Welcome to Yale Cancer Center Ground Rounds.

I'm Doctor Miriam Lustberg and I have the privilege of introducing our two speakers today. Doctor Elena Ratner is a professor of obstetrics and gynecology and reproductive sciences and cochief of the section of Gynecological Oncology. She's a board certified gynecologist.

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and early cancer detection.

She's the current codirector of Discovery to Cure, Director of discovery to Cure Early ovarian cancer detection program and a founder and director of the Sexuality, intimacy and Menopause program.

Her expertise? Is cytoreductive surgery for patients with advanced ovarian cancer minimally invasive procedures for patients with gynecologic malignancies or complex benign gynecologic conditions and robotic fertility sparing surgery for young patients with cancer? Doctor Ratner’s laboratory is working
00:01:13.365 --> 00:01:16.325 on new targeted drugs for ovarian cancer in order to provide patients with truly personalized care.

00:01:23.490 --> 00:01:25.350 reversing chemotherapy resistance in ovarian and uterine cancers.

Our second speaker is Doctor Alessandro Santine.

Dr. Santine is a professor of obstetrics and gynecology and reproductive sciences and cochief of the section of Gynecology oncology.

His clinical interests include cancer of the ovary, uterus,
vagina, cervix, and the vova.

Interperitoneal chemotherapy,
tumor genetics, immunology and immunotherapy,
tumor angiogenesis,
radiation biology and experimental therapeutics, and gynecologic oncology.

Dr. Santine's current research interests include immunotherapy for ovarian,
cervical and endometrial carcinomas, refractory to standard treatment modalities,
and development of therapeutic vaccines.

Against the human papilloma virus, infected genital tumors and the use of monoclonal antibodies.

against chemotherapy resistant
gynecologic malignancies.

Santine has more than 300 original research and peer reviewed publications and has written extensively on various topics including cancer of the ovary, Endometrium, cervix as well as on tumor immunology and immunotherapy.

I thank both speakers for sharing their expertise with us and I welcome Dr. Ratner to the podium.

Thank you.

Let me bring us to the beginning the oldfashioned way. I’m just going to bring it.
we’re sure this more sophisticated way.

Here we go. So we are so excited to speak with you today. Thank you for giving us opportunity to present to you the work of our division and to discuss the state of the union of gynecological cancers especially in the State of Connecticut. Just like everything else in the Centina and I do, we are going to double team this. I will start with clinical presentation and Doctor Centine will discuss his very impressive research, so ovarian cancer. Continues to be unacceptably deadly.
It’s the survival of ovarian cancer. Interestingly, shockingly and unacceptably has really changed very little over the past 20-30 years. The reason for this is multiple call there continues to be a profoundly late detection ovarian cancers. There is a lot of research that says that ovarian cancers by the time that diagnosed usually have been there for as long as 24 months and frequently women has seen six other physicians, six other providers prior to actually finally being diagnosed.
And that is why advocacy is so important, that’s why education is so important and that is why we so profoundly and strongly support encourage personalized care, personalized care to patients in the setting of early detection, in the setting of prevention, which as I mentioned to you is so important in the disease because early detection is so difficult because the symptoms are so vague. Personalized care in terms of surgery, surgery in this disease and it’s incredibly important and we will talk today about stratifying patients. To who is able to have this
surgery minimally invasive and
we’ll talk briefly about hypec,
something that one of our colleagues Bargain
and Dekean is very passionate about.
And then the Constantine will
talk about the importance of
personalized care and the treatment,
The management,
the maintenance of these women.
We are incredibly blessed to be in
a wonderful supportive environment.
We are so happy that some of our
team is here today.
We have the most incredible research
and the most incredible clinical
team and none of this would be possible for sure without them.

So very briefly, we don’t have much time. So I’m going to be skipping through a lot of things, but just kind of to set the stage today, we’re going to be talking about epithelial cancers, ovarian cancers. Ovarian cells in general have different kinds of cells, and epithelial cancers are the ones we’re going to talk about today. Those are the most common ones. And when you hear about people...
talking about ovarian cancer, usually it’s about epithelial, which is serious serous endometrioid clear cell we use in this or carcinosarcoma. Nowadays, things like genomics and things like mutations that drive the cancers is so much more important actually that the kind of Histology that the cancer has and again the Constantine will share all that with us. But in terms of prevention, in terms of early detection, in terms of treatment, in terms of clinical presentation,
so much time and effort now is being spent on understanding predisposition. You know, we have not succeeded in curing these cancers. We have not succeeded not because of lack of trying in early detection. So the next best thing, and really just the best thing is prevention. We know that there’s certain genetic mutations that increase the risk of bearing cancers. BEAR, C1, BEAR, C2 and Lynch all profoundly increase the risk. And that is why it is so important that women know their predisposition. We do a lot of advocacy and a lot of talks
to talk to women about know your genes,
know your predisposition, know what kind of genetic mutations you might carry, because a lot of these women could be saved not by cure, not by early detection, but actually by prevention. And so much now in treatment depends on the pathophysiology of these high grade serious cancers. And we know so much now about different DNA mechanisms that drive these cancers. One of the biggest one is homogeneous recombination.
That is something that we have really explored widely over the past five, seven years and where a lot of the targeted drugs play a role.

So briefly, ovarian cancer, second most common malignancy of the general tract, by far the deadliest. The incidence is actually not that high 1.3%, but as you see 21,000 women get diagnosed and 13,000 women die. So incredibly deadly cancer.

