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https://reachmd.com/programs/cme/precision-through-the-continuum-applying-biomarker-guided-therapies-in-ovarian-cancer/56953/

Released: 07/07/2026
Valid until: 07/07/2027
Time needed to complete: 60 minutes

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Precision Through the Continuum: Applying Biomarker-Guided Therapies in Ovarian Cancer

Opening:
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Chapter 1

Dr. Campos:
We're going to talk specifically about approved ADCs in platinum-resistant disease. And so the mother of all ADCs in ovarian cancer is mirvetuximab, and this is an ADC that targets the folate receptor alpha, and specifically, this has a payload that's an antimicrotubule. It's about 100- to 1000-fold more potent than vinca alkaloids. Now, in terms of folate expression in wild-type cells in epithelial ovarian cancer, it's on the order of 0 to 25%, but in contrast, tumor cells overexpressing the folate receptor alpha can be anywhere between like 76 to 89%.

So, although there are many trials that actually led to this pivotal trial, the FORWARD trial, the SORAYA trial, the pivotal trial was indeed the MIRASOL trial. And this was published by Dr. Katie Moore, presented by Dr. Katie Moore. And it's a phase 3 study of mirvetuximab versus investigator's choice chemotherapy in platinum-resistant ovarian cancer, specifically in patients that have a high folate receptor alpha expression. And as you can see, the eligibility criteria is they had to have platinum-resistant disease, a high folate receptor alpha, defined as greater than or equal to 75% cells that were staining greater than or equal to 2+. They could have had prior bev and prior PARP inhibitors.

The trial was a simple design. It was 453 patients randomized either to mirvetuximab or investigator's choice, which could have been paclitaxel, liposomal doxorubicin, or topotecan. The primary endpoint of the trial was progression-free survival, while secondary endpoints were overall response rate, overall survival, and patient-related outcomes. And you can see from this study and the patient characteristics that they were quite balanced between that of individuals on mirvetuximab versus that of chemotherapy.

I think to highlight here is these folks also were previously exposed to bev, PARPs, taxanes. They had had prior therapies, and in terms of like prior systemic therapies, the majority of these individuals had had about two to three prior lines of therapy.

So what were the results of MIRASOL, both in progression-free survival and overall survival?

In terms of progression-free survival, you can see that the curves separate, and they separate very nicely very early on. And in terms of median progression-free survival, it was in favor of mirvetuximab at 5.62 months versus the chemotherapy that was 3. 98 months,

statistically significant. In a likewise fashion, so was overall survival. You see the overall survival curve splitting quite nicely and very early on, and you see about a 4-month gain in overall survival in favor of the mirvetuximab.

Now, overall response rate. Now, often we don't talk about overall response rate, but it's still quite important if your patient is indeed symptomatic. Overall response rate was about 42% with MIRV and about 15% with chemotherapy. Now, this was a difference of about 26.4, and the odds ratio was 3.81.

Now, what about tumor reduction? The investigators looked at tumor reduction and progression by subgroups, and you can see the best tumor change from baseline. In the mirvetuximab group, you can see the tumor reduction in the MIRV arm occurred in about 81% of patients, as opposed to chemotherapy, where it was only about 55%. And when you look at disease progression or death by prior therapy status, it was mostly in favor of that of mirvetuximab.

Now, in terms of toxicities, you could take a look at hematologic toxicities. In essence, chemotherapy was far more hematologically toxic than that of MIRV in general. Indeed, we did see peripheral neuropathy more so with MIRV, almost approximating that of paclitaxel. Some patients do have alopecia, not all. There is gastrointestinal issues, diarrhea specifically. Often patients complain about diarrhea about 3 to 4 days after having had mirvetuximab.

What is different here is that of the ocular toxicity. And blurred vision, keratopathy, and dry eyes is clearly seen more in mirvetuximab, and I think most of us know that patients have to be seen by either an optometrist or an ophthalmologist. They need to have a slit lamp examination every other cycle. They also adhere very, very nicely to that of some eye drops, both steroid drops, vasoconstrictor, and lubricating drops. It's quite important. It's a little algorithm. At least in my practice, I'll tell you, this has not been a problem. I would certainly like to discuss that.

So, that's the first ADC that is indeed approved.

What is the second ADC? I think we're all pretty much familiar with this, and this is trastuzumab DXd, and this is an ADC that targets HER2/neu. In this particular setting, the payload is that of a topoisomerase inhibitor. So when you think back and you ask yourself the question, how much HER2/neu was really expressed on gynecologic malignancies, specifically that of ovarian cancer? Well, in terms of IHC 3+ expressed, it’s somewhere between 2 to 5%. In terms of IHC 2+, it can be anything from 8 to 18%. And I think we also know that the expression of HER2/neu is associated with basically an aggressive phenotype.

Now, this is an important thing to remember, that trastuzumab DXd is recommended by the NCCN guidelines for platinum-resistant ovarian cancer, both IHC 2+ as well as 3+. And in contrast to other disciplines, if you have an IHC that is 2+, you do not have to reflex to that of FISH. All you need is IHC 2+ or 3+ in platinum-resistant ovarian cancer.

So what was the study that actually really brought this to the attention of the ovarian discipline? It was the phase 2 DESTINY-PanTumor02 trial. This particular trial was done in several solid tumors. Patients had to have greater than one prior lines of systemic therapy, and they had to be either 2+ or 3+.

Two hundred sixty-eight patients were in this trial in multiple disciplines, and patients were given trastuzumab DXd of 5.4 mg/kg. Primary endpoint was that of overall response rate, and secondary endpoints is duration of response and disease control rate. What you can see from the patient characteristics is that a majority of these folks were actually 2+ expressors, but interestingly, 35% of these individuals had had prior therapies, so they were heavily pretreated. And additionally, about 10% of these folks had had prior HER2/neu therapy, in this case trastuzumab or pertuzumab. Patients had a good performance status.

When the results were tabulated, it's quite impressive, although it was only an N of 40 individuals. When investigators looked at overall response rate by IHC or the number of prior lines, you can see in all patients it was about 45%. When overall response rate was looked at by prior HER2/neu and topo-I inhibitor therapy, anyway, it was overall about 45%. And when they looked at it by biomarker status, regardless if they were BRCA positive, not BRCA positive, HRD mutated or not mutated, you can see response rates that hovered somewhere between 33 to almost 75%. So you can see that the overall response rate in this particular cohort was indeed quite robust.

