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# Optimizing Multidisciplinary Approaches in the Guideline-Driven Management of Cervical and Endometrial Cancers

**Opening:**
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**Dr. Slomovitz:**
Good afternoon, everyone. Thank you very much for the opportunity to present to you today. My name is Dr. Brian Slomovitz. I'm a Gynecologic Oncologist in Miami Beach, Florida at Mount Sinai Medical Center. I also serve within the GOG Foundation as the Director of the Clinical Trial Program in Uterine Cancer, and I serve on the Board of Directors, as well.

It's really an honor for me and a privilege to have the opportunity to speak with your group today. Today, we'll be talking about optimizing the multidisciplinary approaches in the guideline-driven management of cervical and endometrial cancers. As a warning, there's a lot of information we're going to get through. Rather than really focusing on all the minor details of the slides, I want to go through, and as we go through, I want to sort of tell you a story just so you could better understand some of the things that we have ongoing for the management of this disease. And there's a lot of new things that are going on. And at the end, we'll be talking about different cases to help remember some of the things that we're talking through.

Here are some disclaimers about the program. There will be some discussion of unlabeled use as we move forward.

And here are my disclosures.

So, let's get going. So, when we talk about the incidence and mortality of endometrial cancers, the most common gynecologic cancer is uterine cancer; 67,000 cases per year, followed by ovarian cancer, and third is cervical cancer. It's interesting, of the uterine cancers, and we'll go through this later, two-thirds of those I consider one and done, treated with surgery alone. One-third have advanced or recurrent disease. When we see on the right, it's really interesting and a bit troublesome as well, the cases of ovarian cancer and cervical cancer is going down. However, given obesity and other comorbidities, the number of cases of uterine cancer are going up, and we need to do better to help treat those cancers and help prolong overall outcome for those patients who are suffering from uterine cancer, particularly to decrease the incidence of this disease.

When we think about endometrial cancer in particular, it's important for us to know the differences in biology and difference in response to therapy across racial disparities. What do I mean by that? Women of color have more aggressive histologies, they have more advanced stage disease. They're less likely to receive guideline-concordant treatment, and overall, their outcomes are worse.

Specifically, black women who have endometrial cancer are twice as high, likely two-times the risk of death due to disease, than other races and white women. So, it's something that we really need to do better. And as a clinical trialist, I'm really focusing on that in my career to help come up with better treatment options for our patients, all patients, across different disparities.

When we're focusing on the multidisciplinary management of cervical and endometrial cancers, really the number one key is the compliance with NCCN guidelines. Following these guidelines is associated with improved survival rates, making it a valuable indicator of quality cancer care. Lower rates of adherence to guideline-based treatments is seen amongst black women. This may be one of the reasons why there's poorer outcomes. And also, guidelines are lower in those in lower socioeconomic groups.

Failure to adhere to treatment guidelines is significantly linked to reduced survival compared to those who receive adherent therapy.

When we're focusing on the multidisciplinary expertise, you know it's just not one oncologist treating our patients; it takes a team. Pathology, molecular analysis, imaging or radiologist, surgery, radiation with their oncologist, oncology, medical radiation. Obviously, I'm a gynecologic oncologist. A little bit different of a field. We do surgery and we do our chemotherapy and obviously our nursing team. And a shout out to our nurse practitioners and our physician assistants. Particularly in my practice, they play a crucial role in offering the best care for my patients.

Okay, we're going to get going. Start with cervical cancer and then go into endometrial cancer. A lot's been changing in the world of cervical cancer, and we'll focus on this as we go through the talk.

Cervical cancer was one of the most common causes of death for women in the US. Thanks to screening, greater than 50% decrease in incidence and mortality since the 1970s. Knowing about cervical cancer and screenings really does help save lives.

Screening recommendations. Under age 21, screening not recommended. Cervical cancer is rare before this age. Age 21 to 29, screening with cytology alone every 3 years. When I say cytology, it's the PAP test. There's some organizations, the ACS also recommend starting at the age 25.

Truthfully, in my practice, what I do is I start screening once sexually active. I think that once sexually active, that exposes them to human papillomavirus. That is a necessary risk factor for the development of over 95% of the cancers. The other thing, while I'm thinking about it, is vaccinate, vaccinate, vaccinate. The best way to eradicate a disease is to give HPV vaccinations prior to sexual debut. And the other factoid that I like to share is not only vaccinating women, or those who are affected from disease, but also vaccinating men who, in the world of immunity, we talk about herd immunity. You can not only vaccinate those affected, but those that could spread it as well.

Sorry to go on a tangent there. Continuing on, age 30 to 65, screening every 3 to 5 years, depending on the test. If it's an HPV test, negative HPV can be screened every 5 years, PAP alone every 3 years, co-testing every 5 years as well.

