Welcome everyone, I'm right here. Still be the moderated today. Just as we started this remind everyone that this Friday from 8:00 to 12:30 is our annual review of ASCO. And I'm very excited this is the 10th year I'll be doing it, but we had it in place a number of years before that. Eddie used to run it and it should be very nice of you, Barbara. Already one of you are probably speaking on hearing that cancer. So, uh, another chance to hear, and then it'll be very special.
NOTE Confidence: 0.78131855
00:00:33.890 --> 00:00:35.620 3540 minutes around 11:00 o’clock,
NOTE Confidence: 0.78131855
00:00:35.620 --> 00:00:37.958 where Vince Devita and his daughter Elizabeth
NOTE Confidence: 0.78131855
00:00:37.958 --> 00:00:40.786 and a few questions for myself as well.
NOTE Confidence: 0.78131855
00:00:40.790 --> 00:00:43.454 We’ll discuss a little bit about the 50th
NOTE Confidence: 0.78131855
00:00:43.454 --> 00:00:45.617 anniversary of the National Cancer Act,
NOTE Confidence: 0.78131855
00:00:45.620 --> 00:00:47.690 so that should be very excited.
NOTE Confidence: 0.78131855
00:00:47.690 --> 00:00:50.280 So now I’m going to introduce today’s
NOTE Confidence: 0.78131855
00:00:50.280 --> 00:00:52.518 speakers on introduce all three of you,
NOTE Confidence: 0.78131855
00:00:52.520 --> 00:00:54.590 and then I’ll let Barbara moderate
NOTE Confidence: 0.78131855
00:00:54.590 --> 00:00:55.970 through the the presentations,
NOTE Confidence: 0.78131855
00:00:55.970 --> 00:00:58.890 and then we’ll have questions at the end.
NOTE Confidence: 0.78131855
00:00:58.890 --> 00:01:01.123 And one of the things we’ve been
NOTE Confidence: 0.78131855
00:01:01.123 --> 00:01:02.957 doing is we’ve been highlighting
NOTE Confidence: 0.78131855
00:01:02.957 --> 00:01:05.764 our darts or disease teams at these
NOTE Confidence: 0.78131855
00:01:05.764 --> 00:01:08.755 grand rounds and it’s a great way to
develop multi modality discussions.

An interaction between the disease programs and the research programs with Cancer Center. So we’re very excited.

We have a group today, a tremendous team. First speaker will be Doctor Barbara Burtness, Barbara Professor of medicine and medical in country and disease aligned research team leader for head and neck cancer. She was recently named as interim Associate cancer Director for Diversity. Congratulations Barber Chief Medical
00:01:36.912 --> 00:01:39.447 degree from SUNY at Stony Brook
00:01:39.447 --> 00:01:41.806 completed a residency at Yale and our
00:01:41.872 --> 00:01:44.397 Fellowship at Memorial Sloan Kettering.
00:01:44.400 --> 00:01:45.828 Is that on faculty?
00:01:45.828 --> 00:01:47.256 Of course that yeah,
00:01:47.260 --> 00:01:49.766 she left in and she’s come back.
00:01:49.770 --> 00:01:51.955 Doctor Bernice is an internationally
00:01:51.955 --> 00:01:54.738 recognized leader in the treatment of head
00:01:54.738 --> 00:01:57.290 and neck cancer and as chair of the Ikago,
00:01:57.290 --> 00:01:59.438 Akron and Therapeutics Committee since 2006.
00:01:59.440 --> 00:02:00.210 Pioneering biomarker,
00:02:00.210 --> 00:02:02.520 guided treatment and treatment at the
00:02:02.520 --> 00:02:04.090 intensification studies in this disease.
00:02:04.090 --> 00:02:05.875 She also leads the Yellowhead
00:02:05.875 --> 00:02:07.303 and explore recently awarded.
Finished just finished the first year, which addresses critical barriers to treatment of head and neck squamous cell carcinoma due to resistance to immune DNA damaging and targeted therapy. So welcome Barbara. And also on the panel this morning or this afternoon is already Bhatia. Doctor Bhatia is an assistant professor of medicine and medical oncology. She received her medical degree from Toccoa National Medical College and her MPH from the University of Texas School of Public Health. She played her residency at Johns Hopkins University Sinai Hospital and
I fell asleep at Temple University, Fox Chase Cancer Center. Dr Bhatia treats patients with head and neck cancers and a research interest include exploring novel therapies for patients. She designs and conducts clinical trials and also serves as a site PI for several multi center studies and then last but not least from radiation oncology. We have Melissa Young and Doctor Young is an assistant professor of therapeutic radiology and chief of the head and neck radiotherapy program.
She completed her MD PhD training as part of the Medical Scientist Training program at the University of Texas Southwestern Medical Center in Dallas. She then continued her training in radiation oncology, yeah, and stayed and joined our faculty in 2015. Doctor Young treats patients as part of their head in their cancers. Multi disciplinary clinic at the Smile Cancer Hospital Care Center in Trumbull and also specializes in breast and gynecological agencies. So finally, just a quick word. The head and neck cancers dark provides expert multidisciplinary care.
for head and neck cancer patients.

Names to advance new research and the force of the next generation of neddex cancer translational researchers through a developmental research program. Career enhancement program. An interaction in collaboration with the wider spore and head and neck squamous cell Cancer Research communities. So what an amazing team. I’ve used up five of your minutes introducing you. You’re also qualified. I’m going to stop by to turn over to you. Barbara,
one of the best things that ever happened here at yell for me in my 10 years, is when you came and joined us and Barbara and I worked together 20 years ago in the early ages, so Texas map. So Barbara thank you for all you’ve done and the floor is yours.

OK, well thank you for that very kind introduction and for recruiting me back and I’m also very grateful to have the opportunity to talk about what we’ve been doing in the head neck DART. As you heard, the way we’re going to do this is.

My team I’m gonna spend about half an
00:04:50.548 --> 00:04:53.751 hour trying to do a world whirlwind tour

00:04:53.751 --> 00:04:57.419 of some of what our dart has been up to,

00:04:57.420 --> 00:04:59.737 then turn it over to Doctor Bhatia

00:04:59.737 --> 00:05:02.348 to talk about some of the clinical

00:05:02.348 --> 00:05:04.278 trials she's been developing in

00:05:04.278 --> 00:05:06.879 her collaboration with the sporlan,

00:05:06.880 --> 00:05:08.564 then to Doctor Young,

00:05:08.564 --> 00:05:10.669 who leads our therapeutic radiation

00:05:10.669 --> 00:05:12.000 efforts in this area.

00:05:12.000 --> 00:05:14.364 So just a brief introduction to

00:05:14.364 --> 00:05:15.546 our clinical membership.

00:05:15.550 --> 00:05:18.469 The nature of of head neck cancer.

00:05:18.470 --> 00:05:21.010 Given its anatomic complexity,

00:05:21.010 --> 00:05:24.185 its tendency to treatment resistance.

