New Drug Updates in Solid Tumors: PARP Inhibitors in Ovarian Cancer, Immunotherapeutics, and Other Agents

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CHRIS Good evening, everyone and welcome back. I hope you all had a lovely evening and enjoyed that extra hour of sleep. We are going to dive right into day four of the meeting. As a gentle reminder before we begin, please remember to silence your phone.

Also, one thing I wanted to point out, for those of you that use the app, which I'm sure is everyone, the slides right now are not showing up for this. But they will likely by the end of the day. Right now there's a six-page drug overview table that looks really nice, but the slides will go up later.

Our first talk this morning is a BCOP-certified lecture on "New Drug Updates in Solid Tumors: PARP Inhibitors in Ovarian Cancer, Immunotherapeutics, and Other Agents." Please join me in welcoming Dr. Ed Li from the University of New England College of Pharmacy.

EDWARD

Today I'll be talking about the new drugs for solid tumors, especially focusing on four different areas, PARP inhibitors being one of the big ones; we have three in this area. We'll talk about IOs because when do we never talk about IOs anymore? And other agents as well. Today's learning objectives: I'm going to talk about the pharmacology indications of these medications that's approved pretty much from last year at this time until about 3 or 4 weeks ago when the slides were due.

And we'll also talk about the pivotal clinical trial data considered by the FDA when approving these oncologics. What I'm going for here is breath, not depth, because you're going to see how many new drugs were approved in the last year. And you can see just how many there are, and we won't be able to get into those in-depth because of time. But we'll talk about the signs and symptoms of severe or life-threatening adverse events of these new therapies, and we'll also describe the impact of these drugs on advanced practice.

Here are my financial disclosures. And with that, I'd like to start with a little bit of history. I'm a bloviating professor nowadays, so I need to start with history lessons here. Just to get a land-to-land of looking forward into the future, we need to know where we are. And we know that since the 1940s, we know that chemotherapy has been used and tested in our patients, and you can see the timeline of starting off with nitrogen mustard through developing that further and having combination chemotherapy. And then, the commercialization of oncology agents really started in the 1990s, specifically with paclitaxel; that was probably considered to be our first commercialized chemotherapy product in the United States at least.

And after the turn of the century, we had targeted therapies, specifically trastuzumab, imatinib. Those were really important. And we started talking about targeted therapies as being much, much more important starting in 2000. And so, this continues being today, continues with the theme of targeted therapies for the treatment of cancer. And at the same time, we know that depending on the type of product that's approved, it changes our practice paradigm. So, again, in the

1960s or so, we started having these agents approved then and we can start using them as clinical practitioners.

Once we had more and more chemotherapy agents, depending on the toxicity profile of the agent, we actually had to mitigate those toxicities. Remember cisplatin, one of the major adverse effects is nausea and vomiting; you deal with that all the time. We really started talking a lot about the management of chemotherapy-induced nausea and vomiting with combination chemotherapy; that's when we really started talking about myelosuppression and managing febrile neutropenia. And that's where supportive care management was really, really important in terms of myeloid growth factors and preventing febrile neutropenia.

We started talking about pharmacogenomics a lot with the targeted therapy, and we really start to understand *EGFR* mutations and all sorts of other mutations. We really started talking about pharmacogenomics and we're going to continue to talk about pharmacogenomics in the future. There were lots of sessions on targeted therapies at this meeting, so you know the importance of that.

And starting in 2010 or so, probably 2008/2009 is when the first save hit, but between 2011 and 2014, we had 18 new just oral oncology agents approved. So, now the big discussion right now that I'm sure you're working through is how do you get your patients to adhere to these medications? How do we implement the monitoring plans in our population so that the population of patients who you're taking care of has better outcomes?

We're also talking about immune-oncology as well and the challenges with immune-oncology. We didn't really have good immune-oncology agents pretty much until 2010 or so when the first autologous cellular therapies, sipuleucel-T, was approved, so that really opened up the cancer treatment paradigm to IOs. And we really started talking about adverse events, severe immune-related adverse events, with the first checkpoint inhibitor approved—that was ipilimumab—and then now we're talking about—we have a serious discussion about the concept of pseudoprogression and how do we monitor progression with IOs, right? So, using the immune-related response criteria instead of the traditional RECIST criteria to evaluate the responses to these PD-1 inhibitors.

And so, now we're in the era of cost containment of IOs and we're also talking about invasive monitoring for specific products like CAR T cells and their impact on cytokine release syndrome. These new products changed the way that we practice and what we have to do. So that's just a little history lesson, just a reminder of the fact that these can really impact us.

The other part of that—I set this up saying that we have these new products that changed the way that we practice, but if you look at the column here with novel mechanisms of action versus established mechanisms, in the last year, we've really only had established mechanisms in place. So, these are what we would consider to be what we call "me-too" types of drugs. And we used to call them me-too before it was #metoo. So these are the therapies that are approved.

I'm not going to talk about olaratumab today. This is a monoclonal antibody for that, it's targeted against the platelet-derived growth factor receptor for soft tissue sarcomas. I don't really have time to talk about that today; this was over a year old. So we're going to focus on the new drugs today that are established mechanisms.

With that I do want to talk about the other regulatory events that are not the new molecular entities that are approved. There were a whole series of regulatory events. A lot of these were changing the accelerated approval over to regulatory approval for some specific agents, like osimertinib and palbociclib; ceritinib, as well, but we also had expanded edifications into urothelial carcinoma. We're going to talk about urothelial carcinoma quite a bit because we had two new IOs approved specifically for urothelial carcinoma.