When the investigators looked at progression-free survival as well as overall survival, what you can see here, the dark blue line is IHC 3+. The median progression-free survival was 12.5 months. IHC 2+ was 4.1 months. Overall survival, again, the IHC 3+ was 20 months,

and the IHC 2+ was 13 months. So again, very robust data, not only in overall response rate, but in progression-free survival as well as overall survival.

Now, how enticing this particular drug is, no matter how, it does have some toxicity that we should speak about. There's hematologic toxicity. It is a highly emetogenic drug, so often we use three agents before the chemotherapy. It can cause fatigue.

It is trastuzumab, and so left ventricular dysfunction , it has to be monitored quite closely, both at baseline and every three to four cycles. Patients can have GI distress, and some patients—not all patients—can have alopecia. So I have to remind myself every so often to make sure that I make that known.

One toxicity that we do pay very close attention to is interstitial lung disease, and recognizing this can be quite important. It can be quite difficult also. We get these incidental findings on routine scans, and we sometimes don't know what to do about it. I've gotten in the habit, if I do suspect ILD, I talk to my pulmonologist, we sometimes get a high-resolution CT. But the important thing is to know how to manage it. If it's a grade 1 and patients are asymptomatic, you can hold the agent. You can resume it once these symptoms have resolved. You can consider systemic steroids at 0.5 mg/kg. And then if the symptoms go away within 28 days, you can just resume at the same dose, but greater than 28 days you dose reduce.

However—and this is however—in contrast, if the patient has a grade 2 toxicity, they are symptomatic, you absolutely discontinue the trastuzumab, and you start steroids at 1 mg/kg.

So, quite important drug in the management of ovarian cancer, but knowing and how to mitigate some of the side effects is exceptionally important.

Chapter 2

Dr. Campos:
So we have just a couple minutes to talk about this. Let me ask you, Debbie, in the MIRASOL trial, the response rate in the control arm was around 16%. How does that feel to you in respect to, like, what we might expect today?

Dr. Richardson:
Well, I think what we expect today is going to be a lot higher, because we just got two FDA approvals of taxane-based, where we're seeing ORR over 30%.

That being said, I also think you have to look at how many lines are we talking about. So, in the B96 regimen, it was only one to two priors. In ROSELLA was one to three priors, but that ORR is about 36%, although when the FDA relooked at it, it's more about 24% when they looked at it with their own data.

But I think, honestly, topotecan will go away. I don't think it's an active drug, and I'm not sure why we're still using it. I think PLD is a great drug to use with carboplatin. Again, it's not very active, and so I think what you're seeing in that is that it's being driven by those two drugs.

I do think weekly Taxol is active up to about five prior lines with an ORR expected somewhere closer to 30%, although again, both in B96 and ROSELLA, if you look at the FDA data, it's maybe a little bit lower, and that's probably because of some of the other treatments patients have had.

Dr. Coleman:
And Susana, you brought up T-DXd and there's no doubt that when that got a pan-tumor approval it kind of took the world by storm. And so here we have two drugs that have been linked to biomarkers. So tell us a little bit about your biomarker testing strategy. Like, when do you do it? Do you repeat it? That kind of thing.

Dr. Campos:
Yeah. Oh, this is very good question. So we test for folate receptor alpha right at the beginning. We do next-generation sequencing. We just send it off.

In terms of HER2/neu, that's a little bit different. Sometimes we'll have it when patient initially presents, and sometimes we order it when the patient actually relapses. But I think a very good point is, is that don't always just simply trust your HER2/neu expression if it's 0 or 1. Always re-biopsy. There's tremendous heterogeneity with HER2/neu expression, and I have changed the management of several individuals by simply retesting it and being able to give this drug to the individual, so quite important. Yeah.

Dr. Richardson:
And can just ask, at your institutions, are you guys using gastric scoring or breast scoring?

Dr. Campos:
Yes, and that's something that I did not say. Actually the DESTINY-PanTumor did use the gastric scoring system. Yeah, absolutely.

Dr. Coleman:
Yep. So with respect to the adverse events, I think you gave us a good spectrum of the two drugs that we have now. How do you counsel patients, I guess, as to what to anticipate? Is there something that we can tell them in terms of timing? You mentioned ocular toxicity. You mentioned alopecia.

Dr. Campos:
Exactly. You know with mirvetuximab, I think most patients are used to hematological toxicity, neurotoxicity. They've learned to live with this over the course of time. Oculotoxicity, however, just really does make people see things in a different light, no pun intended, right?

Although you know when you actually tell individuals, you're going to see the optometrist, the ophthalmologist, every other cycle. You have to use these agents if- and most people do accommodate very well, very well actually.

And in my clinical practice, yes, I've seen one or two people with dry eyes, but this has been mild in comparison. I've also had patients who refused to go on the drug because of the ocular toxicity, only to come back to the drug to use it at a later time. Yeah.

Dr. Coleman:
Are there any questions from the audience? I'm just going to stop before I keep going. Okay. Yeah, go ahead please. Yeah. Let's get you a mic'd so that we can hear you.

Mr. Ahmed:
Wanted to understand the challenges associated with getting fresh biopsies of ovarian cancer patients, particularly in metastatic settings where there are multiple lesions. And from the data that I've seen, it sounds like each of these metastatic sites are very different—

Dr. Coleman:
Can be.

Mr. Ahmed:
Genomically or biomarker or protein expression-wise, which my understanding is if you're doing immunohistochemistry of the primary tumor, that's very limited even if you get a fresh biopsy. So if you can give a little bit of color as to is this a challenge, how severe is it, and what are some of the solutions? I know the ctDNA for blood, but for protein expression?

Dr. Coleman:
Right.

Mr. Ahmed:
How are you guys thinking about this?

Dr. Coleman:
Great question. Yeah, do you want to?

Dr. Richardson:

I mean, I think for some of the assays, at least, they've done some of that work, like mirvetuximab has done that for folate receptor. It's been done for NaPi2b. It's been done for a few of the other things, and actually there's not that much drift. I mean, there definitely is some. Both. There can be some heterogeneity in the tumor, and then it can also change somewhat over time, but in general many of these markers, especially for the IHC, kind of stay stable.

Now, one of the things that will change in high-grade serous ovary cancer is CCNE1 amplification. So if you had a drug that was targeting that, that's probably something you would want a fresh biopsy. We definitely do fresh biopsies, but some patients for ovary cancer never even get measurable disease because they have carcinomatosis, and sometimes they have recurrences in places that are just too difficult to safely biopsy.