It is very interesting, there’s for sure geographic distribution, there’s for sure high risk populations. Women with Caucasian populations,
women that come from smaller family size, higher socioeconomic status and high fat diet all play a role. And what’s interesting is that when women move from the region that’s of lower incidence to a region of higher incidence, most sadly they acquire the higher risk of. So it’s now where you’re born, it’s where you grow up, where you where you live, which is very interesting. So there’s many different studies, of course, that talk about predisposition. And you know, we know that obesity plays a role.
We know that women who have their periods start early, their menopause come late, women who do not have kids, women who have endometriosis. We know these women have a predisposition, and the reason for that is because there’s two different theories. One is that every time a woman ovulates, some sort of a process happens. And the more time she ovulates, the higher is her risk of developing ovarian cancer. That’s why certain things are so protective.
women who have had five pregnancies and breastfeed each child for one year have a 50% reduction rate. I’ve worked on the plan very, very different. The most same option is the birth control pills. So similar, any woman who uses birth control pills for five years has a reduction of 50%. So very, very impressive. Women who have used OCP’s birth control pills for 10 years have reduction as high as 80%. And that is all cumulative and that’s all respective to the woman personalized risk. So even somebody who has a BRC.
mutation and has a 40% risk,
NOTE Confidence: 0.949598185714286
if they have used OC PS;
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for five years,
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the risk goes down to 20%.
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They’ve used it for 10:15,
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it goes to 10:00 and 8:00.
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So with different modifications,
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we actually can do risk
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adjustment and decrease the risk.
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And then we know there’s also
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inflammatory factors such as
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pelvic inflammatory disease and
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endometriosis that play a role as well.
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The second theory of ovarian cancer
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is actually that these cancers
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are not potentially not even
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00:10:21.670 --> 00:10:23.420 ovarian cancers to begin with.
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00:10:23.420 --> 00:10:25.980 They’re actually fallopian tube cancers,
NOTE Confidence: 0.949598185714286
00:10:25.980 --> 00:10:28.218 especially in women with genetic mutations.
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00:10:28.220 --> 00:10:29.914 And these cancers start in the Philippine
NOTE Confidence: 0.949598185714286
00:10:29.914 --> 00:10:31.860 tubes and only then spread to the ovaries.
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00:10:31.860 --> 00:10:34.068 And that is why nowadays there’s such a
NOTE Confidence: 0.949598185714286
00:10:34.068 --> 00:10:36.129 culture of actually removing fallopian
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00:10:36.129 --> 00:10:38.060 tubes at different opportunities,
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00:10:38.060 --> 00:10:40.215 because that creates a risk
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00:10:40.215 --> 00:10:43.050 reduction as high as 50 to 70%.
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00:10:43.050 --> 00:10:45.048 So here within our our institution,
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00:10:45.050 --> 00:10:46.625 we actually have been able
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00:10:46.625 --> 00:10:47.885 to influence the culture.
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00:10:47.890 --> 00:10:49.890 And in the older days,
NOTE Confidence: 0.949598185714286
00:10:49.890 --> 00:10:50.679 10 years ago,
when people when women used to have their tubes tied, they literally have their tubes tied. Now we actually remove the fallopian tubes, especially in women with higher predisposition to cancers. We are able to provide a very substantial risk reduction just by that simple technique. In the older days, anytime we left ovaries when somebody would have a hysterectomy. Nowadays, for sure fallopian tubes would be removed because we know that there's a huge component of risk
00:11:18.396 --> 00:11:20.178 reduction by removing the fallopian tube and it’s a very easy adjustment.

00:11:20.178 --> 00:11:22.670

00:11:22.670 --> 00:11:24.190 But of course, out of all those things,

00:11:24.190 --> 00:11:28.310 the most highest risk is the family history.

00:11:28.310 --> 00:11:31.572 Anybody who has a family first degree family member who has ovarian cancer,

00:11:31.572 --> 00:11:34.374 that increases that woman’s lifetime risk to 4 to 5%.

00:11:34.374 --> 00:11:36.238 And as I showed you before,

00:11:36.238 --> 00:11:38.029 this hereditary breast and ovarian syndromes,

00:11:38.030 --> 00:11:39.548 which account for 20% of ovarian cancers,

00:11:39.550 --> 00:11:42.310 but we really think,

00:11:42.310 --> 00:11:44.907 they of course carry the the

00:11:44.910 --> 00:11:45.970 We just don’t yet know exactly which ones.

00:11:45.970 --> 00:11:47.030 They of course carry the the

00:11:47.030 --> 00:11:51.748
most highest risk.

Very briefly.

There’s a very profound and very meaningful and very important racial health disparities in ovarian cancer.

We have known this forever.

We have known forever that women of color do worse. And we used to think that it’s just because of the Histology of the cancer that the women who are non Caucasian get Histology that are more aggressive and that is indeed. Case, but unquestionably and deniably confirmed by many different studies, especially recently.
We also know the women of color get worse care. They have more profound delays in diagnosis and chemotherapy. They don’t get necessarily this term of care surgery now with the joint oncologist and another very important component is that women of color are under enrolled in clinical trials. Only 17% of clinical trial participants represent racial or ethnic minorities and African American women’s participation only reached 9/11, 10%, nine percent.
00:13:03.955 --> 00:13:06.055 a very important role and that is
NOTE Confidence: 0.9553487
00:13:06.055 --> 00:13:08.681 why so much effort is being being
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00:13:08.681 --> 00:13:10.790 made to improve this cruel into
NOTE Confidence: 0.9553487
00:13:10.790 --> 00:13:13.990 trials and open it to women of color.
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00:13:13.990 --> 00:13:16.924 So very briefly just the state of our union.
NOTE Confidence: 0.9553487
00:13:16.930 --> 00:13:18.970 You an ecology here at Yale is very,
NOTE Confidence: 0.9553487
00:13:18.970 --> 00:13:19.674 very busy.
NOTE Confidence: 0.9553487
00:13:19.674 --> 00:13:22.490 We have a great number of surgical cases,
NOTE Confidence: 0.9553487
00:13:22.490 --> 00:13:25.575 new patients and it continues
NOTE Confidence: 0.9553487
00:13:25.575 --> 00:13:28.450 to increase every year.
NOTE Confidence: 0.9553487
00:13:28.450 --> 00:13:30.106 Our biggest we cover the entire
NOTE Confidence: 0.9553487
00:13:30.106 --> 00:13:31.733 state of Connecticut all the way
NOTE Confidence: 0.9553487
00:13:31.733 --> 00:13:33.85 from Greenwich all the way to New
NOTE Confidence: 0.9553487
00:13:33.85 --> 00:13:34.982 London with the great majority of
NOTE Confidence: 0.9553487
00:13:34.982 --> 00:13:37.226 our care that happens here in New
NOTE Confidence: 0.9553487
00:13:37.226 --> 00:13:39.566 Haven and then Bridgeport Hospital.
And as you see the number of our new patient visits and surgeries grows. Each and every year, and this is the territory that we cover again, all the way from New York all the way to New London, so very profoundly so there. One of the things that have changed drastically in the care of joining College of Patients, something that I’m going to talk about briefly, is how much we are able to do surgically in a minimally invasive way.
So when you look at that data that I just pulled up and the data that you know, I study very closely and extensively, the culture of this field is changing to become almost predominantly outpatient field. Great majority of our women used to have the surgeries and have a prolonged inpatient stay. And now great majority of women are able to have the same kind of radical debalking surgeries in a minimally invasive way that I’ll show you in a little bit and are able to be discharged home literally same day. And that is why so much of our financial
representation has now become an outpatient service versus the inpatient. So surgery is very, very important. Let me just get rid of that. I don’t know if that’s supposed to be here. There we go. So surgery in gynecology is of paramount importance. We know for many different reasons that women who have had very radical surgery and their cancer was removed entirely with no residual disease, have done profoundly better.
You can see here the overall survival is significantly better for women who have had 0 millimeters of disease left at the completion of surgery. This is kind of what things look like when we begin. This is kind of how ovarian cancer presents. This is the cancer that spreads over the bowel or momentum over the peritonal surfaces. And very frequently we hear especially Yale give new adjuvant chemotherapy, which is chemotherapy before the surgery to increase the chances of successful debalking to no residual disease. So I want to talk briefly about approach to surgery and again why this has to be
so personalized and so individualized.

