NEW DRUG UPDATES IN SOLID TUMORS

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MS. JEFFERS Good morning everyone. Hope everyone had a great night last night and got to enjoy a little bit of the outside. It was cooler last night with the rain coming in. So, welcome back to our fourth day of JADPRO Live, our last day of the conference. My name is Kate Jeffers and I am an oncology pharmacist at UC Health Memorial Hospital in Colorado Springs.

So, we're going to dive right in this morning for day four. Just as a gentle reminder, please silence your cell phones if you have not done so already.

Our first talk this morning is a BCOP lecture, which is very exciting for all the pharmacists in the room and this is on New Drug Updates on Solid Tumors. So, please join me in welcoming Dr. Patrick Kiel from Indiana University, Simon Cancer Center.

DR. KIEL Somebody started drinking at the bistro early this morning. Well thanks, Kate, thanks JADPRO for having me. This is always a unique time in oncology. If you could start the clock, this is part of the spiel too, otherwise, I'll go over. Oncology has become very educational-heavy in the past probably 3 years, and I think it's fantastic that there's activities that JADPRO puts on to keep up. So, part of my gestalt for this talk is going to say, I'm covering new drugs in oncology, basically from the last year's meeting. So anything that's been FDA approved in the last 24 hours, or 4 weeks, I'm not going to touch on, okay? To give you an idea of the complexity of what's happening, in the last 12 months

there's been 45 new drug approvals by the FDA, 24 have been in oncology, probably another 12 to 15, if you listened to the talk earlier, have been for hematology, which leaves like eight for everybody else. So, if you're in critical care medicine, you pretty much have zero drug approvals in the past 12 months.

These are the learning objectives we're going to go through. Discuss what's been FDA approved for the last year. Go through the pivotal clinical trial data—we're talking meat and potatoes. There's going to be some drugs on here that are FDA approved, but some of it is based on phase 1 or phase 2 trials with 90 or 100 patients. I haven't put in the data, but I've put it in Excel table for you. Go over symptoms, signs and symptoms of toxicity profiles between drugs in a class, life-threatening adverse events, and describe these agents in the impact of practice.

These are my disclosures. And for the sake of time, I'm going to preface this with I've got 72 slides to go through in 50 minutes to give you guys 10 minutes of questions. And I don't want to be late for the next presenter, okay?

So, this is the timetable looking at the history of cancer drugs approved in the United States. Starting in the ’40s with Goodman and Gillman. Goodman and Gillman were the pharmacologists, the premier pharmacologists, in fact, the textbook still says, *Goodman and Gillman, The Pharmacologic Basis of Therapeutics.* They took nitrogen mustard gas and gave it to patients with lymphoma and were able to induce responses. It was the most impure form because you were pretty much using the same drug they used on the battle lines during World War I and World War II.

Moving up to FDA approving cyclophosphamide in the late ’50s, which was a pro drug of these mustard gases. And, moving to the ’60s, which if you've read the books, *The Emperor of All Maladies*, going through how drugs were developed for ALL, if you haven't read it, please go through and look at it. Cisplatin approved in 1978, one of my mentors and premier oncologists, Dr. Lawrence Einhorn, who I had the pleasure of working with at IU, brought cisplatin and a few other drugs to market to help cure testicular cancer.

Moving on to more targeted therapy with trastuzumab. Trastuzumab is the premier monoclonal antibody. I had the pleasure of working with Dr. Cobleigh in Chicago who helped bring this to market.

And then, imatinib; imatinib has been the magic silver bullet in oncology, where we have a drug that is taken orally that can block ATP intracellularly and actually looking at the newer data, you can get 85%10-year survival rates. This is novel because we're looking at a disease in which 95% of patients with CML are characterized by a genomic aberration. We're finally moving into the era of precision medicine, genomic targets, but those targets aren't there 95% of the time. We're looking at small slices of the pie, making incremental improvements. That's what a lot of these drugs are going to be FDA approved on.

So, if you look at approvals and the paradigm practice, I'm sure this is a slide everybody's seen before, going from the ’40s to alkylator-based therapy, to combination chemo in the ’70s and ’80s. Really improving upon supportive care in the ’90s and early 21st century with antiemetics, other supportive care just with antibiotics, how we treat neutropenic fever, antifungals, into the era of proteomics

and pharmacogenomics. When gefitinib came out in the late ’90s, early 21st century, we gave it to everybody with minimal biopsies from lung cancer and then we kind of found out, hey, this works best in females, Asian descent, nonsmoking. And now we know, hey, there's something there, there are activating mutations in which these patients should be selected for. And now, with the explosion of 24 oncology drugs in the year 2018, we're going to have a lot more sea coming down the pipeline.