We also had the MSI-high approval here that was agnostic of tumor type. And so, that's really important as well because in 2018, we're going to have to start talking about this whole issue of genetic abnormalities across various tumors where we have at least one or two products that are probably going to be approved in 2018 that are agnostic of tumor sites.

Then we have these other regulatory events, so we are using other drugs—BRAF inhibitors in non–small cell lung cancer as well, MSI-high, again, specifically with nivolumab in colorectal cancer. We had our very first biosimilar approved for the active treatment of cancer in 2017; that was just a few months ago. So that was bevacizumab-awwb and the indications were pretty much across the board compared to the branded product. The only issue here is that

this won't be available for a number of years because of patent exclusivity and they still have to fight things out in court. So we're not going to see it for a little while.

We also had PD-L1 positivity in gastric cancer as well with pembrolizumab. I do like to see the fact that we have biomarkers when we use IOs; that's really good to help us select out the patients who would actually respond to these agents.

The drugs that I'll be talking about today, the nine drugs that I'll be talking about today, again, continues the theme of oral administration. And you can see the seven out of the 10 are orally administered and they're small molecule drugs—mostly tyrosine kinase inhibitors—but we also have CDK4/6 inhibitors as well. And, also, we have the parental administration specifically with the IO therapies, the PD-L1 inhibitors. And it seems to be a running theme now. That's the parenterally administered products that we have out are IOs versus the other therapies that we have are more orally administered.

And I think this is a really good thing because I think orally administered products—you know, it's great for patient convenience. And I think really the reason why we've been having a lot of these orally administered drugs approved in the marketplace is two-fold: number one, we understand more of the genetic abnormalities in these tumor types; but, two, we now have a mechanism to pay for them. It really hasn't been that long since Medicare Part D got up and running, and now patients actually have some sort of mechanism to pay for it instead of being solely on them in terms of out-of-pocket costs.

I'm going to start off with the PARP inhibitors first, specifically focusing on rucaparib, niraparib, and olaparib. It's interesting, olaparib has been around for a while now—a few years now—about 3 years; the original approval date was in 2014. They changed the formulation over to tablets and got an additional indication as such. So I'm really just going to be talking about the new indication for olaparib in context with the other newly approved PARP inhibitors as well.

Rucaparib is the first one that I'll be talking about, which is approved for monotherapy in patients with *BRCA* mutations and that's associated with advanced ovarian cancer treated with two or more chemotherapies. And, again, olaparib has that same type of indication, but in terms of the new indications, niraparib and olaparib also have this indication for maintenance of recurrent epithelial ovarian cancer. That's in patients who have a complete or partial response to platinum-based chemotherapy, and this is outside of whether or not they have these *BRCA* mutations. And I'll go through the data with that in terms of why that actually is.

Before we get into that, we have to talk about the pharmacology of PARP inhibition. And when olaparib was introduced, we really talked about synthetic lethality. In terms of this being more beneficial for patients who have *BRCA* mutations because they have this loss of homologous recombination. And so, what happens here is you have PARP that essentially is a protein that repairs single-stranded breaks in the DNA. So when you have these breakages in DNA, that's not a good thing; you need a mechanism to repair that. PARP normally repairs those single-strand breaks and everything is fine and dandy there.

But when we have introduced here PARP inhibitors, what happens is that there's an accumulation of double-stranded breaks now. Single-stranded breaks will accumulate into double-stranded breaks and in most normal cells. This is a non-tumor cell, a tumor cell or a normal cell that does not have a *BRCA* mutation. This cell can still repair these double-stranded breaks through a process called homologous recombination, and so the cell can still live on. These normal cells, these non-tumor cells, can still live on even in the setting of PARP inhibitors.

But when you have a *BRCA*-mutated cell like a tumor cell, ovarian cancer cell, they don't have this homologous recombination, there's no repair, and that results in cell death. This is what we call synthetic lethality because it's taking advantage of an issue that the tumor cell has to and we introduce another mechanism that actually causes that death.

This is what we've been talking about with PARP inhibitors for 3 years now, but we have to realize that there are other functions of PARP as well. We've been talking about the issues with DNA repair, but they also regulate transcription and cause, basically growth of tumor cells. They are important in chromosomal stability, they're involved in mitosis, and also cell death as well. There's many, many other functions of PARP, and that's probably why we're talking about the ability for these products to be used outside of whether or not these patients' tumor types have any loss of homologous recombination or BRCA mutations. So that's the rationale behind how that would work.

In terms of the clinical trials, these are the major clinical trials that at least led to the approval of these products. Rucaparib was a phase II trial. This was an

open-label study of rucaparib in patients with recurrent platinum-sensitive disease. This was the ARIEL2 study. The next phase of this is actually looking at three lines of chemotherapy, but the phase that I'll be talking about is actually after one to two lines of chemotherapy. And that was stratified according to how much of the homologous recombination deficiency patients actually had. So if we go back to this slide, there were stratifying patients based off of either this process or some other process that results in homologous recombination and loss of homologous recombination. So we'll take a look at that.

We'll also look at niraparib and olaparib specifically for the maintenance situation. These are patients who have recurrent platinum-sensitive disease. They respond to chemotherapy and then they go on maintenance therapy within 8 weeks after completing their platinum-based chemotherapy.

The first study that I'll be talking about, again, is rucaparib, again, for recurrent disease specifically with the ARIEL2 study. And you can see on the far left-hand column there you have these different stratifications. So you have your *BRCA* mutation–positive patients, but then you also have patients who have wild-type *BRCA,* so they don't have the *BRCA* mutations, but they do exhibit some loss of heterozygosity, which is actually what I was talking about with some loss of homologous recombination as well. So even though these patients don't have *BRCA* mutations, they lose some of their ability for that double-strand repair.