As a GYN oncologist, I'm sent a higher risk group of patients, a risk group that oftentimes already has PAP abnormalities. So, my screening or my PAP testing and HPV testing is more frequent. But again, that's not for screening. That's for follow-up.

Now, over the age of 65, most recommendations say stop screening. Patients who've been screened regularly in the previous 10 years with negative results, it's OK to stop screening. This is a common question amongst my patients. A lot of times patients come in, they're used to getting their pap every year. So, it's important that we do pelvic exams every year, but it doesn't include pap testing. And we need to better educate our patients about this.

A multi-pronged approach to lowering cervical cancer risk. I mentioned this, I'll mention again, HPV vaccination. I actually vaccinate into mid-40s and those patients that are not in a monogamous relationship because they're at risk for HPV. It's important to get screened in order to find pre-cancers and cancers. Smoking doubles the risk of cervical cancer. And obviously, to avoid HPV infection.

Okay, so we talked about prevention and screening strategies. Let's dive into it and go right into the summary of treatments for cervical cancer. The nice thing about cervical cancer, it has a slow indolent course, meaning that a pre-cancer takes several years to develop into a cancer. Not to say we have time to miss something, but we definitely have time to intervene, many opportunities to intervene, if, in fact, abnormalities aren't picked up right away. CIN 2-3, which is high-grade dysplasia, these are usually treated with a cone biopsy,

cryotherapy, laser therapy, or a LEEP, or an excision of the cone.

Early-stage disease, which includes FIGO IA1, IA2, IB2, and IIA, these are amenable to surgical resection. We've actually gone away from radical hysterectomies on all of our patients. Some of the lower-risk cervical cancers actually do well with a simple hysterectomy. As we go on in the talk, I'll talk about locally advanced disease. These affect about 36% of the cases. These are treated with chemoradiotherapy. Surgery, if feasible, but I'm going to highlight some newer therapies that we're working with. And then, for stage IVB disease, platinum-based therapy with pembrolizumab, and with bevacizumab. Second-line therapy, immunotherapy agents, if not previously treated, this includes pembrolizumab and cemiplimab. Tisotumab vedotin, I was involved with this trial. This is a tissue factor antibody drug conjugate that's FDA approved in this disease. We have the tumor agnostic study, I'll talk about that a couple times during this talk, of trastuzumab deruxtecan in those patients that have second-line recurrence. For trastuzumab deruxtecan, IHC 3 or 2 in order to get treated; 3+ is an FDA indication, 2+ is NCCN guideline.

And then all single-agent chemotherapies as well.

The other thing I want to highlight here, is there's better options for fertility preservation. Sometimes the cone biopsy procedures are enough and help women maintain fertility by maintaining the uterus. In addition, there's recent data that shows doing a simple hysterectomy as opposed to radical surgery is just fine for these patients and obviously minimizes the risks of surgery by doing simple hysterectomies without the more radical approach.

Locally advanced disease. How do we manage these? First is a biopsy and a referral to GYN oncologist. Staging is done clinically as well as with imaging. We've incorporated looking at the nodes as well as part of the staging. Once we have this information, the cases are presented at a multidisciplinary team. This includes the gynecologic oncologist, the radiation oncologist, the pathologist, the radiologist, extenders, and also medical oncologist, if in fact the GYN oncologist does not give their own treatment.

Then we go into planning, followed by chemo radiation, chemotherapy with radiation therapy. And it's important when we're talking about this, for AE (advsere event) management as well.

So, let's starting off, GOG 120 was in 1999. Established cisplatin plus radiation therapy in locally advanced cervical cancers. We can see here that the groups that had cisplatin had higher progression-free survival and overall survival. At 2 years, 67% of the patients were alive in those patients treated with cisplatin in radiotherapy, as opposed to 46% treated with hydroxyurea, making cisplatin with radiation the standard of care.

Adding immune therapy. Here's a cartoon on the immune dynamics. I'm not going to spend much time on this. But giving immunotherapy, cytokine and chemokine release results in activation of adaptive immune system. E6 and E7 induced somatic mutations, increased PD-L1 and cytokine expression. Neoantigen release really activates innate immune system. These are all ways that are sort of squashed when given with chemoradiation. And we could see, based on this immune response, there's an increase in PD-L1, and giving checkpoint inhibitors here, there's an opportunity to have them work a bit better with the chemoradiation.

There are four immune checkpoint inhibitors in cervical cancer that have been developed: pembrolizumab, a PD-1 inhibitor, cemiplimab, I'm not going to talk about this one as much. There was a positive Phase 3 trial led by my friend, Dr. Tewari at University of San Diego. This led to a *New England Journal of Medicine* article, however, not further developed here in the US, but still on the NCCN listing. Durvalumab, which is a PD-L1 inhibitor, was evaluated in a locally advanced trial.