How many of you are familiar with immuno-oncology? Okay, awesome. So, this has been an explosion. We're going to have more of this in this talk, so just to kind of go through. Cytokine, cytokines are Latin for cell movement. It's how T cells, B cells communicate with each other. I'm going to really be going through, from Dr. Good, discovering the immune system in the ’60s and ’70s, all the way up to the Nobel Prize, which was awarded this year for the CTLA-4 discovery, and, now we're moving on to CAR Ts to be more targeted in precision and with this comes a plethora of immune-related toxicities, fatigue being the most common with these drugs. But we're talking about the -itises: pneumonitis, hepatitis, colitis being the most common, down to rarer things, and now we're seeing cytokine released with some of these agents at higher doses as well as with CAR T therapy. I feel like there should be a buh-bump-bump after this because, we don't actually have any new classes approved this year. I would encourage you to stay tuned for next year because there's a lot of TRUCKs and immunotherapy in the pipeline, but the four that I will point out, for biosimilar trastuzumab was FDA approved at the end of last year. I won't go into the details

of the approval. As far as those with established mechanism of action, we're looking at apalutamide for prostate cancer, encorafenib and binimetinib for melanoma.

So looking through regulatory events, the way FDA approval language is, is some of these get fast-tracked approval and then once they're approved, they can gain FDA approval for new indications, or it's cemented as a formal FDA approval process once more data comes out. I've kind of lumped the first two tables together for immunotherapy, so I'll just kind of highlight the salient ones, nivolumab for metastatic small-cell lung cancer in patients who were previously treated with a platinum. It's published as a phase 1/2 trial. I didn't include it, but you're more than welcome to pull the article.

We'll go through nivo and ipi combinations, as the slide goes on. Immunotherapy emerging as adjuvant therapy for melanoma. Pembrolizumab in metastatic PD-L1 cervical cancer, published in about 90 patients, which is FDA approved and you should easily be able to get for your advanced stage patients.

Carbo/pem squared, or carboplatin, pemetrexed, pembrolizumab for non–small lung cancer in the first-line setting, and durvalumab, which was also spoken about at a symposium this morning for breakfast.

CDK 4/6 inhibitors – I know everybody has been seeing this in their practice in the metastatic setting for breast cancer. We're now moving them up into first-line combination therapy with antihormonals and we'll go through some of the data. Olaparib is an oldie but a goodie, it's been used for ovarian cancer,

for about 8 to 10 years and now, we're finally seeing it get into metastatic breast cancer. Lenvatinib for hepatocellular and cabozantinib for first-line renal cell.

And then we'll go through some of the lung cancer data with alectinib, afatinib. I'll focus more on osimertinib because that seems to be more of a game changer, at least in my practice, and at least in the Midwest. And then the newer agents for castrate-resistant and castrate-sensitive prostate cancer with abiraterone being FDA approved for castrate-sensitive prostate and enzalutamide for castrate-resistant prostate cancer. Pertuzumab in combination with trastuzumab – I know we've all be using this as of the end of 2017.

And then, uniquely, it's not a drug approval, but it was FDA approved, Foundation One's 324-gene panel for solid tumors. How many of you are doing genomic practice in your sites? Okay. How many of you are using Foundation? How many of you feel comfortable reading those reports? Yeah, I get the same answer all the time.

Okay, so immune therapy. When we're looking at immune therapy, we're looking at the brakes and the gas pedals, as probably what's been reiterated the most through the conference. What's pushing the T cells to turn on and what's turning the T cell off? And, for the most part, FDA-approved drugs are targeting CTLA4 with ipilimumab, PD-L1, PD-1, as I go through the agents on the presentation. Things on the forefront, LAG3, IDO inhibition, which is related to tryptophan pathways, there's a lot, it's not just these two. There's usually two ways that I explain this to patients with regards to activation and effective function. One is, if you remember the old TV shows with Spanky and the Gang,

the he-men, women-hating club? If you don't know the secret handshake, you're not going to get in the club, okay? So, essentially, a lot of the secret handshakes that are going on between CTLA4 and then PD-1 – programmed death ligand 1 – with PD-1. When T cells come around and they start touching stuff, if you're a virus or you're a bacterial infection and you don't know the secret handshake, they attack you. With cancer cells, they still come from normal cells, so they still know the secret handshakes. When you're giving immunologic drugs, you're breaking that secret handshake and the T cells think, “Hey, I don't know you, you don't belong here, we should attack you.”