00:05:24.190 --> 00:05:27.067 It has been that very clearly outcome
00:05:27.067 --> 00:05:29.854 is improved when patients get surgery
NOTE Confidence: 0.8714161
00:05:29.854 --> 00:05:32.800 and radiation at high volume centers,
NOTE Confidence: 0.8714161
00:05:32.800 --> 00:05:35.495 and so we have a dedicated focus
NOTE Confidence: 0.8714161
00:05:35.495 --> 00:05:38.347 on trying to have pockets of
NOTE Confidence: 0.8714161
00:05:38.347 --> 00:05:40.495 excellence around the state.
NOTE Confidence: 0.8714161
00:05:40.500 --> 00:05:44.126 So in addition to the program, it’s Milo.
NOTE Confidence: 0.8714161
00:05:44.126 --> 00:05:47.750 There are hubs for head and neck cancer,
NOTE Confidence: 0.8714161
00:05:47.750 --> 00:05:48.654 multidisciplinary care,
NOTE Confidence: 0.8714161
00:05:48.654 --> 00:05:51.366 including at Trumbull Ann Lawrence Memorial.
NOTE Confidence: 0.8714161
00:05:51.370 --> 00:05:55.114 I know Emily Collier is going to be.
NOTE Confidence: 0.8714161
00:05:55.120 --> 00:05:57.170 Joining us at Saint Francis.
NOTE Confidence: 0.8714161
00:05:57.170 --> 00:06:00.040 So it’s a it’s a terrific team.
NOTE Confidence: 0.8714161
00:06:00.040 --> 00:06:03.730 A lot of fun to work with with everybody.
NOTE Confidence: 0.8714161
00:06:03.730 --> 00:06:05.610 The patients who present with
NOTE Confidence: 0.8714161
00:06:05.610 --> 00:06:08.028 with head neck cancer often come
NOTE Confidence: 0.8714161
00:06:08.028 --> 00:06:09.880 with locally advanced disease,
so local, regionally invasive and not meta static and may present many times in a curative state or cure, potentially curable stage. But these tumors are located in areas that are very critical for speech and swallowing and taste and appearance and. And many of the things that we do to interact with with other people. So having a conversation, sharing a meal, singing all of these things can be impacted by either the cancer or the treatment for the cancer.
Treatments are further constrained by some anatomic peculiarities, like the carotid artery in the base of the skull, and even patients who are successfully treated may be left with very significant impairment, functional restriction, and actually may succumb to the consequences of their treatment even when they are cured. So there is a lot of work to do to improve our standard of care even when it's curative as well. There are a lot of areas of I think difficulty in the science underlying or the biology underlying head neck cancer.
So Roy mentioned that he and I first worked together in the context of cetuximab and it was a thrill when we saw that lead to responses as a single agent in head neck cancer. But it's clear that both constitutive resistance and adaptive resistance greatly limit the utility of EGFR inhibitors and another. Her family inhibitors the genome of head neck cancer is dominated by mutations in tumor suppressor genes, so this has been very difficult to target there. There are not a lot of successes.
00:07:52.571 --> 00:07:54.971 with kinase inhibitors of activated oncogenes in this disease.
NOTE Confidence: 0.8009887

00:07:54.971 --> 00:07:57.015 Although we have activity for immune checkpoint inhibition and I'll briefly show you some of those data.
NOTE Confidence: 0.8009887

00:08:00.002 --> 00:08:01.990 The effective immunotherapy is more modest in head and neck cancer than in many other solid tumors.
NOTE Confidence: 0.8009887

00:08:06.810 --> 00:08:09.343 And part of this story certainly lies in the tumor microenvironment, which is hostile to immune effector cells because of hypoxia.
NOTE Confidence: 0.8009887

00:08:11.690 --> 00:08:16.190 Expression of Ido macrophage polarization.
NOTE Confidence: 0.8009887

00:08:16.190 --> 00:08:20.280 Very high abundance of Milo drive suppressor cells, an lymphocyte excluded phenotypes.
We have a new kind of head neck cancer. Over the past 1520 years which is driven by human papilloma virus, which gives us both an immune target and and maybe also a way to interfere with. The signaling that drives these cancers, but there has been pretty low success in targeting HPV as a driver of head neck cancer. We see very grave disparities in outcome in HPV. Negative cancers between black patients and other groups, and although much of this is
explained by socioeconomic factors,

it's becoming clearer that their ancestry based differences in treatment response as well, and these have kind of been lost in a pool of trials that did not include a lot of patients of African ancestry. And then the field as a whole has historically suffered from underinvestment in clinical trials and low access to new patients. So what I'd like to quickly do is talk a little bit about multidisciplinary clinical care here,
our catchment area,
afew highlights of our clinical research portfolio,
some of the correlative and translational science that is going on.
Some of our translation to the cooperative group network.
Engagement with policy and then career development and then part of career development will be turning it off to my two very talented junior colleagues.
Multidisciplinary care I mentioned that high high case volume is important and so you see here, at least from the pre pandemic numbers.
are surgical volumes for oral cavity, pharynx and larynx cancer. We have a multidisciplinary tumor board. That brings together surgery, radiation, medical oncology, neuro radiology, pathology and speech language pathology which helps us to make treatment recommendations that optimize both our drive for cure and the need to think about the functional consequences of treatment for our patients. We’ve rolled out chemoradiation supportive care order sets across that the health system. We work very closely with
speech language pathology. And function preservation beginning with pre him before the surgery or or chemoradiation even begins and we have dedicated social work to help with many of the problems with employment. That and and other socio economic problems that this group of patients encounters. Several marijuana var or the leader of our head and neck surgical oncology program introduced to clinic clinical care pathway for reducing ICU. Usage in head neck cancer microvascular reconstruction and you can see here these absolutely stunning data not
only lowering the average length of stay to a week for very complicated large reconstructive surgeries, but also bringing ICU stays from 100% to 6% and dramatically reducing unplanned 30 day re admission. Within our catchment area, New Haven County is well documented to have excess rates of tobacco use relative to national rates and in lower income adults in New Haven uses twice as high oral cavity. Cancer is increasing dramatically. In Connecticut, Ann is 50% higher in the Latin X population in the state, so we have a very significant focus on
the on the tobacco associated malignancies.

We have trials and Artie Patio will speak later about. About one of them, moving forward in the cooperative groups, international trials focused on HPV negative disease. Two of the projects in our head and explore focus on HPV, negative disease and in the E con Akron health Head Neck Committee that that I lead. We are now developing HealthEquity coast studies with many of our larger clinical trials.
For HPV negative head neck cancer
NOTE Confidence: 0.8516818
are among the most dramatic for
NOTE Confidence: 0.8516818
any solid tumor and a collaborator
NOTE Confidence: 0.8516818
of mine from my time at Fox Chase.
NOTE Confidence: 0.8516818
Camille Reagan, who is now part of our spore,
NOTE Confidence: 0.8516818
has demonstrated that African ancestry
NOTE Confidence: 0.8516818
informative markers are associated with
NOTE Confidence: 0.8516818
overexpression of DNA polymerase beta
NOTE Confidence: 0.8516818
and that this in turn is associated
NOTE Confidence: 0.8516818
with platinum and radiation resistance.
NOTE Confidence: 0.8516818
She’s got a large collection of patients
NOTE Confidence: 0.8516818
in the temple system that she’s sequencing.
NOTE Confidence: 0.8516818
It’s highly enriched for African American
NOTE Confidence: 0.8516818
patients and we’re collaborating with her.
NOTE Confidence: 0.8516818
To bring forward.
NOTE Confidence: 0.8516818
Patient drive tissue resources for
00:13:18.365 --> 00:13:20.505 studying alternative therapies to platinum and radiation in these patients.

00:13:20.505 --> 00:13:23.340 We have a large clinical trial portfolio.

00:13:26.160 --> 00:13:29.787 I don’t want to go through it in detail, but I’ll just emphasize that we always prioritize investigator initiated trials.

00:13:29.790 --> 00:13:32.576 Doctor Bhatia will talk about the Phantom, so tuck some AB work.

00:13:32.576 --> 00:13:34.220 I’ll talk a little bit about a trial for pembrolizumab in primary radiation resistance and the five Aza work we have particularly focused on HPV,

00:13:34.220 --> 00:13:37.034 phase one trials particularly focused on HPV, therapeutic vaccines for HPV.

00:13:37.040 --> 00:13:42.068 I’ll talk a little bit about a trial for pembrolizumab in primary radiation resistance and the five Aza work we have particularly focused on HPV,

00:13:42.068 --> 00:13:44.057 phase one trials particularly focused on HPV, therapeutic vaccines for HPV.

00:13:44.057 --> 00:13:47.294 associated cancer.
practice changing trials including.

Not that we let it,

but contributed to the cabins

antonym in radioiodine.

Refractory thyroid cancer study that

was presented at ASCO this year and I

think is really going to change the

standard of care for Len Bat neighbor

factory disease and on going late phase

trials in the chemoradiation setting.

So let me tell you a little bit

about this radioresistance trial.

This was started by Zen Hussain when

when he was here before he left for

Toronto and the idea was that we

had patients in our practice HPV.
Negative cancers predominantly, who had presented with very advanced disease and had primary radio resistant disease. At that time there was no standard of care with immunotherapy for those patients, and so he put together a Phase two trial for moving them right on to Pember Lizum app with the advantage that we would have baseline tissue tissue from the biopsy that prove persistent disease and if the patient had become resectable by the end of four cycles of Pember lism and they would,
they would go on to reception.