This was a big poster that was hanging in the office.

Of my mentor and previous boss.

And when I was younger, not that much younger.

It was a big point of debate.

The greater the surgeon, the bigger the incision.

Certainly not the case.

Granted, I now have his office and his job, so there's that.

So many studies have showed the approach to ovarian cancers.
and gero logic cancers not only safe but completely appropriate.

We know that complications are less, We know that efficiency is the same.

We know that effectiveness is the same.

So again, everything has to be done in a very personalized way that has to make sense,

the biggest thing in joint oncology surgery and something that we care so passionately about.

Is that masses do not get spilled because when the mass ruptures, that’s upstages the patient and worsens their prognosis.

So all kinds of things are done
to prevent that. And again, in the older days used to be a big point of debate and big point of discussion. So I want to share some of the videos of mine and some of our partners Sudo Zodi that show how we deal with some of these concerns. So you know in ovarian cancer, because our patients are women, we use frequently the vaginal orifice as a site of removal. So this is a young patient who had Carson Sarcoma that had isolated periodic mass. That you know in the older days,
again few years back would have just been removed with a big incision, with a huge resection and huge recovery because of the concern both for the complexity of the case.

So as you can see this is the great vessels, this is the ureter, this is the mask that was entirely resected and then the concern would have been how do you remove a mask like this. This is something that we're able to just play something right through the vagina, place the back into the vagina.
that is only very, very small, small 10 millimeter incision and then remove it like this. And this patient was able to go home same day. This patient also had a metal diverticulum that we resected at the same time. And also was removed similarly like that as you can see. So this is the the bowel surgery, the reticulum similarly placed in the bag, similarly placed in the vagina similarly patient went home same day and had minimal minimal recovery from something that
00:18:52.914 --> 00:18:54.799 would have been very extensive.
NOTE Confidence: 0.911545551333333
00:18:54.800 --> 00:18:57.404 Natural or laparoscopy is so important
NOTE Confidence: 0.911545551333333
00:18:57.404 --> 00:19:01.035 and again we are lucky to be able to use
NOTE Confidence: 0.911545551333333
00:19:01.040 --> 00:19:04.246 vaginal orifice in our patients for this.
NOTE Confidence: 0.911545551333333
00:19:04.250 --> 00:19:06.488 So at times, again, you know,
NOTE Confidence: 0.911545551333333
00:19:06.490 --> 00:19:07.650 everything has to make sense.
NOTE Confidence: 0.911545551333333
00:19:07.650 --> 00:19:09.922 You know, this is the older patient who
NOTE Confidence: 0.911545551333333
00:19:09.922 --> 00:19:12.822 had a very many medical comorbidities
NOTE Confidence: 0.911545551333333
00:19:12.822 --> 00:19:15.737 who would not have withstanded.
NOTE Confidence: 0.911545551333333
00:19:15.740 --> 00:19:17.112 Overall, big large laparotomy,
NOTE Confidence: 0.911545551333333
00:19:17.112 --> 00:19:19.579 which is what we would have done
NOTE Confidence: 0.911545551333333
00:19:19.579 --> 00:19:21.655 usually for this 12 centimeter mass.
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00:19:21.660 --> 00:19:22.860 But at the same time,
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00:19:22.860 --> 00:19:24.948 we of course want to be very careful and
NOTE Confidence: 0.911545551333333
00:19:24.948 --> 00:19:26.980 not rupture the mass and not leak it.
NOTE Confidence: 0.911545551333333
00:19:26.980 --> 00:19:29.708 So we do all kinds of special techniques
00:19:29.708 --> 00:19:32.239 again in a very truly personalized way
to be able to provide our patients with
the best care specifically for them.
So this patient,
everything was protected and then
the mask was insulated and we were
actually able to see inside the
mask and then we were able to see
that this was a malignant mask.
Once the fluid was removed in the
contained way and that nothing was removed,
nothing was leaked.
And then same same way we were able
to just tie something around it
to make sure that nothing leaks.

Remove it and then remove it similarly to the vagina like I showed you before and all the lymph nodes and everything else could be done laparoscopically.

And again the spatial with multiple comorbidities was able to go home next morning with minimal recovery.

We nowadays use something called high pack, which is what I mentioned to you before. Which is there’s a lot of conceptual thinking that hyper hypothermia and neoplasia at the time of aggressive debalking really improves.
the overall survival.
And this is again, this is before debalking.
This is after debalking, we remove all the disease and then we're able to place a cyst plan into the belly for 90 minutes that improves direct permeation of the tumors. And there's some very, very strong literature that supports it in this population with pretty, pretty significant improvement and progression free survival.
In the next two minutes that I have left, I promised I consenting that
I was going to be on time.

I want to talk briefly about survivorship.

So survivorship is so important.

We for generations have undervalued under address the importance of survivorship in this population.

It’s because forever we, we thought the women get this cancers and then they die.