And then you have, also, on the far left are a control group, which is the *BRCA* wild type and LOH low as well. So, clearly, you can see that those patients with *BRCA* mutations had an objective response rate that was high: 80%

progression-free survival. So, actually, if you look at progression-free survival compared to the control group, clearly, it's increased progression-free survival with a hazard ratio of 0.27, which is really, really, really good. We talk about the minimum cutoff of being clinically significant, and that is just bare minimum cutoff of being clinically significant as a hazard ratio of .8. So, .27 is really, really good in terms of a hazard ratio.

The duration of response was pretty long; we had about 9.2 months there. This is the FDA-approved indication here with the *BRCA* mutations. But the issue here now becomes the *BRCA* wild type and a LOH high where you actually still saw some effect. The hazard ratio is 0.62 compared to the control group, but the objective response rate was only 29%, which was still there. It's higher than your control group, but the magnitude of benefit isn't as great as with the *BRCA* mutations. So this is not an FDA-approved indication, and some people are talking about how, perhaps, we could use it for these patients. But really the jury isn't out right now about this patient population and whether or not we would routinely use that in this patient population.

The next PARP inhibitors that we're going to talk about are niraparib and olaparib, specifically, again, for the maintenance. We have niraparib that has a phase III study versus olaparib that has a phase II study. And if you look at niraparib, and they did kind of the same thing, where they looked at *BRCA* mutation–positive patients and then *BRCA* mutation wild type, but they also had this deficiency in their homologous repair. And then you had the control group, which was *BRCA* wild type. And you can actually see in this phase III study the

hazard ratio—remember, this is compared to placebo for maintenance—the hazard ratios were all very, very good across the board across these whole cohorts.

So even though you saw a better benefit in terms of progression-free survival with your *BRCA* mutation–positive patients, those who were wild type also benefited as well. From here, we can conclude that we can use niraparib regardless of the *BRCA* mutation status. And the same thing for olaparib; this was a phase II study, but you also saw that the hazard ratios were pretty much in line with what niraparib had. And so there's going to be more fluctuations here because it's phase II and the precision for evaluating the magnitude of benefit is not going to be as good.

In this phase II study, they looked at and collected overall survival data. Now, we have to take that in stride because the overall survival in a phase II study is not the primary endpoint, so it wasn't statistically designed to detect a difference. Even though this *P* value is less than .05 that we typically look at, that still didn't reach the threshold for statistical significance. We don't really look at overall survival data all that much in a phase II study anyway, even though we do look at it; we tend to look at that as being descriptive in nature.

Even though this looks good, we still have to interpret that with caution as to whether or not that overall survival benefit really is there. So we're going to have more data released, I'm sure, about overall survival in the near future that will give us a little bit more confidence about these products. But right now we can talk about progression-free survival being improved with these products.

So when you line these up side by side in terms of the toxicities, we're talking about fatigue and these general toxicities as being the big issue. Fatigue is pretty much a huge issue across the board with all of these, as is nausea, abdominal pain, and those GI toxicities, diarrhea. We have issues with infections as well; upper respiratory infections, UTIs, headaches, myalgias, and taste disturbances and the like.

And the thing about monitoring for PARP inhibitors—I'm sure a lot of you know that bone marrow suppression is a big issue with olaparib, and that extends out to the other products as well, niraparib and rucaparib. And you can see the percentages there with neutropenia, anemia, and thrombocytopenia; they're all pretty much in line with olaparib. So we can essentially say that this is a class effect.

Increased serum creatinine was a specific issue with rucaparib, as that was markedly higher compared to niraparib and olaparib; so that's something to watch out for. Liver function tests and the increase in liver functions tests was also seen with rucaparib and niraparib as well. Niraparib actually has this interesting toxicity of hypertension. So 20% of patients actually had issues with hypertension, and about 10%, almost 10%, had grade 3 to 4 hypertension. So that's something to really watch out for with niraparib.

If you were to line up the special monitoring in the prescribing information with these products, what would you see? Well, the transformation to MDS and AML is a class-wide effect, something that we have to watch out for with all the PARP inhibitors. So we have to monitor for that and discontinue if patients

transform into MDS or AML. Bone marrow suppression specifically was called out for niraparib, but you had a significant amount of patients with rucaparib that actually had dose reductions based off anemia. So that's something that—it's not that you ignore that for rucaparib and olaparib, but it's just explicitly stated for niraparib. But cardiovascular toxicity is an issue that you have to worry about, with niraparib, specifically blood pressure. Monitoring blood pressure pretty much intensifies for the first year, so they recommend monthly, and then periodically after treatment after a year and use antihypertensive medications as needed. And the last is pneumonitis specifically with olaparib, so this is very similar to *EGFR* type of monitoring, as well, in terms of looking at if patients get these respiratory symptoms of dyspnea, fever, cough, or wheezing.

The place in therapy with PARP inhibitors and where do we see these PARP inhibitors fitting into the guidelines? If we were to just really, really briefly summarize the NCCN Guidelines, what would we have here? For this maintenance—if you have a person who had complete remission following completion of chemo and then they had a relapse 6 months or greater after that—and the cytoreductive surgery is there if that's indicated. But if they get platinum-based chemotherapy for six cycles and then they get a complete response or a partial response, then they would qualify for maintenance therapy with niraparib or olaparib regardless of their *BRCA* status.