So we are doing immuno profiling on the specimens from this trial and also started sequencing them in the first two cases that we sequenced. Both had this. Very unusual finding of whether new emergence or enrichment for mutation in tenascin R1 of the. Tenascin family proteins that controls EMT and can be involved in an immunosuppressive microenvironment. So we have just gone back and received funding to finish sequencing. All the cases here and think that this is potentially a very
interesting lead into the biology of primary radioresistance. The pictures at the bottom just show you one of our patients who had a CR. He’s now four years out. Just to switch gears now to some of the correlative work along time ago, the Kaag committee had demonstrated that for patients who had undergone margin negative resection, but who had disruptive mutation of TP53 that they continued to have a pretty poor outcome despite getting risk based appropriate postoperative therapy. And that was done with older sequencing.
technology as next Gen sequencing came on and a number of new algorithms for calling P53 mutation became available. We undertook a comparison of all of these different classifying schemes in the specimens from that ekonk trial, finding that our original rule, which was DNA binding domain mutations or truncation mutations, somewhat supplemented with information about splice variants, really was the best predictor of bad outcome. And since, P53 mutation is quite prevalent in head neck cancer. And difficult to target this has,
I think, really helped us focus on the importance of understanding the biology of these people.

Barbara did we lose Barbara? Yeah, look. Her Internet is down. OK, well these things happens. Barbara you're muted. It’s the storms. Who’s ready to step up? Oh, here she is. Barbara you’re muted. Sorry about that. So we sequenced these or characid sequenced over these or characid sequenced over HPV negative cancers.
We classified the P53 mutation using a variety of different schemes ever.

You need to share your slides again, sorry.

Will give you 2 extra minutes at the end of the hour, don’t worry.

Alright, am I doing better now?

There’s this better perfect looked at CDK into mutations and then calculated tumor mutation burden.

So what was quite interesting here was that either P53 or CDK mutation was associated with higher tumor mutation burden, with the exception of when that P53 mutation was a gain of function, not loss of function mutation,
but that the Co-occurrence of P53, CDK and 2A.

Mutation was associated with the HYEST tumor mutation burden and this came into the 15 mutations per megabase range, which has been informative for response to immunotherapy.

But it’s been understood for a long time that there’s a range of TMB across different kinds of both HPV positive and HPV negative head, neck cancers, both smokers and nonsmokers that this is associated with response to pembrolizumab and more recently in a
randomized trial of development that was actually negative for all comers. If you focused on the group with high TMB there was a survival advantage for the use of immunotherapy, so I think one thing this points us to is the early use of immunotherapy. In P53 mutated head neck cancer and I’ll maybe take a brief detour here because this is. This is work that Yale investigators participated in before I arrived here. And then I’ve been very involved with the keynote 012 trial, which was the first large scale study of immune checkpoint inhibition.
00:20:27.761 --> 00:20:30.848 in head and neck cancer was done with pembrolizumab.

NOTE Confidence: 0.8312539

00:20:30.848 --> 00:20:31.730 We had a big focus on including both HPV negative and HPV positive cancer.

NOTE Confidence: 0.8312539

00:20:31.730 --> 00:20:34.898 and you can see.

NOTE Confidence: 0.8312539

00:20:34.898 --> 00:20:37.707 That durable responses were seen in both types of head neck cancer.

NOTE Confidence: 0.8312539

00:20:37.710 --> 00:20:39.130 Really, what the next five years of research into immunotherapy in head neck cancer has has played out as because there are early and deep responses, and there are somewhat slower responses.

NOTE Confidence: 0.8312539

00:20:40.905 --> 00:20:43.332 and looking at the spider plot, I think that you see.

NOTE Confidence: 0.8312539

00:20:43.332 --> 00:20:45.559 00:20:48.220 I think that you see.

NOTE Confidence: 0.8312539

00:20:45.560 --> 00:20:48.606 Really,

NOTE Confidence: 0.8312539

00:20:48.606 --> 00:20:51.308 what the next five years of research into immunotherapy in head neck cancer has has played out as because there are early and deep responses, and there are somewhat slower responses.

NOTE Confidence: 0.8312539

00:20:51.308 --> 00:20:53.050 00:20:55.150 cancer has has played out as because there are early and deep responses, and there are somewhat slower responses.

NOTE Confidence: 0.8312539

00:20:53.050 --> 00:20:55.150 00:20:57.369 there are early and deep responses, and there are somewhat slower responses.

NOTE Confidence: 0.8312539

00:20:55.221 --> 00:20:57.369 00:20:59.130 there are early and deep responses, and there are somewhat slower responses.
But that are deep and very durable.

But there’s a subset of patients who not only don’t respond to immunotherapy, but appear to almost have accelerated. Disease growth and so we need to understand what’s suppressive in the tumor microenvironment that leads to this resistance and what it might be in the tumor microenvironment that’s PDL one expressing that it’s actually bad to turn off.

So I think there’s some. Some work to be done there, but given the strong signal with 18% response rate and durable CRS in the treatment refractory setting,
we move this forward as a first line trial in metastatic recurrent disease and this had a little bit of a complicated design because we recognized that the standard of care which was chemotherapy with Cytoxan had a higher response rate than pembrolizumab monotherapy, but it didn’t have the same duration and it didn’t have the same complete response rate. So we had to experimental arms. One was Pember Lism AB alone and one was purple is made with chemotherapy, each of them independently compared
to the standard of care

NOTE Confidence: 0.8051728

chemotherapy with cetuximab and

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then we undertook a biomarker driven

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analysis because the hypothesis was

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that those cases that express PD,

NOTE Confidence: 0.8051728

L1 the most richly might be

NOTE Confidence: 0.8051728

the most likely to respond,

NOTE Confidence: 0.8051728

and there the advantage over chemo cetuximab

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would be more readily apparent.

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Actually, Pember Lism had

NOTE Confidence: 0.8051728

performed better than.

NOTE Confidence: 0.8051728

Then we could have imagined,

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but so this is the CPS 20 group,

NOTE Confidence: 0.8051728

the highest PDL one expressing an

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you see here a hazard ratio of

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in favor of Pember Lism AB.
We now have four year data showing that this group has over a 20% for your survival. This is all PDL one. Expressing cancers, hazard ratios of 0.78 and this was also statistically significant compared with the control arm. And then if you took all comers so that includes the 15% that are PDL, one negative Pember Lizum app was noninferior to chemotherapy cetuximab. Going back and looking at that PDL one subset they do substantially worse with Pember Lizum app then with chemotherapy cytoxan and so
they should not get pembrolizumab in monotherapy and then pembrolizumab plus chemotherapy superior to the reference regimen across all regimens, across all biomarker subgroups. So this study has been very fruitful. Subsequent publications coming out about patient-reported outcomes. The PDL1 subsets. In long term survival. I would like to introduce you to our head export team so spores are. Programs of research excellence usually centered around a given disease type. They need to have at least three projects and cores.
and developmental projects, and we received very generous support from the Cancer Center in the medical school to jumpstart these projects and. The first review had some some comments that we had to address, but we were funded late last year, so we have three projects, one on targeting the EGFR family. An artifact will talk about that more in a couple of minutes, one on synthetic lethal therapy for predominantly P53 mutated cancer. I'll speak about that a little bit, and then Karen Anderson and Del Yarbrough.
Looking at demethylation to trigger a pevec induced synthetic lethality, and I'll introduce them briefly as well. So I've been talking about P53 mutant cells really being sort of one of the last bastions of undruggable head neck cancer, and we know that these cells exhibit impaired regulation of G1 S checkpoints, increasing their dependence on the G2 M transition to repair replication damage, creating vulnerability to inhibitors of these processes through DNA damage, restrictive mitotic entry and we have had.
An interest in this for a long time going back to work when I was at Fox Chase demonstrating that Aurora kinase overexpression in the nuclear compartment was associated with worse overall survival, we know that Aurora is regulated by P53, and so we began to look at using Aurora as an inhibitor. Both preclinically and in the clinic and...
the clinic it hit a 9% response rate, so that was obviously pretty disappointing. And what we found when we gave it clinically and this is with an agent called ellisor tip is that it did actually aggregate phosphorylation of Aurora. It did change the function of Aurora, so we got these. And yet what happened was that the cells, I’m sorry, but the cells entered really a cell cycle arrest that was mediated through phosphorylation of CDK. One is, you see here that that inhibitory phosphorylation is placed by we won,
and so we combine the Aurora inhibitor with the wee one inhibitor we want is a regulator of mitotic entry and you see here when you give the wee one inhibitor, you accelerate mitotic entry and find these cells that are. Sort of held up in late mitosis, but when you give the two agents together, you precipitate mitotic catastrophe and the cells undergoing a punit cell death. As you can see here with the Nixon 5 and Cliff Park, we treated animals with the combination. Their survival was markedly improved compared to either of the amount of therapies.
and tumor growth was really controlled.