Chemoradiation with durvalumab. And atezolizumab was evaluated in a distant metastatic trial. Not ready for prime time yet, and we'll talk through that.

Locally advanced cases. How do we improve upon the care? I talked about the history. There's different strategies that we've looked at, immunotherapy. In addition, we've looked at adding chemotherapy either before the treatment or after the treatment. After the treatment, we looked at a study called ALPACA, and that was a negative trial. And what about maintenance therapy? And we'll go through the different options there.

Let's dive into it. KEYNOTE-A18, first-line trial, locally advanced patients, adding to – and you can see the schema here – adding to external beam radiation, followed by brachytherapy with cisplatin. Treating patients with either pembrolizumab 200 milligrams every 3

weeks for 5 cycles, or placebo. The maintenance period here was pembrolizumab for 15 cycles versus placebo for 15 cycles. Accrued over 1,000 patients. Really, a large population. Obviously, in the US compared to globally, we don't see as many of these patients, but it's still an appropriate treatment. We actually, we still need to have better treatment options for those patients with cervical cancer, and it is a great cause of deaths and morbidity in the United States.

Here's a primary analysis. In the pembrolizumab arm, which is in green, again, these are the patients treated with pembrolizumab with chemo radiation followed by pembrolizumab maintenance versus the placebo arm. Patients who had events, there are more events or recurrences or deaths in the placebo arm. When we look at median progression-free survival, the progression-free survival with pembrolizumab was 47.6 months vs 47.5 months in the placebo arm. As far as the 24-month, PFS 70.6% and 59.7%. You can see here, a hazard ratio of 0.7, or 30% risk reduction given immunotherapy, and that was statistically significant.

Overall survival at interim analysis 2, there's a survival advantage, hazard ratio of 0.67, with the confidence interval not crossing 1, statistically significant. Twenty percent of the patients with placebo had events versus 14%. Game-changing, right? Helping us to incorporate in the first-line setting, pembrolizumab in locally advanced patients.

Looking at the interim analysis to the final analysis, we can see that the difference is pretty held strong. With longer-term outcome, the curves do come together in what we call a traditional banana-shaped curve, as opposed to in the interim analysis staying apart. But clearly here, we could see a difference in the separation of curves, again, demonstrating the overall survival advantage.

Patient-reported analyses were obsessed in KEYNOTE-A18. There was no clinically meaningful differences between those patients receiving pembrolizumab compared to placebo. Similar percentages of patients treated with pembrolizumab or placebo experienced improved or stable scores. As far as global health status, 81% and 82% respectfully, and improved physical functioning, 81% and 83% respectfully.

Safety data in patients with cervical cancer receiving pembrolizumab and chemo RT, adverse events occurred at a higher incidence of grade 3 to 5 severity. You can see here, leukopenia 13% with pembrolizumab and chemoradiation versus 11%. Really not much of a difference there when treated with placebo and chemoradiation.

There's a comparable study you can see here on the bottom left, CALLA. CALLA was using durvalumab, a PD-L1. It didn't have the same risk factors. You could see in the top box on the right, KEYNOTE-A18 must have had two pelvic nodes or more. It allowed for a PET scan to evaluate. The CALLA study only included one pelvic node. So, a little bit less of population risk factors.

The lymph node size remained unchanged for lymph nodes, according to RESIST 1.1, which is 1.5 centimeters in the shortest dimension. In the CALLA study, it allowed 1 centimeter. Those are pretty much the main differences here of randomized prospective trial.

Here is the results of CALLA on the left. Not statistically significant. The confidence interval there of a hazard ratio of 0.84, but the confidence interval did in fact cross 1. As opposed to pembrolizumab, again, 30% reduction as shown earlier.

Key differences. CALLA had lower-risk patients, I mentioned that. Similar progression of disease, death events from primary analysis, in the two groups, and the similar maturity. But another big difference is the PD-1 versus the PD-L1.

What about advanced metastatic disease? This is talking about the local disease, but what about advanced metastatic? In the past, we demonstrated that cisplatin and paclitaxel was active in cervical cancer. We changed the world with bevacizumab in GOG 240. And then, most recently, we evaluated both pembrolizumab and atezolizumab and let’s take a dive into that.

One of the things I like talking about when I talk about cervical cancer, the world's not going to change in a day, it’s going to be baby steps. You can see here the response rates. Chemotherapy, 29%. Add bevacizumab, 48%. Add pembrolizumab in IO with bevacizumab, 69%.