Remember, rucaparib doesn't have this particular indication—we don't have the data for that as of right now—versus if we have patients with recurrence. So if they have these *BRCA* mutations and received at least two or

more chemotherapy regimens, we could go a number of ways; we could go to rucaparib regardless if it's platinum resistant or not. And the NCCN Guidelines actually say preferred if platinum resistant. And so this would be after two or more chemotherapy regimens. Or you can do another third chemotherapy regimen and then go to olaparib after that. You could also put rucaparib here as well.

But that's how I see the differentiating points with these different PARP inhibitors. They're overlapping a bit. I'm pretty confident that they're all going to have very similar data and they'll be aligned in the near future in terms of the indications, but this what we have right now.

The summary with PARP inhibitors. There's absolutely new advances here. We have these three drugs with very similar or the same mechanism of action. Olaparib and niraparib are used in the similar situation, such as maintenance. Rucaparib, as well as olaparib, are used for patients with *BRCA* mutations as well. We saw that increase in progression-free survival. We're not really sure about the overall survival right now specifically in that maintenance phase, but we're going to wait until the data is mature with that.

So that, in a nutshell, is PARP inhibitor. We're going to move on to the next class of medications, which is our CDK4/6 inhibitors, which, remember, we had ribociclib approved earlier this year. And then me having to scramble to incorporate abemaciclib.

That's good because now we have two of these therapies, and it's interesting that they actually have different indications. And, remember, we have

already a CDK4/6 inhibitor previous to these drugs approved in the marketplace, which was palbociclib. And so, the question is where do these products fit in relative to palbociclib? And I'll talk about that in just a little bit.

Ribociclib is in combination with an AI, aromatase inhibitor; these are all going to be for HR-positive *HER2*-negative patients. And this is that first-line almost endocrine-based therapy-naive patients versus abemaciclib is given with fulvestrant for those patients who progressed after endocrine therapy or as monotherapy following what I'm calling basically very, very last-line therapy. They've received endocrine therapy, they've received multiple endocrine therapy, and they received prior chemotherapy as well. Interestingly, palbociclib has this indication and it also has this indication right here. So, there's, again, some overlapping indications across these three different products here that we're just going to have to keep track of.

Just to review the role of CDK4/6 in the cell cycle and the pharmacology of this and how it works. And this is good because it'll help us understand the toxicities a lot better, too, and how to manage that. But I want to start with the end in place here, which is the retinoblastoma gene here and retinoblastoma protein. Basically, this is a tumor suppressor gene and it actually hits the brake on the DNA for the expression and progression from part of the cell cycle to the next. And so, if this is a brake, there's something that has to lift the brake off of that and part of that is cyclin D and CDK4/6. So when CDK4/6 binds to cyclin D, that basically lifts the brake off of this and allows the transcription of the DNA to

occur, which then allows the cell to progress into the next part of the cell cycle. So that's the normal process that happens.

And the interesting part of this, cyclin D and CDK4/6, is that this is heavily influenced by the mutagen activation kinase pathway here, which we know as the RAS/RAF, right? These are all legitimate targets that we have. We have products that actually legitimately target these specific proteins, but also, here as well, estrogen receptor. When estrogen binds to the estrogen receptor, it will actually upregulate cyclin D, which causes this positive feedback loop in terms of progression and growth of these breast cancer cells.

In these articles, they talk about how hormone receptor–positive *HER2*-negative is kind of that prototypical—the best laboratory to experiment with the CDK4/6 inhibitors in terms of whether or not that would work. But the other part of that is that that's not the only clinical application of CDK4/6 inhibitors. So we have a lot of studies that are coming out in patients that are not necessarily HER-positive and for other indications as well, so we might actually be seeing the indications of CDK4/6 inhibitors expand in the near future.

This is a little bit complicated, but I just basically explained these two here, which is the RB protein is the break on the DNA, the cyclin D is this Pac-Man here, it binds to the CDK4/6. And it basically lifts that brake off of the DNA, so it allows the cell to go from the G phase to the S phase to rest in the cell cycle.

But when we have a ciclib here, it binds to either the cyclin D or CDK4/6 complex or the CDK4/6 itself, which essentially leaves the brake in place, which

doesn't allow the cell to progress from the G phase to the S phase, which leads to what we call G1 arrest, so it stops the growth of the cell.

So we have these three different CDK4/6 inhibitors approved in the marketplace today. Remember, palbociclib is what we've been working with for over a year now, probably close to 2 years or so. Abemaciclib is a little bit different than the others in that this is dosed on a continuous basis versus ribociclib and palbociclib are based off of a cycle-based dosing scheme here. They all have a little bit of slight differences in their selectivity against the CDK protein, so palbociclib inhibits four and six versus abemaciclib inhibits nine as well. But it's very, very selective against CDK4 as is ribociclib is very selective against CDK4, which actually goes and translates into their toxicity profile as well. The more selective you are against CDK4, the less neutropenia that you'll actually have.

So when you look at the dosing here you can see the frequency of dosing. And the dose here—we have the range of dosing for abemaciclib based off of the indication and then the toxicity profile in general, which we'll talk about in just a little bit. The drug interactions are the same across the board. So when we look at the clinical trial data for the CDK4/6 inhibitors, again, this is HR-positive *HER2*-negative advanced breast cancer patient. We have ribociclib given with letrozole as that initial endocrine space therapy in post-menopausal patients and that was a phase III study.