The other analogy that I typically use in clinic, because I live in Indiana, is it's like camouflage. If you have PD-L1 overexpression it's like camouflage. I get a lot of patients who are hunters and essentially immunotherapy takes off that camouflage, hides it, T cells notice you, they rub off and they attack you.

Okay, so looking at approved agents, nivolumab was first FDA approved in 2015, based on the CheckMate 25 for advanced renal cell carcinoma in patients receiving standard of care, antiangiogenic agents. Flash forward to this year and we're looking at combination, nivolumab, ipilimumab, based on CheckMate 214 in patients with intermediate to poor renal cell carcinoma. And now, with the caveat, we've had, not only numerous immunotherapies come on the market, but we've also had dose changes to those agents on the market. Originally, 3 mg/kg for nivolumab, which was changed to 240 every 2 weeks to 480 every 4. How many of you guys are still using the mg/kg weight-based

dosing? Anybody? No? 240 every 2? 480 every 4? Okay, so we've got a wide spread between the last two.

If you're looking at ipi/nivo in renal cell carcinoma, in the first-line setting it was compared to sunitinib in CheckMate 214. They were all treatment-naive patients and they were stratified by the International Metastatic Renal Cell Carcinoma Database, so their performance status, what was their time from diagnosis to treatment, their laboratory values as far as some complete blood counts and calcium levels, which help give you a score that's typically derived from studies on angiogenesis agents. Patients were randomized to get nivo 3 mg/kg plus ipi 1 mg/kg every 3 weeks. Ipi was just for four doses and then you got kind of a maintenance nivolumab compared to sunitinib, and the treatment was continued until progression or unacceptable toxicity.

If you look at the responses, the combination nivo-ipi for overall response rates, the CRs plus PRs, 42% versus 27% of the sunitinib group.

Looking at median progression-free survival, in the combination immunotherapy arm, 11.6 months versus 8.4 months in sunitinib, which is statistically significant.

If you look at overall survival, and this is something we really haven't seen too often in renal cell carcinoma, it's not reached in the combination arm, versus 26 months for sunitinib. So, this has quickly been developing as the standard of care.

Nivolumab also has some additional approvals. Looking at patients with microsatellite instability high or mismatch repair deficiency in 12 year olds and

above – I don't do Peds, so please don't ask me any pediatric questions at the end of this. Although, I have five kids, I'm not allowed to treat them, based on my wife's recommendations.

Dosing is what you would expect. Uniquely the trial for CheckMate 142 gave patients monotherapy with nivolumab in combination with nivo-ipi. So, this first slide is really looking at monotherapy with nivolumab. It's based on 74 patients. Looking at the objective response 31%, okay? Disease control 69%. The responses were seen irrespective of PD-L1 expression, Lynch syndrome and then for colorectal cancer, we also worry about *KRAS* mutations and *BRAF* mutations because they tend to be more aggressive cancers. Twelve-month progression-free survival is about 50%, so the median PFS is about 50%.

Uniquely enough, we are also getting in the era of patient-reported outcomes. If you look at some of the PROs, coming out of Memorial Sloan-Kettering's Group, we're at an era now to where we have to better communicate with the patient and mitigate their drug toxicity because these are leading to advances in overall survival. And there is published data on that in *JAMA Oncology*, but what this trial did, is also they looked at the global health status for the quality of life of patients receiving nivolumab. Any grade toxicity, 70%. Grade 3/4, 20%, which is a little bit higher than I think you would expect, but if you look overall at the trend to zero as your baseline, down is your mean change so patients have a worse quality of life, you go up, patients have a better quality of life, I think overall what this slide is really showing us is treating patients that

have a better overall quality of life, which adds to the armamentarium of immunotherapy in this patient population.

A same trial but looking at patients with combination therapy, nivolumab plus ipilimumab. Median follow-up of about 13.5 months, so about the same. Objective response rates are higher, 55%; disease control, higher, 80%; and although it was not randomized to power or difference between these two because there are actually six subcohorts in this study, the blue line at the top is combination therapy, nivo-ipi, the bottom yellow line is monotherapy with nivolumab, you do see a difference in 12-month progression-free survival, about a 21% benefit in progression-free survival with the combo, and the overall survival, you're seeing a little benefit as well. But, again, it's not powered to detect a difference.