As you see that as we’re getting better in diagnosis is we’re getting better in surgery as we’re getting better in treatment, women are living longer and when they live longer, it is so important that we provide them with
NOTE Confidence: 0.871449994090909
00:21:45.898 --> 00:21:47.987 survivorship techniques to support them.
NOTE Confidence: 0.871449994090909
00:21:47.990 --> 00:21:50.118 I'm actually so happy to see that we
NOTE Confidence: 0.871449994090909
00:21:50.118 --> 00:21:52.742 have our teal team here that help
NOTE Confidence: 0.871449994090909
00:21:52.742 --> 00:21:54.982 us concentrate on nutrition this
NOTE Confidence: 0.871449994090909
00:21:54.982 --> 00:21:57.200 population because this is yet another
NOTE Confidence: 0.871449994090909
00:21:57.200 --> 00:22:00.092 one of those aspects that really has
NOTE Confidence: 0.871449994090909
00:22:00.092 --> 00:22:02.188 been undervalued and underaddressed.
NOTE Confidence: 0.871449994090909
00:22:02.190 --> 00:22:06.794 So in Galactic Cancers survivorship
NOTE Confidence: 0.871449994090909
00:22:06.794 --> 00:22:09.949 has so many different aspects,
NOTE Confidence: 0.871449994090909
00:22:09.950 --> 00:22:12.710 fear recurrence, toxicities from surgery,
NOTE Confidence: 0.871449994090909
00:22:12.710 --> 00:22:14.618 toxicities of chemo and radiation and
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NOTE Confidence: 0.871449994090909
00:22:16.990 --> 00:22:18.550 Psychological body image and
NOTE Confidence: 0.871449994090909
00:22:18.550 --> 00:22:20.110 then sex and intimacy,
NOTE Confidence: 0.871449994090909
00:22:20.110 --> 00:22:23.702 which is a very profound aspect of women’s
NOTE Confidence: 0.871449994090909
NOTE Confidence: 0.871449994090909
00:22:25.949 --> 00:22:28.813 and then our legal team to help
NOTE Confidence: 0.871449994090909
00:22:28.813 --> 00:22:31.744 us with the legal issues that come from
NOTE Confidence: 0.871449994090909
00:22:31.744 --> 00:22:34.176 cancer.
NOTE Confidence: 0.871449994090909
00:22:34.176 --> 00:22:36.814 Our team is here to support you,
NOTE Confidence: 0.871449994090909
00:22:36.814 --> 00:22:38.744 to help you navigate these challenging times.
experiences that here at Yale we are very passionate about the dressing so I’ll let this I’ll leave this with Doctor Sentine to with one minute to spare. So in the one minute then I have I’m not going to I’m not going to give away the minute what separates us here at Yale. Is that we are truly patient driven and we are truly believe in the importance of personalized care. You know, we nobody, nobody treats the cancer anymore. We truly treat the women that we see. We see their lives, we see their experiences and then we do. Everything we can to address their
personal experience from diagnosis to surgery to treatment and we'll talk about and then to the survivorship and supporting them through their journey both during treatment and then after. And again we're only able to do it because of the amazing team that we have. Thank you so. Alina has already done a very nice introduction and this light for me is only to remind you that regardless to the how sophisticated our surgery can be and Alina show you minimally invasive approaches, sometimes we have to do ultra radical
surgery to remove the tumor again.

regardless the adjuvant treatment they were able to offer such as radiation as well as chemotherapy.

A significant number of our patients still develop progression and recurrent disease. Of the 100,000 diagnosis with a gynecological cancer in the US, about 1/3 of women still die every year because of this difficult to treat cancer.

So the question is what can we do to improve the outcome of this patient? And this again and what I'm going to...
show you here is our scientific vision and goals that we really started thinking about how we could really face up with some medical need many years ago and we developed or we tried to develop a program, adding to what Alina show you, so this excellent clinical and surgical care, adding a translational research program above that in particular targeting the difficult to treat gynecological cancer. And when I say difficult to treat it means that the problem is really in our specialties not to take care of
a well or moderately differentiated uterine cancer. Is really to take care of the biologically aggressive such as the uterine serous carcinoma or the ovarian that are widespread and so on. So we thought to really the one of the winning strategies was to provide access to our patient in particular this group of patient to precision medicine through a pipeline of both pharma as well as yield developed treatment. Again validated within rigorous clinical trial that I’m going to show you in a minute.
But the other thing was really to be able to build a multidisciplinary approach because if you want to be successful in a big Cancer Center, again the surgical is important, the chemotherapy or addition therapy is important by if you want to do one step farther and going to translational personalized medicine. This is really a team approach that goes outside our division. And that is what we try to build here. We involve and interact with other.
successful clinical as well as the research program present in our Yale Cancer Center and also of course take advantage of the cutting edge resources that we have available at Yale. And I want to mention the genomic course sequencing facility that we have in the West Campus. As well as again the pathology corps, Doctor RIM is here that is doing an excellent job is providing tissue to all the research area of the Yale Cancer Center to be able to do what I’m going to show you internal personalized treatment. So a lot of people talk about personalized treatment.
00:27:00.302 --> 00:27:02.960 treatment but what is personalized treatment,
NOTE Confidence: 0.93421556
00:27:02.960 --> 00:27:05.834 what is precision medicine in the
NOTE Confidence: 0.93421556
00:27:05.834 --> 00:27:08.180 division of gynecological oncology Yale.
NOTE Confidence: 0.93421556
00:27:08.180 --> 00:27:09.972 As Alina show you,
NOTE Confidence: 0.93421556
00:27:09.972 --> 00:27:12.660 everything start with the surgical part.
NOTE Confidence: 0.93421556
00:27:12.660 --> 00:27:15.936 So we are surgeon but ovarian uterine
cancer are surgically staged tumor.
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00:27:15.936 --> 00:27:18.459 So we that is the first time,
NOTE Confidence: 0.93421556
00:27:18.460 --> 00:27:20.140 and as Alina told you,
NOTE Confidence: 0.93421556
00:27:20.140 --> 00:27:21.960 the first moment in the
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00:27:23.420 --> 00:27:24.620 And as Alina told you,
NOTE Confidence: 0.93421556
00:27:24.620 --> 00:27:27.550 we try to remove all the disease that we can
NOTE Confidence: 0.93421556
00:27:27.620 --> 00:27:29.696 see to improve the outcome of this patient.
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00:27:29.700 --> 00:27:32.092 But one of the thing that we’ve been
NOTE Confidence: 0.93421556
00:27:32.092 --> 00:27:34.188 doing now for quite a long time.
NOTE Confidence: 0.93421556
Starting probably as one of the First Division in the US and worldwide was to consent our patient at the time of surgery before surgery also to donate a piece of tissue to go to our research laboratory and this piece of tissue was used to sequence the DNA of the tumor of this patient with the ultimate goal. At that time point the commercial entity that we were using to receive a some
sort of FDAGMP approved report was Foundation Medicine but at the same time in parallel we are also able to perform. All Axon sequencing at the West campus, as you know all Axon sequencing is quite expensive, was very expensive about 10-15 years ago when we started is still expensive now. So the question that some of you can ask me, but there’s something how have you been able to do that 100 or gynecological cancer patient without asking you. know the patient to pay for it. The answer is that we. You know,
We had this collaborative research program at Yale between Yale and Gilead Science. And this was a huge program, $70 million in 10 years provided to us through Doctor Schlesinger, who was the Chair of pharmacology that was able to establish this collaborative research agreement. And thanks to this significant amount of money, we were able again to sequence over 800 gynecological cancer. Again all Axon sequencing, 21,000 gene encoded protein. Another thing that we have been doing for the last 10 years is a little...
A piece of this fresh tissue was going to my lab and in my lab we were trying to establish primary cell line as well as patient derives senokra. So in few words the viable tumor tissue was both placed in the Petri dish. As well as in an animal with the ultimate goal again to establish the disease in these avatar animals. Why is that important is because as I’m showing you here, the ultimate goal was to develop the patient to get the pathology report to start the patient on the standard treatment that as we discussed.
unfortunately sometime is unable to cure the patient and having the genetic sequencing data available. To be able to identify potential draggable marker, test this potential drug in the avatar animal on the tumor of the patient when she was receiving the standard of care and be ready for her in case the disease come back or become resistant. We already had tested in for that specific patient a certain number of drug to provide her again with personalized treatment at the time of occurrence. Another thing that we’ve been able to do in the last 5-6 years
00:30:58.412 --> 00:31:00.632 is also to provide personalized
diagnostic to our patient.