If you looked at these mirroring tumors under the microscope, you saw that the combination increased cleaved caspase reduced proliferation. Looking in the leading edge of these tumors using Aqua, we could count phospho CDK one and it was markedly reduced. We’ve now moved to a more selective second generation Aurora inhibitor, which we think will be easier ‘cause it’s not as myelosuppressive and been able to replicate these findings and so part of our score is to take this
Combination forward as a window trial in HPV, negative disease, going for resection with those escalation, and then an expansion cohort. Collaborating with the Glamis lab, we've done a high throughput screen to identify additional synergistic pairs or additional partners for agave, assertive and our strongest hit was with the check. One check two inhibitor prex assertive. When I first saw that come out, I was pretty discouraged. 'Cause that's a pretty myelosuppressive agent in the clinic,
and I was fearful that we wouldn’t be able to use it in combination. But if you look here, you can see that even at 25 nanomolar we get clonogenic survival effects in combination, so these pairs are going to be tested in animal models as part of our sport project. I think in the interest of time I will skip this. This sort of side branch story that we have trying to explore these therapies for patients with Fanconi anemia who developed head neck cancer at very high rates in adulthood. But let me introduce you to Karen Anderson and Dell Yarbrough’s project in the spore.
There's an observation from the TSJ that they're striking differences in metalation between HPV negative and HPV positive head neck cancers, and else lamp had done work demonstrating that this metalation induces immune silencing and if you give a demethylating agent like 5 Aza, you downregulate HPV and MMP expression. You stabilize P53 and you induce a pop ptosis so we ran a window trial of Viveza siding and HPV negative of Viveza siding and HPV negative and HPV positive cancer. No effects in the HPV negative cancers.
but in the HPV positive cancers. We saw. Activation of Type One interferon signaling. Upregulation of the gene editing protein apobec 3B which increased double strand DNA breaks and there was activated T cell infiltration within tumors and you see here. Photomicrographs before and after that were stained in David Rims Lab, looking for CD4 CD 8 and CD 20 cells and I just Representative Lee have shown you the CD eight counts within the tumor mask before and after five days of siding. So we are taking this.
Forward now in a store window, trial either 5/8 sided, being alone nivolumab alone or the combination in the new edgmont setting and are. Also hoping to add to this 18 F energy pet for noninvasive quantitation of activated T cell infiltration across the course of the new engine therapy and collecting samples for tumor neoantigen expression. The cooperative groups are, I think, an important venue for asking questions that are closer to practice, and I’ve talked a lot about HPV,
negative disease in HPV positive disease.

Are questions center more on?

How can we enhance function

preservation and these are data we

just presented at ASCO this year,

showing that if you take patients

with resectable stage HPV

associated cancer to transoral

resection and then you have that.

Pathologic staging from the surgical

material in hand that really permits

much more dramatic treatment.

The intensification than if

you have to rely on.

Clinical variables and so here you see

that for favorable risk surgical staging
without any post operative therapy, we have three year progression free survival approaching 97% for the intermediate risk group. So this is node positive but no extranodal extension. Whether we gave 60 Gy of radiation or 50 grey Anne Frank, the fields we maintain three year progression free survival of about 94% and then even the very high risk patients we were able to intensify therapy by going to weekly chemotherapy in the post op setting.
You’ll see here that about a third of the patients on the trial ended up needing Tri modality therapy that is not the goal of treatment. The intensification and so one question is, how can we better identify the patients who have higher risk of let’s say any or positive margin from going on to a surgical trial because they ought to probably go straight to chemoradiation. Ben Khan, who’s now a junior faculty member at the Farber but was a radiation oncology resident here, undertook a machine learning project
where he developed a deep neural network algorithm for identifying extranodal extension from a baseline CT scan. We’ve now validated that on the cooperative group trial in 76 patients, and this has moved on to part of the University of Pittsburgh head next door that I’m a Co investigator on where we’re going to be linking radio MIC. To genomic signatures so that we hopefully can have a better means of identifying these high risk patients at baseline. In terms of policy there, I think have been.
a paucity of FDA approvals

The approvals of pembrolizumab in Nevala

And these trials have become more difficult.

Certainly for the HPV associated cancers, where the event rates are quite low, and designing randomized trials where

you’re looking to have something happen that’s better than 94% at three years really becomes prohibitive in terms of size and duration.

And although we see many ways that immunotherapy and targeted therapy could allow us to intensify trials,

there is no accepted regulatory strategy
NOTE Confidence: 0.84220314
00:33:41.970 --> 00:33:44.119 for demonstrating that that’s the case.
NOTE Confidence: 0.84220314
00:33:44.120 --> 00:33:46.496 So the goals of Project 2025.
NOTE Confidence: 0.84220314
00:33:46.500 --> 00:33:50.490 Are to find harmonized surrogate
NOTE Confidence: 0.84220314
00:33:50.490 --> 00:33:56.220 endpoints that the FDA will accept they.
NOTE Confidence: 0.84220314
00:33:56.220 --> 00:33:58.390 You know want to have public meeting
NOTE Confidence: 0.84220314
00:33:58.390 --> 00:34:00.161 with all the stakeholders present
NOTE Confidence: 0.84220314
00:34:00.161 --> 00:34:02.870 that that will kind of refine PFS?
NOTE Confidence: 0.8097394
00:34:02.870 --> 00:34:03.920 Probably looking better
NOTE Confidence: 0.8097394
00:34:03.920 --> 00:34:05.320 than local regional control.
NOTE Confidence: 0.8097394
00:34:05.320 --> 00:34:07.070 What’s the role of following
NOTE Confidence: 0.8097394
00:34:07.070 --> 00:34:08.470 each PV circulating DNA?
NOTE Confidence: 0.8097394
00:34:08.470 --> 00:34:10.285 How do functional endpoints get
NOTE Confidence: 0.8097394
00:34:10.285 --> 00:34:12.837 defined to permit approval in the D
NOTE Confidence: 0.8097394
00:34:12.837 --> 00:34:14.507 intensification trial and then the
NOTE Confidence: 0.8097394
00:34:14.507 --> 00:34:16.929 last thing that I think is really
NOTE Confidence: 0.8097394
important for us is career development.

And before I turn it over to RT,

I just want to highlight that

the sport does have developmental

research and career enhancement.

Programs that offer up to 50K pilot funding.

Our pay line is pretty good.

We give out seven awards a year.

We just had a cycle but please

think about us next year.

So with that I'm going to.

I think not introduce my two Co

speakers 'cause Roy Herbst did very

nice job with that just mentioned

that obviously this work was done

by many many people besides myself.
Thank my funding agencies and stop sharing so that I can turn it over to Doctor Bhatia.

Good afternoon everyone. Thank you for the opportunity to present here today. I'll be talking briefly about research strategies that we have undertaken at Yale to overcome cetuximab resistance and head neck cancers. This approval was based on improved locoregional control and survival.