But I do a lot of phase 1 clinical trials, and some of those mandate biopsies, and so certainly there are many patients who can be biopsied. And so I think it depends on how long has the patient been alive, etc. There are definitely times when, if somebody doesn't have much to target, I will consider re-biopsying something else to see, can I find something that I can give them.

Dr. Campos:
I have to say I have one patient's going back to surgery for a lap because she has such little disease and I've known her for 20 years; I just don't know her folate receptor expression or HER2/neu, so I'm not giving her these drugs without, because I just simply don't know it. And she's never mounted enough disease that's visible on CT in order to mandate a biopsy.

Yeah.

Dr. Coleman:
Yeah, the one thing about ovary cancer is that if most of those patients do get surgery at some point, either in the primary setting before they get chemo or as an interval, so some of the invaluable samples are coming from the neoadjuvant patients, where they send basically fibrotic tissue, so it's harder to get good biomarkers there. But I kind of say, like, if I get a hit that's positive, I like keep it. If I get one that's negative, then I go looking. And so-

Dr. Richardson:
I think just for that point, like, so, at my institution, at a new diagnosis of ovary, if we're giving neoadjuvant, we take them to the OR and get tissue. Like, I don't send them to IR for a biopsy unless they're really too sick to go to the OR for a laparoscopic biopsy, so I'd actually have enough tumor to do testing in case they have a dramatic response and there's nothing left at interval debulking, or not enough to send NGS.

Dr. Coleman:
Exactly. Yeah. So it's the same thing— we've adopted doing laparoscopic procedures to assess for the ability to do complete gross resection, and that's an ideal time to get good tissue in primary and metastatic sites.

Dr. Campos:
I also torment my IR division. Okay. I send biopsy requests all the time. Nine out of 10 times they'll say no, but once in a great while they say yes, yes.

Chapter 3

Dr. Richardson:
Thank you. Okay, so CDH6 is highly expressed in ovary cancer, especially high-grade serous ovary cancer. On this slide it says 70%, but in our trials for R-DXd, we're actually seeing it as high as 90% expressed if you define it at 1% or higher. You will see it in some other of the cell types, mostly when they're advanced stage, so stage III or stage IV, but it is highly expressed.

And these are basically the two CDH6-directed ADCs under development right now. On the top we have R-DXd, and on the bottom we have CUSP06. R-DXd is a little bit further along in its development. Both of them are topo-I payloads. You'll notice that R-DXd is the same payload as T-DXd, so if you know how to use T-DXd, you can pretty much figure out how to use R-DXd, because the toxicity is not from its target, but it's really from its payload, and the linker is the same, so it has a very similar side effect profile to T-DXd.

CUSPO6 has an exatecan linker. We've seen this before as well. There's many drugs actually under development than exatecan. One of the examples in GYN cancer right now is Rina-S, which is a FOLR-directed ADC.

And this is the REJOICE-Ovarian01 study design. This was a phase 2/3 multicenter international randomized trial of R-DXd in patients with PROC high-grade- well, it's PROC high-grade serous or endometrioid primary peritoneal or fallopian tube cancer. In the phase 2, it was one to three priors. In the phase 3, it's now one to four priors. Patients do have to have prior MIRV if they were MIRV eligible, aka FOLR high, 2+ or 3+ at 75%. They could not have had prior CDH6-targeting agents or an ADC with a linked DXd. There was no selection by tumor CDH6 expression, though tumor was collected. In fact, for the phase 2, they did undergo fresh biopsies. On the phase 3, that is not required, it's just archival tissue.

There are multiple stratification factors for the phase 2. It's lines of therapy, one versus two to three, and whether the CDH6 expression is greater than or equal to 75% or less than 75%.

And the phase 2 was basically dose optimization. They were randomized to three different doses: 4.8 mg/kg, 5.6 mg/kg, or 6.4 mg/kg. And the primary endpoint was ORR per BICR, with multiple key secondary endpoints. And the phase 3 is R-DXd at the recommended phase 3 dose, which I'm going to show you is 5.6, versus treatment physician's choice, which is basically weekly paclitaxel, topotecan, or PLD.

And these are the baseline characteristics. You can see, basically, this was presented by Dr. Ray-Coquard at ESMO. We did in the US enroll in the phase 2 extension, but this is the data from the dose optimization. So this included 107 patients, the majority of whom were diagnosed with ovarian cancer. They had pretty good performance status. You can see the majority of them had had bevacizumab 83%, PARP inhibitor 70%. That fits with a different European label as far as PARPs, I think, than the United States. And only a couple of patients had had MIRV, which also fits with where this cohort enrolled, because even though MIRV has been approved, it's not available widely all over the world yet.

And you can see that the last platinum-free interval, less than 3 months in 44%, and 3 to 6 months in 56%. And you can see any positivity, 94% of these patients were positive for CDH6 expression, and for most of them were more than 75%.

And this is the results based on the doses. So what we decided, and I'll show you also with the toxicity, is that 5.6 was the recommended phase 3 dose. It really balanced well, response, so we didn't really lose any efficacy, but it is a better toxicity profile when I show you that data. So we're looking at about a 50% response rate for 5.6. It was a little bit higher in the 6.4, 57%. We did have two CRs, and they both happened in the 5.6, and there was actually one in the 4.8. And disease control rate in the 5.6 was 80%.

And basically, what you see is that it's a very rapid response, so that you're seeing responses at the first CT scan, which was basically at 6 weeks, two cycles.

And this is our waterfall plot. I mean, it's a beautiful waterfall plot, right? You want to get your patients on drugs that are active. And so I guess to go back to your question that you asked me during the panel discussion. I mean, we're going to be having control arms of 50% response rate in the near future, right? Once some of these ADCs with topo-I payloads hit market. So very nice waterfall.

And I think another key thing is that obviously for mirvetuximab, right, we see a difference in response rates depending on how much FOLR is expressed, and it's only FDA approved if you're FOLR high. Now, we do have NCCN guidelines that say you can give MIRV with BEV, as long as the FOLR is 25% or higher. In this particular trial with CDH6, basically it didn't really matter what your CDH 6 expression level was. We did see across-the-board responses. And that kind of fits with what we see with T-DXd, right? Like, you can see some responses even when you have low expression of HER2. I think that just talks to the bystander effects of these drugs.

And this is why we went with the 5.6. It's really the tolerability. It really balances safety. So if you look here as far as drug discontinuation, it was much lower in the 5.6 than 6.4, and same thing with dose reduction and dose delays. And in addition, ILD; we're again aware of this as a problem with a lot of ADCs. T-DXd has pneumonitis, so we've learned a lot from that. And in the 5.6 we did not have any grade 3 or higher ILD, and only one patient, 2.8%, had ILD. So this was definitely the thing that we felt was safest to move forward. And so we're moving forward 5.6.