KEYNOTE-826 looked at the standard of care, which was chemotherapy plus/minus bevacizumab versus chemotherapy plus/minus bevacizumab and pembrolizumab. A large, randomized Phase 3 trial, dual primary endpoints of overall survival and progression-free survival.

Here, you can see the differences. On the left, the progression-free survival significantly favors the pembrolizumab arm, hazard ratio of 0.58. And that was in the CPS ≥1, or PD-L1 population positive. In all-comer population, hazard ratio of 0.61, representing a 39% decrease in risk of recurrence.

Overall survival carried out an overall survival advantage with pembrolizumab in the metastatic recurrent setting. PD-L1 positive, 0.60. PD-L1 negative, 0.63. Remarkable results. Again, two studies show overall survival advantages.

Bevacizumab use, as mentioned, was optional. Two-thirds of the patients received bevacizumab. One-third did not. As far as reasons for bevacizumab exclusion, it could shown here most of the time it was for medical reasons; GI perforation, hemorrhage, hypertension. Without bevacizumab, there's still an advantage to pembrolizumab. That's the bottom line.

Another trial similar, the BEATcc trial with the atezolizumab. The prospective, randomized phase 3 trial. Here, the dual primary endpoint of progression-free survival was met, hazard ratio of 0.62. The confidence interval did not cross 1 and was clinically, statistically significant. Atezolizumab and bevacizumab plus chemotherapy versus bevacizumab/chemo alone. As far as the overall survival advantage, that was also seen here, 0.68. As with the confidence interval, did not cross 1.

Key differences here, BEATcc was ENGOT, the European group, with participation of the GOG. BEATcc was investigator-initiated. There was similar eligibility, but what does this mean in the context of global approval of KEYNOTE-826? I think the familiarity, as I'm sure in your practice, the familiarity of pembrolizumab helps push 826 into the lead here, being probably used a little bit more, at least here in the United States and in my practice. All the patients of note were IO naive.

After first-line therapy, second-line therapy options – this is a study that I was a GOG lead for, which led to a *New England Journal of Medicine* paper. The tisotumab vedotin versus standard of care chemotherapy. Standard of care here was either topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed. Bottom line, overall survival, the hazard ratio is 0.7, representing a 30% decreased risk of death in the second or third-line setting in those patients treated with tisotumab vedotin.

Again, game-changing. Again, what I'd like to highlight here, it's not going to be a big win, particularly in cervical cancer, it's going to be these small baby steps we saw with chemotherapy. Then, we added bevacizumab, and then we added pembrolizumab, and then now, in the second-line setting, tisotumab vedotin. So, you know some raised the question, the difference in median survivals. I actually think that the more important endpoint here is hazard ratios. And being significant, significant, significant, a 30% decrease in the risk of death.

What's in the future? There's some good, promising data looking at a TROP2 antibody-drug conjugate. This is sac-TMT – basket trial. When we looked at the cervical cancer cohort, again, TROP 2 antibody drug conjugate, sac-TMT, overall response rate of 24%. What's compelling is when given with pembrolizumab, sac-TMT and pembrolizumab, we see that the response rate here was 57%. So, really remarkable. You could see the remarkable swimmer's plot and waterfall plot on the right, 57% demonstrating the good synergy between the two agents.

Before we go to endometrial cancer, ongoing studies. There's a second-line trial of sac-TMT versus standard of care. Interestingly, the standard of care there does include tisotumab vedotin, to see which one will win out. And we just recently opened a first-line trial. This one, I had the fortune of being the global lead on, looking at five therapies. This is for patients with metastatic disease, distance disease. Carboplatin paclitaxel plus/minus bevacizumab, plus/minus pembrolizumab, and in the maintenance setting, we're adding in sac-TMT to see if we could mirror or duplicate the results, or a similar trend of the results of pembrolizumab and sac-TMT in this first-line setting.

Let's now move on to endometrial cancer. As mentioned, I had the great fortune of leading the endometrial cancer portfolio for the GOG. A take-home point here is, if you can, we need patients on trials. The best way to treat patients with cancer is clinical trials, and we need your help in putting patients on trials.

I went through some of this a bit earlier. Endometrial cancer, here's the two 2025 numbers, 69,000 new cases. Fortunately, two-thirds of these are what I consider one and done, requiring surgery alone. It's the one-third with advanced or metastatic disease that we need to do better. We need to come up with better treatment options. Thirteen-thousand deaths due to this disease.

I talked earlier about the uptrend. I want to re-highlight, there are more deaths due to endometrial cancer now than there are ovarian

cancer. That's one of the take-home points I really want to impress upon you, that the number of deaths for endometrial cancer are more than ovarian cancer. And that just shows that we need to do better.