As we all know, so toxic members in monoclonal antibody against EGFR an it's the only approved targeted therapy for patients with head and neck cancers. This approval was based on improved locoregional control and survival.
when it was given concurrently with radiation in the locally advanced setting and do to improve PFS and OS when administered in combination with chemo in the recurrent metastatic setting. However, these effects are modest and radiation is proven inferior to chemoradiation. Its clinical utility is limited primarily by either inherent or acquired resistance to therapy, like and binding of EGFR needs to **** and Heterodimerization with other her family receptors or other.
00:36:17.941 --> 00:36:21.388 receptors in kinases such as met and
00:36:21.388 --> 00:36:23.256 subsequent downstream signaling of
00:36:23.342 --> 00:36:25.592 MAP kinase K3 kinase mtor pathway
00:36:25.592 --> 00:36:28.948 rest Ref Mac or Pathway or Jack stat.
00:36:28.948 --> 00:36:31.258 And resistance can be mediated
00:36:31.258 --> 00:36:33.918 either by over expression of EGFR,
00:36:33.920 --> 00:36:37.061 or it’s like ends as we see in hidden
00:36:37.061 --> 00:36:40.094 cancers and in response to smoking it can
00:36:40.094 --> 00:36:43.620 be mediated by nuclear translocation of EGFR,
00:36:43.620 --> 00:36:45.822 where it stabilizes P CNA and
00:36:45.822 --> 00:36:48.060 enhances DNA repair and synthesis,
00:36:48.060 --> 00:36:49.242 or increase headers.
00:36:49.242 --> 00:36:50.818 Dimerization with other members
00:36:50.818 --> 00:36:52.510 of the her family,
00:36:52.510 --> 00:36:54.530 her two and her three,
or with cross talk with other receptors in kinases such as Seemeth. In bed rest and identifying effective means of sensitizing hidden cancers to EGFR inhibition is an important goal for us. An important part of our sport project to prior research at Yale. Done on tissue microarrays that were constructed from oropharyngeal cancer specimens showed a significant association of nuclear EGFR with membranous EGFR expression. An with nuclear P CNA, and that suggested that EGFR functions as a tossing pennies in the nucleus where it stabilizes PC na.
The nuclear activity will could therefore constitute a novel therapeutic target.

Subsequent to that, we designed a phase two trial using a chemo backbone and dual EGFR blockade with cetuximab and or lachnit. The rationale was that dual EGFR blockade would overcome EGFR overexpression, and it’s like an independent downstream signaling an show improved responses.

The tumor biopsies were planned at baseline font treatment, at disease progression. An encore native analysis, we found that nuclear PC na staining.
A decrease in the standing actually correlated with clinical response to treatment for several patients who had matched pre and post treatment biopsies and that suggested that nuclear EGFR may also be inhibited with this combination. As a follow up to that study, we proposed and received an CC and funding for a phase two trial of cetuximab and afatinib in patients with platinum and mostly immune checkpoint inhibition had neck cancers were really no effective. An approved treatments exist. This trial is ongoing for a target accrual of 50 patients.
We have already approved 38 tissue for correlatives is being obtained both pre and post treatment for most patients. An existing funding from NC, CNN, the Patterson Foundation will support quantitative immunohistochemical assessment of the known biomarkers of resistance to EGFR inhibition, namely P-10, Phospho, AKT and PCN. A tumor biopsies from patients on this trial will also be used in project one of the sport to establish PDX is an immune deficient mice and recent structural insights into TKI.
binding have shown that stabilization of receptor activation states. For instance, after Heterodimerization with her three produces EGFR confirmations that do not bind inhibitors like Patna benefit net and that could lead to resistance. So the goal is to identify TK eyes that bind to EGFR confirmations that are occurring in head, neck cancers or those that are not restricted by confirmation. State dependent binding and to test the effectiveness of these compounds in head neck cancers. So PDX is derived from.
Biopsies from patients on the trial will be treated with EGFR directed TK Eyes, which retain efficacy against her three EGFR heterodimers. We also received a recent Department of Defense funding to define the relationship between TP 53 genotype, Aurora kinase expression, and response to EGFR inhibition using patient samples from the same NSN trial. In the absence of TP 53, or in the presence of TPX 2 Aurora kinase, it provides an alternative mechanism of downstream signaling of EGFR using the tissue samples from the trial.
We will be able to determine if the combination.

I’m sorry whether TP 53 mutation will predict for baseline or post treatment resistance,

an weather Aurora kinase and TPX 2 levels are predicted.

Biomarkers of non response to dual EGFR inhibition and correlate with a shorter survival.

Also using posttreatment biopsies, we can determine whether a rise in Aurora kinase levels will predict for disease progression following.

Progression clinical progression on treatment.
Yale is also participated in a multi institutional IIT of an hepatocyte growth factor cement pathway inhibitor similar to the map in combination with Cytoxan map in patients who have previously progressed onset eczema. There is cross talk between EGFR and the cement pathways and it’s a known tumor intrinsic resistance mechanism, a phase one trial of this combination showed a response rate of 17% in syntax map resistant patients. And the subsequent randomized phase two trials showed a response rate of 38% in HPV negative patients.
and these results were presented at ASCO this year. So while keynote over 8 has established the role of immune checkpoint inhibition in the first line, treatment of head neck cancers, so toxic map continues to hold a place in the treatment of this disease and it is one of the most frequently chosen second line treatment in combination with chemotherapy. For patients who came off keynote over 8 on the Pembroke monotherapy arm. We now seek to explore the best second line treatment options for head and neck cancers and multiple lines of
00:42:26.162 --> 00:42:28.622 Evidence has suggested that head and neck tumors are frequently hypoxic.

00:42:28.622 --> 00:42:31.082 An have elevated VEGF signaling, which is associated with immunosuppression.

00:42:31.090 --> 00:42:33.240 The object via the stat three signaling pathway or impairment of dendritic cell maturation induction of immunosuppressive populations, such as MDF, season T regs, and reduce recruitment of cytotoxic effectors, including CD 8 cells.

00:42:39.490 --> 00:42:41.566 Dendritic cell maturation induction of immunosuppressive populations, such as MDF, season T regs, and reduce recruitment of cytotoxic effectors, including CD 8 cells.

00:42:43.130 --> 00:42:45.710 Such as MDF, season T regs, and reduce recruitment of cytotoxic effectors, including CD 8 cells.

00:42:47.610 --> 00:42:48.560 And reduce recruitment of cytotoxic effectors. Including CD 8 cells.

00:42:50.012 --> 00:42:52.808 CD 8 positive T cells and natural killer cells.

00:42:53.890 --> 00:42:56.200 So we postulate that VEGF blockade...
with bevacizumab will reverse these suppressive mechanisms and lead to improved antitumor immunity and clinical responses in patients who were previously treated with the checkpoint inhibition. The combination of immunotherapy and veg F inhibition has also shown excellent clinical efficacy in other solid tumor types, including renal, cell, lung, and hepatocellular, and was recently approved as first line treatment for HCC. Anne in head neck. We had a Phase 1B trial looking at the combination of Pedro and.
NOTE Confidence: 0.8379239
00:43:27.801 --> 00:43:29.908 botnet which showed a response rate
NOTE Confidence: 0.8379239
00:43:29.908 --> 00:43:33.190 of 36% and the PFS of 8.2 months.
NOTE Confidence: 0.8379239
00:43:33.190 --> 00:43:35.430 So we designed a Phase 2 slash
NOTE Confidence: 0.8379239
00:43:35.430 --> 00:43:36.880 3 trial through ekach.
NOTE Confidence: 0.8379239
00:43:36.880 --> 00:43:39.886 There will be 3 arms in the initial phase.
NOTE Confidence: 0.8379239
00:43:39.890 --> 00:43:41.570 Two portion of this study.
NOTE Confidence: 0.8379239
00:43:41.570 --> 00:43:43.943 We chose chemo and cetuximab as a
NOTE Confidence: 0.8379239
00:43:43.943 --> 00:43:46.101 control arm because that was the
NOTE Confidence: 0.8379239
00:43:46.101 --> 00:43:47.891 regimen most patients coming off
NOTE Confidence: 0.8379239
00:43:47.891 --> 00:43:50.439 of keynote over 8 went on to an
NOTE Confidence: 0.8379239
00:43:50.439 --> 00:43:52.242 the two experimental arms are chemo
NOTE Confidence: 0.8379239
00:43:52.242 --> 00:43:54.419 and Beves is a map anitys alisme
NOTE Confidence: 0.8379239
00:43:54.419 --> 00:43:56.926 AB Inbev’s is a map 216 patients
NOTE Confidence: 0.8379239
00:43:56.926 --> 00:43:59.062 will be randomized in the initial
NOTE Confidence: 0.8379239
00:43:59.062 --> 00:44:01.337 phase two part of the trial and
NOTE Confidence: 0.8379239

72
the winner of the phase two.