As far as the most common treatment-emergent adverse events, not surprising. Again, we know that DXd is highly emetogenic, and so

you have to be a little bit aggressive about nausea management. So we do recommend triple antiemetics. And then it's no surprise that there's going to be myelosuppression with a topo-I payload. You're going to see some fatigue, et cetera, but I would say overall pretty manageable as far as side effects go.

And we already have talked about—Dr. Campos went over very nicely how to manage pneumonitis with T-DXd, so it's going to be the same basically for R-DXd. If you see ground-glass opacities on your CAT scan, which I live in Oklahoma most of the year. There's a lot of wind. I have patients that get CAT scans who are on no drugs, who have ground-glass opacities, so it can be a little bit of a challenge, right, to decide who has pneumonitis, who doesn't. And that's where like, you need to have a good friend that's a pulmonologist to say, can you look at this, are you worried or not? But if there is any question of whether or not the patient has pneumonitis, you should hold the drug. And I will tell you, even for grade 1, I do usually start steroids, mostly because I want to get it resolved as fast as possible so I can resume, because quite frankly, it's very rare to get the findings on the CT gone in 28 days. Like, they just don't go away. And for when you're talking about a grade 1 pneumonitis, it's findings on a CT scan. Those ground-glass opacities are there for at least, usually in my experience, 28 days. So I'm just trying to get them to resolve as fast as possible so I can resume a drug that's helping my patient.

And this is the study design of the phase 3. I've already kind of told you that, but now we're up to one to four priors. There's no biopsy required. It is R-DXd at 5.6 mg/kg every 3 weeks versus physician's choice chemotherapy: weekly paclitaxel, topotecan, or PLD. You can see the stratification factors with the primary endpoint of PFS by BICR, and we will be assessing OS as well. And it's actively recruiting, so please, if you have a patient, send them. We want to get these patients on active therapy.

And also I will point out that R-DXd has been granted Breakthrough Therapy, I believe, as of December by the FDA, and it was for CDH6-expressing PROC, which is only defined as 1%. So again, in our trial it was 94% of those patients were expressing, who had received prior bevacizumab or were ineligible for bevacizumab, and that's because that's how we had done the phase 2 part.

Chapter 4

Dr. Richardson:
And now that brings me to CUSP06. This was the first-in-human phase 1a and 1b dose-escalation expansion study in platinum-refractory resistant ovary cancer. They also enrolled some renal cell carcinoma and other advanced CDH6-positive solid tumors.

This is the publicly available data. ECOG had to be PS 0 or 1, and pre-screening for CDH6 expression was required for those patients with solid tumors, but not for ovarian cancer or renal cell cancer.

And you can see the dose escalation. After they went up to 5.6, they came down to 4, and then intermediate dose of 3.6, and then expanded 4 and 4.4 mg/kg with G-CSF.

And these were the baseline characteristics. This comprised 37 patients, the majority of whom were ovary cancer patients. And you can see these patients were heavily pre-treated with median prior lines of four but range from one to nine. And the majority of these were platinum resistant. You can see they had all had prior platinum taxane, about 77% had prior BEV, and a little bit more patients in this trial had had prior MIRV, 23%.

And we did see durable clinical benefit across the doses. The arrows show the patients that were still ongoing but you can see some patients were on for a long time. Six patients with PROC and one patient with renal cell received CUSP06 for more than 6 months, and three patients were approaching a year when this data cut-off occurred.

And this is the waterfall plot. Overall, in high-grade serous ovary cancer, the response rate was 36%, but when we look at the G-CSF cohorts, which were those higher doses of four and 4.4, the response rate was 50%. Again, these are kind of small numbers. This is very early data.

And safety, again, not really surprising, but you do see myelosuppression. You can see that neutropenia. But when we look in the patients who got prophylactic G-CSF, there were significantly reduced grade 3 neutropenia. It was 16% compared to 35% before the G-CSF had been added.

But for drug discontinuation for AEs it was only 8%, so that's very reassuring that we can manage the side effects and keep patients on trial. There were about 1/3 needed to have dose delay, and 24% required a dose reduction. There were two grade 5 events. One was a multi-organ failure, which was unrelated to the drug, and there was a febrile neutropenia at 5.6 mg/kg, which was deemed drug related. There are two cases of pneumonitis. One was a grade 1 and one was a grade 2.

Chapter 5

Dr. Coleman:
We didn't really get into this, but maybe each of you kind of tell me, when we talk about—I heard you say platinum refractory, I heard you say platinum resistant. We defined it differently. Tell us, what do we mean when we say platinum-resistant ovarian cancer?

Dr. Campos:
It can be anything, and then some. You know what I mean? Some people feel as though platinum refractory is basically 3 months, and then others feel as though it's probably on therapy. If you progress while on therapy. I've always known it to be within 3 months, but this is variable. Yeah. How about you?

Dr. Coleman:
Yeah, what about you?

Dr. Richardson:
I mean, I think per the trials, they're defining it. Most of the trials are now defining platinum refractory as recurring within 3 months of last platinum, but I was always traditionally taught that you had to recur on platinum or within a month of ending your upfront platinum, by the way. Platinum refractory was never a thing in subsequent lines of therapy, but now you'll see that those terms are used quite frequently. Platinum refractory, but they're on second or third line platinum, and I'm like, well, everybody should really get that if they're platinum sensitive. We should be forcing patients to progress on platinum before we put them on something else. Right?

Dr. Coleman:
And I think that's material to why the investigator choice chemotherapy arms are structured the way they are as physician choice. You don't see platinum in there because the anticipated response to platinum in patients that we are selecting for this trial would be almost unethical because they progressed on it.

So, but I think that the terminology is variable, and so just for those of you who are in this, are seeing these types of patients, we used to say there is this 6-month magical date that happens that patients magically become platinum sensitive after 6 months, and I always go back to the story—this true story—that when we were running a series of screening trials within the NRG at GOG at the time, we had a queue of phase 2 trials that essentially were plug and play. It was the same statistical design, same eligibility, but you just put in a new compound, and then we used the same decision rules for go/no-go. Well, the cut-off for that was 6 months or 183 days, so I had a patient who came in who was right before that window on Thursday, and so she would have been eligible for trial, but her scan was out of window, so I had to repeat it, and she couldn't get it done until Monday when she became magically platinum sensitive, and I was unable to go on the trial.