And with abemaciclib, their phase III study was with a combination with fulvestrant of when patients progress on adjuvant or that first-line endocrine

therapy, typically in AI. And that, again, was their phase III randomized controlled trial there. And abemaciclib has this phase II trial for patients that were refractory to prior endocrine therapy and one to two chemotherapy regimens; it's given as a single agent. And, again, that was a phase II open-label single-arm study.

These studies' names, including the palbociclib studies, are named very, very interestingly so that you can remember them; MONARCH, MONALEESA, right, PALOMA? Those are the kind of things that you would remember.

The clinical trials with ribociclib looking specifically at the MONALEESA-2 trial; this was, again, their phase III study. When you looked at the progression-free survival and the fact that the median progression-free survival was not yet reached, which was good, which means that 50% had not had that event occur yet. But the hazard ratio was about .5 or so, which was basically right in line with the palbociclib data and what their hazard ratio was when they got approval.

Overall survival data was not yet available for ribociclib. But, again, this palbociclib study was a phase II study, so you have to interpret the overall survival data with caution. We don't really have that available as of right now to look at with palbociclib either. So, again, we're still waiting for the overall survival data for this first-line with an aromatase inhibitor for breast cancer.

We look at abemaciclib, and, again, their studies here—I guess the phase III study we'll start with, which is that second-line with fulvestrant. And you look at the response rates for that, that was higher with the abemaciclib arm. And you look at the hazard ratio for progression-free survival—again, which was .5—which is really, really good for that. And when you look at their last-line, again, as

a single agent, you can see that—this was just a single-arm study, so we don't have any numbers to compare to, we don't have any hazard ratios. So the response rate was 20% progression-free survival, 6six months, and the overall survival was 17 months. And so, you may look at that and say, "Well, that doesn't look very great at all; how can they approve that based off of this data?"

You have to remember, if you go back about 20 years and pull the data with letrozole and when letrozole was first approved for this exact situation, the numbers are incredible; they're almost exactly the same as that, about—response rate is 20%, progression-free survival 6 months, and overall survival around the same. And we know how impactful letrozole is today, so the fact that they can get these numbers in the last line is actually very good.

If you look at the comparison of the toxicities here, they're all slightly different in kind of how they select CDK4/6, and so they're going to have slight differences in their toxicity profile as well. If we look at palbociclib and where we are today—if you look at fatigue and nausea, those are—fatigue is about the same. Nausea is going to be a little bit more with abemaciclib, as are these other GI toxicities. Look at diarrhea; diarrhea is really, really a big side effect with abemaciclib and that matches its CDK4/6 selectivity profile.

So you're going to see a lot more diarrhea with abemaciclib. Ribociclib's going to be about the same; abdominal pain. And decreased appetite is going to be a little bit more with abemaciclib. But when you look at the laboratory abnormalities and you look at neutropenia, abemaciclib is far less in terms of causing grade 3 or 4 neutropenia. Look at this grade 3, 4; about 65%, which is

far, far lower with abemaciclib. Ribociclib is going to be about the same as palbociclib in terms of neutropenia.

And then anemia and thrombocytopenia are about the same with these products. Ribociclib has issues with QT prolongation. Increased serum creatinine is an issue with abemaciclib and ribociclib as well. Hypokalemia is an issue and hyponatremia is an issue with abemaciclib. I think probably that's related mostly to the issues with diarrhea, so you're going to have to watch out with that.

Febrile neutropenia was about the same across the board, which is essentially a nonissue with CDK4/6 inhibitors. Remember, we don't use myeloid growth factors with CDK4/6 inhibitors; if patients get neutropenic, you basically hold the dose until they come back. There is no need for myeloid growth in this situation because, again, febrile neutropenia is essentially a nonissue. That's basically just noise right there in terms of febrile neutropenia.

When you look at the special monitoring as per the package inserts, what are the common themes that emerge here? Well, neutropenia is a common issue across all of these. Remember, abemaciclib probably has the lowest issue with neutropenia. Although it's still there, the rates are lower with grade 3 to 4 neutropenia with abemaciclib, but it trades off increasing toxicities of diarrhea, GI toxicities, and VTEs as well. So, diarrhea, again, is a big issue with abemaciclib. You have to monitor patients, initiate antidiarrheal therapy, increase oral fluids, and have patients check in if they get that diarrhea.

Venous thromboembolism; again, same very standard issues of monitoring for thrombus, pulmonary embolism. Hepatic toxicity is also an

emerging theme with all of these as well, so you have to look at liver function tests on a very clear schedule for monitoring LFTs. And with ribociclib specifically it has issues with QT prolongation, so you're going to look at EKGs, monitor electrolytes, and there's a clear schedule for doing that as well for ribociclib. So those are the differences across the CDK4/6 inhibitors in terms of their special monitoring of their toxicities.

The place in the therapy with CDK4/6 inhibitors. Where do we have these? I think what you're seeing is most patients—now, if you have that kind of newly diagnosed metastatic patient or that patient who just had metastatic disease, you're probably giving an AI plus palbociclib at this point in time, right, correct? I would say probably the vast majority of our patients are going to that. Ribociclib is just an alternative that you could use instead of palbociclib. So you can do either palbociclib or ribociclib there.

You're also probably seeing these patients who were on adjuvant endocrine therapy, right? And they failed adjuvant endocrine and they need to go on something, so you're probably doing palbociclib plus fulvestrant at this point in time for those patients, correct? So what you could do is just do fulvestrant plus abemaciclib as well. And the specific product choice would be up to you in terms of the toxicity profile, but that's an alternative in terms of what patients could get at that treatment note.

