lose the ability to remove the

NOTE Confidence: 0.819094598293304

00:13:52.633 --> 00:13:54.289 inhibitory phosphorylation from

NOTE Confidence: 0.819094598293304

00:13:54.289 --> 00:13:57.699 CDK one and that will result in

NOTE Confidence: 0.819094598293304

00:13:57.699 --> 00:14:00.195 cell cycle arrest that we can

NOTE Confidence: 0.819094598293304

00:14:00.200 --> 00:14:02.670 counter that by inhibition of

NOTE Confidence: 0.819094598293304

00:14:02.670 --> 00:14:05.140 we won so that phosphorylation

NOTE Confidence: 0.819094598293304

00:14:05.229 --> 00:14:07.864 isn't placed and accelerate these

NOTE Confidence: 0.819094598293304

00:14:07.864 --> 00:14:10.499 cells into mitosis where given

NOTE Confidence: 0.819094598293304

00:14:10.587 --> 00:14:13.347 the spindle disruption that's been

NOTE Confidence: 0.819094598293304

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,

NOTE Confidence: 0.819094598293304

00:14:49.290 --> 00:14:51.482 and you can see that all of them

NOTE Confidence: 0.819094598293304

00:14:51.482 --> 00:14:53.408 increase the expression of arorae

NOTE Confidence: 0.819094598293304

00:14:53.408 --> 00:14:55.160 relative to either fibroblasts

NOTE Confidence: 0.819094598293304

00:14:55.160 --> 00:14:56.970 or normal epithelial tissue.

NOTE Confidence: 0.819094598293304

00:14:56.970 --> 00:14:59.966 And when I was at Fox Chase,

NOTE Confidence: 0.819094598293304

00:14:59.970 --> 00:15:03.130 we worked on a Aqua essay and insight

NOTE Confidence: 0.819094598293304

00:15:03.130 --> 00:15:05.819 to fluorescence assay for Aurora that

NOTE Confidence: 0.819094598293304

00:15:05.819 --> 00:15:08.549 could be applied to tissue microarrays.

NOTE Confidence: 0.819094598293304

00:15:08.550 --> 00:15:11.438 And so you see here that green is

NOTE Confidence: 0.819094598293304

00:15:11.438 --> 00:15:14.111 for carrot and defines where these

NOTE Confidence: 0.819094598293304

00:15:14.111 --> 00:15:16.913 head neck cancer nests are within

NOTE Confidence: 0.819094598293304

00:15:17.002 --> 00:15:19.708 the tissue core Blues for dampit.

NOTE Confidence: 0.819094598293304

00:15:19.710 --> 00:15:23.148 So that will be your nucleus and red is

NOTE Confidence: 0.819094598293304

00:15:23.148 --> 00:15:27.008 for Aurora and in this Aurora high cancer.

NOTE Confidence: 0.819094598293304

00:15:27.010 --> 00:15:28.840 What you can particularly appreciate

NOTE Confidence: 0.819094598293304

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

NOTE Confidence: 0.819094598293304
00:16:01.576 --> 00:16:03.739 data we went to Millennium.
NOTE Confidence: 0.819094598293304
00:16:03.740 --> 00:16:05.246 And argued that.
NOTE Confidence: 0.819094598293304
00:16:05.246 --> 00:16:08.258 Aurora could potentially be a good
NOTE Confidence: 0.819094598293304
00:16:08.258 --> 00:16:10.926 target in head and neck cancer.
NOTE Confidence: 0.790267467498779
00:16:10.930 --> 00:16:14.074 They were doing a trial of AI assertive,
NOTE Confidence: 0.790267467498779
00:16:14.080 --> 00:16:17.140 which is in Aurora a inhibitor.
NOTE Confidence: 0.790267467498779
00:16:17.140 --> 00:16:18.740 Val asserted monotherapy across
NOTE Confidence: 0.790267467498779
00:16:18.740 --> 00:16:20.740 a bunch of solid tumors,
NOTE Confidence: 0.790267467498779
00:16:20.740 --> 00:16:22.924 and we were able to convince
NOTE Confidence: 0.790267467498779
00:16:22.924 --> 00:16:25.940 them to add a head neck cohort,
NOTE Confidence: 0.790267467498779
00:16:25.940 --> 00:16:28.250 but this was crushingly disappointing
NOTE Confidence: 0.790267467498779
00:16:28.250 --> 00:16:31.022 because the response rate for Aurora
NOTE Confidence: 0.790267467498779
00:16:31.022 --> 00:16:33.338 monotherapy in in head and neck
NOTE Confidence: 0.790267467498779
00:16:33.338 --> 00:16:35.930 cancer turned out to be about 9% and
NOTE Confidence: 0.790267467498779
00:16:35.930 --> 00:16:37.490 given the increasing experimental
NOTE Confidence: 0.790267467498779

00:16:37.490 --> 00:16:39.909 evidence that are or inhibition may
NOTE Confidence: 0.790267467498779

00:16:39.909 --> 00:16:41.537 always be intrinsically limited.
NOTE Confidence: 0.790267467498779

00:16:41.540 --> 00:16:43.940 Limited by this kind of compens
NOTE Confidence: 0.790267467498779

00:16:43.940 --> 00:16:45.540 atory cell cycle arrest.
NOTE Confidence: 0.790267467498779

00:16:45.540 --> 00:16:48.764 We were then interested in what would be.
NOTE Confidence: 0.790267467498779

00:16:48.770 --> 00:16:51.750 The rational combination with
NOTE Confidence: 0.790267467498779

00:16:51.750 --> 00:16:54.730 Arora's inhibition that could.
NOTE Confidence: 0.790267467498779

00:16:54.730 --> 00:16:57.268 Optimize the targeting of what we
NOTE Confidence: 0.790267467498779

00:16:57.268 --> 00:17:00.276 continued to think was likely to be
NOTE Confidence: 0.790267467498779

00:17:00.276 --> 00:17:02.742 an important target in this disease,
NOTE Confidence: 0.790267467498779

00:17:02.750 --> 00:17:05.550 and so any Mendez and colleagues at the
NOTE Confidence: 0.790267467498779

00:17:05.550 --> 00:17:07.693 University of Washington together with
NOTE Confidence: 0.790267467498779

00:17:07.693 --> 00:17:09.973 Dell Yarbrough are former colleague
NOTE Confidence: 0.790267467498779

00:17:09.973 --> 00:17:12.880 here had undertaken a functional kind,
NOTE Confidence: 0.790267467498779

00:17:12.880 --> 00:17:13.680 ohmic screen.
NOTE Confidence: 0.790267467498779

00:17:13.680 --> 00:17:14.480 In P53,

NOTE Confidence: 0.790267467498779
00:17:14.480 --> 00:17:16.880 mutated head and neck cancer and
NOTE Confidence: 0.790267467498779
00:17:16.956 --> 00:17:19.917 actually Aurora came out of that screen.
NOTE Confidence: 0.790267467498779
00:17:19.920 --> 00:17:22.302 But another thing that came out
NOTE Confidence: 0.790267467498779
00:17:22.302 --> 00:17:24.296 was this mitotic checkpoint kinase
NOTE Confidence: 0.790267467498779
00:17:24.296 --> 00:17:25.976 that I just alluded to.
NOTE Confidence: 0.790267467498779
00:17:25.980 --> 00:17:27.078 We want and.
NOTE Confidence: 0.790267467498779
00:17:27.078 --> 00:17:28.908 People have been interested in
NOTE Confidence: 0.790267467498779
00:17:28.908 --> 00:17:31.403 the idea that inhibitors of G1
NOTE Confidence: 0.790267467498779
00:17:31.403 --> 00:17:33.513 will abrogate the G2 checkpoint.
NOTE Confidence: 0.790267467498779
00:17:33.520 --> 00:17:34.258 You have.
NOTE Confidence: 0.790267467498779
00:17:34.258 --> 00:17:36.103 The G1 checkpoint is already
NOTE Confidence: 0.790267467498779
00:17:36.103 --> 00:17:38.567 advocated by P53 mutation and that
NOTE Confidence: 0.790267467498779
00:17:38.567 --> 00:17:40.707 this might accelerate cell death,
NOTE Confidence: 0.790267467498779
00:17:40.710 --> 00:17:42.978 particularly in the presence of DNA
NOTE Confidence: 0.790267467498779
00:17:42.978 --> 00:17:45.866 damage such as you might generate with
NOTE Confidence: 0.790267467498779

00:17:45.866 --> 00:17:48.470 cisplatin and they showed in animal
NOTE Confidence: 0.790267467498779

00:17:48.470 --> 00:17:51.078 models that we one inhibitor MK 1775,
NOTE Confidence: 0.790267467498779

00:17:51.080 --> 00:17:54.264 which is now known as the data sorted,
NOTE Confidence: 0.790267467498779

00:17:54.270 --> 00:17:56.375 was synergistic with platinum in
NOTE Confidence: 0.790267467498779

00:17:56.375 --> 00:17:59.040 P53 mutated head neck cancer models.
NOTE Confidence: 0.790267467498779

00:17:59.040 --> 00:18:01.315 Eddie Mendez then took this forward as
NOTE Confidence: 0.790267467498779

00:18:01.315 --> 00:18:03.647 a window trial and head neck cancer,
NOTE Confidence: 0.790267467498779

00:18:03.650 --> 00:18:05.834 so a small number of patients treated
NOTE Confidence: 0.790267467498779

00:18:05.834 --> 00:18:08.311 with a DAB assertive together with
NOTE Confidence: 0.790267467498779

00:18:08.311 --> 00:18:10.279 low dose weekly chemotherapy.
NOTE Confidence: 0.790267467498779

00:18:10.280 --> 00:18:13.152 And you can see here that the majority
NOTE Confidence: 0.790267467498779

00:18:13.152 --> 00:18:15.354 of patients had some diminution in
NOTE Confidence: 0.790267467498779

00:18:15.354 --> 00:18:18.569 tumor size and a number of them had
NOTE Confidence: 0.790267467498779

00:18:18.569 --> 00:18:20.629 rather major pathologic responses,
NOTE Confidence: 0.790267467498779

00:18:20.630 --> 00:18:21.752 and most intriguingly,
NOTE Confidence: 0.790267467498779

00:18:21.752 --> 00:18:24.370 you can see that there was evidence

NOTE Confidence: 0.790267467498779
00:18:24.443 --> 00:18:25.799 of target engagement,
NOTE Confidence: 0.790267467498779
00:18:25.800 --> 00:18:28.188 and so among those patients who
NOTE Confidence: 0.790267467498779
00:18:28.188 --> 00:18:28.984 had responses,
NOTE Confidence: 0.790267467498779
00:18:28.990 --> 00:18:31.425 there was a decrease in
NOTE Confidence: 0.790267467498779
00:18:31.425 --> 00:18:32.886 phosphorylation of CDK.
NOTE Confidence: 0.790267467498779
00:18:32.890 --> 00:18:35.900 There was a decrease in
NOTE Confidence: 0.790267467498779
00:18:35.900 --> 00:18:38.910 fast focus Stone Age 3.
NOTE Confidence: 0.790267467498779
00:18:38.910 --> 00:18:41.640 And potentially you could see
NOTE Confidence: 0.790267467498779
00:18:41.640 --> 00:18:44.954 some increase in gamma, H2, ax.
NOTE Confidence: 0.790267467498779
00:18:44.954 --> 00:18:48.326 They also were able to correlate
NOTE Confidence: 0.790267467498779
00:18:48.326 --> 00:18:50.715 both pathologic and clinical
NOTE Confidence: 0.790267467498779
00:18:50.715 --> 00:18:54.207 response with the presence of P53
NOTE Confidence: 0.790267467498779
00:18:54.207 --> 00:18:57.781 mutation in the HPV negative cancers
NOTE Confidence: 0.790267467498779
00:18:57.781 --> 00:19:00.089 and across the board.
NOTE Confidence: 0.790267467498779
00:19:00.090 --> 00:19:02.722 These P53 mutations are
NOTE Confidence: 0.790267467498779

00:19:02.722 --> 00:19:04.696 disruptive or deletions.
NOTE Confidence: 0.790267467498779

00:19:04.700 --> 00:19:07.166 So we've been exploring whether or
NOTE Confidence: 0.790267467498779

00:19:07.166 --> 00:19:10.530 not you can combine Aurora A and we
NOTE Confidence: 0.790267467498779

00:19:10.530 --> 00:19:12.585 want inhibition and observe synergy
NOTE Confidence: 0.790267467498779

00:19:12.585 --> 00:19:15.278 in P53 mutated head neck cancer,
NOTE Confidence: 0.790267467498779

00:19:15.280 --> 00:19:19.078 and you see here a picture of John Wooley,
NOTE Confidence: 0.790267467498779

00:19:19.080 --> 00:19:21.200 my colleague in the lamp,
NOTE Confidence: 0.790267467498779

00:19:21.200 --> 00:19:24.154 who has done the majority of these
NOTE Confidence: 0.790267467498779

00:19:24.154 --> 00:19:26.698 experiments and so you'll see MLN,
NOTE Confidence: 0.790267467498779

00:19:26.700 --> 00:19:28.500 that's the Aurora inhibitor,
NOTE Confidence: 0.790267467498779

00:19:28.500 --> 00:19:31.200 Azd 1775 that's the wee one
NOTE Confidence: 0.790267467498779

00:19:31.280 --> 00:19:33.610 inhibitor and we see synergy.
NOTE Confidence: 0.790267467498779

00:19:33.610 --> 00:19:36.130 In terms of cell viability,
NOTE Confidence: 0.790267467498779

00:19:36.130 --> 00:19:38.565 soft auger oncosphere formation and
NOTE Confidence: 0.790267467498779

00:19:38.565 --> 00:19:41.569 this was present in two separate
NOTE Confidence: 0.790267467498779

00:19:41.569 --> 00:19:44.491 HPV negative head neck cancer cell

NOTE Confidence: 0.790267467498779
00:19:44.491 --> 00:19:47.190 lines that bear P53 mutations.
NOTE Confidence: 0.790267467498779
00:19:47.190 --> 00:19:49.914 Trying to figure out whether or
NOTE Confidence: 0.790267467498779
00:19:49.914 --> 00:19:51.730 not our our guests
NOTE Confidence: 0.809300720691681
00:19:51.829 --> 00:19:54.739 about the mechanism was correct.
NOTE Confidence: 0.809300720691681
00:19:54.740 --> 00:19:59.474 You can see here that when you give the.
NOTE Confidence: 0.809300720691681
00:19:59.480 --> 00:20:01.675 Aurora inhibitor there's a dramatic
NOTE Confidence: 0.809300720691681
00:20:01.675 --> 00:20:04.190 increase in phosphorylation of CDK one.
NOTE Confidence: 0.809300720691681
00:20:04.190 --> 00:20:06.734 This happens in a slightly different
NOTE Confidence: 0.809300720691681
00:20:06.734 --> 00:20:09.349 timeline in the two South and
NOTE Confidence: 0.809300720691681
00:20:09.349 --> 00:20:11.454 the two different cell lines,
NOTE Confidence: 0.809300720691681
00:20:11.460 --> 00:20:14.456 but seems to be a reproducible phenomenon,
NOTE Confidence: 0.809300720691681
00:20:14.460 --> 00:20:16.698 and that's abrogated by the addition
NOTE Confidence: 0.809300720691681
00:20:16.698 --> 00:20:19.689 of the wee one inhibitor and completely
NOTE Confidence: 0.809300720691681
00:20:19.689 --> 00:20:23.014 abolished when you gives it to together.
NOTE Confidence: 0.809300720691681
00:20:23.020 --> 00:20:26.452 This results in an increase in the number
NOTE Confidence: 0.809300720691681

00:20:26.452 --> 00:20:29.959 of mitotic figures that's abnormal to the.