00:31:00.632 --> 00:31:02.248 What does it mean?

00:31:02.250 --> 00:31:03.722 It mean to detect the present of
circulating tumor DNA that is
mutated DNA coming from the tumor
and this was again possible because
through the sequencing.

00:31:06.455 --> 00:31:08.650 We add knowledge about the potential
driver mutation present in this patient,
present the tumor of this patient.

00:31:08.650 --> 00:31:11.450 We design specific probe able to
amplify this mutation present in the
circulation of this patient and using
a not invasive method that is a simple
collection of five to 10CC we were able and this is a tumor inform assay to detect the presence of the mutated DNA. That correlate with the presence of this in the patient. So this is a new approach of course to monitor and is called again personal like diagnostic type of approach because allow us to see the presence of tumor DNA in the circulation. But even more important being a tumor inform approach this type of technology become about 10 to 100 fold more sensitive. Then the standard approach of looking to again the Press of DNA when you don’t know what type of mutation is pressed.
So using this approach, let me show you a little bit the progress that we have done for the last again few years taking care in particular the difficult to treat patient and one of the most difficult uterine cancer. They were dealing with in the clinic are uterine seros. They are rare tumor 3:00 to 9:50 to 10% over all of all uterine cancer, but they kill over 40% of our patient. Why is that is because they are biologically aggressive, they can start spreading very early and they’re usually difficult to
treat in thermal chemotherapy.

One of the important thing is that.

The Gynong division at Yale has been a long time a really a place where this patient were affair.

And this is because of course and this is because of the work of Doctor Schwartz, that work here for the last 50 years.

Doctor Schwartz has a specific interest in studying this tumor. And when he asked me to join him 16 years ago, I kept on going and and work in specifically against this biologically aggressive tumor. So this is to say we see a lot of this.
rare tumor and because of that we were able to collect a lot of specimen and we perform and we reported the first comprehensive genetic landscape analysis of the rare manigancy and this was published. Again, over 10 years ago, what we found in this study there was by the way before the TCGA data, published before the TCGA data, about six months before the first major comprehensive analysis done by the Tumor Cancer Atlas Network,
important chronologically to say that this is what we found, we sound, we found something very interesting, namely. A small minority of this biological aggressive cancer called uterine series had this characteristic year. They had a huge number of mutation. They were ultra mutated, but they were Microsoft and lie stable. They didn’t have any mismatch repair deficiency. So what were this tumor? We didn’t know at that time, but they had this genetic characteristic, the remaining group. There was again the striking majority
00:34:52.420 --> 00:34:55.140 90% where normal mutated tumor, very low number of mutation, MSI stable and cold meaning minimal inflammation, minimum inflammatory cell present in the tumor microenvironment.

00:35:06.820 --> 00:35:10.154 So of course we start looking to the 92%, right. And what I’m showing you here was our finding, we look to this 21,000 genes we found specific pathways. That this aggressive tumor was using to survive hemotherapy and then come back after treatment and one of these pathways that I’m you know I’m.

00:35:19.410 --> 00:35:21.960
highlighting here was the hair to new
NOTE Confidence: 0.930428735769231

PAKAKT enter pathway over 1/3 of
NOTE Confidence: 0.930428735769231

this patient had amplification on on
NOTE Confidence: 0.930428735769231

the C RB2 gene that encode for the
NOTE Confidence: 0.930428735769231

epidermal glow factor type 2 receptor.
NOTE Confidence: 0.930428735769231

This is well known in oncology.
NOTE Confidence: 0.930428735769231

Why? Because there are specific
NOTE Confidence: 0.930428735769231

treatment they target this pathway.
NOTE Confidence: 0.930428735769231

The target have to new trust is
NOTE Confidence: 0.930428735769231

monoclonal antibodies one of those.
NOTE Confidence: 0.930428735769231

But the problem is that this was
NOTE Confidence: 0.930428735769231

an antibody available for the
NOTE Confidence: 0.930428735769231

treatment of breast cancer patient
NOTE Confidence: 0.930428735769231

and later on gastric cancer patient.
NOTE Confidence: 0.930428735769231

But there was really no report,
NOTE Confidence: 0.930428735769231

no literature in the treatment
00:36:16.050 --> 00:36:17.826 of uterine serous carcinoma.

00:36:17.830 --> 00:36:20.166 So we decided to fill that gap and

00:36:20.166 --> 00:36:22.146 we designed a study here at Yale,

00:36:22.150 --> 00:36:25.280 we designed an investigator initiated

00:36:25.280 --> 00:36:28.385 trial there was again through a

00:36:28.385 --> 00:36:30.518 consortium of institution because as

00:36:30.518 --> 00:36:33.670 I just told you this is a rare cancer

00:36:33.670 --> 00:36:35.945 and we were and we were targeting

00:36:35.945 --> 00:36:37.992 about 30% of this rare cancer the

00:36:37.992 --> 00:36:39.590 one over expressing her to new.

00:36:39.590 --> 00:36:42.350 So we needed multiple side to do that.

00:36:42.350 --> 00:36:44.793 So we had eleven side going from

00:36:44.793 --> 00:36:47.258 John Hopkins to higher state and.