So yeah, just use some judgment on that, but all the trials essentially will have to have some criteria for what's considered platinum resistant or platinum refractory, as you mentioned.

I know we only have one second, but I have one more question. So topotecan has been around a long time, right? It was FDA approved, right?

Dr. Richardson:
A long time ago.

Dr. Coleman:
Yeah, and now you tell me it's not active, so why are we seeing activity with a topo-I isomerase inhibitor as an ADC, but it was no longer active as a non-ADC?

Dr. Richardson:
Yeah, I wish I knew the answer to that, but I do think that these drugs, these payloads are far more potent, and I think truthfully, like topotecan is, the way that it's more active is day 1 through 5 every 21 days, and it's incredibly myelosuppressive, and no patient wants to get day 1 through 5 chemotherapy if they have some other option, right? So I think from that reason, like most people then get topotecan, because usually when you have topo as the control arm it's investigator choice, also day 1 through 5 or weekly, and everybody chooses weekly, and I don't think weekly topo, as a dose that we use, is active, and I think that it gets so myelosuppressive they get dose reduced, and they're not getting any activity, whereas an ADC, especially a good ADC that has good chemistry, is able to deliver a lot more payload, which actually is killing the cancer.

Chapter 6

Dr. Coleman:
Alright, so I'm going to talk a little bit about immunotherapy in the PD-L1-positive platinum-resistant ovarian cancer. I called it hype or hope, and I hope you'll see why as I go through this.

So, we've known for quite a long time about this idea of immune education of the tumor microenvironment. There's a priming phase governed by CTLA4 and a number of other checkpoints, and then there's an effector phase guided by the PD-1 and PD-L1 as its targets for immunotherapy. But we know that in the heterogeneous environment of ovarian cancer, we have this issue. You can see this T cell going after one cancer cell but leaving the other one completely alone. And so this is the heterogeneity that we deal with in ovarian cancer. We believe that some of the responses to this has to do with the clonal expansion of ovarian cancer, which in most cases, especially in resistant disease, is a expansion of subclonal populations. So we do see this in kind of the tumor microenvironment.

But we've known for a long time that there are immune cells in the tumor microenvironment. This is a paper that's now more than 20 years old from George Coukos' lab that showed that there were intratumoral T cells t that were present, and when they were present in these tumors, they had a better survival outcome, both for progression-free and for overall survival.

And so because of that, and of course all of the impressive data that was emerging across multiple different tumor types, there was a rapid adoption of immunotherapy into ovarian cancers. Like, we threw everything at it because we felt that, why not? It seemed to be working in every other disease.

I think we did this a little prematurely, and you can see that our single-arm trials of different immune checkpoint inhibitors of both CTLA4 and PD-1 and PD-L1 inhibitors basically are very modest in response, most of them being around 15% or less.

But there were a few patients that had long-term outcomes. And because of that, there was a rapid adoption to move this not only in the platinum- resistant domain, we did it in the platinum-sensitive recurrent domain and in the frontline domain. We went all in. And these are just some examples in the platinum-resistant. All of these phase 3 trials are negative, and in fact, there's some evidence that these may have been actually harmful, that we had adverse events and overall survival which was less than anticipated. And once again, you can see that our response rates were quite low.

So it was really about, okay, listen, are we just beating a dead horse? Why are we going to go up and do this again? Well, we thought it was still moving, so we launched B96. Like, okay, listen, we just think we have a better situation with a better handle. This is an unmet medical need area. So we designed this phase 3 trial that was going to combine our best chemotherapy backbone at the time, which was paclitaxel given weekly, and we were going to allow for bevacizumab. Now, this is a global trial, so the bevacizumab was actually provided, so there was no discrimination on the availability of bevacizumab. If you liked it, you could use it. If you didn't like it, you didn't have to. So essentially it was in a +1 design with pembrolizumab being the +1.

And you can see we did this in patients with confirmed recurrent ovarian cancer who had either one or two prior lines of treatment and at least one platinum-based therapy. We did allow for prior PD-1, PD-L1, and of course PARP and bevacizumab were permitted according to the label.

And, as I mentioned in the last discussion, the radiological evidence of progression needed to be within 6 months in this particular trial. In this particular trial, patients who had platinum-refractory disease, which was defined as progression during first-line therapy only, those patients were not allowed. They were not eligible, and they had to have good performance status.

And the primary endpoint of this trial was progression-free survival, but it was balanced on the expression of PD-L1. And so the analysis and the algorithm was to look at this in the PD-L1-positive cohorts, the intent-to-treat cohorts, and to do that both for PFS and for overall survival.

So the four analytical subgroups of this particular trial, so all of them had alpha allocated to it, so they were studied with the intent to demonstrate statistical superiority.

Okay, so this is the baseline characteristics. So, typical ovarian cancer patient population, actually a decent representation of Asians, which we don't see frequently in a lot of trials. In this particular trial, we had a good global representation. You can see that a little bit higher than we expected. That's about over 70% of the patients in the study were PD-L1-positive, based on the 22C3 assay that is well known for pembrolizumab. You can see that most of these patients presented with advanced-stage disease.

Bevacizumab use in the frontline setting was higher than we normally see at 73%, so it represents a decently treated cohort of patients that could have had that in the frontline or that could have had it in recurrence. So platinum-sensitive recurrent patients globally is an opportunity to use bevacizumab because there's usually only one opportunity to use it. In the US, we can obviously use it more than one time.

The number of lines of therapy was two. Two lines of therapy was over 60% of the cohort, and you can see the other highlighted platinum-free interval. Most of these patients were relatively short duration between their last platinum and their inclusion on the trial.

So this was the very first analysis. So the way that this trial was set up was to look at an interim analysis, and in the super tiny print on the third line down there in the bottom, you can say is the observed p-value crossed the prespecified nominal boundary at 0.0166.

So frequently trials will do this when they have a high informative fraction, meaning that if they had not made this particular cut-point, they would have subtracted this small degree of alpha from the total amount of alpha that was applied to the analysis, which was 0.05 two-sided. So they looked at this early on, but you can see that the informative fraction here is 88%. And what that means is that when we design these trials, we say we have to hit a certain number of events to call the trial fully mature—so fully, that we can evaluate. So this is the proportion of those events that they were targeting that they actually hit.

So while it's an interim analysis, it's really pretty far along the line, and this is one of the issues we see when we're looking at overall survival and progression-free survival at the same time. So waiting for those overall survival events to occur allows the accumulation of progression events, and that's why this is so high.