NOTE Confidence: 0.809300720691681

00:20:29.960 --> 00:20:32.546 The. Presence of of really only

NOTE Confidence: 0.809300720691681

00:20:32.546 --> 00:20:34.801 single digit normal mitotic figures

NOTE Confidence: 0.809300720691681

00:20:34.801 --> 00:20:37.495 in the presence of the combination.

NOTE Confidence: 0.809300720691681

00:20:37.500 --> 00:20:40.034 So if you just walk through here,

NOTE Confidence: 0.809300720691681

00:20:40.040 --> 00:20:42.206 these are the normal mitotic figures.

NOTE Confidence: 0.809300720691681

00:20:42.210 --> 00:20:44.737 When you give the wee one inhibitor,

NOTE Confidence: 0.809300720691681

00:20:44.740 --> 00:20:47.110 you get some dis aggregation of

NOTE Confidence: 0.809300720691681

00:20:47.110 --> 00:20:49.063 chromatin reflected here in the

NOTE Confidence: 0.809300720691681

00:20:49.063 --> 00:20:50.899 fast food Stone Age 3 stain.

NOTE Confidence: 0.809300720691681

00:20:50.900 --> 00:20:53.066 When you give the Aurora inhibitor,

NOTE Confidence: 0.809300720691681

00:20:53.070 --> 00:20:55.492 you get the formation of these multipolar

NOTE Confidence: 0.809300720691681

00:20:55.492 --> 00:20:57.409 spindles three to four spindles,

NOTE Confidence: 0.809300720691681

00:20:57.410 --> 00:20:59.660 Purcell, and when you give the

NOTE Confidence: 0.809300720691681

00:20:59.660 --> 00:21:02.288 two together you get a, uh.

NOTE Confidence: 0.809300720691681

00:21:02.288 --> 00:21:05.880 Abnormal catastrophic mitotic figure.

NOTE Confidence: 0.809300720691681

00:21:05.880 --> 00:21:09.380 We also showed in using Annexin 5

NOTE Confidence: 0.809300720691681

00:21:09.380 --> 00:21:12.985 flow and looking for cleaved PARP that

NOTE Confidence: 0.809300720691681

00:21:12.985 --> 00:21:16.790 there's an increase in a pop ptosis.

NOTE Confidence: 0.809300720691681

00:21:16.790 --> 00:21:19.562 And we wanted to compare this

NOTE Confidence: 0.809300720691681

00:21:19.562 --> 00:21:21.410 to Aurora B inhibition,

NOTE Confidence: 0.809300720691681

00:21:21.410 --> 00:21:24.890 which completely cuts off mitotic entry

NOTE Confidence: 0.809300720691681

00:21:24.890 --> 00:21:27.210 by aggregating the phosphorylation

NOTE Confidence: 0.809300720691681

00:21:27.296 --> 00:21:30.152 of histone H3 and there was no

NOTE Confidence: 0.809300720691681

00:21:30.152 --> 00:21:32.182 synergy between these two agents

NOTE Confidence: 0.809300720691681

00:21:32.182 --> 00:21:34.360 and and you can see there.

NOTE Confidence: 0.809300720691681

00:21:34.360 --> 00:21:37.948 The lack of fastball, histone H3,

NOTE Confidence: 0.809300720691681

00:21:37.950 --> 00:21:41.740 an increase in DNA damage.

NOTE Confidence: 0.809300720691681

00:21:41.740 --> 00:21:44.820 Taking this into xenograft models here at

NOTE Confidence: 0.809300720691681

00:21:44.820 --> 00:21:48.698 either of two doses of the wee one inhibitor,

NOTE Confidence: 0.809300720691681

00:21:48.700 --> 00:21:51.244 the standard dose of the Aurora

NOTE Confidence: 0.809300720691681

00:21:51.244 --> 00:21:53.455 inhibitor tumors continued to grow
NOTE Confidence: 0.809300720691681

00:21:53.455 --> 00:21:55.655 not too differently from vehicle,
NOTE Confidence: 0.809300720691681

00:21:55.660 --> 00:21:58.705 but when we gave the two together,
NOTE Confidence: 0.809300720691681

00:21:58.710 --> 00:22:02.091 there was control of tumor growth and
NOTE Confidence: 0.809300720691681

00:22:02.091 --> 00:22:03.540 actually statistically significant
NOTE Confidence: 0.809300720691681

00:22:03.607 --> 00:22:06.289 improvement in survival for the animals.
NOTE Confidence: 0.809300720691681

00:22:06.290 --> 00:22:08.964 Looking at the tumors under the microscope
NOTE Confidence: 0.809300720691681

00:22:08.964 --> 00:22:11.857 when we gave the two agents together,
NOTE Confidence: 0.809300720691681

00:22:11.860 --> 00:22:14.326 there was a decrease in proliferation
NOTE Confidence: 0.809300720691681

00:22:14.326 --> 00:22:16.240 reflected in decreased Ki 67,
NOTE Confidence: 0.809300720691681

00:22:16.240 --> 00:22:18.844 there was increased cleaved caspase and
NOTE Confidence: 0.809300720691681

00:22:18.844 --> 00:22:21.809 there was a decrease in fast for CDK,
NOTE Confidence: 0.809300720691681

00:22:21.810 --> 00:22:24.428 one within tissue and if we did
NOTE Confidence: 0.809300720691681

00:22:24.428 --> 00:22:26.469 Aquaphor phospho CDK one and
NOTE Confidence: 0.809300720691681

00:22:26.469 --> 00:22:28.574 counted the amount of phosphorus,
NOTE Confidence: 0.809300720691681

00:22:28.580 --> 00:22:31.756 IDK one signal in the tumor leading edge.

NOTE Confidence: 0.809300720691681
00:22:31.760 --> 00:22:35.330 You can see this was dramatically decreased.
NOTE Confidence: 0.809300720691681
00:22:35.330 --> 00:22:37.568 Ellisor to has been a difficult
NOTE Confidence: 0.809300720691681
00:22:37.568 --> 00:22:39.939 drug to work within the clinic.
NOTE Confidence: 0.809300720691681
00:22:39.940 --> 00:22:41.860 It's associated with Mila suppression,
NOTE Confidence: 0.809300720691681
00:22:41.860 --> 00:22:43.775 and there's been a negative
NOTE Confidence: 0.809300720691681
00:22:43.775 --> 00:22:45.307 phase three monotherapy trial,
NOTE Confidence: 0.809300720691681
00:22:45.310 --> 00:22:46.120 and lymphoma,
NOTE Confidence: 0.809300720691681
00:22:46.120 --> 00:22:49.360 and so we were concerned that the development
NOTE Confidence: 0.809300720691681
00:22:49.434 --> 00:22:51.835 of that agent might not go forward.
NOTE Confidence: 0.809300720691681
00:22:51.840 --> 00:22:52.199 However,
NOTE Confidence: 0.809300720691681
00:22:52.199 --> 00:22:54.712 there's been a number of 2nd generation
NOTE Confidence: 0.809300720691681
00:22:54.712 --> 00:22:57.018 or or inhibitors that have come
NOTE Confidence: 0.809300720691681
00:22:57.018 --> 00:22:59.764 forward and we've had access to a
NOTE Confidence: 0.809300720691681
00:22:59.764 --> 00:23:02.158 compound from Taiho called task 119
NOTE Confidence: 0.809300720691681
00:23:02.158 --> 00:23:04.506 recently been acquired by Bit Track.
NOTE Confidence: 0.809300720691681

00:23:04.506 --> 00:23:07.180 And it's gonna be called Vic 1911
NOTE Confidence: 0.809300720691681

00:23:07.265 --> 00:23:10.170 moving forward and once again across a
NOTE Confidence: 0.809300720691681

00:23:10.170 --> 00:23:13.691 range of P53 mutated cell lines we see
NOTE Confidence: 0.809300720691681

00:23:13.691 --> 00:23:16.347 dramatic synergy for the two agents.
NOTE Confidence: 0.809300720691681

00:23:16.347 --> 00:23:17.261 Once again,
NOTE Confidence: 0.809300720691681

00:23:17.261 --> 00:23:20.003 we see synergy in xenograft models.
NOTE Confidence: 0.809300720691681

00:23:20.010 --> 00:23:23.465 This is confocal microscopy that
NOTE Confidence: 0.809300720691681

00:23:23.465 --> 00:23:26.920 again shows you the multipolar
NOTE Confidence: 0.809300720691681

00:23:27.030 --> 00:23:30.252 spindle formation with the use of
NOTE Confidence: 0.809300720691681

00:23:30.252 --> 00:23:32.400 task 119 is the
NOTE Confidence: 0.815518438816071

00:23:32.515 --> 00:23:34.379 Aurora inhibitor.
NOTE Confidence: 0.815518438816071

00:23:34.380 --> 00:23:37.089 But with the cells really arresting in
NOTE Confidence: 0.815518438816071

00:23:37.089 --> 00:23:39.847 that or becoming quiet sent in that
NOTE Confidence: 0.815518438816071

00:23:39.847 --> 00:23:42.127 multipolar spindle state an as they
NOTE Confidence: 0.815518438816071

00:23:42.204 --> 00:23:44.766 then attempt to enter mitosis in the
NOTE Confidence: 0.815518438816071

00:23:44.766 --> 00:23:47.785 in the presence of both the wee one

NOTE Confidence: 0.815518438816071
00:23:47.785 --> 00:23:49.700 inhibitor and the Aurora inhibitor,
NOTE Confidence: 0.815518438816071
00:23:49.700 --> 00:23:51.232 developing these very catastrophic
NOTE Confidence: 0.815518438816071
00:23:51.232 --> 00:23:53.116 mitotic phenotypes, an notice that
NOTE Confidence: 0.815518438816071
00:23:53.116 --> 00:23:56.210 I'm sort of running out of time here,
NOTE Confidence: 0.815518438816071
00:23:56.210 --> 00:23:58.884 so I won't March you through this,
NOTE Confidence: 0.815518438816071
00:23:58.890 --> 00:24:01.954 but the mechanism looks to be identical here,
NOTE Confidence: 0.815518438816071
00:24:01.960 --> 00:24:04.840 as what we saw with assertive.
NOTE Confidence: 0.815518438816071
00:24:04.840 --> 00:24:06.630 I'm working with our Columbus
NOTE Confidence: 0.815518438816071
00:24:06.630 --> 00:24:08.420 is Lambert at Fox Chase.
NOTE Confidence: 0.815518438816071
00:24:08.420 --> 00:24:10.200 We undertook a high throughput
NOTE Confidence: 0.815518438816071
00:24:10.200 --> 00:24:12.970 screen to see if we could find
NOTE Confidence: 0.815518438816071
00:24:12.970 --> 00:24:15.260 additional partners that would be.
NOTE Confidence: 0.815518438816071
00:24:15.260 --> 00:24:17.888 Both hindering and an fostering mitotic
NOTE Confidence: 0.815518438816071
00:24:17.888 --> 00:24:21.119 entry again with the attempt to exploit
NOTE Confidence: 0.815518438816071
00:24:21.119 --> 00:24:23.449 these multiple regulators of G2,
NOTE Confidence: 0.815518438816071

00:24:23.450 --> 00:24:25.772 M and another hit that appeared
NOTE Confidence: 0.815518438816071

00:24:25.772 --> 00:24:28.548 very strong was the check one
NOTE Confidence: 0.815518438816071

00:24:28.548 --> 00:24:30.276 inhibitor Prexasertib agent.
NOTE Confidence: 0.815518438816071

00:24:30.280 --> 00:24:32.890 It's not really moving forward in
NOTE Confidence: 0.815518438816071

00:24:32.890 --> 00:24:35.739 the clinic because of its toxicity,
NOTE Confidence: 0.815518438816071

00:24:35.740 --> 00:24:39.058 but I wanted to show this just
NOTE Confidence: 0.815518438816071

00:24:39.058 --> 00:24:42.079 because with very low dose Ng and
NOTE Confidence: 0.815518438816071

00:24:42.079 --> 00:24:45.320 a single dose we saw a profound.
NOTE Confidence: 0.815518438816071

00:24:45.320 --> 00:24:47.042 Energetic survival effects that make us
NOTE Confidence: 0.815518438816071

00:24:47.042 --> 00:24:49.308 hopeful that with a number of these pairs,
NOTE Confidence: 0.815518438816071

00:24:49.310 --> 00:24:51.886 we might be able to go to very
NOTE Confidence: 0.815518438816071

00:24:51.886 --> 00:24:53.740 low doses in the clinic.
NOTE Confidence: 0.815518438816071

00:24:53.740 --> 00:24:56.050 So test 119 has completed
NOTE Confidence: 0.815518438816071

00:24:56.050 --> 00:24:57.436 two clinical trials.
NOTE Confidence: 0.815518438816071

00:24:57.440 --> 00:25:00.206 There's a recommended phase two dose.
NOTE Confidence: 0.815518438816071

00:25:00.210 --> 00:25:03.290 The toxicity seems to be very manageable

NOTE Confidence: 0.815518438816071

00:25:03.290 --> 00:25:05.750 with diarrhea and eye disorders.