The last thing is we never had anything here where you had those patients who you've been treating for a very, very long time. They've had the full gamut of endocrine therapies, right? They also had some chemotherapy and they just

never qualified for a CDK4/6 inhibitor because they were not diagnosed at the opportune time. Their stage of and where they are in their treatment pathway was far, far later than the studies for palbociclib, right? And so, this actually is really good because you can actually use abemaciclib as a single agent for those patients.

I think really what this tells us is that a patient with HR-positive *HER2*-negative breast cancer should get a CDK4/6 inhibitor somewhere along their treatment pathway; whether or not it's up front, in the middle, or at the end, they'll benefit from a CDK4/6 inhibit. So I think this is kind of that last line. You probably have a lot of patients that fall into that that could now benefit from CDK4/6 inhibitor and you don't have to worry so much that they don't fall within the first-line or second-line cohorts.

The summary here is that we have a lot of these. These are basically becoming standard of care. I keep saying to my students that CDK4/6 inhibitors are to aromatase inhibitors the same way aromatase inhibitors were to tamoxifen, in terms of transforming how we treat HR-positive breast cancer.

Ribociclib is another option. I think that is therapeutically equivalent to palbociclib in the first-line setting. We can say the same thing about abemaciclib and how that's therapeutically equivalent to palbociclib in the second-line setting. But they have different toxicity profiles that you have to be aware of and manage that. But the interesting thing is abemaciclib being used as monotherapy in those last-line patients who wouldn't otherwise quality for CDK4/6 inhibitors.

I'm going to move on to IOs. And it's interesting because we've kind of slowed down in our discussion of immune-oncology agents, specifically in the solid tumor setting. I think it's because now with these two, we have our fourth and fifth PD-1/PD-L1 inhibitors in this space. And you can see that most of these are competing for urothelial carcinoma, this niche setting of locally advanced metastatic disease progression during or following platinum-based chemotherapy.

It's interesting because all five of the PD-1/PD-L1 inhibitors have this indication, which really makes for a fantastic, fantastic experiment in terms of evaluating these for formulary consideration and how you would do that. So we'll talk about this in just a little bit. Avelumab also has metastatic Merkel cell carcinoma as well as another indication.

Just to review the pharmacology, remember that these checkpoints are essential for maintaining self-tolerance and especially for modulating duration and amplitude of those immune response in peripheral tissues. And the reason why we have these checkpoints is to minimize collateral tissue damage; we need that. If we just let our immune system go wild and start attacking these antigens and these peripheral tissues, then we're going to have some sort of disseminated inflammatory response that will eventually kill us. So we actually have these checkpoints in place to modulate that and to keep them in check.

And the two clinically relevant checkpoints that we have today—and it's important to note there's literally hundreds of these different checkpoints. We only have two clinical applications today, which is CTLA-4 and PD-1 or PD-L1 as

well. CTLA-4, remember, that's our ipilimumab that downregulates the T-cell function. That's essential for having that homeostasis in your immune system. This is what I call the circuit breaker panel in your house. It's more attune to the circuit breaker panel in your house versus PD-1 or PD-L1 is limited to kind of these specific peripheral tissues or antigen-presenting cells and dampens the T-cell response specifically in peripheral tissues. And so, I liken that to a light switch in one of the rooms in your house.

The way that we modulate this is that we can affect CTLA-4 so that we basically turn on the lights in our whole house or we can look at a PD-1 or PD-L1, which is essentially that one room analogy. And so, the thing about PD-1 or PD-L1 is that PD-1 is highly expressed on these T regulator cells and it interacts with the ligand to downregulate T-cell function. So here you have this PD-1/PD-L1 interaction to downregulate the effect of the T cell. But we also have this in peripheral issues as well. And this is what the tumors actually take advantage of, is that it expressed PD-L1 to dampen the response of the T cell from in the tumor microenvironment.

What we're trying to do here is develop monoclonal antibodies that block this specific interaction where they're not as PD-L1 or PD-1. At least therapeutically right now we think they're about the same in terms of the clinical response, but this is essentially what we're doing with these new drugs.

The drugs that I'm going to be talking about today are the PD-L1 inhibitors, which is blocking this receptor over here. The clinical trials for PD-L1s that we have—again, avelumab and durvalumab—we have the Merkel cell

carcinoma. This was an open-label single-group phase II study, so these are patients with chemotherapy-refractory MCC. And we also have the urothelial carcinoma indication, which essentially every single IO PD-1 or PD-L1 IO has this exact indication, which is progression after platinum-based chemotherapy, and they're unselected for PD-L1 expression as well.

This was a phase I study and this was a phase I/II study, which is interesting because all of these therapies have differences in terms of the level of data for urothelial carcinoma. So when we look at the Merkel cell carcinoma data—again, this is stage IV Merkel cell—and you can see the response rates here with avelumab. So, again, single arm, we don't have any comparisons; that looks pretty good, especially when you look at it compared to pembrolizumab and their 26 patients. It was about right in line with that, so we can say that looks pretty good. Again, this is a rare but serious disease with no other options at this point in time. So we'll take something like that for this particular setting.

And when you look at specifically—I do want to spend most of the time talking about urothelial carcinoma because this is interesting because remember, we've had these products approved for a little while now in this particular setting, which is, again, that advanced or metastatic after progression of platinum-based chemotherapy. And you can see that the data with these three drugs ranged from either a phase I trial to a phase III trial, so depending on what product you were looking at, it was either a phase I, II, or III trial. And when you look at the range of the response with these three drugs, you're talking about a median overall

survival of anywhere—about a year or so. And then the progression-free survival is about 2.1 to 2.8 months or so with response rate of up to 24% or so.