Endometrial cancers change. We used to classify these into two classifications, what we call type 1 and type 2. We've really redefined that. This is based on some of the TCGA (The Cancer Genome Atlas) data in 2012, led by Doug Levine, who was at Sloan Kettering at the time, and also there's a PROMISE trial. Dividing into four different subgroups. POLE gene mutation; these are the most rare, however, they have the best overall prognosis.

We haven't completed them yet, but there's some ongoing trials of de-escalation in this population of patients, meaning taking away therapy. And honestly, I don't always do POLE gene mutation testing in my patient population. But if the de-escalation trials are positive, then I most certainly will to take away toxic therapy, especially if there's no benefit.

Microsatellite instability. Now, these two categories on the left, we consider these what we call hot tumors. Those tumors that are going to be most amenable to single-agent immunotherapy. Microsatellite instability-high or dMMR-deficient mismatched repair proteins. This is the loss of expression of MLH1, MSH2, MSH6, and PMS2. It can happen in about 30% of the patients. These are hypermutated phenotype, very responsive to immunotherapy. The two on the right, the cold tumors, the differentiator here is a *p53* mutational status. Copy-number low, *p53* wild-type, no specific molecular profile. Forty to 50% of endometrial cancers. A better prognosis than the *p53*-mutated group. Often aligned with AKT, P10, PI3-kinase in abnormalities, as well as ER expression is pretty high here; *p53*, abnormal. These are aligned with the more aggressive histology findings, not the obesity-driven cancers, not the hormonally responsive cancers, but you know they make up 10% of the cases and they account for 50% of the diseases. These are the aggressive cases where, again, we need to come up with better treatment options.

It's important to note if you look at the PROMISE criteria, which is outcome data, not only are there molecular differences in these four groups, but prognosis plays out. The best outcomes in the poly-mutated group, 7 to 10% of endometrial cancers. The worst players, OK, the worst players are the *p53* mutated group. And in the middle, we have the dMMR and the copy number-low group which have that middle prognosis.

This is where we were and where we're going with endometrial cancer. I like this slide. We started off treating with progestins. In early 1970s, we finally got an approval of endometrial cancer with progesterone therapy. That was the last FDA approval in about 30 to 40 years. The next FDA approval after progestins was actually for pembrolizumab in the IO setting. We used chemotherapy. Again, we used chemotherapy. That was an NCCN listing, it was not necessarily on FDA approval. So, now we're sharing more, and I'll share with you the data. We're seeing more and more FDA approvals in this setting, but we need to do better.

And you know again, highlighting here, progestin therapy, then chemotherapy, immunotherapy we'll go through, and then now we're in the era of antibody drug therapies.

Now, I want to prove to you that all women with endometrial cancer deserve immunotherapy, all women. I'm going to start with you in the second-line. KEYNOTE-158 is one of the four trials list here in addition to single-agent durvalumab, dostarlimab, and avelumab. Biomarker-positive population, meaning dMMR-positive. Response rate of 48% with pembrolizumab, 43% with durvalumab, 44% within the GARNET dostarlimab trial, 27% with the avelumab trial. So, right now, second-line setting, dMMR, 30% of the tumors, single-agent immunotherapy as the best treatment option. Second-line setting, IO-naive.

Now, the similar studies in biomarker-negative patients didn't work, so we needed to do better. What did we need to do better? What did we do? We, based on the work of Vicki Makker at Sloan Kettering, we added a dirty tyrosine kinase inhibitor, lenvatinib, to the pembrolizumab. First, there was a preliminary study, then followed by this study. This is study 309, KEYNOTE-775 with pembrolizumab, demonstrating that lenvatinib and pembrolizumab worked in patients with pMMR tumors, better than chemotherapy and overall survival advantage.

Okay, you can see here on the left in the pMMR population, a hazard ratio of 0.70. It did not cross 1. In the all-comer population, a hazard ratio of 0.65. That was boosted, obviously, with the dMMRs that were included. So, pMMRs, a 30% decreased risk of death over traditional chemotherapy.

Right there, there you go. Second-line setting. I just proved to you, all patients deserve immunotherapy, whether biomarker positive or

not. What about first-line therapies for the management of this disease? First-line immunotherapy.

Here, just to start off with, this is the old regimen, chemotherapy, carboplatin paclitaxel. This is a study that was led by David Miller, done by the legacy GOG. We call it NRG, now. Carboplatin paclitaxel versus TAP regimen, a triplet taxane Adriamycin platinum. Non-inferiority trial, and as you can see from the curves on the right, they're exactly the same. About a 51, 52% response rate in the first-line chemo-naive setting. You can say, Slomovitz, wait a minute, 48% with pembrolizumab in the second-line setting. That's how active immunotherapy agents are. Comparable results here. Better efficacy, therefore making carboplatin paclitaxel the standard of care.