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

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

NOTE Confidence: 0.815518438816071

00:25:39.291 --> 00:25:41.191 the fabulous colleagues who were
NOTE Confidence: 0.815518438816071

00:25:41.191 --> 00:25:43.511 part of the team that they put
NOTE Confidence: 0.815518438816071

00:25:43.511 --> 00:25:45.741 the head and explore in and then
NOTE Confidence: 0.815518438816071

00:25:45.741 --> 00:25:47.376 acknowledging all the people whose
NOTE Confidence: 0.815518438816071

00:25:47.376 --> 00:25:49.139 work I've just talked about,
NOTE Confidence: 0.815518438816071

00:25:49.140 --> 00:25:51.005 particularly John Wooley Jannike Parameshwar
NOTE Confidence: 0.815518438816071

00:25:51.005 --> 00:25:53.520 on in Teresa Sandoval Schaefer in the lamp.
NOTE Confidence: 0.815518438816071

00:25:53.520 --> 00:25:55.220 So thank you very much.
NOTE Confidence: 0.815518438816071

00:25:55.220 --> 00:25:55.610 Barbara,
NOTE Confidence: 0.815518438816071

00:25:55.610 --> 00:25:56.390 thank you.
NOTE Confidence: 0.834983050823212

00:25:56.390 --> 00:25:57.707 That's fabulous work.
NOTE Confidence: 0.834983050823212

00:25:57.707 --> 00:26:00.341 Congratulations on all of it and
NOTE Confidence: 0.834983050823212

00:26:00.341 --> 00:26:02.713 and folks can submit questions on
NOTE Confidence: 0.834983050823212

00:26:02.713 --> 00:26:05.780 the on the chat box of of the zoom,
NOTE Confidence: 0.834983050823212

00:26:05.780 --> 00:26:08.524 but I wanted to ask, you know,
NOTE Confidence: 0.834983050823212

00:26:08.524 --> 00:26:10.906 with regard as you look through

NOTE Confidence: 0.834983050823212
00:26:10.906 --> 00:26:12.895 the combination of an Aurora
NOTE Confidence: 0.834983050823212
00:26:12.895 --> 00:26:14.765 kinase and we want inhibitors,
NOTE Confidence: 0.834983050823212
00:26:14.770 --> 00:26:18.680 do you have a sense of 1st what might emerge?
NOTE Confidence: 0.834983050823212
00:26:18.680 --> 00:26:21.020 I'm even when you're getting response
NOTE Confidence: 0.834983050823212
00:26:21.020 --> 00:26:23.758 because of the complexity of those pathways.
NOTE Confidence: 0.834983050823212
00:26:23.760 --> 00:26:25.436 What might emerges mechanism?
NOTE Confidence: 0.834983050823212
00:26:25.436 --> 00:26:27.531 Resistance that will occur when
NOTE Confidence: 0.834983050823212
00:26:27.531 --> 00:26:30.186 you have dual inhibition of any and
NOTE Confidence: 0.834983050823212
00:26:30.186 --> 00:26:32.552 then the second question I have is
NOTE Confidence: 0.834983050823212
00:26:32.552 --> 00:26:34.540 what do you anticipate will be the
NOTE Confidence: 0.834983050823212
00:26:34.540 --> 00:26:36.300 toxicity profile or the therapeutic
NOTE Confidence: 0.834983050823212
00:26:36.300 --> 00:26:38.060 therapeutic window for the combination
NOTE Confidence: 0.827964603900909
00:26:38.060 --> 00:26:40.496 clinically. So the we want inhibitors
NOTE Confidence: 0.827964603900909
00:26:40.496 --> 00:26:42.527 been quite tolerable 'cause I'm
NOTE Confidence: 0.827964603900909
00:26:42.527 --> 00:26:44.585 going to take the second question
NOTE Confidence: 0.827964603900909

00:26:44.585 --> 00:26:46.269 first 'cause I've already wrestled
NOTE Confidence: 0.827964603900909

00:26:46.269 --> 00:26:48.613 with X and a lot that we want.
NOTE Confidence: 0.827964603900909

00:26:48.620 --> 00:26:49.928 Inhibitors been quite tolerable
NOTE Confidence: 0.827964603900909

00:26:49.928 --> 00:26:52.339 in the clinic but when it was
NOTE Confidence: 0.827964603900909

00:26:52.339 --> 00:26:53.899 combined with PARP inhibition,
NOTE Confidence: 0.827964603900909

00:26:53.900 --> 00:26:56.036 diarrhea really became the dose limiting.
NOTE Confidence: 0.827964603900909

00:26:56.040 --> 00:26:58.860 Side effect, and so this second
NOTE Confidence: 0.827964603900909

00:26:58.860 --> 00:27:01.123 generation Aurora inhibitor did have
NOTE Confidence: 0.827964603900909

00:27:01.123 --> 00:27:04.140 about a 25% rate of high grade diarrhea
NOTE Confidence: 0.827964603900909

00:27:04.140 --> 00:27:06.720 at the recommended phase two dose.
NOTE Confidence: 0.827964603900909

00:27:06.720 --> 00:27:09.810 So the two things that were
NOTE Confidence: 0.827964603900909

00:27:09.810 --> 00:27:12.220 sort of hoping is 1.
NOTE Confidence: 0.827964603900909

00:27:12.220 --> 00:27:15.271 That will get away with lower doses as we
NOTE Confidence: 0.827964603900909

00:27:15.271 --> 00:27:18.570 have in the animal models and second of all,
NOTE Confidence: 0.827964603900909

00:27:18.570 --> 00:27:20.772 the diarrhea as it dose limiting
NOTE Confidence: 0.827964603900909

00:27:20.772 --> 00:27:23.640 toxicity is one of the easier ones to

NOTE Confidence: 0.827964603900909

00:27:23.640 --> 00:27:26.737 manage and so that if we're on top of

NOTE Confidence: 0.827964603900909

00:27:26.737 --> 00:27:29.152 this with an Imodium regimen early on,

NOTE Confidence: 0.827964603900909

00:27:29.160 --> 00:27:31.778 hopefully that will be helpful in terms

NOTE Confidence: 0.827964603900909

00:27:31.778 --> 00:27:33.591 of resistance mechanisms with this

NOTE Confidence: 0.827964603900909

00:27:33.591 --> 00:27:35.481 is not something that we've really

NOTE Confidence: 0.827964603900909

00:27:35.481 --> 00:27:37.638 gone into with the combination yet,

NOTE Confidence: 0.827964603900909

00:27:37.640 --> 00:27:40.720 but is well studied for both of the

NOTE Confidence: 0.827964603900909

00:27:40.720 --> 00:27:42.587 agents independently and one of the.

NOTE Confidence: 0.827964603900909

00:27:42.590 --> 00:27:44.605 Resistance mechanisms to the Aurora

NOTE Confidence: 0.827964603900909

00:27:44.605 --> 00:27:47.758 agents has been a kind of conformational

NOTE Confidence: 0.827964603900909

00:27:47.758 --> 00:27:49.890 dependence on the inhibitor,

NOTE Confidence: 0.827964603900909

00:27:49.890 --> 00:27:52.512 so inhibitor binds to the activated

NOTE Confidence: 0.827964603900909

00:27:52.512 --> 00:27:56.274 form of Aurora A and if you get a

NOTE Confidence: 0.827964603900909

00:27:56.274 --> 00:27:58.868 an adaptive process where the cell

NOTE Confidence: 0.827964603900909

00:27:58.868 --> 00:28:01.738 just generates more inactive Aurora,

NOTE Confidence: 0.827964603900909

00:28:01.740 --> 00:28:04.698 the current generation of inhibitors may
NOTE Confidence: 0.827964603900909

00:28:04.698 --> 00:28:08.577 not work as well and there is a group.
NOTE Confidence: 0.827964603900909

00:28:08.580 --> 00:28:11.298 Kevan Shokat lab has been developing
NOTE Confidence: 0.827964603900909

00:28:11.298 --> 00:28:13.600 novel Aurora inhibitors that maybe.
NOTE Confidence: 0.827964603900909

00:28:13.600 --> 00:28:16.528 More able to bind the inactive
NOTE Confidence: 0.827964603900909

00:28:16.528 --> 00:28:21.144 confirmation as well. And in terms
NOTE Confidence: 0.827964603900909

00:28:21.144 --> 00:28:28.480 of we want inhibitors there there is.
NOTE Confidence: 0.827964603900909

00:28:28.480 --> 00:28:35.900 Suggestions that? The the.
NOTE Confidence: 0.827964603900909

00:28:35.900 --> 00:28:40.760 Do you need damage effects of?
NOTE Confidence: 0.827964603900909

00:28:40.760 --> 00:28:45.350 That we want inhibitors may have an S phase.
NOTE Confidence: 0.827964603900909

00:28:45.350 --> 00:28:48.675 Could actually upregulate some checkpoints
NOTE Confidence: 0.827964603900909

00:28:48.675 --> 00:28:53.220 that are earlier in the cell cycle.
NOTE Confidence: 0.827964603900909

00:28:53.220 --> 00:28:54.590 But it's a good question.
NOTE Confidence: 0.827964603900909

00:28:54.590 --> 00:28:55.678 Probably something we should
NOTE Confidence: 0.827964603900909

00:28:55.678 --> 00:28:56.766 devote more effort to.
NOTE Confidence: 0.831635475158691

00:28:57.380 --> 00:28:59.420 Yeah, well, I'm sure it'll

NOTE Confidence: 0.831635475158691
00:28:59.420 --> 00:29:00.646 it'll definitely emerge.
NOTE Confidence: 0.831635475158691
00:29:00.646 --> 00:29:03.908 Emerge as you get samples from your trial.
NOTE Confidence: 0.831635475158691
00:29:03.910 --> 00:29:05.586 So it's really exciting.
NOTE Confidence: 0.831635475158691
00:29:05.586 --> 00:29:08.799 And congratulations so I know we're at 12:31.
NOTE Confidence: 0.831635475158691
00:29:08.800 --> 00:29:10.840 Wherever so why don't we
NOTE Confidence: 0.831635475158691
00:29:10.840 --> 00:29:12.880 will turn out to people?
NOTE Confidence: 0.831635475158691
00:29:12.880 --> 00:29:15.328 Can submit questions to Barbara Online,
NOTE Confidence: 0.831635475158691
00:29:15.330 --> 00:29:18.098 but will turn now to our second speaker
NOTE Confidence: 0.831635475158691
00:29:18.098 --> 00:29:20.716 and very fortunate to have another
NOTE Confidence: 0.831635475158691
00:29:20.716 --> 00:29:23.488 valued member of our faculty speaking.
NOTE Confidence: 0.831635475158691
00:29:23.490 --> 00:29:25.956 Doctor Elizabeth Klaus is a professor
NOTE Confidence: 0.831635475158691
00:29:25.956 --> 00:29:27.600 of Biostatistics and neurosurgery.
NOTE Confidence: 0.831635475158691
00:29:27.600 --> 00:29:30.222 Focused not only on brain tumors
NOTE Confidence: 0.831635475158691
00:29:30.222 --> 00:29:31.970 but also the Epidemiology,
NOTE Confidence: 0.831635475158691
00:29:31.970 --> 00:29:33.718 most notably the genetic
NOTE Confidence: 0.831635475158691

00:29:33.718 --> 00:29:35.466 Epidemiology of these malignancies.
NOTE Confidence: 0.831635475158691

00:29:35.470 --> 00:29:38.806 She received her MD and PhD from Yale
NOTE Confidence: 0.831635475158691

00:29:38.806 --> 00:29:41.499 and completed her surgery here in
NOTE Confidence: 0.831635475158691

00:29:41.499 --> 00:29:44.151 their surgery and through her work
NOTE Confidence: 0.831635475158691

00:29:44.237 --> 00:29:46.841 she really has been an international
NOTE Confidence: 0.831635475158691

00:29:46.841 --> 00:29:49.454 leader in in the investigation of
NOTE Confidence: 0.831635475158691

00:29:49.454 --> 00:29:51.639 the Epidemiology of CNS Malignancy's,
NOTE Confidence: 0.831635475158691

00:29:51.640 --> 00:29:54.262 most notably serving as the leader
NOTE Confidence: 0.831635475158691

00:29:54.262 --> 00:29:56.010 of the Meningioma consortium,
NOTE Confidence: 0.831635475158691

00:29:56.010 --> 00:29:57.974 that meningioma Genome Wide
NOTE Confidence: 0.831635475158691

00:29:57.974 --> 00:29:58.956 Association study.
NOTE Confidence: 0.831635475158691

00:29:58.960 --> 00:29:59.365 Also,
NOTE Confidence: 0.831635475158691

00:29:59.365 --> 00:30:02.605 a leader of the AL Acoustic neuroma study,
NOTE Confidence: 0.831635475158691

00:30:02.610 --> 00:30:05.730 and we again were so pleased to have
NOTE Confidence: 0.831635475158691

00:30:05.730 --> 00:30:08.233 talented people who bridge the gap
NOTE Confidence: 0.831635475158691

00:30:08.233 --> 00:30:10.705 of Epidemiology in biology of cancer

NOTE Confidence: 0.831635475158691

00:30:10.785 --> 00:30:13.564 and Elizabeth thank you so much for

NOTE Confidence: 0.831635475158691

00:30:13.564 --> 00:30:17.388 sharing your work with us today.

NOTE Confidence: 0.831635475158691

00:30:17.390 --> 00:30:18.326 Thanks very much.

NOTE Confidence: 0.831635475158691

00:30:18.326 --> 00:30:19.892 Can you see my slides?

NOTE Confidence: 0.831635475158691

00:30:19.892 --> 00:30:20.204 OK,

NOTE Confidence: 0.831635475158691

00:30:20.204 --> 00:30:20.828 yes great.

NOTE Confidence: 0.850167512893677

00:30:20.830 --> 00:30:22.090 So I'm going to

NOTE Confidence: 0.850167512893677

00:30:22.090 --> 00:30:24.088 talk a little bit about something

NOTE Confidence: 0.850167512893677

00:30:24.088 --> 00:30:26.403 we've been working on an I do want

NOTE Confidence: 0.850167512893677

00:30:26.403 --> 00:30:28.571 to note that this is work done in

NOTE Confidence: 0.850167512893677

00:30:28.571 --> 00:30:30.386 collaboration with Jeff Townsend's Group

NOTE Confidence: 0.850167512893677

00:30:30.386 --> 00:30:33.040 who I think you all know very well.

NOTE Confidence: 0.850167512893677

00:30:33.040 --> 00:30:34.605 And Vincent Kenna Tarot as

NOTE Confidence: 0.850167512893677

00:30:34.605 --> 00:30:35.857 well as Steven Gaffney.

NOTE Confidence: 0.850167512893677

00:30:35.860 --> 00:30:37.425 So despite all the things

NOTE Confidence: 0.850167512893677

00:30:37.425 --> 00:30:38.990 that we've attempted to do,
NOTE Confidence: 0.850167512893677

00:30:38.990 --> 00:30:40.868 we still don't know much about
NOTE Confidence: 0.850167512893677

00:30:40.868 --> 00:30:42.120 risk factors for glioma.
NOTE Confidence: 0.850167512893677

00:30:42.120 --> 00:30:43.940 And we wanted to take a look
NOTE Confidence: 0.850167512893677

00:30:43.940 --> 00:30:45.939 and see if they were different
NOTE Confidence: 0.850167512893677

00:30:45.939 --> 00:30:47.854 methods that we could use.
NOTE Confidence: 0.850167512893677

00:30:47.860 --> 00:30:50.184 To see if we could tease out
NOTE Confidence: 0.850167512893677

00:30:50.184 --> 00:30:51.998 both environmental and then also
NOTE Confidence: 0.850167512893677

00:30:51.998 --> 00:30:54.230 another hot topic is sex specific
NOTE Confidence: 0.850167512893677

00:30:54.230 --> 00:30:56.150 signatures of glioma causation.
NOTE Confidence: 0.850167512893677

00:30:56.150 --> 00:30:59.548 So you all know that gliomas are the most
NOTE Confidence: 0.850167512893677

00:30:59.548 --> 00:31:01.810 common type of malignant brain tumor,
NOTE Confidence: 0.850167512893677

00:31:01.810 --> 00:31:04.826 accounting for about 1/3 of all brain tumors,
NOTE Confidence: 0.850167512893677

00:31:04.830 --> 00:31:07.086 and the majority of malignant tumors.
NOTE Confidence: 0.850167512893677

00:31:07.090 --> 00:31:09.226 But they proved to be very
NOTE Confidence: 0.850167512893677

00:31:09.226 --> 00:31:11.899 heterogeneous and we have not done a

NOTE Confidence: 0.850167512893677

00:31:11.899 --> 00:31:13.864 great job identifying risk factors,

NOTE Confidence: 0.850167512893677

00:31:13.870 --> 00:31:17.055 be they genetic or environmental for glioma.

NOTE Confidence: 0.850167512893677

00:31:17.060 --> 00:31:19.364 And so we were interested in doing that,

NOTE Confidence: 0.850167512893677

00:31:19.370 --> 00:31:21.694 particularly in light of the poor outcomes

NOTE Confidence: 0.850167512893677

00:31:21.694 --> 00:31:24.476 that we see with this group of patients.