Portion will then move to phase three against the standard chemo’s attacks ARM and another 214 patients will be randomized in phase three for a total sample size of 430.

Expected study duration is about four and a half years.

We expect this study to actually be activated soon.

We are collaborating with Jeff Ishizuka on that issue Correlatives an at the end of the phase three portion we hope to have a clear answer for best second line treatment moving forward.

Uhm,
that’s all I have for my work here so far. I’ll pass it on to Melissa. Screen sharing. Alright now and thank you. I’ll try to get my screen up. Next and I am again I want to thank everyone here for the opportunity to discuss. It’s such an honor to be able to speak in combination with Doctor Burtness and Doctor Bhatia, and I look forward to the years that we have in the future to continue these projects that we’re all excited about. Part of what I wanted to do today in terms...
00:45:23.119 --> 00:45:26.255 of my brief presentation was to really also.
NOTE Confidence: 0.8404386
00:45:26.260 --> 00:45:27.845 While we're focusing a lot
NOTE Confidence: 0.8404386
00:45:27.845 --> 00:45:29.840 on the head and neck dart,
NOTE Confidence: 0.8404386
00:45:29.840 --> 00:45:32.440 Anan the spore that we have funding for,
NOTE Confidence: 0.8404386
00:45:32.440 --> 00:45:34.150 and how we're incorporating that
NOTE Confidence: 0.8404386
00:45:34.150 --> 00:45:35.860 to the clinical trial progression
NOTE Confidence: 0.8404386
00:45:35.913 --> 00:45:37.683 at Yale didn’t want to discount
NOTE Confidence: 0.8404386
00:45:37.683 --> 00:45:40.888 the the contribution that the
NOTE Confidence: 0.8404386
00:45:42.615 --> 00:45:43.650 and we work very collaboratively
NOTE Confidence: 0.8404386
00:45:43.650 --> 00:45:44.789 two organizations and arts,
NOTE Confidence: 0.8404386
00:45:44.790 --> 00:45:47.294 so I wanted to kind of highlight some
NOTE Confidence: 0.8404386
00:45:47.294 --> 00:45:49.987 of the trials that we do have open,
NOTE Confidence: 0.8404386
00:45:49.990 --> 00:45:52.006 and some of the hope that that
NOTE Confidence: 0.8404386
00:45:52.006 --> 00:45:54.209 will be able to help contribute,
00:45:54.210 --> 00:45:56.866 both with supporting the head and neck dart.

00:45:56.870 --> 00:45:59.374 But also with the head and neck score,

00:45:59.380 --> 00:46:01.592 I have no disclosures and I am

00:46:01.592 --> 00:46:04.088 not going to spend a lot of time.

00:46:04.090 --> 00:46:06.916 I know we’re running a little short on time,

00:46:06.920 --> 00:46:08.873 but as everyone here knows that you

00:46:08.873 --> 00:46:10.750 know head and neck squamous cell

00:46:10.750 --> 00:46:13.025 carcinoma is very common with at least

00:46:13.086 --> 00:46:15.036 64,000 cases in the United States

00:46:15.036 --> 00:46:17.402 and this is reiterating some of what

00:46:17.402 --> 00:46:19.172 Doctor Burtness had previously already

00:46:19.172 --> 00:46:21.297 mentioned is that the head and neck

00:46:21.297 --> 00:46:23.016 location of cancer is very sensitive

00:46:23.016 --> 00:46:25.144 part of the body and it’s very

00:46:25.144 --> 00:46:27.330 important with how we interact with society.

76
Maintain nutrition, communicate.

Anan, it's what, especially in a pandemic.

How we visualize each other to how we, how we see each other and communicate orally.

So currently as we know that in order to provide curative treatment for people who are nonmetastatic, that is usually some form of local therapy which may be surgery or radiation, or sometimes a combination of both, which carries a lot of potential risk for functional impairment.

Whether it’s related to surgical changes, scar tissue from both, surgery radiation.

I’m swallowing dysfunction pain dry mouth.
You know, complications that can arise from dental health and other things that come down the line after. As a consequence of the curative intent treatment. So while patients may be cured, they could be left with lifelong implications of their treatment and some of the goals that we have both at Yale but also across the country in the world or to understand how we can try to reduce the morbidity of that treatment without compromising cure rates. But also importantly,
we still have a long ways to go in certain disease sites.

We've already heard a lot about the P-16 negative population. And how can we overcome treatment resistance but also prevent further morbidity of the treatment that we provide? Some of what’s been touched on already, as is the importance in recognition of immune checkpoint inhibitors. Certainly other disease sites and FDA approvals have come along showing activity. An other disease sites and we now see data showing the efficacy that immune checkpoint inhibitors.
inhibitors appear to have, both also in head and neck cancer as well, and therefore, while a lot of initial data has indicated efficacy in the metastatic setting, we’re also now looking to see how this might be incorporated. In the upfront definitive setting and whether or not that might also provide some opportunity for either reduced dose of radiation, reduced need for cytotoxic chemotherapy, but still maintaining. Equivalent cure rates as to what we already have,
so a lot of these trials are now moving into the definitive setting, looking at multiple different immune checkpoint inhibitors that I’ve got listed here. Some of the former trials that we are now in either actively enrolling on through the head and neck DART, but also previously open trials that are now in their follow-up phase, have used immune checkpoint inhibitors in the upfront setting whether it was in keynote for 12, where. Checkpoint inhibitor Kimbrough was added in conjunction with CHEMORADIATION.
but also in the maintenance phase.

We are currently enrolling on the ikago Akron 3161 that is looking at addition of atrovent you know therapy after an initial phase of definitive chemoradiotherapy and there have been some phase one trials including H NO3 that have looked at how immunotherapy may play some role and also safety and the adjuvant setting after surgery. One of the trials that we currently have open through the radiation oncology DART is looking at how immunotherapy may perhaps improve
efficacy in a high risk population.

So specifically, this is looking at patients who have positive margin or extranodal extension after initial surgical resection of locally advanced head and neck cancer, and patients are currently standard of care is radiation cisplatin.

but this is now heading into the phase three design. An activation and this is now exploring the combination of Docetaxel subtaxa with radiotherapy versus cisplatin with the addition of immunotherapy, this one being a tease.

Oh, and this has been.
Unfortunately, I must admit, a high accruing trial. In part, I think. Again, we're seeing this. A phenomenon of increased. Higher stage disease, more locally advanced disease, especially as patients have had maybe some delays in their care from COVID. And so we have. We have actually been accruing to this at a rather high rate, and we look forward to the results to come. We are also, as I alluded to, looking at how. We might be able to improve our definitive intent,
and there's certain populations where we have some room to improve, and one of that population is a cisplatin ineligible group of patients has already been alluded to, so I won't get into the details of the data. But as was previously mentioned, the Bonner Trials had indicated some improvement over radiotherapy alone, but when compared to cisplatin, it is inferior, although we do have that group of patients that are ineligible for cisplatin instead of eczema, maybe that therapy that we have.
And so H&O four is now looking at whether or not we can take those patients who are ineligible for cisplatin and compare how they might do. And compared to Subtaxa ma’am. So this is using a derbe as an immunotherapy, and whether or not this might also provide meaningful outcomes help radiosensitizing those patients who are not otherwise eligible for cytotoxic chemotherapy. This is open to more advanced P. and higher risk P. 16 positive population, but also the P-16 negative population. Both stage three and stage four cancers.
I mean and also a trial that we have been enrolling on with at least about 7 patients currently in its current state. And then lastly, in terms of the intensification, it is certainly one of our goals as is also been mentioned, the HPV population. Has been recognized as having a better prognosis than that of the P-16 population and across the country. We’re now trying to tease out how. How might we be able to safely D intensify in therapy and the ikago Akron, or this I should say,
the COGS 3311 is kind of one example of where there might be some opportunity to reduce. Treatment, but the outcomes and the number of failures are low because this is a relatively good prognosis population, so we have to think about this meaningfully an carefully an whether or not that’s some combination of reducing radiation dose whether or not it’s a combination of surgery with reduced radiation dose.