So when you look at these studies with avelumab and durvalumab, they were pretty much in line with the other studies, and you have the 1-year survival rates. These look maybe a little bit higher, but, again, the issue here is the different studies designs, and you can't really make many inferences in terms of which one is better at this point in time because of that. But everything else was pretty much in line in terms of response rates, and the grade III adverse events were about, again, in line with the other therapies as well.

When you look at the safety profile and you put all of these side by side and look at the toxicities of all of these—and so, again, the fatigue is the big issue across the board with these agents. Infusion-related reactions start to become an issue when you're talking about avelumab, but then you have the arthralgias, diarrhea, right? Rashes, which is also important as well. Those were pretty much consistent across the board with these agents. Hypertension starts to be an issue, again, with avelumab here.

When you look at the special monitoring, these are pretty much, again, in line with our other IOs. So pneumonitis, hepatitis, colitis—those being the big three that we worry about—as we do with endocrinopathies. Infusion reactions is an issue with avelumab and that requires premedication with acetaminophen and antihistamine at least for the first four infusions. So we're used to dealing with immune-muted pneumonitis, right? So you would watch out for those symptoms. We're used to dealing with immune-muted hepatitis and colitis as well, and then

we're used to dealing with immune-muted endocrinopathies. And so, again, we're used to dealing with all of these. The rates are pretty low, as you can see, but, again, about in line with the other IOs that we've been dealing with for quite some time now.

The place in therapy with avelumab and durvalumab—I think what this does is it competes with the other products that we have in the space; specifically, in Merkel cell, it competes with the other therapies. But the interesting thing is in the urothelial carcinoma, all five of these have this on occasion, so the question is are you preferring one over the other or is it just one that you like? Or how are you deciding which one to use for your patients; is it based off of insurance or something like that? So that's going to be the big question.

Toxicity profile and—you know, we see this, again, with all of the other drugs in the space, those include those immune-muted adverse reactions that we've been dealing with for quite some time now. And avelumab has that issue with infusion-related reactions that requires premedications.

The last class that I'll be talking about are the tyrosine kinase inhibitors, specifically brigatinib and neratinib. They're slightly different in terms of what they do, but I'm going to talk about them in context with each other. Brigatinib is used for all positive non–small cell lung cancer for patients who have progressed on crizotinib, and neratinib is the extended adjuvant treatment for *HER2*-positive breast cancer patients following trastuzumab adjuvant therapy. And, remember, this is the pharmacology of *EGFR* and *ALK,* and we have this tyrosine kinase

family of proteins here that has all of these subsequent downstream effects on the intracellular space, but essentially, these promote growth of the tumor cell. And when we have this *ALK* mutations, we're talking about these translocations that causes this fusion protein and, again, the end result is the proliferation and dissemination of these tumor cells.

The one thing that I think we really need to be aware of with these products is that brigatinib is not just an ALK inhibitor; it inhibits all of these other tyrosine kinases as well, so *ROS1, EGFR*—some specific *EGFR* mutations that erlotinib doesn't really cover. So that's really interesting and important to know. The other thing is that we're firmly transitioning into a space where we're not just talking about does a patient have an *ALK* mutation or not? We're asking the question of which *ALK* mutation does the patient actually have, right?

So when you look at this table and look at the relative affinity and effect on all of these different *ALK* mutations here, you can see that brigatinib actually has sensitivity to a lot of these different *ALK* mutations that the newer ones, quite frankly, don't really have coverage of. So we're talking about alectinib and using that up front now compared to crizotinib, and having alectinib superseding crizotinib now in terms of being first line. And so, there's some that brigatinib covers that erlotinib or alectinib does not. So this is something that we're actually going to have to look at is it not just simply is it an *ALK* mutation and have they received crizotinib, but which *ALK* mutation do they actually have?

The other thing I want to talk about with neratinib is the slight differences between that and lapatinib. Neratinib is an irreversible binding to—it's a pan-

EGFR inhibitor, so it inhibits *EGFR1*, *HER2*, and *HER4* as well. This is blank here because that's not published, but we know that it does inhibit *HER4*. So, it's irreversible and it's a pan-inhibitor and it's very, very similar to afatinib, actually, so it's much, much more similar to afatinib than it is to lapatinib.

When we look at these clinical trials here with brigatinib versus neratinib, right now we're focusing on the *ALK*-positive patients. The studies that we have here, this phase II study with brigatinib, receiving 90 mg or escalated up to 180 mg if they can tolerate that, so that's the major study that we'll be talking about. They also have this study looking at *ALK*-positive patients resistant to crizotinib as well. So right now we're talking just about crizotinib-refractory patients.

With neratinib we're talking about that early *HER2*-positive breast cancer. They received trastuzumab chemotherapy and they were disease free for up to 2 years after completing that trastuzumab therapy. This was a phase III multi-center randomized double-blind placebo-controlled trial, which is a good quality trial. So when you look at the brigatinib studies and being—again, these are crizotinib-refractory patients—you see these very, very good high response rates. This is really good in terms of looking at that for these patients who have refractory disease or no other good options as well.

So, again, this is enough for FDA approval here, specifically when you're talking about accelerated approval, and so, this represents another option for patients. But, again, the issue in my mind is what specific mutation do they have and can we target that a little bit more precisely?