If you look at the adverse events with the combination cohort, grade 3/4 toxicity, about 32%. So, you're seeing nearly a double of toxicity with the combination nivolumab/ipilimumab. So, part of this is picking apart which patient is the ideal patient. And I don't think these combinations are going to go away. We're seeing a lot of the combination therapy emerging, although not FDA, necessarily FDA approved for non–small cell lung cancer and small cell lung cancer, to where we still don't know which patients are going to benefit based on baseline characteristics for combination versus mono agent.

Moving on to combination therapy with chemotherapy in the frontline setting, carboplatin, pemetrexed, pembrolizumab, or I usually call it carbo-pem squared. KEYNOTE-47 trial took patients who were treatment naive with

metastatic non–small cell lung cancer. Patients received carbo, paclitaxel at standard dosing plus pembrolizumab, compared to carbo-pem as the standard of care. Uniquely, we're moving in a lung cancer with coprimary endpoints, overall survival and progression-free survival. Immunotherapy has really been the class that is pushing overall survival advantages in non–small cell lung cancer. Even if you go and look at targeted therapy in lung cancer, for ALK, ROS1, EGFR, those are typically based on progression-free survival, so we're going in the right direction.

Baseline characteristics between the two groups are pretty much the same. A median age of about 65, 7% never smoker, mostly squams and PD-L1 greater than 1%, 63% of patients in both arms.

Looking at the primary outcome since it is essentially coprimary, overall survival and progression-free survival. Progression-free survival has a hazard ratio of 0.56, so what does that mean? All patients are likely to progress or die on the study but if you receive pembrolizumab in combination with chemo, you are 44% less likely to die or progress, okay? Progression-free survival is also a notable statistical difference.

So, now we're moving from stage IV disease to stage III disease. Durvalumab, which is a PD-L1/PD-1 blocker, was evaluated in a prospective randomized trial for stage III non–small cell lung cancer, the majority were stage IIIA, stage IIIB. They had to have not progressed following platinum chemo/radiation, so as a standard, all patients get platinum or chemo/radiation for a few cycles and with the life expectancy greater than 12 weeks. The

comparative for this arm is placebo because once you get platinum and chemo/rad – or platinum with radiation, there is no standard of care, so there's nothing to compare this drug to. And, again, coprimary endpoints, which is now the trend and probably the expectation of the FDA moving forward of progression-free survival and overall survival.

If you look at durvalumab, median progression-free survival is 16.8 months versus placebo 5.6 months. Very uniquely this is one of the first times in stage III non–small cell lung cancer, you have a drug where these curves separate and stay separated, and this is practice changing, as well.

Looking at safety concerns, so instead of going through each trial and giving you all the toxicities, I picked out the salient toxicities for you. So, fatigue by far is the most common. Anywhere from about 28% to 50% of patients are going to feel fatigued. Infusion reactions are exceedingly rare but are most common with avelumab. Sorry. My mouth's getting dry just saying all the mAbs, over and over. Atezolizumab, nivo, pembro, and durval are the least likely to have infusion reactions. And then when you start to look at immunotherapy, it's still about less than 5% with all of the agents across the board.

CDK4/6 inhibitors. They were initially approved in the relapse setting for patients who have progressed on hormonal therapy for metastatic breast cancer. Now, looking at ribociclib and abemaciclib, we're moving them up as initial therapy. Ribociclib can be used in pre- and perimenopausal women with hormone receptor–positive HER2-negative as initial endocrine based therapy. And in combination with fulvestrant for postmenopausal metastatic following

progression on endocrine-based therapy. I've got another table on this at the end, don't worry. Abemaciclib in combination first line with an aromatase inhibitor, which I'm pretty much going to call an AI for the rest of the talk.

If you look at CDK4/6 cycle, there's a lot of interplay with the Ras/Raf/ERK pathway and part of this to be druggable is that you have to have an intact retinoblastoma gene, which is one of the guardians of the genome, because that's one of the master regulators. The way that I always think about this is, CDK4/6 is really the alarm clock. This is what is forcing cells to go from G0 to G1 and go into S phase. So, going back to biology class, G-0, cells in a resting phase, it's normal, G1, you're prepping to go to S phase so you're increasing microtubulin, you're increasing your cytoplasm, messing with your organelles. When you get to S phase, you're doubling your DNA, so I'm normally a 46,XY chromosome male, they're going to double that before they go to G2. G2 are where we're checking all the DNA with BRCA1, BRCA2, ATM, P53, and then we go into mitoses for prophase, interphase, metaphase, anaphase, geophase. That'll be the most boring that the talk gets, hopefully.