NOTE Confidence: 0.850167512893677

00:31:24.480 --> 00:31:28.296 So we do know that there are sex specific

NOTE Confidence: 0.850167512893677

00:31:28.296 --> 00:31:31.065 differences in glioma risk and outcome and

NOTE Confidence: 0.850167512893677

00:31:31.065 --> 00:31:34.656 the plots I have here are for all gliomas,

NOTE Confidence: 0.850167512893677

00:31:34.660 --> 00:31:36.284 an then glioblastoma or

NOTE Confidence: 0.850167512893677

00:31:36.284 --> 00:31:38.314 sort of an IDH positive.

NOTE Confidence: 0.850167512893677

00:31:38.320 --> 00:31:39.256 Excuse me,

NOTE Confidence: 0.850167512893677

00:31:39.256 --> 00:31:41.596 IDH negative tumor and then

NOTE Confidence: 0.850167512893677

00:31:41.596 --> 00:31:43.000 lower grade gliomas.

NOTE Confidence: 0.850167512893677

00:31:43.000 --> 00:31:44.760 The males being the blue,

NOTE Confidence: 0.850167512893677

00:31:44.760 --> 00:31:47.040 the females being the red.

NOTE Confidence: 0.850167512893677

00:31:47.040 --> 00:31:49.068 And it's interesting in that we
NOTE Confidence: 0.850167512893677

00:31:49.068 --> 00:31:50.904 see this sex specific difference
NOTE Confidence: 0.850167512893677

00:31:50.904 --> 00:31:52.979 across the entire age range,
NOTE Confidence: 0.850167512893677

00:31:52.980 --> 00:31:55.206 so it's a little bit different
NOTE Confidence: 0.850167512893677

00:31:55.206 --> 00:31:56.690 than we see with,
NOTE Confidence: 0.850167512893677

00:31:56.690 --> 00:31:57.434 for example,
NOTE Confidence: 0.850167512893677

00:31:57.434 --> 00:31:59.294 meningiomas where we see the
NOTE Confidence: 0.850167512893677

00:31:59.294 --> 00:32:00.770 women having greater risk,
NOTE Confidence: 0.850167512893677

00:32:00.770 --> 00:32:02.858 but the risk difference decreasing once
NOTE Confidence: 0.850167512893677

00:32:02.858 --> 00:32:04.850 women passed through the menopause.
NOTE Confidence: 0.850167512893677

00:32:04.850 --> 00:32:07.028 Whereas here we see the sex
NOTE Confidence: 0.850167512893677

00:32:07.028 --> 00:32:08.920 differences for glioma across the
NOTE Confidence: 0.850167512893677

00:32:08.920 --> 00:32:11.158 age spectrum and across all subtypes,
NOTE Confidence: 0.850167512893677

00:32:11.160 --> 00:32:13.260 and so that obviously suggests
NOTE Confidence: 0.850167512893677

00:32:13.260 --> 00:32:15.360 that other mechanisms in addition
NOTE Confidence: 0.850167512893677

00:32:15.432 --> 00:32:17.469 to a good sex hormones must be.

NOTE Confidence: 0.850167512893677

00:32:17.470 --> 00:32:19.222 Are behind the difference men are

NOTE Confidence: 0.850167512893677

00:32:19.222 --> 00:32:21.187 at greater risk of being diagnosed

NOTE Confidence: 0.850167512893677

00:32:21.187 --> 00:32:22.297 with the disease.

NOTE Confidence: 0.850167512893677

00:32:22.300 --> 00:32:22.992 And again,

NOTE Confidence: 0.850167512893677

00:32:22.992 --> 00:32:24.722 that's across pretty much all

NOTE Confidence: 0.850167512893677

00:32:24.722 --> 00:32:26.861 the subtypes and they also have

NOTE Confidence: 0.850167512893677

00:32:26.861 --> 00:32:28.591 lower survival in general then

NOTE Confidence: 0.850167512893677

00:32:28.591 --> 00:32:30.560 for females across all subtypes.

NOTE Confidence: 0.850167512893677

00:32:30.560 --> 00:32:32.919 So we've looked at this a little

NOTE Confidence: 0.850167512893677

00:32:32.919 --> 00:32:35.351 bit and I've been lucky enough

NOTE Confidence: 0.850167512893677

00:32:35.351 --> 00:32:38.045 to collaborate with a group of

NOTE Confidence: 0.850167512893677

00:32:38.045 --> 00:32:39.919 individuals called the glioma.

NOTE Confidence: 0.850167512893677

00:32:39.920 --> 00:32:41.548 International Case Controls Consortium,

NOTE Confidence: 0.850167512893677

00:32:41.548 --> 00:32:43.990 and that's led by Melissa Bondy,

NOTE Confidence: 0.850167512893677

00:32:43.990 --> 00:32:46.839 initially at MD Anderson, then it Baylor.

NOTE Confidence: 0.850167512893677

00:32:46.840 --> 00:32:49.276 Now she heads up the Epidemiology

NOTE Confidence: 0.850167512893677

00:32:49.276 --> 00:32:50.494 section at Stanford,

NOTE Confidence: 0.850167512893677

00:32:50.500 --> 00:32:53.027 but we were able to gather over

NOTE Confidence: 0.850167512893677

00:32:53.027 --> 00:32:55.390 10,000 cases and 10,000 controls,

NOTE Confidence: 0.850167512893677

00:32:55.390 --> 00:32:58.102 and so these are essentially looking

NOTE Confidence: 0.850167512893677

00:32:58.102 --> 00:32:59.910 at constitutional or germline

NOTE Confidence: 0.850167512893677

00:32:59.980 --> 00:33:01.348 risk alleles by sex.

NOTE Confidence: 0.850167512893677

00:33:01.350 --> 00:33:03.660 So if I can draw your attention

NOTE Confidence: 0.850167512893677

00:33:03.660 --> 00:33:05.479 to the table over here,

NOTE Confidence: 0.850167512893677

00:33:05.480 --> 00:33:07.316 these are the variants that we

NOTE Confidence: 0.850167512893677

00:33:07.316 --> 00:33:09.019 found to be significantly different

NOTE Confidence: 0.850167512893677

00:33:09.019 --> 00:33:10.288 males versus females.

NOTE Confidence: 0.850167512893677

00:33:10.290 --> 00:33:11.666 Males being the blue,

NOTE Confidence: 0.850167512893677

00:33:11.666 --> 00:33:13.386 an females being the red.

NOTE Confidence: 0.850167512893677

00:33:13.390 --> 00:33:15.454 So we did certainly find differences

NOTE Confidence: 0.850167512893677

00:33:15.454 --> 00:33:16.830 at the germline level,

NOTE Confidence: 0.850167512893677

00:33:16.830 --> 00:33:18.762 but we were also interested in

NOTE Confidence: 0.850167512893677

00:33:18.762 --> 00:33:20.853 looking at things at the tumor

NOTE Confidence: 0.850167512893677

00:33:20.853 --> 00:33:22.325 or their cinematic level.

NOTE Confidence: 0.850167512893677

00:33:22.330 --> 00:33:25.090 0 Sex is a biologic variables I mentioned.

NOTE Confidence: 0.850167512893677

00:33:25.090 --> 00:33:27.148 This is a very hot topic.

NOTE Confidence: 0.841646373271942

00:33:27.150 --> 00:33:29.607 Now we obviously know there are biologic

NOTE Confidence: 0.841646373271942

00:33:29.607 --> 00:33:31.359 differences between males and females.

NOTE Confidence: 0.841646373271942

00:33:31.360 --> 00:33:33.328 There's also some thought as to

NOTE Confidence: 0.841646373271942

00:33:33.328 --> 00:33:34.640 whether there's variation in

NOTE Confidence: 0.841646373271942

00:33:34.695 --> 00:33:36.390 the prevalence of risk factors,

NOTE Confidence: 0.841646373271942

00:33:36.390 --> 00:33:37.865 and then also whether there's

NOTE Confidence: 0.841646373271942

00:33:37.865 --> 00:33:40.204 a difference in sort of a gene

NOTE Confidence: 0.841646373271942

00:33:40.204 --> 00:33:41.407 by environmental interaction.

NOTE Confidence: 0.841646373271942

00:33:41.410 --> 00:33:42.415 So, for example,

NOTE Confidence: 0.841646373271942

00:33:42.415 --> 00:33:44.425 and this has long been postulated,

NOTE Confidence: 0.841646373271942

00:33:44.430 --> 00:33:46.470 but it's really been pretty difficult
NOTE Confidence: 0.841646373271942

00:33:46.470 --> 00:33:48.807 to prove that males in particular are
NOTE Confidence: 0.841646373271942

00:33:48.807 --> 00:33:51.353 more likely to be exposed to work like
NOTE Confidence: 0.841646373271942

00:33:51.353 --> 00:33:53.810 toxins that might be associated with risk,
NOTE Confidence: 0.841646373271942

00:33:53.810 --> 00:33:56.546 and so that was one of the things
NOTE Confidence: 0.841646373271942

00:33:56.546 --> 00:33:58.826 we wanted to look at as well.
NOTE Confidence: 0.841646373271942

00:33:58.830 --> 00:34:01.510 And in part, why we divided our analysis.
NOTE Confidence: 0.841646373271942

00:34:01.510 --> 00:34:03.390 By sex.
NOTE Confidence: 0.841646373271942

00:34:03.390 --> 00:34:05.484 So there's two goals and what
NOTE Confidence: 0.841646373271942

00:34:05.484 --> 00:34:07.850 I'm going to talk about today.
NOTE Confidence: 0.841646373271942

00:34:07.850 --> 00:34:10.454 We wanted to look at the relative
NOTE Confidence: 0.841646373271942

00:34:10.454 --> 00:34:12.451 contribution and this is based on
NOTE Confidence: 0.841646373271942

00:34:12.451 --> 00:34:14.935 some of the work that I know you've
NOTE Confidence: 0.841646373271942

00:34:14.935 --> 00:34:17.530 already appreciated with Jeff Townsend,
NOTE Confidence: 0.841646373271942

00:34:17.530 --> 00:34:19.385 but we're applying it specifically
NOTE Confidence: 0.841646373271942

00:34:19.385 --> 00:34:20.498 now to glioma,

NOTE Confidence: 0.841646373271942
00:34:20.500 --> 00:34:22.360 but looking at the relative
NOTE Confidence: 0.841646373271942
00:34:22.360 --> 00:34:24.220 contribution of cancer cell lineages,
NOTE Confidence: 0.841646373271942
00:34:24.220 --> 00:34:25.708 proliferation and survival of
NOTE Confidence: 0.841646373271942
00:34:25.708 --> 00:34:26.824 single nucleotide mutations,
NOTE Confidence: 0.841646373271942
00:34:26.830 --> 00:34:29.062 and we divided our study subjects
NOTE Confidence: 0.841646373271942
00:34:29.062 --> 00:34:30.550 up by IDH mutation.
NOTE Confidence: 0.841646373271942
00:34:30.550 --> 00:34:32.776 And, as most of you know,
NOTE Confidence: 0.841646373271942
00:34:32.780 --> 00:34:35.012 IDH mutation is one of the
NOTE Confidence: 0.841646373271942
00:34:35.012 --> 00:34:36.500 key dividers into the.
NOTE Confidence: 0.841646373271942
00:34:36.500 --> 00:34:38.915 The higher in the lower grade tumors,
NOTE Confidence: 0.841646373271942
00:34:38.920 --> 00:34:40.640 and certainly a prognostic factor,
NOTE Confidence: 0.841646373271942
00:34:40.640 --> 00:34:43.745 as well as a factor in response to treatment.
NOTE Confidence: 0.841646373271942
00:34:43.750 --> 00:34:45.470 We also wanted to quantify,
NOTE Confidence: 0.841646373271942
00:34:45.470 --> 00:34:47.535 and this is something that is a
NOTE Confidence: 0.841646373271942
00:34:47.535 --> 00:34:49.199 little bit new to Epidemiology
NOTE Confidence: 0.841646373271942

00:34:49.199 --> 00:34:51.670 in terms of how we've tried to
NOTE Confidence: 0.841646373271942

00:34:51.670 --> 00:34:53.059 identify risk exposures.
NOTE Confidence: 0.841646373271942

00:34:53.060 --> 00:34:54.975 Typically we've done things like
NOTE Confidence: 0.841646373271942

00:34:54.975 --> 00:34:56.890 large case control studies where
NOTE Confidence: 0.841646373271942

00:34:56.950 --> 00:34:58.931 we look at large numbers of people
NOTE Confidence: 0.841646373271942

00:34:58.931 --> 00:35:00.310 that have the disease,
NOTE Confidence: 0.841646373271942

00:35:00.310 --> 00:35:02.035 compare them to large numbers
NOTE Confidence: 0.841646373271942

00:35:02.035 --> 00:35:03.760 of people without the disease,
NOTE Confidence: 0.841646373271942

00:35:03.760 --> 00:35:05.842 and look at things like questionnaire
NOTE Confidence: 0.841646373271942

00:35:05.842 --> 00:35:06.883 or work pic.
NOTE Confidence: 0.841646373271942

00:35:06.890 --> 00:35:09.626 Exposure and see if we can figure out
NOTE Confidence: 0.841646373271942

00:35:09.626 --> 00:35:11.757 differences between the cases and controls.
NOTE Confidence: 0.841646373271942

00:35:11.760 --> 00:35:13.500 So what we're doing now,
NOTE Confidence: 0.841646373271942

00:35:13.500 --> 00:35:15.565 and this is sort of an emerging
NOTE Confidence: 0.841646373271942

00:35:15.565 --> 00:35:17.330 field in cancer Epidemiology,
NOTE Confidence: 0.841646373271942

00:35:17.330 --> 00:35:19.787 is to look at the cosmic cancer

NOTE Confidence: 0.841646373271942
00:35:19.787 --> 00:35:21.511 mutational signatures in tumors and
NOTE Confidence: 0.841646373271942
00:35:21.511 --> 00:35:23.618 see if we can then backtrack match
NOTE Confidence: 0.841646373271942
00:35:23.618 --> 00:35:25.677 it to possible risk exposures,
NOTE Confidence: 0.841646373271942
00:35:25.680 --> 00:35:27.787 and one of the things we're hoping
NOTE Confidence: 0.841646373271942
00:35:27.787 --> 00:35:30.870 to do in the future is to go back to
NOTE Confidence: 0.841646373271942
00:35:30.870 --> 00:35:33.127 our cohorts and studies for which
NOTE Confidence: 0.841646373271942
00:35:33.127 --> 00:35:35.262 we collected good occupational data
NOTE Confidence: 0.841646373271942
00:35:35.262 --> 00:35:38.556 and see if we can match it up to.
NOTE Confidence: 0.841646373271942
00:35:38.560 --> 00:35:42.131 Mutational signatures So the methods
NOTE Confidence: 0.841646373271942
00:35:42.131 --> 00:35:44.153 I'll talk a little bit about.
NOTE Confidence: 0.841646373271942
00:35:44.160 --> 00:35:45.516 I am highlighting here.
NOTE Confidence: 0.841646373271942
00:35:45.516 --> 00:35:47.940 Jeff's paper that he had in J&CI
NOTE Confidence: 0.841646373271942
00:35:47.940 --> 00:35:48.888 two years ago,
NOTE Confidence: 0.841646373271942
00:35:48.890 --> 00:35:50.962 and I think you've seen some of
NOTE Confidence: 0.841646373271942
00:35:50.962 --> 00:35:52.949 these sorts of methods applied,
NOTE Confidence: 0.841646373271942