So you can see it did meet it. So this is an analytical endpoint at the first interim analysis for progression-free survival in the CPS greater than 1. So because of that, the alpha was all passed—the 0.05 was passed—over to the ITT population, and you can see that the p-value here is less than 0.001. And again, in the third line in the middle of that sentence, the nominal boundary for here was 0.0023. So this was also positive. So positive for PD-L1-positive, positive for ITT. Again, highly mature data.

This is the subgroup evaluation in the study. You can see that the appropriate way to read a subgroup analysis is to look at the dark gray vertical bar that's back there. And what you're looking for are subgroups that are wholly outside of that bar, meaning that the point estimate and the 95% confidence interval are outside. If they are, it raises the hypothesis that one of those subgroups may be different. Doesn't say it is, it says it might be. So you can see basically every single one of the subgroups was within that 95% confidence interval of the primary study result.

And so what we appropriately conclude is that the events were stable across all of these specific subgroups. That's how we make that analysis. So this was in the CPS greater than 1 and in the intent-to-treat population. So both of them, you can see, very consistent.

And you can see that with members I mentioned, bevacizumab was provided. So about 75% of the patients in both of these populations chose to use bevacizumab. So this would have been a pac/BEV versus pac/BEV/pembro comparison. So going back to what our expectations are for the control arm, this is probably among the most active control-arm regimens that we would have ever compared against, which is why I asked that question earlier.

Chapter 7

Dr. Coleman:
Okay, so because the IA1 was positive, this was mostly just informative. Here now, this is the second interim analysis. There's no p-value here because it was already assessed, so we don't need to know. But frequently what we'll do on studies when we do a later follow-up before the final is to just to see how the tail of the censored events fared out. And so you can see now the curves have very little tick marks because events have happened, and for progression so very, very consistent with the primary. We would not expect this to change the hazard ratio point estimate.

But because the interim analysis at IA1 for overall survival was not met, we waited until this release at ESMO last year, which was the overall survival at Interim Analysis Two, and you can see the informative fraction is almost 100%, so it's 90% of the available information that was needed to do a final analysis was already available at this point in time.

And you can see now, because the curves don't have—except for the tail of this curve are very stable through, obviously, through about 70% of the information, and it, of course, was positive at 0.0053, hazard ratio 0.76. And again, if you go down to that third line midway through, you can see the nominal *P*-value that it needed to beat at this analysis was 0.0083, so it did. So it was then alpha passed now for the fourth analysis in the ITT population, and that was also positive.

These are the subgroups in that analysis for overall survival in the CPS greater than 1 cohort. Again, across prior exposure and age, platinum-free interval, all consistent right through the analysis for overall survival. And then we also—oh, I guess I don't have the ITT in here. So, we were also interested in looking at objective responses. I mentioned we were looking at our most active control arm, so this is weekly pac, and 3/4 of the patients were getting BEV with it. So you can see that in the control arm, it's a 46% response rate; 7.8% of these patients had a complete response rate to weekly pac plus or minus BEV, mostly BEV. And you can see that in the duration of response on the right-hand side, what those values were.

So this was improved slightly with the addition of pembrolizumab, but you can see the biggest effect was on the duration of the response. So whatever was happening in the tumor microenvironment was impacted with maintaining response and delaying progression with the use of the immune checkpoint inhibitor. And this is in the second interim analysis. Again, of course very similar to what I just shared with you at the first interim analysis.

So, adverse events. Obviously, now we're looking at a two- to three-drug regimen versus a one- to two-drug regimen, and you can see that adverse events were frequently reported, that either grade 3 events were also frequently reported across the board. Fortunately, the number of adverse events leading to death were very low, and certainly the ones that led to treatment discontinuation were slightly higher in the two- to three-arm, the pembro arm versus the placebo arm, which would have been pac plus or minus BEV. But the immune-related adverse events you can see were fortunately very low.

And I think what's happening, and maybe we can talk about this in discussion, is like how comfortable we're getting with the use of pembro across our portfolio, because now we're using it in all three of the diseases that we commonly treat.

So this is the breakdown of those adverse events at the second interim analysis.

This is a very mature safety report showing the outcomes among the specific elements that were more than 20% in either arm. You can see the grade and the high grade are the lighter-colored boxes at the top there. What we see is consistency with the taxane base, which was consistent in both arms, some of the epistaxis related to the bevacizumab use, and then, of course, here the immune-related adverse events, and these are again very much what like we expect. I don't like to say there's no new safety signals, because I think that undermines the safety, but what we do see is that the safety profile is consistent with what we've seen in the past.

The frequency seems to be consistent with what we expect to see with the use of pembro in this patient population of platinum-resistant ovarian cancer who have had prior lines of treatment. Fortunately, it's very low, and again, like I said, it's low and anticipated.

So on February 10th we got this information from the FDA that this regimen was then approved. It was approved in the CPS greater than 1.

Now, what I didn't share with you, because it wasn't shared widely, was what was the results in the CPS less than 1, which would be the complement, obviously, to the CPS greater than 1 in the ITT population. But there was very close between the CPS greater than 1 and the ITT with respect to those point estimates. So we would expect that in that population there would have been a similar outcome.

However, the FDA, using this companion diagnostic, the 22C3, as I mentioned, which is used broadly across indications for pembrolizumab, that's what got its indication. And of course this was also aligned with the bevacizumab label, which is one to two prior systemic therapy. So CPS greater than 1, one to two prior lines of therapy.

So ovarian cancer is, in general, is considered a cold tumor. A lot of this - Although our recent experience has been maybe we're getting better at identifying patients who might benefit, this was an eye-opening trial for us, given the prior history. We really have not seen a positive trial for immunotherapy in ovarian cancer. I know we've looked at some experience with dual CTLA4/PD-L1 or PD-1 treatment, as was one of the choices, but none of that has moved forward into further development.

We think this might be due to the subclonal population that is prevalent in most of recurrent platinum-resistant ovarian cancer, but there are patients who have clonal expansion, and those patients seem to be sensitive to this line of therapy. So I think much more work needs to be done to continue to identify who these people are that are responding so well, and then ultimately safety will come with greater experience.

Chapter 8

Dr. Campos:
Alright, so oldies and goodies, we'll take you back. We'll close this up on some data that we've all pretty much known, but we certainly can review, and that's what first-line therapy is, maintenance therapy for patients that are BRCA-positive or HRD-positive.

These are the NCCN Guidelines recommendations for PARP inhibitors as frontline for maintenance therapy. In this particular case, it says stages II to III in ovarian cancer. Now, the NCCN Guidelines are listed here, and you and I can both read them. They are slightly more liberal than that of the FDA approvals, and we'll talk a little bit about that.