CDK4/6 is the alarm clock that triggers that G0 to G1 to S phase mentality. I always think back in the ’80s, the Dunkin Donuts commercial where the guy gets up and says it's time to make the donuts. That's CDK4/6, okay? When it's amplified, it's like the alarm clock is going off at 6 o’clock, and 8 o’clock, and 9 o’clock, and 12 o’clock and promoting carcinogenesis.

If you look at a comparison between the three agents, abemaciclib, palbo and ribo, there is a different selectivity for CDK4 versus CDK6. Palbo is equal for

CDK4 and 6, abema favors CDK4 ninefold; ribo favors CDK4 fivefold. Abemaciclib is really dosed continuously and then for the other two, you get 3 weeks on, 1 week off. Toxicity is a little bit different, which we'll get to exact percentages in another table, and drug interactions, they're hepatic, CYP3A4 so you worry about your tuberculosis meds, your HIV meds, and your antiepileptic drugs, and then voriconazole, posaconazole.

Not all the data was published at the time so some of this is really taken from abstract data or FDA approval websites. Looking at the MONLEESA trials, which are associated with ribociclib, and the MONARCH trials, which are associated with abemaciclib. Looking at ribo with fulvestrant and postmenopausal first line, and then pre and perimenopausal with an AI. And then most of these are going to be with an AI. Regardless of what drug you're looking at, the natural comparator was the antihormonal therapy that it's combined with. Fulvestrant or an AI and when you're looking at progression-free survival, in this patient population, essentially across the board, giving a CDK4/6 inhibitor with antihormonal therapy is a double in PFS, okay? So, all of these have become the standard for a first-line combination regimen.

Median overall survival, not available. Why? Because metastatic breast cancer patients do well for a very long time. Changing one regimen up front when they've got five to eight downstreams, probably one, not going to be noticeable, and two, going to take you about a decade to figure out. So as things continue to change, we'll have more information, probably in 20 or 30 years.

Looking at the safety profile, so this is more clinical adverse events. The next slide will be laboratory abnormalities. The things that I like to point out are that palbo and ribociclib have a little bit more less, I guess less nausea profile than abemaciclib. Abemaciclib typically has a lot more GI-related toxicities: nausea, diarrhea, even a little bit more stomatitis – that's kind of a take-away point for abemaciclib. It's also not uncommon to recommend these patients stop at a pharmacy on the way home and pick up some type of antidiarrheal agent, whereas ribo and palbo have more of an effect on the white blood cell count. So, checking CBC is more of an issue because you can get more grade 3/grade 4 toxicities with neutropenia with ribo and palbo versus abema. So abema toxicity is what? GI. Everything else, you worry more about? Good job.

So special monitoring, all of these can prolong the QTc interval. What we worry most about is ribociclib. Abemaciclib again, more issues with GI-related toxicity, there is some concern with venous thromboembolism. Monitoring for signs and symptoms and then, for the most part, the rest of them are pretty similar across the board.

Looking at their place in therapy, we're now moved up to newly diagnosed in postmenopausal females who have not received chemo giving a CDK4/6 inhibitor with an AI. Which one should you use first? Well, there's no comparator trials to date on which one's better; a lot of this is going to be relating the toxicity profiles. Essentially, the patient who has more GI-related toxicities at baseline, Crohn’s, ulcerative colitis, IBS, you probably don't want to give them abemaciclib.

Olaparib, so we're finally in breast cancer to where we're catching up with ovarian cancers. So, olaparib was approved in patients with deleterious for suspected germline *BRCA*-mutated HER2-negative breast cancer, those who have been treated with chemotherapy and neoadjuvant, adjuvant or metastatic setting.

PARP inhibitors are really, they've been around for a while but they're still a little bit misunderstood, I think. If you look at the cell cycle again, and we're going through G2, the main regulators are protectors of the genome for making sure there are no DNA errors are BRCA1 and BRCA2, most important, clearly for gynecologic, oncologic malignancies in breast cancer. And through homologous recombination they can repair single strand and double stand, more complex breaks than anything else. When you lose BRCA, you're relying on other pathways or the cancer cells are relying on other pathways to repair DNA. PARP, CHEK, ATR; PARP has become the most druggable because it's relied upon the most heavily in repairing single strand breaks. And the concept is that you rely on something called synthetic lethality, to where the cancer cells cannot do major repairs with BRCA anymore because it's lost, so PARP has become the kid on the block that is keeping the cancer cell genome repaired. The way that I usually explain this in clinic to patients is, it's like a four-legged table. If you have a table with four legs, one of them is BRCA and you take it off, you got a three-legged table. Everybody's been in college where you have a not-so-good hand-me-down or Ikea furniture that has a three-leg table in the corner holding your stuff up. PARP is that third leg. When you take out that third leg, that table's going to fall.