00:35:52.950 --> 00:35:55.000 in particular to actually head
NOTE Confidence: 0.841646373271942

00:35:55.000 --> 00:35:56.230 and neck cancer.
NOTE Confidence: 0.841646373271942

00:35:56.230 --> 00:35:58.670 So the Cancer Genome Atlas,
NOTE Confidence: 0.841646373271942

00:35:58.670 --> 00:36:01.100 and others, including the glioma
NOTE Confidence: 0.841646373271942

00:36:01.100 --> 00:36:02.558 Longitudinal Analysis Consortium,
NOTE Confidence: 0.841646373271942

00:36:02.560 --> 00:36:05.969 or Glass, which is led by roll.
NOTE Confidence: 0.841646373271942

00:36:05.970 --> 00:36:06.968 Their Hokage,
NOTE Confidence: 0.841646373271942

00:36:06.968 --> 00:36:11.330 Jackson Labs and which I'm also a member of.
NOTE Confidence: 0.841646373271942

00:36:11.330 --> 00:36:13.810 So these groups have identified
NOTE Confidence: 0.841646373271942

00:36:13.810 --> 00:36:16.838 the most common genetic changes in
NOTE Confidence: 0.841646373271942

00:36:16.838 --> 00:36:19.604 primary glioma tumors including TP 53,
NOTE Confidence: 0.841646373271942

00:36:19.610 --> 00:36:20.080 IDH,
NOTE Confidence: 0.841646373271942

00:36:20.080 --> 00:36:22.430 EGFR with the relative importance
NOTE Confidence: 0.841646373271942

00:36:22.430 --> 00:36:25.403 of these mutations and how they
NOTE Confidence: 0.841646373271942

00:36:25.403 --> 00:36:26.927 relate to tumorigenesis.
NOTE Confidence: 0.841646373271942

00:36:26.930 --> 00:36:28.366 Is not well known,

NOTE Confidence: 0.841646373271942
00:36:28.366 --> 00:36:31.053 so one of the things that we've
NOTE Confidence: 0.841646373271942
00:36:31.053 --> 00:36:32.400 been working on,
NOTE Confidence: 0.841646373271942
00:36:32.400 --> 00:36:34.878 and Jeff has been a leader in
NOTE Confidence: 0.841646373271942
00:36:34.878 --> 00:36:35.940 is defining this
NOTE Confidence: 0.841837286949158
00:36:36.025 --> 00:36:37.489 cancer affect size.
NOTE Confidence: 0.841837286949158
00:36:37.490 --> 00:36:39.686 So this metric of the relative
NOTE Confidence: 0.841837286949158
00:36:39.686 --> 00:36:41.641 overabundance of variance due to
NOTE Confidence: 0.841837286949158
00:36:41.641 --> 00:36:43.349 their contributions to survival,
NOTE Confidence: 0.841837286949158
00:36:43.350 --> 00:36:44.914 indivision versus what you're
NOTE Confidence: 0.841837286949158
00:36:44.914 --> 00:36:46.869 actually seeing in the tumor.
NOTE Confidence: 0.841837286949158
00:36:46.870 --> 00:36:49.607 So we're quantifying the cancer affect size.
NOTE Confidence: 0.841837286949158
00:36:49.610 --> 00:36:51.560 We're using single nucleotide mutations,
NOTE Confidence: 0.841837286949158
00:36:51.560 --> 00:36:54.535 and then we basically do a scaled
NOTE Confidence: 0.841837286949158
00:36:54.535 --> 00:36:56.974 selection coefficient for the for the
NOTE Confidence: 0.841837286949158
00:36:56.974 --> 00:36:59.140 different variants we look at it.
NOTE Confidence: 0.841837286949158

00:36:59.140 --> 00:37:01.288 By sex and by IDH subtype.
NOTE Confidence: 0.841837286949158

00:37:01.290 --> 00:37:04.107 And so we're trying to get a feel for
NOTE Confidence: 0.841837286949158

00:37:04.107 --> 00:37:06.482 whether this would help us explain
NOTE Confidence: 0.841837286949158

00:37:06.482 --> 00:37:08.467 any differences in the glioma,
NOTE Confidence: 0.841837286949158

00:37:08.470 --> 00:37:11.350 risk and outcome that we see by sex.
NOTE Confidence: 0.841837286949158

00:37:11.350 --> 00:37:13.854 And then we're going to move on to
NOTE Confidence: 0.841837286949158

00:37:13.854 --> 00:37:16.542 the cosmic mutations so I won't go
NOTE Confidence: 0.841837286949158

00:37:16.542 --> 00:37:18.527 into the gory statistical detail.
NOTE Confidence: 0.841837286949158

00:37:18.530 --> 00:37:20.678 This is drawn from Jeffs paper,
NOTE Confidence: 0.841837286949158

00:37:20.680 --> 00:37:22.056 but basically you're comparing
NOTE Confidence: 0.841837286949158

00:37:22.056 --> 00:37:23.776 expected to observed so expected
NOTE Confidence: 0.841837286949158

00:37:23.776 --> 00:37:25.349 number of synonymous mutations,
NOTE Confidence: 0.841837286949158

00:37:25.350 --> 00:37:27.282 and then we're looking at the
NOTE Confidence: 0.841837286949158

00:37:27.282 --> 00:37:29.330 rate at which the mutations.
NOTE Confidence: 0.841837286949158

00:37:29.330 --> 00:37:30.282 Actually occur.
NOTE Confidence: 0.841837286949158

00:37:30.282 --> 00:37:33.138 The data that we're using here,

NOTE Confidence: 0.841837286949158
00:37:33.140 --> 00:37:35.804 our whole exome sequencing data from a pretty
NOTE Confidence: 0.841837286949158
00:37:35.804 --> 00:37:38.225 good size data set in terms of glioma,
NOTE Confidence: 0.841837286949158
00:37:38.230 --> 00:37:40.132 so about 1100 and these are
NOTE Confidence: 0.841837286949158
00:37:40.132 --> 00:37:41.083 all adult patients.
NOTE Confidence: 0.841837286949158
00:37:41.090 --> 00:37:42.290 There's no pediatric patients
NOTE Confidence: 0.841837286949158
00:37:42.290 --> 00:37:44.830 in here and we drew it from the
NOTE Confidence: 0.841837286949158
00:37:44.830 --> 00:37:46.178 Cancer Genome Atlas study.
NOTE Confidence: 0.841837286949158
00:37:46.180 --> 00:37:47.356 And as I mentioned,
NOTE Confidence: 0.841837286949158
00:37:47.356 --> 00:37:50.246 I know some of you may be aware of
NOTE Confidence: 0.841837286949158
00:37:50.246 --> 00:37:52.110 what glasses, so it's an effort.
NOTE Confidence: 0.841837286949158
00:37:52.110 --> 00:37:54.440 As I mentioned led by role Verhaag,
NOTE Confidence: 0.841837286949158
00:37:54.440 --> 00:37:56.760 but which yell is also a member of
NOTE Confidence: 0.841837286949158
00:37:56.760 --> 00:37:59.210 looking at not only the initial tumors,
NOTE Confidence: 0.841837286949158
00:37:59.210 --> 00:38:00.510 but the humours overtime.
NOTE Confidence: 0.841837286949158
00:38:00.510 --> 00:38:02.135 So how do they change?
NOTE Confidence: 0.841837286949158

00:38:02.140 --> 00:38:04.018 In terms of their genetic makeup,
NOTE Confidence: 0.841837286949158

00:38:04.020 --> 00:38:06.516 when we do nothing to them when we
NOTE Confidence: 0.841837286949158

00:38:06.516 --> 00:38:08.399 do chemotherapy or we do radiation,
NOTE Confidence: 0.841837286949158

00:38:08.400 --> 00:38:11.176 or a combination of all the above and
NOTE Confidence: 0.841837286949158

00:38:11.176 --> 00:38:13.615 what changes do we see and what do
NOTE Confidence: 0.841837286949158

00:38:13.615 --> 00:38:15.995 we learn from that in terms of what
NOTE Confidence: 0.841837286949158

00:38:15.995 --> 00:38:18.103 we should or should not be doing?
NOTE Confidence: 0.841837286949158

00:38:18.103 --> 00:38:20.920 And then we also used a lot of data.
NOTE Confidence: 0.841837286949158

00:38:20.920 --> 00:38:22.798 All of this is readily available
NOTE Confidence: 0.841837286949158

00:38:22.798 --> 00:38:23.737 off the Internet,
NOTE Confidence: 0.841837286949158

00:38:23.740 --> 00:38:25.618 but we use tissue specific mutational
NOTE Confidence: 0.841837286949158

00:38:25.618 --> 00:38:26.870 covariance and this helped.
NOTE Confidence: 0.841837286949158

00:38:26.870 --> 00:38:29.040 Just figure out what sort of mutation
NOTE Confidence: 0.841837286949158

00:38:29.040 --> 00:38:30.619 rate calculations we should use.
NOTE Confidence: 0.841837286949158

00:38:30.620 --> 00:38:32.881 Gave us a little bit of information
NOTE Confidence: 0.841837286949158

00:38:32.881 --> 00:38:33.850 about replication timing.

NOTE Confidence: 0.841837286949158
00:38:33.850 --> 00:38:35.794 And some of the other datasets
NOTE Confidence: 0.841837286949158
00:38:35.794 --> 00:38:37.090 that are listed here.
NOTE Confidence: 0.841837286949158
00:38:37.090 --> 00:38:39.166 So here's some of the results.
NOTE Confidence: 0.841837286949158
00:38:39.170 --> 00:38:42.275 Just to take you through it a little bit.
NOTE Confidence: 0.841837286949158
00:38:42.280 --> 00:38:44.776 So I have a divided by tumor type
NOTE Confidence: 0.841837286949158
00:38:44.776 --> 00:38:47.118 and it's by seksan by mutation.
NOTE Confidence: 0.841837286949158
00:38:47.120 --> 00:38:49.402 So the wild type tumors who would
NOTE Confidence: 0.841837286949158
00:38:49.402 --> 00:38:51.620 be considered the higher grade are
NOTE Confidence: 0.841837286949158
00:38:51.620 --> 00:38:53.570 primarily the glioblastoma tumors are
NOTE Confidence: 0.841837286949158
00:38:53.570 --> 00:38:56.465 in the first 2 rows and the IDH mutant,
NOTE Confidence: 0.841837286949158
00:38:56.470 --> 00:38:57.850 which would more typically
NOTE Confidence: 0.841837286949158
00:38:57.850 --> 00:38:59.575 be the lower grade tumors.
NOTE Confidence: 0.841837286949158
00:38:59.580 --> 00:39:01.995 And then I have males versus females,
NOTE Confidence: 0.841837286949158
00:39:02.000 --> 00:39:03.017 males versus females,
NOTE Confidence: 0.841837286949158
00:39:03.017 --> 00:39:05.051 and then there's sort of a
NOTE Confidence: 0.841837286949158

00:39:05.051 --> 00:39:06.499 cancer affect size here.
NOTE Confidence: 0.841837286949158

00:39:06.500 --> 00:39:08.588 The blue is non coding region.
NOTE Confidence: 0.841837286949158

00:39:08.590 --> 00:39:10.445 And the red is coding so you
NOTE Confidence: 0.841837286949158

00:39:10.445 --> 00:39:12.446 can see the patterns are quite
NOTE Confidence: 0.841837286949158

00:39:12.446 --> 00:39:14.714 different for what might be called
NOTE Confidence: 0.841837286949158

00:39:14.714 --> 00:39:16.688 the low and the high grade,
NOTE Confidence: 0.841837286949158

00:39:16.690 --> 00:39:19.060 the IDH mutant tumors had few
NOTE Confidence: 0.841837286949158

00:39:19.060 --> 00:39:20.245 unique recurrent substitutions.
NOTE Confidence: 0.841837286949158

00:39:20.250 --> 00:39:22.567 All of them were in coding regions,
NOTE Confidence: 0.841837286949158

00:39:22.570 --> 00:39:24.220 whereas the wild type tumors,
NOTE Confidence: 0.841837286949158

00:39:24.220 --> 00:39:26.201 and obviously this is in part what
NOTE Confidence: 0.841837286949158

00:39:26.201 --> 00:39:28.643 makes them so hard to manage is
NOTE Confidence: 0.841837286949158

00:39:28.643 --> 00:39:30.175 they exhibited many substitutions,
NOTE Confidence: 0.850281715393066

00:39:30.180 --> 00:39:32.028 but they were primarily
NOTE Confidence: 0.850281715393066

00:39:32.028 --> 00:39:33.876 in non coding regions.
NOTE Confidence: 0.850281715393066

00:39:33.880 --> 00:39:35.444 So here's another picture.

NOTE Confidence: 0.850281715393066

00:39:35.444 --> 00:39:38.270 A little busy but divided once again,

NOTE Confidence: 0.850281715393066

00:39:38.270 --> 00:39:40.986 the IDH mutant or the lower grade

NOTE Confidence: 0.850281715393066

00:39:40.986 --> 00:39:42.660 tumors are presented first.

NOTE Confidence: 0.850281715393066

00:39:42.660 --> 00:39:44.650 The wild types are second,

NOTE Confidence: 0.850281715393066

00:39:44.650 --> 00:39:47.107 and there's female male, female, male,

NOTE Confidence: 0.850281715393066

00:39:47.107 --> 00:39:51.220 and So what we're looking at here is that.

NOTE Confidence: 0.850281715393066

00:39:51.220 --> 00:39:53.105 Items that top the list

NOTE Confidence: 0.850281715393066

00:39:53.105 --> 00:39:54.613 are the most important.

NOTE Confidence: 0.850281715393066

00:39:54.620 --> 00:39:57.428 The size of the circle that is attached

NOTE Confidence: 0.850281715393066

00:39:57.428 --> 00:39:59.401 to them measures the prevalence

NOTE Confidence: 0.850281715393066

00:39:59.401 --> 00:40:02.173 so there can be kind of this.

NOTE Confidence: 0.850281715393066

00:40:02.180 --> 00:40:04.622 Disconnect as to what is important

NOTE Confidence: 0.850281715393066

00:40:04.622 --> 00:40:06.947 and how frequently it occurs so

NOTE Confidence: 0.850281715393066

00:40:06.947 --> 00:40:09.443 we can see that in the low grades

NOTE Confidence: 0.850281715393066

00:40:09.522 --> 00:40:11.627 it's pretty much as expected.