Then we did a series of four trials. Four trials incorporating immunotherapy, ok, with chemotherapy. Carboplatin paclitaxel plus/minus immunotherapy or placebo. First-line management of this disease. Four trials.

GY018 or KEYNOTE-868, carboplatin paclitaxel plus/minus pembrolizumab. RUBY, carboplatin paclitaxel plus/minus dostarlimab. AtTEnd, carboplatin paclitaxel plus/minus atezolizumab. And finally, the DUO-E trial, led by Shannon Westin and Katie Moore, carboplatin and paclitaxel durvalumab versus carboplatin and paclitaxel placebo. In that study, there's also a third arm looking at the role of PARP inhibitors in this setting.

March 23rd, a Monday afternoon at the SGO meeting, Ramez Eskander presented GY018, the bottom one on the lower left. Mansoor Mirza at the same session, presented dostarlimab with chemotherapy versus chemo and placebo. Changed the world. Not only did they have oral presentations, but they had simultaneous released publications in *New England Journal of Medicine*.

For those that are on there that may be trainees or more junior faculty, if you get an oral presentation, that's awesome. If you get a *New England Journal* paper, that's awesome. Okay. If you get both at the same time, you hit a grand slam home run.

The other trials were positive as well, and JCO Shannon Westin, published durvalumab in the DUO-E trial, and Nicoletta Colombo published atezolizumab in chemotherapy in the AtTEnd trial.

I want to go through these studies. First, I'll start off with GY018. There's a couple of differences here. This is the best statistically designed. The other studies are looking at primarily dMMR and then all comers, and they're making inferential they're making inferential conclusions about the pMMRs. GY018 was designed, two separate statistical designs, two studies in one. This was led by Ramez Eskander. They looked at dMMR, they also assigned alpha to pMMR to come up with a better answer.

The other difference in this study is the primary endpoint was progression-free survival. Okay, with progression-free survival, when the study hit its progression-free survival endpoint, okay, the problem then was the study was over unblinded, so we didn't get longer overall survival data.

Let's go on to the results. KEYNOTE-868/NRG GY018, makes sense. dMMR setting, it works. Hazard ratio of 0.30 on the left, no-brainer. Giving patients with endometrial cancer chemotherapy plus pembrolizumab helped patients longer progression-free survival. You can see on the right, in the pMMR setting, again, carefully designed trial, designed with alpha, given statistical power, hazard ratio of 0.54. Quite remarkable. When we looked at the overall survival differences – I said this, right? Once the study hit PFS, unblinded, so the overall survival data here wasn't as strong as some of the other studies. But in this study that Ramez Eskander published this year in *Nature Medicine*, what he did is he helped to look at the overall survival, adjusting for post-study IOs. And you could still see here, the clear trend of improvement with pembrolizumab in GY018, even though the overall survival difference is not big.

I'm not sure if it's a limitation or not of the trial, but the bottom line is clearly a benefit in PFS and likely this is carried to overall survival.

RUBY trial, very, very similar. Two things; different statistical design. As mentioned, looked at the overall population, the ITT population, in the dMMR setting. Okay? Included carcinosarcomas, another big difference. Allowed for adjuvant therapy, three C2s or greater. Even with no disease, they were allowed to be on trial. The asset here was dostarlimab. Upper left, dMMR setting, same as pembrolizumab, no-brainer, hazard ratio of 0.28. It works. Overall population PFS, hazard ratio is 0.64, very strong. Didn't cross 1. Statistically significant. Overall survival in the dMMR is 0.3. Again, survival here was an outcome, so we have longer data on survival.

Of those patients, interestingly, 39% on the placebo arm and 15% in the dostarlimab arm received subsequent IO. I'm not sure about the role of IO after IO. For those of you that read the *International Journal of Gynecologic Cancers*, I published an article this month. It's

the lead article in the journal about IO after IO. And earlier this afternoon, I did a podcast on the *International Journal of Gynecologic Cancers* discussing that fact exactly, and it'll be an enduring material online if you'd like to refer to that. Overall survival of all-comers, 0.64 hazard ratio or 36% reduction.

Here's in the pMMR setting. Hazard ratio of 0.76, did not cross 1. Overall survival in pMMR, clinically meaningful with a hazard ratio of 0.73 or a 27% reduction. Of note, 16% of the dostarlimab patients did receive subsequent IO. The longer overall survival data here, I talked about this, why it's longer data available, but the difference held true. The longer, more mature data, there were still differences in outcomes, overall survival, whether it be dMMR or pMMR.

I alluded to this trial, the DUO-E trial. This is adding one of the arms had olaparib, as well. The results here, three outcomes. The bottom is carboplatin paclitaxel placebo.