So, just basically, if the patient is in a complete or partial response and has either a germline or somatic mutation, and if BEV was not used during the primary chemotherapy, several PARP inhibitors could be used, whether it be olaparib, niraparib, or rucaparib. And it's also, in terms of stage II disease, because you'll see through the studies that I'll present that the studies were done with stage III and stage IV, you can observe for stage II.

But if BEV was used during the primary therapy, then olaparib plus bevacizumab, or niraparib plus BEV if unable to tolerate olaparib can be used, or simply you could use olaparib, niraparib, or rucaparib. Now, if you're BRCA wild-type and you're HRD-positive, then if you've used BEV, then you certainly could use BEV. If BEV was not used, you could use a PARP inhibitor, olaparib, niraparib, or rucaparib, or observe if they're in complete remission. If you have used BEV before, you can lean on the PAOLA data, which we'll talk about, and we can use olaparib and BEV, or niraparib plus BEV if unable to tolerate the olaparib, or bevacizumab, or olaparib. But if you're BRCA wild-type and you're HRD-negative, if you've used BEV during the course of your therapy, you could continue BEV, or you simply can observe. You'll see that this is a little bit more liberal than that of the FDA requirements.

So let's take us back and look at the SOLO-1 trial. And the SOLO-1 trial was olaparib as maintenance, first-line maintenance therapy in patients with advanced ovarian cancer in a complete or partial response after platinum therapy. It was randomized, it was double-blinded, it was placebo-controlled. So these folks had FIGO stage III or IV high-grade serous or endometrioid, and they had to have a BRCA mutation. They were stratified by response to platinum-based chemotherapy and then randomized in a 2:1 fashion to either olaparib or placebo.

The primary endpoint of SOLO-1 was progression-free survival, and secondary endpoints being PFS2 and overall survival. Patients stayed on olaparib for 2 years if they were NED.

These are the results of 5 years of follow-up. This is progression-free survival presented by Dr. Banerjee and colleagues. And you can see that it's a beautiful piece of art here. Okay. Those curves separate beautifully, okay? And they separate very early on. You're looking at a median progression-free survival of 56 months with olaparib. Compare that and contrast that to that of 13 months, a

difference of 42.2, and a hazard ratio of 0.33, so highly statistically significant.

When Dr. DiSilvestro looked at this in terms of a 7-year follow-up for overall survival, the curves still continued to separate. You'll see that the median overall survival with the olaparib was not reached. The placebo was 75.2 months, a hazard ratio of 0.55, statistically significant.

And it's quite important and not necessarily surprising that more patients in the placebo group versus the olaparib group received subsequent PARP therapy, about 44%, which certainly could affect survival.

So that's the SOLO-1 data, and that is specifically that of BRCA mutation carriers, I should say.

Now the PAOLA trial is a bit different. This was maintenance therapy with olaparib plus BEV in advanced-stage ovarian cancer. Similar eligibility criteria, phase 3 trial, FIGO stage III to IV, high-grade serous and endometrioid. Patients had to be either in a partial response or a complete response after chemotherapy, but the kicker here is that they would have had to have greater than or equal to 3 cycles of BEV. HRD testing was also mandatory.

Patients were randomized once again in a 2:1 fashion to olaparib plus BEV or placebo plus BEV. And olaparib or placebo was continued for 2 years or until progression or unacceptable toxicity, while BEV was continued up to about 15 months in total. And when you look at the patient population as a whole, about 48% of the patient population was HRD-positive, 29% carried a BRCA mutation, and 19% of patients were HRD-positive but BRCA-negative. The primary endpoint of the PAOLA study was progression-free survival, and the secondary endpoints were PFS2 and overall survival.

And once again, if you look at the 5-year progression-free survival in the HRD-positive subgroup, okay, again in favor of the olaparib plus the BEV arm when compared to placebo plus BEV, you're looking at a median progression-free survival of 46 months versus 17 months with the placebo and a 5-year progression-free survival rate of 46% versus 19.2%. This was statistically significant.

The study was criticized on one point, is that there is not an olaparib-only-containing arm, so the magnitude of benefit of BEV was very hard to deduce in this particular study, but this was the progression-free survival in the HRD group as a whole.

Now, Dr. Lorusso and colleagues looked at the PAOLA data and looked at the 5-year overall survival data in high-risk patients. So how did they define a high-risk patient? These were patients that had stage III disease that had undergone upfront surgery and they had residual disease, or had received neoadjuvant chemotherapy, or had basically stage IV disease.

But you can see in the PAOLA trial, in the higher-risk individual group, that there was an advantage to olaparib plus BEV versus that of placebo. You're looking at a 5-year overall survival rate of 55 versus 42% and a median overall survival of 67 months with olaparib and BEV versus that of 54.

Now, when the investigators looked at a lower-risk group—in this particular case a lower-risk group were patients with stage III disease who had undergone upfront surgery and had complete resection—you're looking at a median overall survival that was not reached in either group, but a 5-year overall survival rate of 88% versus 61%.

So basically, olaparib plus BEV was helpful both in the higher-risk group as well as in a lower-risk group. So that's the PAOLA study.

Lastly, the PRIMA study was a study that used niraparib versus placebo in patients with ovarian cancer at high risk. This was a bit of a different trial in terms of the design. This was indeed, however, a randomized double-blind, placebo-controlled trial. Patients were stratified either by neoadjuvant therapy, yes or no, best response to first platinum, and tissue HRD testing, so either deficient versus proficient or not determined.

Now, these individuals had newly diagnosed ovarian cancer but could have had anywhere between six to nine cycles of chemotherapy. Neoadjuvant chemotherapy was allowed. They were randomized in a 2:1 fashion to niraparib at 300 mg qd. However, toxicity was seen and because of patient weights, that could have been decreased to 200 mg qd if the patient's weight was less than 77 kilos or if their platelet count was less than 150,000, or patients were randomized to that of placebo. In this particular case, niraparib was given for 3 years. Primary endpoint was progression-free survival in patients with HRD and the overall population, and secondary endpoints was

overall survival and progression-free survival 2.

And these are the updated progression-free survival and the final overall survival in the HRD population. You can see in the first graph that the curves separate very nicely. You're looking at a median progression-free survival of 24.5 months versus 11.2, statistically significant.

However, to most of our surprise, when they looked at the overall survival, you'll see that those curves are completely superimposable on each other. If you look at the 3-year overall survival rate, the 4-year overall survival rate, or even the 5-year, basically there was no improvement in overall survival.