NOTE Confidence: 0.850281715393066

00:40:11.630 --> 00:40:12.764 Previously reported mutations
NOTE Confidence: 0.850281715393066

00:40:12.764 --> 00:40:15.410 in IDH one and two TP 53.
NOTE Confidence: 0.850281715393066

00:40:15.410 --> 00:40:18.056 Some of the other classics were confirmed,
NOTE Confidence: 0.850281715393066

00:40:18.060 --> 00:40:19.584 but what's interesting is
NOTE Confidence: 0.850281715393066

00:40:19.584 --> 00:40:22.290 if we go here to the IDH.
NOTE Confidence: 0.850281715393066

00:40:22.290 --> 00:40:24.612 Wild type tumors the most important
NOTE Confidence: 0.850281715393066

00:40:24.612 --> 00:40:26.622 with respect to cancer affect
NOTE Confidence: 0.850281715393066

00:40:26.622 --> 00:40:28.968 gene is this low prevalence right?
NOTE Confidence: 0.850281715393066

00:40:28.970 --> 00:40:31.358 You can see that the circle
NOTE Confidence: 0.850281715393066

00:40:31.358 --> 00:40:34.079 that matches up to it is small,
NOTE Confidence: 0.850281715393066

00:40:34.080 --> 00:40:36.824 not large like we see for IDH.
NOTE Confidence: 0.850281715393066

00:40:36.830 --> 00:40:39.602 Is this B RAF V 600 E so we
NOTE Confidence: 0.850281715393066

00:40:39.602 --> 00:40:41.938 know that it's important.
NOTE Confidence: 0.850281715393066

00:40:41.940 --> 00:40:44.022 It turns out that it looks
NOTE Confidence: 0.850281715393066

00:40:44.022 --> 00:40:46.260 like it's the most important,
NOTE Confidence: 0.850281715393066

00:40:46.260 --> 00:40:48.225 but obviously it doesn't occur

NOTE Confidence: 0.850281715393066
00:40:48.225 --> 00:40:49.797 that frequently but interesting.
NOTE Confidence: 0.850281715393066
00:40:49.800 --> 00:40:52.600 What drives some of these gliomas here?
NOTE Confidence: 0.850281715393066
00:40:52.600 --> 00:40:54.584 The other thing we looked at is do
NOTE Confidence: 0.850281715393066
00:40:54.584 --> 00:40:57.175 males and females show the same pattern
NOTE Confidence: 0.850281715393066
00:40:57.175 --> 00:40:58.803 of what significantly overburdened,
NOTE Confidence: 0.850281715393066
00:40:58.810 --> 00:41:01.512 and there were a lot of similarities
NOTE Confidence: 0.850281715393066
00:41:01.512 --> 00:41:04.144 the way that we have this broken
NOTE Confidence: 0.850281715393066
00:41:04.144 --> 00:41:06.860 up here is each panel is a gene.
NOTE Confidence: 0.850281715393066
00:41:06.860 --> 00:41:09.308 The mutants come first in each
NOTE Confidence: 0.850281715393066
00:41:09.308 --> 00:41:11.822 panel and then within each panel
NOTE Confidence: 0.850281715393066
00:41:11.822 --> 00:41:14.629 we've got the females in the mails.
NOTE Confidence: 0.850281715393066
00:41:14.630 --> 00:41:16.854 So we did see some differences,
NOTE Confidence: 0.850281715393066
00:41:16.854 --> 00:41:19.026 although overall most the things the
NOTE Confidence: 0.850281715393066
00:41:19.026 --> 00:41:21.397 males and females showed were similar,
NOTE Confidence: 0.850281715393066
00:41:21.400 --> 00:41:24.400 but we did see differences in the P3K
NOTE Confidence: 0.850281715393066

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.

NOTE Confidence: 0.850281715393066

00:41:59.360 --> 00:42:01.968 We did find a paper by Dan Cahill

NOTE Confidence: 0.850281715393066

00:42:01.968 --> 00:42:04.875 at all at mass general and although

NOTE Confidence: 0.850281715393066

00:42:04.875 --> 00:42:07.530 they didn't report it as such,

NOTE Confidence: 0.850281715393066

00:42:07.530 --> 00:42:09.098 they found something similar

NOTE Confidence: 0.850281715393066

00:42:09.098 --> 00:42:11.450 where the females tended to have.

NOTE Confidence: 0.850281715393066

00:42:11.450 --> 00:42:14.803 Variations in the he local domain and

NOTE Confidence: 0.850281715393066

00:42:14.803 --> 00:42:18.788 the males had them in the kinase domain,

NOTE Confidence: 0.850281715393066

00:42:18.790 --> 00:42:21.230 and so as I said,

NOTE Confidence: 0.850281715393066

00:42:21.230 --> 00:42:23.182 although both domains are

NOTE Confidence: 0.850281715393066

00:42:23.182 --> 00:42:25.134 involved with glioma Genesis,

NOTE Confidence: 0.850281715393066

00:42:25.140 --> 00:42:27.585 there is differential amounts of

NOTE Confidence: 0.850281715393066

00:42:27.585 --> 00:42:30.030 potentiated by these two regions.

NOTE Confidence: 0.850281715393066

00:42:30.030 --> 00:42:32.282 And obviously there's different

NOTE Confidence: 0.850281715393066

00:42:32.282 --> 00:42:34.534 sensitivity to various treatment

NOTE Confidence: 0.850281715393066

00:42:34.534 --> 00:42:36.579 types depending upon domain.

NOTE Confidence: 0.850281715393066

00:42:36.580 --> 00:42:38.500 So back to environmental exposure.
NOTE Confidence: 0.850281715393066

00:42:38.500 --> 00:42:40.705 We have searched and not just our
NOTE Confidence: 0.850281715393066

00:42:40.705 --> 00:42:43.007 group of many groups have searched
NOTE Confidence: 0.850281715393066

00:42:43.007 --> 00:42:45.581 long and hard for environmental and
NOTE Confidence: 0.850281715393066

00:42:45.581 --> 00:42:47.688 genetic risk factors for glioma.
NOTE Confidence: 0.850281715393066

00:42:47.690 --> 00:42:49.988 In terms of genetic risk factors,
NOTE Confidence: 0.879732668399811

00:42:49.990 --> 00:42:52.559 we have found small numbers of families
NOTE Confidence: 0.879732668399811

00:42:52.559 --> 00:42:55.361 with high risk but typically that does
NOTE Confidence: 0.879732668399811

00:42:55.361 --> 00:42:57.809 not relate to the general population
NOTE Confidence: 0.879732668399811

00:42:57.877 --> 00:43:00.037 and so no genetic risk factors
NOTE Confidence: 0.879732668399811

00:43:00.037 --> 00:43:02.298 really explain a large proportion of
NOTE Confidence: 0.879732668399811

00:43:02.298 --> 00:43:05.161 inherited risk and other than high dose
NOTE Confidence: 0.879732668399811

00:43:05.161 --> 00:43:07.269 radiation to which not many people.
NOTE Confidence: 0.879732668399811

00:43:07.270 --> 00:43:08.407 Thankfully are exposed.
NOTE Confidence: 0.879732668399811

00:43:08.407 --> 00:43:11.060 We really haven't found much of an
NOTE Confidence: 0.879732668399811

00:43:11.132 --> 00:43:12.653 Association between environmental

NOTE Confidence: 0.879732668399811
00:43:12.653 --> 00:43:15.188 risk factors in glioma risk.
NOTE Confidence: 0.879732668399811
00:43:15.190 --> 00:43:17.830 There has been reported a fairly
NOTE Confidence: 0.879732668399811
00:43:17.830 --> 00:43:19.590 consistent but low effect,
NOTE Confidence: 0.879732668399811
00:43:19.590 --> 00:43:21.698 an inverse Association with
NOTE Confidence: 0.879732668399811
00:43:21.698 --> 00:43:23.279 history of allergy.
NOTE Confidence: 0.879732668399811
00:43:23.280 --> 00:43:24.736 So the question comes,
NOTE Confidence: 0.879732668399811
00:43:24.736 --> 00:43:26.556 why haven't we found anything?
NOTE Confidence: 0.879732668399811
00:43:26.560 --> 00:43:29.094 Is it that there is no Association?
NOTE Confidence: 0.879732668399811
00:43:29.100 --> 00:43:31.242 Or is it basically statistical power
NOTE Confidence: 0.879732668399811
00:43:31.242 --> 00:43:33.832 that there's so few cases of glioma
NOTE Confidence: 0.879732668399811
00:43:33.832 --> 00:43:36.380 relative to other things we've looked at?
NOTE Confidence: 0.879732668399811
00:43:36.380 --> 00:43:37.114 For example,
NOTE Confidence: 0.879732668399811
00:43:37.114 --> 00:43:39.316 I started my work with breast
NOTE Confidence: 0.879732668399811
00:43:39.316 --> 00:43:41.536 cancer and even just using the
NOTE Confidence: 0.879732668399811
00:43:41.536 --> 00:43:43.654 state of Connecticut as a base,
NOTE Confidence: 0.879732668399811

00:43:43.660 --> 00:43:45.380 you would have enough cases
NOTE Confidence: 0.879732668399811

00:43:45.380 --> 00:43:47.670 for a large study for glioma.
NOTE Confidence: 0.879732668399811

00:43:47.670 --> 00:43:50.198 That is not true and also likely a
NOTE Confidence: 0.879732668399811

00:43:50.198 --> 00:43:53.196 lot of the exposures that we think
NOTE Confidence: 0.879732668399811

00:43:53.196 --> 00:43:55.940 are causing risk are themselves rare.
NOTE Confidence: 0.879732668399811

00:43:55.940 --> 00:43:58.460 So one of the things that people
NOTE Confidence: 0.879732668399811

00:43:58.460 --> 00:44:00.460 have been thinking about doing,
NOTE Confidence: 0.879732668399811

00:44:00.460 --> 00:44:03.476 is there another way to do this now?
NOTE Confidence: 0.879732668399811

00:44:03.480 --> 00:44:06.301 So now that we have these mutational
NOTE Confidence: 0.879732668399811

00:44:06.301 --> 00:44:08.861 signatures that the are listed in
NOTE Confidence: 0.879732668399811

00:44:08.861 --> 00:44:10.986 the Catalogue of Somatic mutations
NOTE Confidence: 0.879732668399811

00:44:10.986 --> 00:44:13.348 and cancer or cosmic can use that
NOTE Confidence: 0.879732668399811

00:44:13.348 --> 00:44:16.005 as a way to match up to exposure,
NOTE Confidence: 0.879732668399811

00:44:16.005 --> 00:44:18.030 particularly if you have previously
NOTE Confidence: 0.879732668399811

00:44:18.030 --> 00:44:19.555 obtained environmental or other
NOTE Confidence: 0.879732668399811

00:44:19.555 --> 00:44:21.195 exposure history in the patients.

NOTE Confidence: 0.879732668399811
00:44:21.200 --> 00:44:23.594 So we did that here with the
NOTE Confidence: 0.879732668399811
00:44:23.594 --> 00:44:25.719 1100 cases that we mentioned,
NOTE Confidence: 0.879732668399811
00:44:25.720 --> 00:44:27.268 we group Jack Sonic.
NOTE Confidence: 0.879732668399811
00:44:27.268 --> 00:44:29.590 SNV and tried to match him
NOTE Confidence: 0.879732668399811
00:44:29.673 --> 00:44:31.647 up to what is in cosmic,
NOTE Confidence: 0.879732668399811
00:44:31.650 --> 00:44:33.974 and so you know that the cosmic
NOTE Confidence: 0.879732668399811
00:44:33.974 --> 00:44:35.640 catalog is rapidly changing.
NOTE Confidence: 0.879732668399811
00:44:35.640 --> 00:44:37.806 New things are always being added,
NOTE Confidence: 0.879732668399811
00:44:37.810 --> 00:44:41.068 but we looked at what existed at this point,
NOTE Confidence: 0.879732668399811
00:44:41.070 --> 00:44:43.080 and obviously they have previously found
NOTE Confidence: 0.879732668399811
00:44:43.080 --> 00:44:45.594 a match up over environmental exposure to
NOTE Confidence: 0.879732668399811
00:44:45.594 --> 00:44:48.670 signatures not only in head and neck cancer,
NOTE Confidence: 0.879732668399811
00:44:48.670 --> 00:44:50.480 but smoking and lung cancer,
NOTE Confidence: 0.879732668399811
00:44:50.480 --> 00:44:51.324 UV exposure,
NOTE Confidence: 0.879732668399811
00:44:51.324 --> 00:44:54.700 and so we looked at that for glioma.
NOTE Confidence: 0.879732668399811

00:44:54.700 --> 00:44:56.068 And so again,
NOTE Confidence: 0.879732668399811

00:44:56.068 --> 00:44:58.348 here's our slide here again,
NOTE Confidence: 0.879732668399811

00:44:58.350 --> 00:45:00.174 broken into IDH Mutant,
NOTE Confidence: 0.879732668399811

00:45:00.174 --> 00:45:02.910 which is the top row IDH,
NOTE Confidence: 0.879732668399811

00:45:02.910 --> 00:45:05.790 Wildtype bottom row and then females
NOTE Confidence: 0.879732668399811

00:45:05.790 --> 00:45:08.598 or first column males or second
NOTE Confidence: 0.879732668399811

00:45:08.598 --> 00:45:11.567 column with each of these bar charts
NOTE Confidence: 0.879732668399811

00:45:11.567 --> 00:45:14.696 relates to is the proportion of our
NOTE Confidence: 0.879732668399811

00:45:14.696 --> 00:45:18.463 cases for whom the majority seem to be
NOTE Confidence: 0.879732668399811

00:45:18.463 --> 00:45:21.270 associated with a certain signature.
NOTE Confidence: 0.879732668399811

00:45:21.270 --> 00:45:23.545 And the overall news is a little
NOTE Confidence: 0.879732668399811

00:45:23.545 --> 00:45:25.853 bit depressing in the sense that
NOTE Confidence: 0.879732668399811

00:45:25.853 --> 00:45:27.541 the primary molecular signature
NOTE Confidence: 0.879732668399811

00:45:27.541 --> 00:45:30.179 identified was age related mutagenesis.
NOTE Confidence: 0.879732668399811

00:45:30.180 --> 00:45:32.210 Basically the older you get,
NOTE Confidence: 0.879732668399811

00:45:32.210 --> 00:45:34.640 the more at risk you are,

NOTE Confidence: 0.879732668399811
00:45:34.640 --> 00:45:37.475 but we did find one thing that
NOTE Confidence: 0.879732668399811
00:45:37.475 --> 00:45:38.690 was quite interesting,
NOTE Confidence: 0.879732668399811
00:45:38.690 --> 00:45:40.886 particularly in light of their such
NOTE Confidence: 0.879732668399811
00:45:40.886 --> 00:45:42.842 a positive risk factors identified
NOTE Confidence: 0.879732668399811
00:45:42.842 --> 00:45:45.410 for glioma and that was occupational
NOTE Confidence: 0.879732668399811
00:45:45.410 --> 00:45:47.998 exposure to something called Halo alkanes.
NOTE Confidence: 0.879732668399811
00:45:48.000 --> 00:45:50.030 Pretty much true across whether
NOTE Confidence: 0.879732668399811
00:45:50.030 --> 00:45:52.060 you are male or female.
NOTE Confidence: 0.879732668399811
00:45:52.060 --> 00:45:53.970 And whether you were IDH,
NOTE Confidence: 0.879732668399811
00:45:53.970 --> 00:45:55.026 mutant or not,
NOTE Confidence: 0.879732668399811
00:45:55.026 --> 00:45:57.490 we did find a little greater rate
NOTE Confidence: 0.879732668399811
00:45:57.566 --> 00:45:59.810 of the signature showing up in
NOTE Confidence: 0.879732668399811
00:45:59.810 --> 00:46:01.970 the males versus the females.
NOTE Confidence: 0.879732668399811
00:46:01.970 --> 00:46:04.392 But we certainly saw them in both
NOTE Confidence: 0.879732668399811
00:46:04.392 --> 00:46:07.043 and then we also saw which we
NOTE Confidence: 0.879732668399811

00:46:07.043 --> 00:46:09.347 haven't quite figured out how to
NOTE Confidence: 0.836727201938629

00:46:09.427 --> 00:46:12.435 explain yet. These UV light signatures an
NOTE Confidence: 0.836727201938629