Okay? That's essentially what we're going for. You guys did have a three-legged table in college, right? No? Okay. Well, I'm a poor kid from the south side of Chicago.

Looking at the OlympiA Trial, this is where patients were randomized with metastatic HER2-negative disease who received no more than two lines of chemotherapy to receive standard of care choice, capecitabine/eribulin/ vinorelbine versus olaparib. About 50% of the patients had a *BRCA1* mutation, and 50% were hormone receptor positive. Primary outcome progression-free survival, top curve, the red line is olaparib, the blue curve, the bottom line is the standard of choice of those three agents, and it is statistically significant for progression-free survival, so it has a ratio of 0.58.

Overall survival, again in metastatic breast cancer, a little bit hard to tease out, but this is based on progression-free survival. Looking at all the PARP inhibitors in general, rucaparib, niraparib, olaparib. The side effect profile across the board is very similar. There's supposedly more upper respiratory tract infections with olaparib and a little bit more headache with niraparib and olaparib, but otherwise, I think across the board they are pretty similar.

Looking at laboratory abnormalities, mild suppression and LFT elevation is the one you worry about the most. There's also some issues with serum creatinine. This is kind of a jumbled bag too, because depending which study you're looking at, these drugs were used in patients who were heavily exposed to cisplatin or carboplatin in ovarian cancer, so there's a lot of gestalt with the creatinine toxicity as well.

One that is being promoted and should be educated to patients is the risk of MDS and AML with these agents. If anybody goes home and does a Google search, from a patient point of view, this is going to pop up. You know, Dr. Google, you have to take his opinion when you're in the clinic as well, or at least talk to the patient about it.

Part of the concern with this has always been is this a drug toxicity or is it a large component that these patients have a deleterious *BRCA* mutation which also contributes to other malignancies, as well? So the chicken or the egg, not sure, but keep that in the back of your head.

That's a lot of talk about females, so men, you're not alone in the audience – and there's not a lot of men in the audience. PARP inhibitors are really being looked at and pushed in prostate cancer now. There's one *New England Journal of Medicine* looking at patients with a multitude of deleterious DNA repair pathways with some efficacy. A lot of the PARP inhibitors are now under formal evaluation with combination therapy of chemo, or compared to placebos monotherapy with androgen deprivation therapy and some immunotherapy. So, PARP inhibitors for prostate cancer in the future, probably germline and even somatic will be on the horizon.

Okay. And this is where you learn to hate cancer even more. Cancer is made from or comes from the same stock as we are. So it's just as smart as your normal cells, if not smarter. There is emerging data now that patients who have deleterious *BRCA* mutations that are pathogenic in normal cell, when you lose your normal BRCA repair mechanisms and you only have deleterious *BRCA*

mutation present, you essentially have the grounds for cancer being developed. So you have your normal cells, you have a pathogenic *BRCA* mutation and you have a functional *BRCA* mutation. There's multiple base repeats for this pathogenic *BRCA* mutation, so there's a lot of strands in there which lead to amino acids that don't make sense, so the BRCA protein is not normal. When you get metastatic cancer prior to a PARP inhibitor, the cancer cell gets smart, it deletes the functional BRCA checkpoint and all you have is this pathogenic mutation with a bunch of TCGAs that don't make sense or GCATs that don't make sense. After treating with a PARP inhibitor, we're now seeing that cancer is getting smart and is actually restoring *BRCA2* function. So, in this scenario, the codons that have been excess repeats that have led to a deleterious *BRCA* mutation, cancer has gone through and deleted and made a normal BRCA repair mechanism, which not infers resistance to PARP. Now this is no means common, but if you have patients progressing on PARP therapy, there is a real chance that even if there's an inherited *BRCA* germline mutation, the cancer cell's correcting it and that will not be observed in genomic sequencing anymore. So, that's what I do in clinic.

Other important regulatory events, I don't want to steal a lot of thunder today, because I know there's more talks coming. Dabrafenib, trametinib for anaplastic thyroid that's *BRAF V600E* mutated. New indications for adjuvant treatment in melanoma.

And then moving onto non–small cell lung cancer, alectinib for first-line *ALK*-positive non–small cell lung cancer. Afatinib and osimertinib in first-line

EGFR-mutated non–small cell lung cancer, and we'll go through some of the antihormonal therapy.