00:36:47.258 --> 00:36:49.130 The primary goal here,

00:36:49.130 --> 00:36:51.248 the primary objective was to understand
if adding trust to the map this
NOTE Confidence: 0.930428735769231
monoclonal antibody to our standard
NOTE Confidence: 0.930428735769231
of care that is based on carbo packet
NOTE Confidence: 0.930428735769231
tax could make the difference in term
NOTE Confidence: 0.930428735769231
of increasing progression free survival,
NOTE Confidence: 0.930428735769231
increasing the objective response
NOTE Confidence: 0.930428735769231
rate and the overall survival
NOTE Confidence: 0.930428735769231
of this patient and so on.
NOTE Confidence: 0.930428735769231
And these are our result.
NOTE Confidence: 0.930428735769231
So we were able to show that
NOTE Confidence: 0.930428735769231
adding this monoclonal antibody.
NOTE Confidence: 0.930428735769231
Without any significant increase
NOTE Confidence: 0.930428735769231
in toxicity when compared to
NOTE Confidence: 0.930428735769231
the Carbo Parkly tax regiment,
NOTE Confidence: 0.930428735769231
we were able to increase of about 5
NOTE Confidence: 0.930428735769231
month progression free survival and
close to six month the overall survival of the entire patient population. They were both advanced stage as well as recurrent patient with uterine serous carcinoma with a benefit even much higher in the chemo naive stage 3 and stage 4 disease so. This study is important because not only ask recognized important, you know, listing it as a major advancement in 2019, one of the five major advancement of that year in the oncology literature, but also because this increase in overall survival caused the revision.
of the National Comprehensive Cancer Network guideline that are widely used as standard. Of care again in oncology by both clinician as well as insurance company and since that time 2019, Carboplatin, Parkly, Taxol and Trastozoma. So the yield regimen is now again recommended in old patient with utransitious carcinoma or expressing her to you in the US as well as worldwide, let me do now. Let me tell you a little bit more about the Poly ultramutated. So we look to this uterines carcinoma. As I told you before,
a small minority, a nine percent had this abnormal alteration in a gene called DNA polymerase epsilon. This is a DNA polymerase at that time. I remind you this was over 10 years ago. Nobody knew what this really gene was doing, but. Look into this tumor, we immediately realize that was really playing a major role in the proofreading capability of the DNA. Why is that? Is because this tumor had a huge number of mutation. So polymerase epsilon in normal cell again is endowed with proofreading capability.
When the cell divide and the DNA duplicate the DNA polymerase epsilon proofread the sequence and if there is an error, a mutation. Stop and repair and fix the error. But if one of the two allele present in the cell encoding for the polymerase mutate and the majority of the special are also multi mutation so acquired during the lifetime, the cell survive but start acquiring error mistakes and start accumulating again mutation to the point where you have this monster tumor they have. 1000 and 1000 mutation much higher than any other human cancer including lung,
Melanoma, bladder cancer that are well known to be, I mean have a high number of mutation. So when we look to this tumor specifically we saw that in the exonuclease domain of the polymerase epsilon, the majority of recurrent mutation with localizing that area and why is that important? Is because even if the majority of the polyultramutated USC, they do well when compared to the other that I told you still some of this patient where they come back with recurring disease and
these tumor are relentless, they are resistant to chemotherapy, they are resistant to radiation treatment and they kill our patient so. Few years ago looking to the set to the genetic characteristic, to the fact they were all permutated, we thought they could be exquisitively sensitive to new checkpoint inhibitor and and again few years ago and here I’m showing you a case report. This is one of my patient treated in two or seven initially for an advanced stage type 2 mix again uterine carcinoma. She was treated with surgery. Chemotherapy or addition treatment,
she did well for a few years, came back in 2012 with recurring disease, multiple metastatic lesion as usual and at that time point she was retrieved with surgery, additional bowel resection, additional chemo and she started progressing. So she was referred to us by an outside medical oncologist for a second opinion. In reality, of course the referral was to for the patient to accept Hospice because there was really nothing that we could offer internal systemic treatment to this patient.
When she came to see us, we sequenced the tumor with foundation medicine and what we found was that she had a Poly hotspot mutation in the exonuclearized domain. This is a lucky patient because at that time was about 2014 we had the program going at Yale with nivolumab. This was a program that doctor Roy Herbs as active in lung cancer at that time point Nivolumab there was the first immune checkpoint inhibitor before before pembrolizumab. OK true that everybody now is using

70
NOTE Confidence: 0.939061272941177
00:42:39.422 --> 00:42:41.425 was only approving Melanoma but
NOTE Confidence: 0.939061272941177
00:42:41.425 --> 00:42:43.770 because of this program I was able
NOTE Confidence: 0.9201268
00:42:43.770 --> 00:42:47.360 to. To the OR through a compassionate
NOTE Confidence: 0.9201268
00:42:47.360 --> 00:42:49.567 base approval to offer to this
NOTE Confidence: 0.9201268
00:42:49.567 --> 00:42:51.217 patient NI voluma for free.
NOTE Confidence: 0.9201268
00:42:51.220 --> 00:42:52.472 She signed a consent.
NOTE Confidence: 0.9201268
00:42:52.472 --> 00:42:54.776 I got the approval for the chief
NOTE Confidence: 0.9201268
00:42:54.776 --> 00:42:56.541 medical officer of the Yale
NOTE Confidence: 0.9201268
00:42:56.541 --> 00:42:58.846 Cancer Center was or Jerry or
NOTE Confidence: 0.9201268
00:42:58.846 --> 00:43:01.340 Lillenbaum and the rest of history.
NOTE Confidence: 0.9201268
00:43:01.340 --> 00:43:03.300 We start treating this patient.
NOTE Confidence: 0.9201268
00:43:03.300 --> 00:43:06.108 I don’t know if you can see this is
NOTE Confidence: 0.9201268
00:43:06.108 --> 00:43:08.756 one of the metastatic deposit as big
NOTE Confidence: 0.9201268
00:43:08.756 --> 00:43:12.047 as a spleen as you can see here 7-8
NOTE Confidence: 0.9201268
00:43:12.047 --> 00:43:14.609 centimeter masses in the Donal cavity.
NOTE Confidence: 0.9201268
This is her bladder nodule or two 3 centimeter growing in the wall of the bladder causing constant bleeding. In a week the bleeding disappear and in about 6 weeks pain disappear. It took about 18 months to completely melt out these pounds of cancer that this patient had on the volume up. The patient is still doing is cure of the disease and I swear two weeks ago in clinic eight years after what I’m showing you here. So this was a terminal patient referred to us for again Hospice. We sequenced the tumor, we found that we are mutation,
we treat the immune checkpoint inhibitor as visit response. And of course we reported this, this is the first report of the successful treatment. Of a polyultramutated endometrial carcinoma and now the word know and everybody is looking to this patient and when they found the polyultramutation for their treatment with immune checkpoint inhibitor. Now the second tumor that I want to tell you in the last 5-6 minutes are carcinos or Comma, the uterus.
The uterus are also biologically aggressive are rare 3 to 5%. But they account for over 20% of all death in uterine carcinoma. And one of the peculiarity about carcinofacoma of the uterine is that for over 150 years this tumor have been a subject of debate. And why is that? Is because they are mixed human, there is both an epithelial component as well as a sarcometus component. And the question is what are these mixed cancers? Are they carcinoma? That undergoes comatus transformation or are sarcoma that
undergo epitilla differentiation such As for instance synovial sarcoma. So we answer that question. This is another paper that we published few years ago. Again we sequenced over 70 carcino sarcoma of the uterus and we published again this high impact journal and what we found here is number one we were able through sequencing. We also perform multiple sequencing, so not only we sequence the 70 specimen from the 70 patient but about five or six of this tumor. We were doing macro dissection and
sequence area of epithelial tumor
and other sarcometus humor tumor
in the same patient and we were
overlapping the old Axon sequencing
data to try to understand are
these tumor epithelial or this
tumor mesenkimal and the answer is.
Unequivocally,
these are all epithelial cancer.
They all start as an epithelia,
uterine carcinoma,
but they go through clonal evolution and
part of the clone during the lifespan,
lifetime of the disease.
They differentiate.
They acquire epithelium,
NOTE Confidence: 0.95534864
00:46:21.167 --> 00:46:22.424 mesenchymal transition and
NOTE Confidence: 0.95534864
00:46:22.424 --> 00:46:24.670 there’s as I’m showing you here,
NOTE Confidence: 0.95534864
00:46:24.670 --> 00:46:27.652 some of these carcinos or coma acquire
NOTE Confidence: 0.95534864
00:46:27.652 --> 00:46:29.391 this epithelium mesenchymal transition
NOTE Confidence: 0.95534864
00:46:29.391 --> 00:46:32.156 in some of the clone relatively early.
NOTE Confidence: 0.95534864
00:46:32.160 --> 00:46:34.878 Some very late during their lifetime.
NOTE Confidence: 0.95534864
00:46:34.880 --> 00:46:37.295 The 2nd and very important finding of
NOTE Confidence: 0.95534864
00:46:37.295 --> 00:46:39.787 the study is that we have identify
NOTE Confidence: 0.95534864
00:46:39.787 --> 00:46:42.140 for the first time some recurrent
NOTE Confidence: 0.95534864
00:46:42.140 --> 00:46:45.653 mutation in Eastern core gene that
NOTE Confidence: 0.95534864
00:46:45.653 --> 00:46:47.718 regulate the transcription of the
NOTE Confidence: 0.95534864
00:46:47.720 --> 00:46:51.848 DNA and these were correlated with
NOTE Confidence: 0.95534864
00:46:51.848 --> 00:46:53.912 the mesenchymal transformation.
NOTE Confidence: 0.95534864
00:46:53.920 --> 00:46:55.840 Now we are clinician, right.
NOTE Confidence: 0.95534864
00:46:55.840 --> 00:46:57.718 So we are very interesting science,
but what we want is translation science, we want to be able to help our patient. One of the thing that we found in carcinofer Com as well as you trying serous carcinoma doing RNA sequencing was that there was a appregulation of the messenger RNA encoding for a specific antigen called trophoblast. And this is the work of two of our recent fellow Dr. Borazebek and Shannen Han. So we look to. Hundreds of this tumor and here of course we have done this with the help of our pathologist in
particular Doctor Natalia Busa and Dr. Pei Wei.