00:46:12.435 --> 00:46:14.979 it's interesting because glioma has been
NOTE Confidence: 0.836727201938629

00:46:14.979 --> 00:46:17.325 associated in the number of instances
NOTE Confidence: 0.836727201938629

00:46:17.325 --> 00:46:19.866 with Melanoma and also with the B RAF.
NOTE Confidence: 0.836727201938629

00:46:19.870 --> 00:46:22.998 So we're trying to sort out whether that.
NOTE Confidence: 0.836727201938629

00:46:23.000 --> 00:46:24.729 Has anything to do with why we're
NOTE Confidence: 0.836727201938629

00:46:24.729 --> 00:46:26.508 just seeing some of those signatures?
NOTE Confidence: 0.836727201938629

00:46:26.510 --> 00:46:29.919 So hello, alkanes are basically used for
NOTE Confidence: 0.836727201938629

00:46:29.919 --> 00:46:33.089 many industrial and day-to-day purposes.
NOTE Confidence: 0.836727201938629

00:46:33.090 --> 00:46:35.496 Of interest there seen in refrigerants,
NOTE Confidence: 0.836727201938629

00:46:35.500 --> 00:46:37.300 fire extinguishers, flame retardants,
NOTE Confidence: 0.836727201938629

00:46:37.300 --> 00:46:40.509 and we thought this was very interesting
NOTE Confidence: 0.836727201938629

00:46:40.509 --> 00:46:43.125 because there's always sort of been
NOTE Confidence: 0.836727201938629

00:46:43.125 --> 00:46:45.670 this theory that in some of these.
NOTE Confidence: 0.836727201938629

00:46:45.670 --> 00:46:47.366 Occupations including for firemen

NOTE Confidence: 0.836727201938629

00:46:47.366 --> 00:46:49.910 and that has been reported that

NOTE Confidence: 0.836727201938629

00:46:49.976 --> 00:46:52.384 there is an increased risk of glioma,

NOTE Confidence: 0.836727201938629

00:46:52.390 --> 00:46:55.120 and so, whether or not this ties

NOTE Confidence: 0.836727201938629

00:46:55.120 --> 00:46:57.520 things together or not is unclear,

NOTE Confidence: 0.836727201938629

00:46:57.520 --> 00:47:00.022 so the signature was basically developed

NOTE Confidence: 0.836727201938629

00:47:00.022 --> 00:47:02.489 by looking at cholangio carcinoma in

NOTE Confidence: 0.836727201938629

00:47:02.489 --> 00:47:05.023 a group of workers that were exposed,

NOTE Confidence: 0.836727201938629

00:47:05.030 --> 00:47:07.412 known, exposed to hello Alkins in

NOTE Confidence: 0.836727201938629

00:47:07.412 --> 00:47:09.832 Japan and so essentially they had

NOTE Confidence: 0.836727201938629

00:47:09.832 --> 00:47:11.737 111 workers that were exposed.

NOTE Confidence: 0.836727201938629

00:47:11.740 --> 00:47:12.520 17 developed.

NOTE Confidence: 0.836727201938629

00:47:12.520 --> 00:47:16.140 Would you all know to be a pretty rare?

NOTE Confidence: 0.836727201938629

00:47:16.140 --> 00:47:16.465 Cancer,

NOTE Confidence: 0.836727201938629

00:47:16.465 --> 00:47:19.065 so it was quite unusual that this number

NOTE Confidence: 0.836727201938629

00:47:19.065 --> 00:47:21.630 of individuals was diagnosed with it.

NOTE Confidence: 0.836727201938629

00:47:21.630 --> 00:47:23.688 They all were working in printing
NOTE Confidence: 0.836727201938629

00:47:23.688 --> 00:47:25.910 companies and they all were known
NOTE Confidence: 0.836727201938629

00:47:25.910 --> 00:47:28.262 to have occupational exposure and so
NOTE Confidence: 0.836727201938629

00:47:28.262 --> 00:47:30.859 essentially what they did was they took
NOTE Confidence: 0.836727201938629

00:47:30.859 --> 00:47:32.604 the tumors from these individuals,
NOTE Confidence: 0.836727201938629

00:47:32.610 --> 00:47:34.474 looked at the molecular.
NOTE Confidence: 0.836727201938629

00:47:34.474 --> 00:47:36.804 Pattern and developed this signature.
NOTE Confidence: 0.836727201938629

00:47:36.810 --> 00:47:39.462 So that's essentially how that the
NOTE Confidence: 0.836727201938629

00:47:39.462 --> 00:47:41.230 signature was initially identified,
NOTE Confidence: 0.836727201938629

00:47:41.230 --> 00:47:43.876 and so that's what we're seeing.
NOTE Confidence: 0.836727201938629

00:47:43.880 --> 00:47:45.536 Basically in our data.
NOTE Confidence: 0.836727201938629

00:47:45.536 --> 00:47:48.020 So conclusions here that the majority
NOTE Confidence: 0.836727201938629

00:47:48.093 --> 00:47:50.865 of cancer causing mutations in these
NOTE Confidence: 0.836727201938629

00:47:50.865 --> 00:47:53.217 gliomas we're seeing primarily as
NOTE Confidence: 0.836727201938629

00:47:53.217 --> 00:47:54.929 a consequence of endogenous,
NOTE Confidence: 0.836727201938629

00:47:54.930 --> 00:47:57.140 rather than actual, exogenous exposures.

NOTE Confidence: 0.836727201938629

00:47:57.140 --> 00:47:59.864 We did think was interesting that

NOTE Confidence: 0.836727201938629

00:47:59.864 --> 00:48:03.037 different domains of jeans in the P3K

NOTE Confidence: 0.836727201938629

00:48:03.037 --> 00:48:06.005 pathway were different for males and females.

NOTE Confidence: 0.836727201938629

00:48:06.010 --> 00:48:08.460 For those of us that have searched

NOTE Confidence: 0.836727201938629

00:48:08.460 --> 00:48:11.117 long and hard for some of these

NOTE Confidence: 0.836727201938629

00:48:11.117 --> 00:48:12.649 risk factors for glioma,

NOTE Confidence: 0.836727201938629

00:48:12.650 --> 00:48:15.240 we are excited that at least potentially,

NOTE Confidence: 0.836727201938629

00:48:15.240 --> 00:48:17.394 there's a new means to try

NOTE Confidence: 0.836727201938629

00:48:17.394 --> 00:48:19.290 and identify even if rare,

NOTE Confidence: 0.836727201938629

00:48:19.290 --> 00:48:20.806 these environmental risk factors

NOTE Confidence: 0.836727201938629

00:48:20.806 --> 00:48:23.806 and it's sort of a whole new aspect

NOTE Confidence: 0.836727201938629

00:48:23.806 --> 00:48:26.088 of glioma that were looking at so

NOTE Confidence: 0.836727201938629

00:48:26.088 --> 00:48:28.149 some of our future directions.

NOTE Confidence: 0.836727201938629

00:48:28.150 --> 00:48:30.400 We're looking now to partner with

NOTE Confidence: 0.836727201938629

00:48:30.400 --> 00:48:32.675 colleagues who have worked with us

NOTE Confidence: 0.836727201938629

00:48:32.675 --> 00:48:34.787 both in the meningioma consortia man,
NOTE Confidence: 0.836727201938629

00:48:34.790 --> 00:48:36.274 the Glioma international Case
NOTE Confidence: 0.836727201938629

00:48:36.274 --> 00:48:37.016 Control Consortium.
NOTE Confidence: 0.836727201938629

00:48:37.020 --> 00:48:39.462 And we also in our international
NOTE Confidence: 0.836727201938629

00:48:39.462 --> 00:48:41.090 low grade glioma registry.
NOTE Confidence: 0.836727201938629

00:48:41.090 --> 00:48:43.400 Looking at cohorts in which we
NOTE Confidence: 0.836727201938629

00:48:43.400 --> 00:48:45.570 have a good occupational history.
NOTE Confidence: 0.836727201938629

00:48:45.570 --> 00:48:48.006 So the San Francisco Bay Area
NOTE Confidence: 0.836727201938629

00:48:48.006 --> 00:48:49.224 Adult Glioma study,
NOTE Confidence: 0.836727201938629

00:48:49.230 --> 00:48:51.666 which is led by Margaret Wrench
NOTE Confidence: 0.836727201938629

00:48:51.666 --> 00:48:52.884 and John Winky,
NOTE Confidence: 0.836727201938629

00:48:52.890 --> 00:48:54.518 they collected extremely detailed
NOTE Confidence: 0.836727201938629

00:48:54.518 --> 00:48:56.553 occupational history for their cohort,
NOTE Confidence: 0.836727201938629

00:48:56.560 --> 00:48:58.996 and they have all the tumors.
NOTE Confidence: 0.836727201938629

00:48:59.000 --> 00:49:02.042 So we're going to try and go back and
NOTE Confidence: 0.836727201938629

00:49:02.042 --> 00:49:04.838 Geno type those tumors and see if

NOTE Confidence: 0.836727201938629
00:49:04.838 --> 00:49:07.550 we can confirm these associations,
NOTE Confidence: 0.836727201938629
00:49:07.550 --> 00:49:09.870 which they found with firefighters.
NOTE Confidence: 0.836727201938629
00:49:09.870 --> 00:49:10.624 And glioma.
NOTE Confidence: 0.836727201938629
00:49:10.624 --> 00:49:14.090 And also they found it with painters as well.
NOTE Confidence: 0.836727201938629
00:49:14.090 --> 00:49:16.981 And so we are also collecting glioma
NOTE Confidence: 0.836727201938629
00:49:16.981 --> 00:49:18.638 patients with occupational histories
NOTE Confidence: 0.836727201938629
00:49:18.638 --> 00:49:21.761 and just sort of throwing it out to people.
NOTE Confidence: 0.836727201938629
00:49:21.770 --> 00:49:24.386 If you're aware of any firefighters
NOTE Confidence: 0.836727201938629
00:49:24.386 --> 00:49:26.494 or similar occupied individuals with
NOTE Confidence: 0.836727201938629
00:49:26.494 --> 00:49:28.587 glioma would love to try and get
NOTE Confidence: 0.836727201938629
00:49:28.587 --> 00:49:29.185 a cohort
NOTE Confidence: 0.812601149082184
00:49:29.254 --> 00:49:31.585 together. The other thing that was
NOTE Confidence: 0.812601149082184
00:49:31.585 --> 00:49:34.449 just sort of luck this past semester.
NOTE Confidence: 0.812601149082184
00:49:34.450 --> 00:49:37.124 So I teach over at the school,
NOTE Confidence: 0.812601149082184
00:49:37.130 --> 00:49:39.874 public health and everything has been remote.
NOTE Confidence: 0.812601149082184

00:49:39.880 --> 00:49:42.922 And so as I was meeting via zoom with
NOTE Confidence: 0.812601149082184

00:49:42.922 --> 00:49:46.404 one of my students for her final project,
NOTE Confidence: 0.812601149082184

00:49:46.410 --> 00:49:48.648 she revealed that she was actually
NOTE Confidence: 0.812601149082184

00:49:48.648 --> 00:49:50.589 the principle project director for
NOTE Confidence: 0.812601149082184

00:49:50.589 --> 00:49:52.549 the Firefighters Cancer Cohort study.
NOTE Confidence: 0.812601149082184

00:49:52.550 --> 00:49:54.860 So we're also hoping to parano.
NOTE Confidence: 0.812601149082184

00:49:54.860 --> 00:49:57.348 NIH is a big directive to try and
NOTE Confidence: 0.812601149082184

00:49:57.348 --> 00:49:59.075 look further at environmental
NOTE Confidence: 0.812601149082184

00:49:59.075 --> 00:50:00.620 exposures and cancer,
NOTE Confidence: 0.812601149082184

00:50:00.620 --> 00:50:03.420 so we're hoping that we can partner with
NOTE Confidence: 0.812601149082184

00:50:03.420 --> 00:50:06.758 some of these folks to look at individuals,
NOTE Confidence: 0.812601149082184

00:50:06.760 --> 00:50:08.720 either living or dead that
NOTE Confidence: 0.812601149082184

00:50:08.720 --> 00:50:09.896 may have undiagnosed.
NOTE Confidence: 0.812601149082184

00:50:09.900 --> 00:50:13.148 With glioma that we now have this exposure.
NOTE Confidence: 0.812601149082184

00:50:13.150 --> 00:50:15.649 So thank you all for your time.
NOTE Confidence: 0.812601149082184

00:50:15.650 --> 00:50:18.149 I wanted to also thank Jeff Townsend,

NOTE Confidence: 0.812601149082184
00:50:18.150 --> 00:50:19.212 Vinston, Canna Terra,
NOTE Confidence: 0.812601149082184
00:50:19.212 --> 00:50:23.152 who was a postdoc in Jeffs lab but now as an
NOTE Confidence: 0.812601149082184
00:50:23.152 --> 00:50:25.650 assistant professor of biology up the road,
NOTE Confidence: 0.812601149082184
00:50:25.650 --> 00:50:27.375 a little bit of Emmanuel
NOTE Confidence: 0.812601149082184
00:50:27.375 --> 00:50:29.929 College and I have to thank him.
NOTE Confidence: 0.812601149082184
00:50:29.930 --> 00:50:31.710 He made all the beautiful
NOTE Confidence: 0.812601149082184
00:50:31.710 --> 00:50:33.134 pictures an Steven Gaffney,
NOTE Confidence: 0.812601149082184
00:50:33.140 --> 00:50:35.276 who also works in Jeff Slab.
NOTE Confidence: 0.812601149082184
00:50:35.280 --> 00:50:36.678 Thank the various.
NOTE Confidence: 0.812601149082184
00:50:36.678 --> 00:50:38.076 Brain tumor associations,
NOTE Confidence: 0.812601149082184
00:50:38.080 --> 00:50:39.745 including the ABCA in the
NOTE Confidence: 0.812601149082184
00:50:39.745 --> 00:50:41.830 NBTS as well as Luglio Anna,
NOTE Confidence: 0.812601149082184
00:50:41.830 --> 00:50:44.050 a Dutch group called Stop Brain
NOTE Confidence: 0.812601149082184
00:50:44.050 --> 00:50:46.346 Tumor for their support and then
NOTE Confidence: 0.812601149082184
00:50:46.346 --> 00:50:48.566 also thank you for Doctor Rolled
NOTE Confidence: 0.812601149082184

00:50:48.566 --> 00:50:50.492 their hacking the Glass consortium
NOTE Confidence: 0.812601149082184

00:50:50.492 --> 00:50:53.082 who allowed us access to the data.
NOTE Confidence: 0.812601149082184

00:50:53.090 --> 00:50:56.138 So happy to take any questions.
NOTE Confidence: 0.865883529186249

00:50:56.860 --> 00:50:58.102 Elizabeth, thank you.
NOTE Confidence: 0.865883529186249

00:50:58.102 --> 00:51:01.000 That was a terrific summary of your
NOTE Confidence: 0.865883529186249

00:51:01.080 --> 00:51:03.258 work and obviously will open it
NOTE Confidence: 0.865883529186249

00:51:03.258 --> 00:51:05.808 up to questions on the chat line.
NOTE Confidence: 0.865883529186249

00:51:05.810 --> 00:51:07.066 But let me ask.
NOTE Confidence: 0.865883529186249

00:51:07.066 --> 00:51:08.950 I found it interesting the the
NOTE Confidence: 0.865883529186249