And this led lots of us to just kind of scratch our heads as to why—why such a very prominent progression-free survival and yet overall survival was not positive. There have been many speculations. About 48% of patients who were originally in the placebo arm eventually got a PARP inhibitor. Was it the toxicity of the PARP inhibitor that led to dose delays? Was it dose intensity? I don't think we all know, but perhaps basically it's probably multifactorial.

When the authors looked at the HRP population, once again, you can see a statistically significant benefit in terms of the niraparib. You're looking at about a 3-month difference in median progression-free survival. But once again, if one looks at the overall survival, the overall survival in the HRP is not statistically significant.

So this is my lovely little cheat sheet, which is a lot more rigid than that of the NCCN Guidelines. This is the current FDA approvals for the PARP inhibitors. Olaparib is approved in BRCA mutation. BRCA mutations, you can give olaparib and BEV. You can give niraparib in monotherapy. In the HRP, there is no indication for any PARP. In the HRD-positive BRCA wild-type, you're looking at olaparib and BEV, and also niraparib in monotherapy.

It's important to note some of the toxicities of these PARP inhibitors. There's some commonality, but there's also some differences. There's more hematological toxicity with niraparib, clearly more thrombocytopenic, more discontinuation rate. Hypertension was more prevalent in the bevacizumab-containing arm, and you know that, which is highlighted here in the little purple box, AML and MDS.

Although we pay a lot of attention to this, and rightfully so, it is still quite low among all of our patient populations.

So, to answer the last question, some very exciting trials are coming up. These are phase 3 trials of ADCs as first-line maintenance therapy in ovarian cancer.

One trial is called the TroFuse study, which is using saci-TMT, and this is a phase 3 maintenance study with or without BEV in newly diagnosed advanced non-HRD-positive ovarian cancer following first-line therapy.

And then trastuzumab DXd in the DESTINY-Ovarian01 trial is again a phase 3 study evaluating trastuzumab DXd plus BEV versus BEV alone as maintenance therapy in HER2/neu-expressing advanced high-grade epithelial cancer following first-line bevacizumab and chemotherapy.

So it's very exciting trials that are coming our way that certainly will bridge what we've already learned in the past.

Chapter 9

Dr. Coleman:
Let me ask Deb. So a couple of you wrote in some questions about circulating biomarkers, one on ctDNA, one on CTCs, circulating tumor cells. Tell us a little bit about what you—how do you see that being used in ovarian cancer?

Dr. Richardson:
Yeah, I mean, I think that's a great question. What I wonder is, could we use it to de-escalate therapy ? So, for example, we don't know how long to use PARP maintenance for in the front line. We're doing a trial of 1 versus 2 years of PARP, but I think that would be a great time to use circulating tumor DNA and see if that would help us figure out who needs longer and who needs shorter and other maintenance therapies as well.

So, I personally think right now, like de-escalation might be our best bet, but it may also help us , like in the gray zone, right, you see something, and you're like, well, is this post-surgical changes, is this disease, you can't quite tell. I think it helps sometimes clinically, like, decide, okay, you do have circulating tumor DNA, and it is going up, so this is, in fact, disease, and not scar tissue on your CAT scan.

So that's mostly how I'm using it in my practice right now, because I think we just don't know how to optimally use it, but I think we're going to learn a lot in the next few years.

Dr. Coleman:
Yeah. How about you?

Dr. Campos:
I think that I've had many conversations with ctDNA, and I often say to them, we can order it. What are we going to do with it? Okay, I don't know what we're going to do with it. There's no evidence of disease clinically, there's no evidence radiographically. You're going to have this level, and you're going to worry about that.

I will tell you, I've ordered it once this past week where I had this 87-year-old woman who came to me for a second consult, who basically had chemotherapy. She has a marker that's 200, keeps climbing, nothing on visible examination. So I said, alright, get a ctDNA, see what it is, what I mean. And I'm not so sure she wants any therapy thereafter, but I thought perhaps that could be informative in that regard, but I think it's part of a clinical trial. Great to de-escalate therapy. Absolutely,

Dr. Coleman:
Yeah, this topic has come up before, first in surveillance. And the question is, if you have a patient who has a biomarker that's positive, will it actually make a difference if you will find out that they'll have disease 3 months later. Is the 3 months helping you? Yeah, so .

Dr. Richardson:
Not so far. I mean, but maybe with new drugs. I mean, that's where I think it's hard to know, right? But, like, we know that from CA-125, like it will precede the finding on CT by 3 months. So I have no doubt that we can make that earlier, but unless we can change the outcome of how long somebody's going to live or how well they're going to live, I don't want to just be giving therapy because somebody has some circulating tumor DNA and no symptoms and no disease on scans.

Dr. Coleman:
Okay, yeah.

Dr. Campos:
Not to mention the anxiety that it caused.

Dr. Coleman:
Yeah, it does cause an anxiety, that's for sure. Yeah.

So there's one question here about, I guess, more around functional status and the use of immunotherapy in our practices. What impact does that play?

Dr. Campos:
Yeah, it's either it does or does not. I think we've all seen this. We've all utilized pembrolizumab in multiple disciplines, and some patients don't even blink at pembrolizumab, and yet others really do have issues, and you really do have to pay attention to even though now we've used it a lot.

And it can. I mean, it's interesting because in one of your slides you showed adrenal insufficiency, okay, and you don't see that very often, and you have to go fishing for this, when you actually do have figured that that may be the case.

But I think for the most part people do very, very well, unless you, of course, have symptoms, like hypothyroidism for example. You

have to be mindful of the fact that you have to test the TSH at start and periodically thereafter. Usually, it's my pharmacist who reminds me of that. But usually it's the fatigue. I think the fatigue is actually perhaps the most relevant element there.

Dr. Coleman:
Yeah, I was going to ask about that, because I do think that that's one of our more difficult side effects to treat. And yeah, and the anemia and fatigue, because it's not easy to manage, and it doesn't have to be very high grade to be completely impactful to activities of daily living.

Dr. Richardson:
I actually do use American ginseng. There is a paper that was published in the *JNCI*, so it's like 1500, I think, mg a day of American ginseng. I have them order it on Amazon. We give them like a little handout. Now, they can't be anticoagulated because that's a contraindication and can increase their bleeding risk, but it does help some of my patients. So.

Dr. Coleman:
Okay, alright, guys, you made it all the way through.

It's been fun to be able to thank you for my two experts here to join me, and it's been fun. Thank you for being here.

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