We did, we did tissue microarray and we found that indeed 60 to 90% of uterine serous carcinoma and the carcinosar coma, they were really overexpressed in tropoblast too.

So in the way that I show you before we generate patient that like sinograph from this patient. And we start testing in the animal the activity of a new agent called Rodelvi that is now a commercial agent approved for breast as well.
as bladder cancer that target
the DROP 2 receptor.
And this is an antibody track conjugate.
So it’s a monoclonal antibody
targeting DROP 2 as a cleavable
linker and attached to the
antibody there is SN38 that is.
A topo isomerase 1 inhibitor and doing
that we were able to show that again
both in vitro as well as in vivo,
this tumor were highly sensitive.
This is actually the tumor in the
animal that complete as you can
see disappear when our control of
course we’re growing and this is the
overall survival of this animal.
So the question is PDX work, is it going to work in patient?

Let me give you an example of that.

This is again another of my patient.

As you can see are 74 years old

uterine serous carcinoma treated with

a gold standard surgery followed by

more chemo to the point where the

patient was progressing on anything.

So at that time we have a Phase 1B

trial ongoing a Yale with Trodelvi,

so as you know calcium sarcoma rare tumor.

So I had to convince the the

medical monitor of the study.
That time, at that time was Immunomedics to approve the treatment of this, you know of this uterine serocarcinoma patient rare tumor in the trial. But I was able to do so patients start receiving T rudelvi and again as you can see here, this is the baseline. She had huge liver, meth as well as carcinomatosis everywhere in the donor cavity and the patient start responding and we gave this patient. As you can see here dramatic shrinkage of all the disease over 66% reduction by this is 1.1 criteria in the in the
inner disease and we have this patient
ten month of very good life with
again because this is also very well
tolerated antibody in term of treatment.
So this was one patient, right.
You cannot change a guideline
You need to design the proper
study and that is what we’ve done.
We had designed an IIT,
so an investigator in shady
trial with his agent,
not easy because Immuno Medics
was purchased by Gilead, right.
So that create a little bit of a problem.
But we were able to convince Gilead to provide us with drug and some money to design and perform this phase two clinker trial with the ultimate goal to evaluate again a response rate as a primary objective, as well as overall overall survival, progression free survival and the safety as a secondary objective.

And these are the result of this trial that I’m going to present in about 10 days at ASCO. This is a presentation. This is a preview. I shouldn’t do that, but I’ll do it anyway.
00:51:10.760 --> 00:51:13.360 this study was designed as a Simon two stage design. That it means to enroll the 1st 21 a valuable patient, see if there was any response and in case of three or more of PROCR, so either complete or partial response would have been able to move to the second stage and enroll a total of 50. So as you can see here over two third of the patient enroll in this trial. Where specifically uterine serous carcinoma and carcinosarcoma, the most difficult to treat uterine carcinoma and we had seven response.
not three so 33 response rate either

CR or PR and so positive stage one and

we are now a rolling the stage two,

so another 30 patient to try to

see in an overall of 50 patient.

How effective this agent is be,

but there is no doubt that there

is a strong signal and again this

So I’d like to conclude analogy

and thanking a lot of people.