00:51:09.022 --> 00:51:11.037 observation I guess from Asia
NOTE Confidence: 0.865883529186249

00:51:11.037 --> 00:51:13.052 about the Association of Halo
NOTE Confidence: 0.865883529186249

00:51:13.123 --> 00:51:15.310 alkanes with cholangiocarcinoma.
NOTE Confidence: 0.865883529186249

00:51:15.310 --> 00:51:16.842 As you may know,
NOTE Confidence: 0.865883529186249

00:51:16.842 --> 00:51:18.374 there's there's a biologic
NOTE Confidence: 0.865883529186249

00:51:18.374 --> 00:51:20.010 difference between intrahepatic,
NOTE Confidence: 0.865883529186249

00:51:20.010 --> 00:51:22.054 an extra paddock cholangio,

NOTE Confidence: 0.865883529186249
00:51:22.054 --> 00:51:24.609 where extra panic actually gave
NOTE Confidence: 0.865883529186249
00:51:24.609 --> 00:51:27.094 IDH mutations but insured don't
NOTE Confidence: 0.865883529186249
00:51:27.094 --> 00:51:29.920 wear the cases that they found
NOTE Confidence: 0.865883529186249
00:51:30.004 --> 00:51:32.356 in Asia with a extra paddock.
NOTE Confidence: 0.865883529186249
00:51:32.360 --> 00:51:32.640 You
NOTE Confidence: 0.871688604354858
00:51:32.640 --> 00:51:34.904 know, I don't know the answer to that.
NOTE Confidence: 0.871688604354858
00:51:34.910 --> 00:51:36.898 I gave a similar talk at UCSF
NOTE Confidence: 0.871688604354858
00:51:36.898 --> 00:51:38.589 and they mentioned this as well,
NOTE Confidence: 0.871688604354858
00:51:38.590 --> 00:51:40.042 so we're trying to gain access
NOTE Confidence: 0.871688604354858
00:51:40.042 --> 00:51:41.700 to some of that information,
NOTE Confidence: 0.871688604354858
00:51:41.700 --> 00:51:43.398 but I don't know at present.
NOTE Confidence: 0.859068708760398
00:51:44.570 --> 00:51:47.586 And then. With regard to the finding of
NOTE Confidence: 0.859068708760398
00:51:47.586 --> 00:51:49.674 the potential differential in mutations
NOTE Confidence: 0.859068708760398
00:51:49.674 --> 00:51:52.970 within pick three CA by gender by sex,
NOTE Confidence: 0.859068708760398
00:51:52.970 --> 00:51:54.515 is there an understanding of
NOTE Confidence: 0.859068708760398

00:51:54.515 --> 00:51:56.439 why those two domains would be
NOTE Confidence: 0.859068708760398

00:51:56.439 --> 00:51:58.049 different between men and women?
NOTE Confidence: 0.859068708760398

00:51:58.050 --> 00:51:59.378 No, and you know,
NOTE Confidence: 0.859068708760398

00:51:59.378 --> 00:52:01.530 we started to look at that a
NOTE Confidence: 0.852207005023956

00:52:01.530 --> 00:52:03.115 little bit and we collaborate
NOTE Confidence: 0.852207005023956

00:52:03.115 --> 00:52:04.700 a bit with Dan Cahill.
NOTE Confidence: 0.852207005023956

00:52:04.700 --> 00:52:06.566 As I mentioned up at mass
NOTE Confidence: 0.852207005023956

00:52:06.566 --> 00:52:08.509 general so we don't know yet,
NOTE Confidence: 0.852207005023956

00:52:08.510 --> 00:52:10.868 but he's going to try to take a look
NOTE Confidence: 0.852207005023956

00:52:10.868 --> 00:52:13.074 into that he he presented the data
NOTE Confidence: 0.852207005023956

00:52:13.074 --> 00:52:15.160 but didn't note the differences,
NOTE Confidence: 0.852207005023956

00:52:15.160 --> 00:52:17.246 so he's going to try to take
NOTE Confidence: 0.852207005023956

00:52:17.246 --> 00:52:19.290 a look and see what that.
NOTE Confidence: 0.852207005023956

00:52:19.290 --> 00:52:20.160 Might entail.
NOTE Confidence: 0.855117380619049

00:52:20.760 --> 00:52:22.510 And then my last question,
NOTE Confidence: 0.855117380619049

00:52:22.510 --> 00:52:24.869 and this is gonna show my naivete

NOTE Confidence: 0.855117380619049
00:52:24.869 --> 00:52:26.360 and understanding brain tumors.
NOTE Confidence: 0.855117380619049
00:52:26.360 --> 00:52:28.385 But instead of the Natural
NOTE Confidence: 0.855117380619049
00:52:28.385 --> 00:52:30.410 History of the low grades.
NOTE Confidence: 0.855117380619049
00:52:30.410 --> 00:52:33.380 Is there an evolution of the
NOTE Confidence: 0.855117380619049
00:52:33.380 --> 00:52:35.944 semantic events such that they
NOTE Confidence: 0.855117380619049
00:52:35.944 --> 00:52:38.389 look more like high grades?
NOTE Confidence: 0.854550182819366
00:52:38.400 --> 00:52:39.366 So it depends.
NOTE Confidence: 0.854550182819366
00:52:39.366 --> 00:52:40.976 They generally remain quite different.
NOTE Confidence: 0.854550182819366
00:52:40.980 --> 00:52:42.995 The IDH mutation stays constant
NOTE Confidence: 0.854550182819366
00:52:42.995 --> 00:52:45.359 throughout and so that's sort of
NOTE Confidence: 0.854550182819366
00:52:45.359 --> 00:52:47.298 been one of the issues is what
NOTE Confidence: 0.854550182819366
00:52:47.298 --> 00:52:49.282 you show up to the party with
NOTE Confidence: 0.854550182819366
00:52:49.282 --> 00:52:51.256 tends to be what you stay within.
NOTE Confidence: 0.854550182819366
00:52:51.256 --> 00:52:53.104 That makes it a little bit
NOTE Confidence: 0.854550182819366
00:52:53.104 --> 00:52:54.499 different to manage them.
NOTE Confidence: 0.854550182819366

00:52:54.500 --> 00:52:56.607 We didn't found find in some of
NOTE Confidence: 0.854550182819366

00:52:56.607 --> 00:52:58.230 the glass consortium work that
NOTE Confidence: 0.854550182819366

00:52:58.230 --> 00:53:00.210 we've looked at that really things
NOTE Confidence: 0.854550182819366

00:53:00.210 --> 00:53:01.897 changed that much whether you
NOTE Confidence: 0.854550182819366

00:53:01.897 --> 00:53:03.512 gave them treatment or whether
NOTE Confidence: 0.854550182819366

00:53:03.512 --> 00:53:05.164 you didn't give them treatment.
NOTE Confidence: 0.854550182819366

00:53:05.164 --> 00:53:06.874 Is a little bit disheartening,
NOTE Confidence: 0.854550182819366

00:53:06.880 --> 00:53:09.640 but we're going to try to look a
NOTE Confidence: 0.841290950775146

00:53:09.640 --> 00:53:11.360 little bit further at that.
NOTE Confidence: 0.841290950775146

00:53:11.360 --> 00:53:12.704 Yeah, yeah, you know,
NOTE Confidence: 0.841290950775146

00:53:12.704 --> 00:53:14.720 judging by the way you describe
NOTE Confidence: 0.841290950775146

00:53:14.786 --> 00:53:16.880 for the presence of Halo alkanes,
NOTE Confidence: 0.841290950775146

00:53:16.880 --> 00:53:18.712 you could imagine they
NOTE Confidence: 0.841290950775146

00:53:18.712 --> 00:53:20.544 may be more ubiquitous.
NOTE Confidence: 0.841290950775146

00:53:20.550 --> 00:53:22.488 In our environment than we might
NOTE Confidence: 0.841290950775146

00:53:22.488 --> 00:53:23.457 otherwise appreciate given

NOTE Confidence: 0.841290950775146
00:53:23.457 --> 00:53:24.957 all the things they are in
NOTE Confidence: 0.846849322319031
00:53:24.960 --> 00:53:26.136 absolutely and it doesn't
NOTE Confidence: 0.846849322319031
00:53:26.136 --> 00:53:27.900 have to just relate to glioma.
NOTE Confidence: 0.846849322319031
00:53:27.900 --> 00:53:29.365 You know could relate to
NOTE Confidence: 0.846849322319031
00:53:29.365 --> 00:53:31.930 lots of different things so.
NOTE Confidence: 0.83347088098526
00:53:31.930 --> 00:53:33.112 Well, very interesting.
NOTE Confidence: 0.83347088098526
00:53:33.112 --> 00:53:36.300 You know we're just about out of time.
NOTE Confidence: 0.83347088098526
00:53:36.300 --> 00:53:37.488 An really appreciate.
NOTE Confidence: 0.83347088098526
00:53:37.488 --> 00:53:39.072 Oh actually, JoJo contest
NOTE Confidence: 0.83347088098526
00:53:39.072 --> 00:53:40.656 hasn't question, forgive me.
NOTE Confidence: 0.83347088098526
00:53:40.660 --> 00:53:42.988 So Joe's question is high dose
NOTE Confidence: 0.83347088098526
00:53:42.988 --> 00:53:44.540 radiation therapy delivered to
NOTE Confidence: 0.83347088098526
00:53:44.603 --> 00:53:47.015 pediatric patients can lead to glioma?
NOTE Confidence: 0.83347088098526
00:53:47.020 --> 00:53:49.714 Have you found evidence that medical
NOTE Confidence: 0.83347088098526
00:53:49.714 --> 00:53:51.988 imaging and radiation exposure in
NOTE Confidence: 0.83347088098526

00:53:51.988 --> 00:53:53.980 this setting is associated? So
NOTE Confidence: 0.861393511295319

00:53:53.980 --> 00:53:55.805 there's actually, and you probably
NOTE Confidence: 0.861393511295319

00:53:55.805 --> 00:53:58.210 even know of these two studies.
NOTE Confidence: 0.861393511295319

00:53:58.210 --> 00:54:00.583 There's a big cohort from Australia as
NOTE Confidence: 0.861393511295319

00:54:00.583 --> 00:54:03.580 well as a second cohort from England,
NOTE Confidence: 0.861393511295319

00:54:03.580 --> 00:54:06.612 and they did find that even exposure to
NOTE Confidence: 0.861393511295319

00:54:06.612 --> 00:54:09.826 head CT's at an early age in children
NOTE Confidence: 0.861393511295319

00:54:09.826 --> 00:54:12.029 was associated with the I mean.
NOTE Confidence: 0.861393511295319

00:54:12.030 --> 00:54:14.718 It's a very small increase in risk,
NOTE Confidence: 0.861393511295319

00:54:14.720 --> 00:54:16.760 but a definite increase in risk
NOTE Confidence: 0.861393511295319

00:54:16.760 --> 00:54:18.940 of both glioma and meningioma,
NOTE Confidence: 0.861393511295319

00:54:18.940 --> 00:54:21.076 and then anything we looked at
NOTE Confidence: 0.861393511295319

00:54:21.076 --> 00:54:24.237 we did find it was a fairly hotly
NOTE Confidence: 0.861393511295319

00:54:24.237 --> 00:54:26.302 contested topic we did find.
NOTE Confidence: 0.861393511295319

00:54:26.310 --> 00:54:28.711 And exposure to bite wings was associated
NOTE Confidence: 0.861393511295319

00:54:28.711 --> 00:54:30.908 with an increased risk of meningioma,

NOTE Confidence: 0.861393511295319
00:54:30.910 --> 00:54:32.750 but that's sort of exposure
NOTE Confidence: 0.861393511295319
00:54:32.750 --> 00:54:34.810 level in terms of dental X,
NOTE Confidence: 0.861393511295319
00:54:34.810 --> 00:54:36.580 Rays generally doesn't exist now.
NOTE Confidence: 0.861393511295319
00:54:36.580 --> 00:54:39.044 But yeah, in terms of head CT's,
NOTE Confidence: 0.861393511295319
00:54:39.050 --> 00:54:41.180 the two big cohorts from Australia,
NOTE Confidence: 0.861393511295319
00:54:41.180 --> 00:54:42.950 anyone to do suggest that,
NOTE Confidence: 0.861393511295319
00:54:42.950 --> 00:54:44.009 although you know,
NOTE Confidence: 0.861393511295319
00:54:44.009 --> 00:54:46.127 even though the risk is increased,
NOTE Confidence: 0.861393511295319
00:54:46.130 --> 00:54:47.198 the absolute numbers
NOTE Confidence: 0.815169589860099
00:54:47.200 --> 00:54:49.110 are small. And then Antonio
NOTE Confidence: 0.815169589860099
00:54:49.110 --> 00:54:51.002 Murray asks, is great talk.
NOTE Confidence: 0.815169589860099
00:54:51.002 --> 00:54:53.246 Have you looked at thyroid hormones,
NOTE Confidence: 0.815169589860099
00:54:53.250 --> 00:54:54.750 thyroid disease and differences
NOTE Confidence: 0.815169589860099
00:54:54.750 --> 00:54:56.250 between men and women?
NOTE Confidence: 0.837125480175018
00:54:57.020 --> 00:54:59.939 So we haven't but one thing that
NOTE Confidence: 0.837125480175018

00:54:59.939 --> 00:55:02.438 is very interesting, and it relates
NOTE Confidence: 0.837125480175018

00:55:02.438 --> 00:55:04.934 a little bit more to meningioma.
NOTE Confidence: 0.837125480175018

00:55:04.940 --> 00:55:07.448 Is a gene that we found,
NOTE Confidence: 0.837125480175018

00:55:07.450 --> 00:55:09.530 and this is a constitutional
NOTE Confidence: 0.837125480175018

00:55:09.530 --> 00:55:11.194 gene on chromosome 10.
NOTE Confidence: 0.837125480175018

00:55:11.200 --> 00:55:14.119 We've found to be associated with meningioma,
NOTE Confidence: 0.837125480175018

00:55:14.120 --> 00:55:16.200 breast, ovarian and also now
NOTE Confidence: 0.837125480175018

00:55:16.200 --> 00:55:20.270 thyroid tumors. Interest.
NOTE Confidence: 0.886166334152222

00:55:20.270 --> 00:55:21.176 Elizabeth, thank you.
NOTE Confidence: 0.886166334152222

00:55:21.176 --> 00:55:23.690 We are at the top of the hour.
NOTE Confidence: 0.886166334152222

00:55:23.690 --> 00:55:25.245 Appreciate both your talk and
NOTE Confidence: 0.886166334152222

00:55:25.245 --> 00:55:26.489 Barbara's really extending work.
NOTE Confidence: 0.886166334152222

00:55:26.490 --> 00:55:28.770 Thank you for sharing all of it with
NOTE Confidence: 0.886166334152222

00:55:28.770 --> 00:55:31.470 us and to everyone who joins us today.
NOTE Confidence: 0.886166334152222

00:55:31.470 --> 00:55:33.528 Thank you for taking the time
NOTE Confidence: 0.886166334152222

00:55:33.528 --> 00:55:35.623 to join grand rounds and we'll

NOTE Confidence: 0.886166334152222

00:55:35.623 --> 00:55:37.579 see you all again next week.

NOTE Confidence: 0.886166334152222

00:55:37.580 --> 00:55:39.648 Have a good day.