Again, this is a picture of the BRAF pathway, so you have the Ras/Raf/ERK/MEK pathway when you get a *BRAF* mutation. It's constitutively active, which can be present in about 50% of melanoma cells and then downstream activation of ERK.

The COLUMBUS trial looked at patients with unresectable or metastatic cutaneous melanoma with *BRAF* mutations and a good performance status, and they were randomized to encorafenib plus binimetinib so your Raf/MEK inhibitors versus your BRAF inhibitor, encorafenib monotherapy versus your old standard of care vemurafenib, primary endpoint was progression-free survival of the combo. If you look at the overall response rates, they go from 40% with monotherapy with vemurafenib as a BRAF inhibitor, to 51% with encorafenib to 63% with a new combo.

If you look at the progression-free survival, so comparing encorafenib plus binimetinib, the top line, the blue line, there's a progression-free survival advantage compared to vemurafenib, which you know, you could easily argue is this really a fair comparison because one arm has a MEK inhibitor and the other one doesn't.

Looking at toxicity, we're starting to see potentially less toxicity with the newer iterations of BRAF inhibitors that are coming out. So, vemurafenib, a little bit more fatigue, more pyrexia, more skin toxicity, which is the most characteristic of toxicities for this patient class of fevers and rashes which you have to keep an

eye on, especially the first month to 2 months. And we are seeing more creatine phosphokinase elevated with encorafenib combination therapy.

Moving on to new drug approvals in non–small cell lung cancer. So, osimertinib has classically been FDA approved in the relapse setting in patients with an *EGFR* mutation with a T790M, so threonine is replaced by methionine at the 790th codon, which is a resistance mechanism to the rest of the TKIs, afatinib, gefitinib, and erlotinib. So, now we've got data in the first -line setting which I'll go over, and afatinib, additionally in the first-line setting as well. A little bit of difference, afatinib causes more GI toxicity than the other agents in the class.

Looking at epidermal growth factors, we're all pretty familiar with this. HER2, HER3, EGFR; EGFR when stimulated leads to multiple self-signaling intracellularly, for the Ras/PI3K/JAK pathway, which leads to cell proliferation and decreased apoptosis or programmed cell death. The way that I explain this, generally, is these cells are essentially receptors. If you're born before 1989 – or before 1989 or 1990, I usually say that back in the day, this is like your neighbor stealing your cable, okay? So, the cancer cells are stealing the signal from the receptors to promote cell growth. If you're a millennial or younger, I don't know what we call younger than millennial now, I usually say it's Wi-Fi because they don't know what cable is anymore.

Looking at osimertinib in the first-line setting, patients with locally advanced or metastatic disease who had documented *EGFR* sensitizing mutation with stable CNS disease were randomized to receive osimertinib or

standard of care agents gefitinib/erlotinib, with the primary endpoint of progression-free survival. So again, note this is PFS, this isn't a co-primary endpoint of overall survival. The baseline characteristics were almost exactly the same between the two: mostly, Asian, mostly never smoker, almost all adenocarcinoma, and then 63% had a 19 exon deletion and 37% with an L858R mutation.

If you look at progression-free survival, 18.9 months with osimertinib versus 10.2 months with standard of line therapy. Overall survival not reached in both arms, which is a good thing in this patient population, okay? Why is this so much better? Don't exactly know why. Osimertinib does have the best penetration for the blood-brain barrier, so you might get a little bit more coverage for the CNS. Issues that this eludes to, is historically if somebody is on erlotinib or gefitinib and then they progress, and you're finding resistance mutations, you can switch to osimertinib and it will cover that. If you start with osimertinib and you develop a mutation resistance, where do you go to next? Generally, this would be more historic chemotherapy or potentially neo therapy or you go fishing for *ALK* and *ROS1* rearrangements.

Other new drug approvals, so moving on to prostate cancer. Abiraterone in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer. And then apalutamide, which is the new kid on the block and enzalutamide in patients with nonmetastatic castration resistant prostate cancer. So, sensitive versus resistant.

Prostate cancer has really been an evolving complexity. We've gone from probably 15 years ago having antihormonal therapies with LHRH superagonists and local androgen testosterone agents, and only having mitomycin. I can remember doing clinic at the VA and one of my favorite patients coming in and having less testosterone and being a little bit more emotionally labile, starting his first dose of mitoxantrone and cursing me out because I made him into a bloody Smurf because he's crying blue tears and peeing blue. So, how many of you have seen mitoxantrone used for prostate cancer? So, this is very much the minority now, okay? We've now moved on to incorporating docetaxel more commonly. We've got newer agents for testosterone targets because testosterone is still the main target of this class. And with PARP inhibitors coming in the pipeline, and PI3KCA inhibitors coming in the pipeline, this is probably becoming just as complex as breast cancer.