When you look at neratinib and the data with this—so we have 240 mg a day for 12 months versus placebo. We talk about how the hazard ratio here is .67, which, again, meets that threshold for clinical significance. But if you really look at things here, we're talking preventing 39 events out of 1,420 patients. So for those of you who can do the math quickly, that's a number needed to treat 36. So what we're talking about is treating 36 patients to prevent one event, okay? And we're committing 36 patients to a therapy that lasts a year and only one of them will actually receive a benefit, okay?

I'm not saying that this doesn't work, but we have to think a little bit about who would be the best patient to actually get this and reducing that number needed to treat. So that's going to be an issue in terms of how do you select out who actually should receive this product?

The general safety here—I just want to talk about this in context with what it does. Neratinib, because it's an EGFR inhibitor, diarrhea is the big thing. This is pretty much in line with afatinib toxicities and the diarrhea. With brigatinib because it inhibits a lot of other kinases, you're a lot more worried about these toxicities here in terms of what it does with these laboratory abnormalities, hyperglycemia, increased lipase, amylase, and all these other issues here, as well. So, cough and dyspnea is an issue with brigatinib as well. And you have these other—rash; again, neratinib being an EGFR inhibitor you're going to expect a rash with that.

When you look at the special monitoring, the interstitial lung disease, again, which we're used to with other EGFR inhibitors, other tyrosine kinase

inhibitors; we watch out for that—the rate is about one in 10 there. Hypertension; we have to worry about all these other cardiovascular toxicities like hypertension, bradycardia, CPK elevation, and those. So, again, you have to monitor blood pressure, heart rate, monitor CPK levels regularly during treatment. We also worry about visual disturbances, pancreatic enzyme elevation, and the hyperglycemia as well. Hyperglycemia is a pretty big issue that we have to worry about here.

And the last is neratinib special monitoring. Again, diarrhea is a huge thing, hepatic toxicity is pretty big as well. So aggressively manage that diarrhea if patients are on neratinib and, again, fluids, electrolytes, antidiarrheal, withholding the drug if necessary.

I'm way over time here, so I'm going to just rush through these last ones, but I'm at the home stretch here. The new place in therapy with TKIs—this represents, again, that advancement in the all positive non–small cell lung cancer refractory to current treatments. But, again, I'm thinking that we're going to move past what they've previously been on and more to something that's more targeted towards what specific genetic mutation they actually have, especially if we're going to change the guidelines now and recommend alectinib first line, what that's going to do to brigatinib? And so, neratinib—I think this is, again, another option. This is probably better for those patients who didn't receive pertuzumab in the adjuvant setting. But, again, the number needed to treat is really, really high, so we'd have to think about which patients would actually be

the right patients to actually use for neratinib, especially a year-long treatment with pretty bad diarrhea.

The summary here is that these agents here are mostly what we call me-too agents; they have some slight differences over our previously approved products. We have these PARP inhibitors emerging in prominence in ovarian cancer; we have CDK4/6 inhibitors; we have more than one now that represents the new standard of care in HR–positive *HER2*-negative breast cancer. We now have five PD-1, PD-L1 inhibitors, specifically for urothelial carcinoma. And we've got more advances with TKIs and drugs that address specific mutations now that we didn't have, so we have a lot more tools in our armamentarium for that.

These new drugs, again, the hazard ratios were really, really good for a lot of these PARP inhibitors. CDK4/6 inhibitors are less, .5, which is really good. Neratinib: we talked about how that looks really good, but the number needed to treat is really, really high with this, so, again, we have to think about how we use that.

The adverse events. We have to think about the slight differences because of their slight differences in pharmacology and how we would manage that. Ribociclib, QT prolongation, abemaciclib with diarrhea, but less neutropenia. And we look at other serious adverse events with brigatinib and neratinib as well.

This is the last thing. Patients with ovarian cancer now have multiple options for maintenance and recurrence; breast cancer patients also now have multiple options; and we continue to advance in non–small cell lung cancer, and breast cancer as well. We've got another niche therapy for those patients with

HER2-positive disease. So, with that, I think we still have about a minute or so left for questions, so we'll take any questions. We have a question over here.

MALE Quick question right back here.

EDWARD Okay, okay.

MALE Might be projecting just a little bit, but taking a look at neratinib plus all of the other agents for metastatic breast cancer—palbo, ribo, everolimus and the TKIs that sort of stuff, I know it's off-label for neratinib at least at this point, but any ideas about adding these agents to patients with ER/PR-positive *HER2*-positive metastatic breast cancer?

EDWARD Yeah. Certainly that's the issue, right? We really want to use these off labels and we want to expand these out to other patients that don't have other options as well. That's a very good question. And the thing is I work a lot with payers—I actually help a company establish cancer treatment pathways—so we're constantly looking at the evidence, the threshold of evidence, and whether or not, from a population-based standpoint, it would be appropriate to use these. I think a lot of that is going to be limited by insurance and whether or not patients will actually get that approved through insurance. And what I can tell you is that unless there's good data that allows it to be incorporated into one of the compendia, specifically the NCCN Compendium, it's really not going to be put on the approved list of indications. So even though we may say that it looks really promising, we want to do this; the problem is that it's probably not going to be paid for.

FEMALE Thank you for your talk. For the PARP inhibition, you had mentioned that there's risk for MDS and AML.

EDWARD Yeah.

FEMALE Is there a dose cap for that where that typically occurs?

EDWARD I'm not really aware if there's an actual dose cap with that, but I think this was a small number of patients, really rare adverse event, right? It's just something to monitor for. I don't think we really know a lot about why that happens or how that happens and in which specific patients it happens. Right now, it's kind of a signal that we just have to monitor patients.

Thanks. All right, thank you.

[END]