I’m not going to be talking about any kind of induction, you know,
systemic therapy followed by your dose

reduced or risk adjusted local therapy,

but certainly a lot of different ways in which this could be explored.

We’re moving to open H and 05, which is looking at our low risk.

P-16 population today.

Intensified protocol, kind of as a jumping point from previously published results of H

and O2 that had shown reasonably good to your progression.

Free survival of 90% with the instead 60 grave radiation with
cisplatin omitting the cisplatin
did did cross to lower progression
free survival so.
Hi,
Hi, no five is looking to keep the 60
Gray with cisplatin arm but also
then looking at a somewhat escalated
or hyper accelerated radiation
60 Gray over 5 weeks
with the addition of immunotherapy
to compare how that may may relate
to the standard of care 70 grain
cisplatin versus 60 Gray and cisplatin.
So we do look forward to opening
this specific population that we
00:54:06.711 --> 00:54:08.923 don’t have a lot of trial opportunity
NOTE Confidence: 0.8304057
00:54:08.923 --> 00:54:11.073 in clinical trial opportunity and
NOTE Confidence: 0.8304057
00:54:11.073 --> 00:54:12.399 look forward to.
NOTE Confidence: 0.8304057
00:54:12.400 --> 00:54:14.935 To providing more options and
NOTE Confidence: 0.8304057
00:54:14.935 --> 00:54:16.963 contributing to important questions
NOTE Confidence: 0.8304057
00:54:16.963 --> 00:54:18.880 nationally and internationally.
NOTE Confidence: 0.8304057
00:54:18.880 --> 00:54:19.396 And then,
NOTE Confidence: 0.8304057
00:54:19.396 --> 00:54:21.460 in terms of the future goals for our
NOTE Confidence: 0.8304057
00:54:21.522 --> 00:54:23.138 therapeutic radiation oncology dart
NOTE Confidence: 0.8304057
00:54:23.138 --> 00:54:25.562 in combination with how we interface
NOTE Confidence: 0.8559582
00:54:25.625 --> 00:54:26.915 with all of the other
NOTE Confidence: 0.8559582
00:54:26.915 --> 00:54:28.205 darts that we work with.
NOTE Confidence: 0.8559582
00:54:28.210 --> 00:54:29.740 But today specifically the head
NOTE Confidence: 0.8559582
00:54:29.740 --> 00:54:31.630 in our head and neck dart,
NOTE Confidence: 0.8559582
00:54:31.630 --> 00:54:33.639 you know our goal is to continue
NOTE Confidence: 0.8559582
00:54:33.639 --> 00:54:35.442 to collaborate with this for a
00:54:35.442 --> 00:54:37.200 lot of the physicians that doctor
00:54:37.200 --> 00:54:38.583 Burtness had previously indicated
00:54:38.583 --> 00:54:40.647 at the beginning of her slides,
00:54:40.650 --> 00:54:42.911 there were at least six physicians just
00:54:42.911 --> 00:54:44.521 from radiation oncology faculty alone
00:54:44.521 --> 00:54:46.558 who are part of this combined effort.
00:54:46.560 --> 00:54:48.772 We have a lot of clinician scientists
00:54:48.772 --> 00:54:50.660 who are actively engaged in DNA.
00:54:50.660 --> 00:54:53.332 Repair and how we might be able to
00:54:53.332 --> 00:54:55.640 improve outcomes in this fits nicely with
00:54:55.640 --> 00:54:58.069 the purpose and an goal of the head.
00:54:58.070 --> 00:54:59.036 And next four,
00:54:59.036 --> 00:55:00.968 and will also be continuing toward
00:55:00.968 --> 00:55:03.253 to support the head and neck dart
00:55:03.253 --> 00:55:05.150 with the trials that were able
00:55:05.150 --> 00:55:07.078 to open our resources as well.
NOTE Confidence: 0.8559582
00:55:07.078 --> 00:55:09.332 Also, we want to continue to open
NOTE Confidence: 0.8559582
00:55:09.332 --> 00:55:10.992 cooperative group trials that will
NOTE Confidence: 0.8559582
00:55:10.992 --> 00:55:13.204 align with the needs of our patient
NOTE Confidence: 0.8559582
00:55:13.204 --> 00:55:14.844 population here in Connecticut and
NOTE Confidence: 0.8559582
00:55:14.844 --> 00:55:17.056 continue to assess that and make sure
NOTE Confidence: 0.8559582
00:55:17.060 --> 00:55:18.926 that we’re opening trials that are
NOTE Confidence: 0.8559582
00:55:18.926 --> 00:55:20.610 appropriate for our Community efforts.
NOTE Confidence: 0.8559582
00:55:20.610 --> 00:55:21.879 And then lastly,
NOTE Confidence: 0.8559582
00:55:21.879 --> 00:55:23.994 is was also alluded to.
NOTE Confidence: 0.8559582
00:55:24.000 --> 00:55:26.520 Outcomes are better at high volume centers,
NOTE Confidence: 0.8559582
00:55:26.520 --> 00:55:28.935 so as we continue to expand an
NOTE Confidence: 0.8559582
00:55:28.935 --> 00:55:30.839 need to serve a greater,
NOTE Confidence: 0.8559582
00:55:30.840 --> 00:55:32.515 expensive community across the entire
NOTE Confidence: 0.8559582
00:55:32.515 --> 00:55:34.800 state of Connecticut and our department,
NOTE Confidence: 0.8559582
00:55:34.800 --> 00:55:37.159 we are working very vigorously of maintaining
high quality at our care center specifically.

Really water for Dan Trumbull.

In addition to our main campus here in New Haven.

So we have extensive efforts in standardizing our radiation treatment planning,

ensuring we have quality across the system.

How we do that is multi factorial, but certainly we have peer review of all of our cases.

We’ve.

Do them regularly whether patients are on or off clinical trial to make sure that we have and maintain quality.

All the physicians that participate
in any head and neck treatment under satellite through also attending these multidisciplinary tumor boards and many of us also attend multidisciplinary clinics as well. So we’re very engaged with with the head and neck team. Like any of the cooperative groups that have external review required as part of our radiation planning, have have identified no concerns with our radiation planning. And then lastly, I think one of the things that is important is that we work very hard to make sure that we have the clinical
NOTE Confidence: 0.8674745
00:56:41.890 --> 00:56:43.788 support services that are key.
NOTE Confidence: 0.8674745
00:56:43.788 --> 00:56:45.527 So the speech, language, pathology,
NOTE Confidence: 0.8674745
00:56:45.527 --> 00:56:47.609 the social work that was mentioned,
NOTE Confidence: 0.8674745
00:56:47.610 --> 00:56:49.595 the surgical resources and expert
NOTE Confidence: 0.8674745
00:56:49.595 --> 00:56:52.447 experts on site so that we can
NOTE Confidence: 0.8674745
00:56:52.447 --> 00:56:54.027 make sure to appropriately.
NOTE Confidence: 0.8674745
00:56:54.030 --> 00:56:55.650 I’m triage our patience is as
NOTE Confidence: 0.8674745
00:56:55.650 --> 00:56:57.320 they go through their treatment,
NOTE Confidence: 0.8674745
00:56:57.320 --> 00:56:59.060 but also have the same high
NOTE Confidence: 0.8674745
00:56:59.060 --> 00:57:00.220 quality surveillance and and
NOTE Confidence: 0.8674745
00:57:00.273 --> 00:57:02.373 also support as they are in their
NOTE Confidence: 0.8674745
00:57:02.373 --> 00:57:03.900 survivorship from heaven and cancer.
NOTE Confidence: 0.8674745
00:57:03.900 --> 00:57:04.713 And I’ll combine.
NOTE Confidence: 0.8674745
00:57:04.713 --> 00:57:06.994 I think this will help continue to improve
NOTE Confidence: 0.8674745
00:57:06.994 --> 00:57:09.276 access as well as improved clinical trial,
NOTE Confidence: 0.8674745

96
trial, enrollment everywhere.