In those patients receiving durvalumab alone, there were still increased activity. Durvalumab and olaparib seemed to perform the best. This study here compared arms A versus B and A versus C, so we can't really statistically – there's no alpha assigned to B versus C, but you can see here the hazard ratio here is 0.78 with a clinically meaningful difference.

dMMR, no question. You don't need olaparib, a PARP inhibitor, in this setting. Durvalumab does all it can. Hazard ratios comparable to the other studies. But in the pMMR setting, durvalumab and olaparib does play out with an advantage. The problem is we don't know which of those patients. We don't know which patients with pMMR tumors, okay, do better with olaparib as opposed to not needing olaparib. It may be *p53* mutation status. More to come on that over the next couple of years as we do more and more translational studies.

Bottom line, dMMR, I've said it once, repetition breeds memory. IO is needed, 0.30, 0.28. This led to three FDA approvals in the dMMR setting; dostarlimab, durvalumab, and pembrolizumab. In the pMMR population, two FDA approvals; pembrolizumab and dostarlimab. Why are some of the differences? Maybe it's a PD-L1 versus PD-1. Maybe there was a higher Asian population in the AtTEnd. We're still determining differences, but we have three approvals in dMMR, two approvals in pMMR.

What about chemotherapy-free options? The two studies on the left haven't reported out yet. This is in the dMMR setting. The one on the left, KEYNOTE-C93, I'm the global PI for. Pembrolizumab versus chemotherapy. Hopefully, it's positive. One of my career goals is to get rid of chemotherapy. Going after dMMR tumors may be a strategy. In the DOMENICA trial, using dostarlimab. We did the LEAP-001 trial, all-comers, lenvatinib and pembrolizumab versus chemo in the first-line setting. Included dMMR and pMMR. Unfortunately, this is a negative trial, as shown here. Written as a superiority trial, so the lines are similar, but clearly not superior.

However, in those patients that had prior neoadjuvant chemotherapy, it appears to make a positive difference. Not a primary endpoint of the study, no alpha assigned to this, but in pMMR patients who received adjuvant chemotherapy, lenvatinib and pembrolizumab had a benefit with a hazard ratio of 0.60, and PMMR and all-comers, 0.52. A 48% improvement.

Adjuvant therapy, KEYNOTE-B21, chemotherapy plus/minus pembrolizumab. High-risk patients. I led this trial for the GOG. Again, negative trial. I'm okay with negative trials because they're answering important questions. Subgroup analysis here, dMMR patients had a hazard ratio of 0.3. Remarkable, remarkable finding. This is in the DSFS population, but as far as disease-free survival, 0.3.

Impressive, okay, and what I'm doing, and according to the current guidelines, in those patients that met the criteria for GY018 advanced disease, in the dMMR population, I'm adding pembrolizumab to their adjuvant therapy. IO after IO. This is the article that I was referring to. Please refer to this. It's in this month's *International Journal of Gynecologic Cancers*. There's not a lot of strong data yet about IO after IO. We're doing current work. There's a case series by Peter Rose showing that in dMMR patients, dMMR, who are on single agent, adding lenvatinib can yield responses.

Towards the end of the talk now, I want to quote, what else is there? Targeting P53, ADCs, hormonal therapy, other targets. ADCs are taking over the world. As mentioned earlier, we have a trastuzumab deruxtecan FDA approval in the second-line setting. We're also studying that in the first-line, the adjuvant setting, in DESTINY-Endometrial01 and DESTINY-Endometrial02.

Second-line trials, we're looking at sac-TMT and sacituzumab govitecan. TROP-2 ADCs. In the future, we're looking at RINA-S, which is an alpha-folate receptor ADC. P-SAM, ADC against B7H4, and another B7H4.

Hormonal therapies. We started in 1961, as I showed you. There's still activity here. I like biomarker-driven therapies. On the left, we have data with ribociclib and letrozole. On the right is some of my work on everolimus and letrozole, both showing activity in this population of patients.

Optimizing safety is important. Effective communication with clinicians and patients is crucial during checkpoint inhibitor therapy. It's important to focus on patient education, multidisciplinary involvement. The management of AEs requires a structured approach based on grading, immunosuppression strategies, and close monitoring. Again, I talked about this earlier. The multidisciplinary team. Based on the side effects, ophthalmologists, radiologists to help me with identifying ILD. Dermatology, gastroenterology, particularly for the diarrhea side effects. Urology, endocrinology for the thyroid. Super important to bring the whole team on board.

Here's just some more information on that, particularly with how it handled the different grades.

We went through a lot of information, a ton of information. I hope you retained some of it. I'm sure you did. Let's go through some of the case-based learnings.