The particular Elena that is here

my cochief they attending of the

Juan oncology division that I listed

here and here in particular I want

to to to emphasize the the the
The role of Doctor Schwartz. A mentor for all of us that has been working here for over 50 years is just retiring as well as of course the group here. The support staff and the clinical trial coordinators again that I'm showing you here that are the reason why again we are successful in providing to our patient clinical trial because they are the one that make this happen. The clinical trial office in the division of gynecological oncology. And finally last man or least the researcher the lab people that are...
00:53:07.777 --> 00:53:10.108 doing they really the work with the
NOTE Confidence: 0.943943513333333
00:53:10.180 --> 00:53:12.469 animals we are to do the sequencing
NOTE Confidence: 0.943943513333333
00:53:12.470 --> 00:53:14.654 and of course these are all as you
NOTE Confidence: 0.943943513333333
00:53:14.654 --> 00:53:16.793 can see young they come they get
NOTE Confidence: 0.943943513333333
00:53:16.793 --> 00:53:19.495 trained in my lab they and after they
NOTE Confidence: 0.943943513333333
00:53:19.495 --> 00:53:21.703 leave to get their faculty position.
NOTE Confidence: 0.943943513333333
00:53:21.710 --> 00:53:25.306 So here is the Fania belona Dr.
NOTE Confidence: 0.943943513333333
00:53:25.310 --> 00:53:29.198 Belona the lab chief of for that has been
NOTE Confidence: 0.943943513333333
00:53:29.198 --> 00:53:31.840 And of course she’s the person that I have to thank the most
NOTE Confidence: 0.943943513333333
00:53:31.840 --> 00:53:33.562 for the work that I just show you
NOTE Confidence: 0.943943513333333
00:53:33.562 --> 00:53:35.476 and I thank you for your attention.
NOTE Confidence: 0.943943513333333
00:53:37.443 --> 00:53:39.277 If there is any question of course we’re here
NOTE Confidence: 0.943943513333333
00:53:49.200 --> 00:53:50.919 SD trial are you looking at the level
NOTE Confidence: 0.943943513333333
00:53:56.200 --> 00:53:58.712 of troop tube or was it just all comers
NOTE Confidence: 0.943943513333333
00:54:01.355 --> 00:54:03.200 and if you can repeat the question.
00:54:03.200 --> 00:54:06.984 Yeah. So Dr. Reem is asking if the.
00:54:06.990 --> 00:54:09.066 The Trudelvi trial that I’m going
00:54:09.066 --> 00:54:11.220 to presented ask whether we have
00:54:11.220 --> 00:54:13.810 look into the expression of the drop
00:54:13.881 --> 00:54:16.563 two that is a target or not and the
00:54:16.563 --> 00:54:19.789 answer David is yes in the phase one.
00:54:19.790 --> 00:54:22.910 So the stage one of this trial we
00:54:22.910 --> 00:54:25.419 specifically look to drop to expression
00:54:25.419 --> 00:54:28.159 and only patient with 50 with expression
00:54:28.159 --> 00:54:31.090 or drop to any expression 1 + 2
00:54:31.090 --> 00:54:33.578 plus or three plus in at least 50%.
00:54:33.580 --> 00:54:35.372 Of the tumor cell we are eligible
00:54:35.372 --> 00:54:36.420 for the stage one.
00:55:00.830 --> 00:55:04.180 This is a good question again the so how
00:55:04.180 --> 00:55:08.300
many of these tumors with recurring disease
they have estrogen or progesterone receptor.
So let me answer to your question this way.
UTRAN cancer is a very heterogeneous
type of tumor, so you have.
From one side, the endometrioid,
so the one that are really resembling
very closely the normal endometrium that can be well,
endometrium that can be well,
moderately or poorly differentiated.
And on the other side of
the spectrum you have the,
the uterine serous carcinoma,
what we call still called type 2,
right, the uterine serous carcinoma,
the carcinosarcoma, the clear cell,
you know uterine cancer,
so in general. If you want you to endometrioid they over express astrogen receptor even when they come back with recurring disease. But those are only a minority of the recurring patient that we are treating in our clinic. Majority of the recurrences as I show you they take place in the uterine serious group, the carcinoso coma group that are the one that usually they do not express. By 20 year experience,
they do not respond to anti-estrogen treatment because most likely the receptor is not active. It's present on the surface but the pathway is not really working.

So what are the side effects of the trudelvides assitu Zumagovita can trial that is using this top poisoner is inhibitor as a toxic payload. So the answer is this is a very well tolerated drug and why am I saying that is because it does not cause the bone marrow toxicity that you know they can cause. And the other thing that we have...
00:57:08.567 --> 00:57:10.795 noticed is that even the GI toxicity
NOTE Confidence: 0.912391133333333
00:57:10.795 --> 00:57:12.679 that is typical of this drug.
NOTE Confidence: 0.912391133333333
00:57:12.680 --> 00:57:14.948 Is much, much smaller and this
NOTE Confidence: 0.912391133333333
00:57:14.948 --> 00:57:17.792 is once again is related to the
NOTE Confidence: 0.912391133333333
00:57:17.792 --> 00:57:19.980 targeted type of approach, right.
NOTE Confidence: 0.912391133333333
00:57:19.980 --> 00:57:23.270 So are only the tumor cell they
NOTE Confidence: 0.912391133333333
00:57:23.270 --> 00:57:26.034 overexpress drop two that they get that
NOTE Confidence: 0.912391133333333
00:57:26.034 --> 00:57:29.240 they get this toxic payload internalized.
NOTE Confidence: 0.912391133333333
00:57:29.240 --> 00:57:31.816 1 important thing that I also am going
NOTE Confidence: 0.912391133333333
00:57:31.816 --> 00:57:35.930 to stress to ASCO is that the Cornell
NOTE Confidence: 0.912391133333333
00:57:35.930 --> 00:57:38.625 toxicity for instance that we are seeing
NOTE Confidence: 0.912391133333333
00:57:38.625 --> 00:57:41.310 with many antibody that are conjugate.
NOTE Confidence: 0.912391133333333
00:57:41.310 --> 00:57:43.626 Is not present with this antibody.
NOTE Confidence: 0.912391133333333
00:57:43.630 --> 00:57:45.191 So that is another great thing because
NOTE Confidence: 0.912391133333333
00:57:45.191 --> 00:57:47.312 as you know we’re getting more and more
NOTE Confidence: 0.912391133333333
approval in terrible treatment with antibody that are conjugate our patient.

But we must have now enough ophthalmology before even starting to look to the corner for this specific type of a DC is not necessary. We don’t, we don’t really see that toxicity those. So it’s overall well tolerated. The only patient that are really experiencing some significant toxicity are the patient that have a polymorphism. In EU GT2B7 that is again this mechanism right that we have in our liver to catabolize at the top of isomerase about,
I’ll say 1-2 out of 10 May have this polymorphism. They are more sensitive to the drug, they usually respond better their cancer, but there we have to do a dose reduction. We go down from 10 usually to 7.5. We have two more answers that yes, so we I show you here our initial work with trust to Zuma and we have shown again for the first time that trust to Zuma added. To chemotherapy helps but in the recurrent setting we have multiple trial using antibody that are conjugate.
So we have used some one that is called symptom 985 that is a I don’t know if you’re familiar but again is the backbone is throstozoma the linker is clivable. The toxic payload is an alkylating semi synthetic calculating agent duocarmising extremely potent but also toxic and so we have seen dramatic response in the recurrence setting intrastuzumab resistant uterine carcinoma over expressing up to new. But the corneltosis it was significant in many of this patient we have to stop treatment for several weeks to allow recovery and that of course.
Was not good because during those sometime more weeks, the tumor will start growing again.

Yes, we do in a very special way. There’s different ways to do it. She’s doing it. So we only do it in the newest. So we already have the diagnosis. We give 3 cycles. We confirm the. But if it’s done different ways, there’s some studies that have it up front. Thank you.
Thank you so much to our wonderful speakers.

Have a wonderful day. Thank you.