And with that I want to.

I'll stop here.

I want to thank everybody again,

I don't have an acknowledgement slide,

but certainly everyone that

Doctor Burtness had mentioned,

plus or clinical trials team has been

very critical in our ability to do

what we've been able to do in serve.

Our patients here in Connecticut.

OK, thanks Melissa.

We have time for a couple questions.

Please put them into the chat or if

you want will unmute you so you can

speak while I'm waiting for you. I'll
00:57:41.990 --> 00:57:44.041 just say Melissa, I was very impressed

00:57:44.041 --> 00:57:46.271 by the multi modality nature of care

00:57:46.271 --> 00:57:48.618 and the fact that you’re writing these

00:57:48.618 --> 00:57:50.736 trials and all the different centers.

00:57:50.740 --> 00:57:52.684 So what’s the secret we need

00:57:52.684 --> 00:57:53.980 You know higher crewing.

00:57:53.980 --> 00:57:55.276 You know where you can can.

00:57:55.276 --> 00:57:58.892 It’s a very prevalent type

00:58:01.000 --> 00:58:02.455 I guess the eligibility criteria

00:58:02.455 --> 00:58:03.910 are quite broad to allow

00:58:06.280 --> 00:58:08.790 Yeah, I think that’s part of it is as we as

00:58:08.854 --> 00:58:10.429 our darts and doctor Burtness

98
can attest to this too.

We really try to understand what’s going to likely accrue for our current patient population,

and I think that’s been key.

But also making sure to advertise it.

And I think because our physicians have been so engaged at the other centers were able to get these opened.

in enrolled at the care centers.

Sometimes we’re able to meet these patients locally.

I think that’s been a huge part of our success.

Is is making sure those patients who, specially if they’re seeing a New Haven,
NOTE Confidence: 0.8262875
00:58:36.150 --> 00:58:38.390 are seeing all of us and and have.
NOTE Confidence: 0.8262875
00:58:38.390 --> 00:58:40.405 Have full venue and access
NOTE Confidence: 0.8262875
00:58:40.405 --> 00:58:42.017 to understanding every every
NOTE Confidence: 0.8262875
00:58:42.017 --> 00:58:43.999 clinical trial available to them.
NOTE Confidence: 0.8262875
00:58:44.000 --> 00:58:44.310 Great
NOTE Confidence: 0.76599836
00:58:44.310 --> 00:58:46.678 thanks. We have a we have a question
NOTE Confidence: 0.76599836
00:58:46.678 --> 00:58:48.761 from Tommy Tommy you want to unmute
NOTE Confidence: 0.76599836
00:58:48.761 --> 00:58:51.130 and will let you ask your question.
NOTE Confidence: 0.9110757
00:58:51.870 --> 00:58:55.210 Yes, first of all.
NOTE Confidence: 0.9110757
00:58:55.210 --> 00:58:58.538 Barbara and I you have and also others.
NOTE Confidence: 0.9110757
00:58:58.540 --> 00:59:03.428 I think that progress in this area is.
NOTE Confidence: 0.9110757
00:59:03.430 --> 00:59:06.550 Very impressed my sections to you.
NOTE Confidence: 0.9110757
00:59:06.550 --> 00:59:10.730 Is all of your services go up to
NOTE Confidence: 0.9110757
00:59:10.730 --> 00:59:13.880 the what is happening after those
NOTE Confidence: 0.9110757
00:59:13.984 --> 00:59:17.998 combination in terms of adverse effect.
NOTE Confidence: 0.9110757
Is it getting worse for the same
Orpik or less? And you know this.
So putting index is the most important part of the treatment.
So could you come in anger and the particular you several, or you’ll be involving using antibody email check.
What’s the impact?
On the enterprise, the combination on the 88.
In other words, anybody you want her?
You go stand by the response.
Is that like getting more or less or or what?
So could you sort of comment on this so so
maybe I'll start and then I'll pass it to Melissa because I think.
Radiation has its own story with toxicity in terms of the combination of Pember Lism AB with chemotherapy. It did not lead to more toxicity than people is made with the taxman and pembrolizumab alone was a lot less toxic than the combination.

There is a suggestion that there is a little bit of intensification of the myelosuppression when you give pembrolizumab chemo relative to the taxman. Although it didn’t lead to a significant increase in the number of deaths, we did see more tumor bleeding when we used pen bro or Pembroke chemo.
And that I think may have to do with.

Loss of immune checkpoint at as regards

the interaction of the activated T

cells with the wall of these damaged

blood vessels within the tumors,

these are these antibodies are

not inducing a a high rate of.

Anti humanized antibody antibodies.

So overall I would say our experience

with toxicity is this the subgroup

with toxicity is this the subgroup

of patients who have high grade

of patients who have high grade

immune related adverse events and

other than that not really worse

than it used to be in the prior era.

And then Melissa,

I don’t know if you want to talk
about is we’ve added the immune checkpoint inhibitors to radiation.

So certainly some of the initial patients that we’ve followed.

I think there’s the immune concern and we certainly are seeing activation of psoriasis skin conditions. You know anything underlying those are the things that I think we’re still learning to manage in terms of toxicity during radiation have not
necessarily seen any worse toxicity during the actual course of radiation and these initial patients that have been on these combined modality. Therapy, but there are different things that we’re having to think about. You know when do we, whether or not we’re needing to add steroids at any point along the way. Different toxicities that we didn’t necessarily have to think about for definitive intent treatment, but I think that is what we are continuing to learn.
And for these trials, the information we get from these trials and toxicity assessments will be very important in determining.

Is this a way of the intensifying?

So I’ll go ahead with just about overtime, but I know my car, which has a question too, but you can do a quick follow up time.

OK. In terms of skin, **** city.

Your EGFR inhibitor, but it caused skin.

And also the other antibody, also called skin.
So what happens if you use combination as?
I think it was mentioned it’s getting worse as that is a quite a very unpleasant this toxicity patient app.
If you have a skin issues.
So I don’t know if Artie wants to address The Phantoms to talk.
Samantha has been associated with a fair bit of skin toxicity that responds to steroids.
So talk some ampem Bros. Been reported now in head neck cancer to be quite active without really much of a difference in the safety signal so you know,
I think there’s obviously still a lot to learn with these regiments that are reported with patients, but I think we’re all quite intrigued by the possibility of the IO anti EGFR combinations. OK, and then the final question. No, not always. Mark Horowitz, so fresh ham it number one. I had an HPV positive tumors that I was hand up along time. Mark Horowitz, yes, so fresh ham it number one. I was my radiation allergist and ‘cause my radiation allergist and
Schumer was eventually recessive as absolute treasure and who oppose them by Sasha Mirror and tell you that I received superior hair? I just change and your experience is just fantastic. So I’m a year and a half out tumor free. Couldn’t be happier. I’m back in my lab in the Department of I work with pleasure. They have voted, but you see, an influx of mafic ages fo a positive cells in or around HPV. Positive tumors in the presence of patients who are treated with the.

01:05:25.580 --> 01:05:28.821 So I think less so than the infiltration of T cells.

01:05:30.930 --> 01:05:33.360 It is well understood that, particularly in the more hypoxic and HPV negative head neck cancers there is at baseline. Quite a lot of.

01:05:45.820 --> 01:05:47.356 Extensive macrophage population and that it’s sort of M2 polarized and make correspond to the macrophage populations that have been defined in preclinical models for predicting hyper progression. For example in non small cell lung cancer.

01:06:00.440 --> 01:06:02.995 So I think still a lot of
work to be done there,

but the response when someone is responding seems to be that

we’re seeing in ingress of T cells.

Well, thank you. Thank you for your wonderful comment and for telling the whole world what how lucky I am to work with these two.

It’s just issue.

Yes issues. Well, well, you know that’s a great way to end

and you know with the patient,

care comes first and the

amazing work that you’re all doing.

And we have an example right here.

So keep it up.
Lab to clinic clinical lab.

You know multi modality care.

It’s exactly what we all aspire to.

So thank you all for coming to grand Rounds today and we’ll see you next week.