Case 1. A 36-year-old woman from an under-resourced community area. Bleeding after intercourse, pelvic discomfort, and bleeding in between periods. Her last pap was several years ago. Real quick. PAP smears, by doing PAP smears alone, you decrease the risk of cervical cancer by 50%. People don't understand that. But that means by going to a doctor, you can decrease your chance of getting cancer. Nothing significant in her past history.

On exam, 4 to 6 centimeter cervical mass, bilateral parametrial involvement. Ultrasound confirmed this mass is highly vascular. Pelvic MRI, solid uterine cervical mass, worrisome for cervical cancer. Bilateral lymph node positive, confirmed on PET scan.

Pathology. Adeno-squamous pathology, IHC is positive for P40 and P16, supporting this diagnosis with a CPS score of 50.

What would you recommend for this patient? Okay, chemoradiation, induction chemoradiation followed by chemoradiation, that's the INTERLACE trial that I alluded to. Chemoradiation with pembrolizumab followed by pembrolizumab maintenance. That's the KEYNOTE-A18 trial. And unsure.

Okay. KEYNOTE-A18. Good.

The other thing about the KEYNOTE-A18 trial, you know they don't allow for CPS score of 0 or negative PD-L1 into that trial, which I'm not excited about. If you read *Gynecologic Oncology*, some of my colleagues, Brad Monk, Coleman, Herzog, and I, and some others wrote an editorial about this.

Cervical cancer can lead to death. You have to give the best therapy first. I believe that giving pembrolizumab for all patients with locally advanced disease is important.

Let's move on.

Following KEYNOTE-A18, the patient started on 5 cycles of pembrolizumab, then 15 cycles of pembrolizumab. Seven months later, she had pulmonary nodules. What would you recommend for this patient? Carboplatin/paclitaxel, carboplatin/paclitaxel bevacizumab, carboplatin/paclitaxel bevacizumab and pembrolizumab, or enroll in TroFuse-036. This is the first-line trial, a TROP 2 ADC for sac-TMT in combination with pembrolizumab in the maintenance setting or E, unsure.

Okay, I think bevacizumab pembrolizumab. Remember, in the KEYNOTE-826 data that we showed, there was an advantage of adding pembrolizumab here, so I think if pembrolizumab is not available in the area, that's not unreasonable, but otherwise, I would go with C. Even with prior pembrolizumab.

This patient was actually treated on study. Twelve months later, she had no evidence of disease.

Let's go to our endometrial case study. A 73-year-old serous carcinoma, uterine serous carcinoma. She had a robotic-assisted

laparoscopic hysterectomy that was sent for lymph node biopsy. She ended up being a stage IIC (FIGO 2023), so high-grade histology limited to the uterus. pMMR, p53 mutated, HER2 2+.

Question: After discussion with the multidisciplinary team, which of the following is most appropriate in the next step according to her biomarker profile? Standard of care, carboplatin and paclitaxel plus/minus bevacizumab, immunotherapy. There's one study that I didn't tell you about, GOG-3122/DESTINY-Endometrial-02 which is looking in the adjuvant setting. Trastuzumab deruxtecan versus standard of care chemotherapy. Or D; unsure.

Outside of trial, I think the answer here would be single-agent carboplatin paclitaxel. KEYNOTE-B21, which is an adjuvant trial that this patient would have been eligible for, was in fact negative. So, even though we used immunotherapy in the first-line setting for this disease, we're not giving it in the adjuvant setting. So, I think C is a great option. Outside of C, I think carboplatin and paclitaxel, which is an A.

She went on the trial. She received standard of care. Ten months later, she had recurrent disease with liver mets and peritoneal carcinomatosis. What would you recommend? Standard of care, carboplatin and paclitaxel immunotherapy. There's another clinical trial, GOG-3098/DESTINY-Endometrial01, looking at trastuzumab deruxtecan and a bispecific, or pembrolizumab versus standard of care. And there's another clinical trial looking at TROP 2 ADCs in the first-line setting, or unsure.

So, I know I didn't have a lot of time to go through the clinical trials here, but you know since she’s HER2-positive, so that maybe take that into consideration when you're considering the direction to go in.

Truthfully, all the answers here are correct.

She enrolled in the DESTINY-Endometrial01 trial. She was randomized to carboplatin paclitaxel pembrolizumab. At 6 months, she had recurrent disease. So, she got adjuvant treatment, then she got recurrent disease. Now, what are options after the second recurrence? Standard of care. There's a trial looking at the TROP 2 ADC in the second-line setting. There's a trial looking at B7H4 ADC in the second-line setting, or unsure.

Again, no wrong answers here. I guess another option here is trastuzumab deruxtecan off-protocol.

Thank you very much for your time.

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