Looking at abiraterone in castrate-sensitive prostate cancer, so these are newly diagnosed patients, high-risk, but castrate sensitive. With bone scans, they can have metastatic lesions and the Gleason score has to be greater than or equal to 8. Patients were randomized to standard androgen deprivation therapy plus placebos. Placebos because abiraterone you give with prednisone and that was compared to ADT plus abiraterone and prednisone and we're going back to co-primary endpoints, although we're also looking at radiographic progression-free survival and overall survival. So metastatic-free disease is going to be become a new term in the subsequent slides.

Looking at overall survival, there is an overall survival advantage with abiraterone, in combination with ADT compared to placebo.

Looking at radiographic progression-free survival versus just chemical, abiraterone does have a radiographic progression-free survival benefit as well.

Looking at apalutamide in nonmetastatic castration-resistant prostate cancer, so if patients were included if they had nonmetastatic disease and a PSA doubling time of less than or equal to 10 months. Again, kind of the same setup: ADT plus apalutamide versus ADT plus placebo. Baseline characteristics that were more unique, but equal in both groups, 76% had a prostatectomy or radiation and 73% were on a first-line antiandrogen already. So this is in my mind second-line therapy.

Looking at the Kaplan-Meier for metastasis-free survival, apalutamide does have a benefit over just ADT monotherapy, has a ratio of 0.28, so all patients, again, are going to progress at some point, but you're 72% less likely to progress if you're on apalutamide plus ADT.

Looking at enzalutamide in nonmetastatic castration-resistant prostate cancer, so M0 castrate-resistant prostate cancer patients, PSA doubling time of less than 6 months or within 6 to 10 months and patients could have a baseline use of bone targeting agents. They were randomized to enzalutamide plus ADT or ADT alone, and the primary endpoint is the MFS or time to radiographic progression or death.

So median metastasis-free survival 36.6 months versus 14.7 months. This terminology is new and is probably going to be used for most agents in the peri-first-line, second-line setting for prostate cancer going forward.

If you look at the time to use of antineoplastic therapy, 39.6 months versus 17.7 months, so you're almost looking at a double of time to decreasing antineoplastics. Overall survival, still immature, can't look at. What's more unique is you do see more hypertension it looks like with this drug, than what's probably more classically thought of. While there's an impressive 2-year median survival, MFS is the new terminology on the block. As far as survival, we're talking prostate cancer patients here, so these patients can do well for a long time and we're probably not going to have the results of that for at least another decade.

Fracture may also be higher in patients compared to placebo so why that is, maybe it's just doing a better job of depleting androgen, increasing risk of fractures, so these patients should especially be on bone-modifying agents. So, again, go back to best practices and ASCO, NCCN guidelines.

Looking at the toxicity profile between the common ones, enzalutamide, abiraterone, and apalutamide just to kind of give you a 30,000-foot view, you see less hypertension with enzalutamide, probably the most with abiraterone, and LFT elevations are the most with abiraterone, as well.

Cabozantinib was also recently FDA approved for the first-line treatment of advanced renal cell carcinoma. Looking at patients with advanced RCC, mostly clear cell, had a measurable disease. And, again looking at that International Risk Stratification for intermediate or poor risk, patients were

randomized to cabozantinib versus sunitinib and looking at the results, median progression-free survival at the top, the yellow curve is cabozantinib 8.2 months, and sunitinib 5.6 months, so there is a benefit. How to interpret these results with immunotherapy at the moment for combination, my gestalt is at least in the clinics that I service, we probably see more immunotherapy used, but really triaging which patient is best based on oral, whether they live in a rural or urban area, how are they going to do with immunotherapy, contraindications to immunotherapy such as rheumatologic conditions should be taken into effect when figuring out which regimen to use first.

Looking at toxicity, the main ones I'm going to point out, more hypertension with cabozantinib over sunitinib and more hepatotoxicity, increased AST, increased ALT is about double. For the most part, otherwise they are very similar and you see a little bit less thrombocytopenia with cabozantinib.

This is the FDA approval that I think throws most of my colleagues for a loop, is bevacizumab being FDA approved for previously untreated ovarian cancer in the first-line setting. So, this trial is a little bit more complicated. You will also know if you're savvy enough, that the reference at the bottom is from 2011, which is in complete contrast to the rest of the agents we talked about. But, GOG-0218 was looking at three arms, carbo and pac plus placebo, arm one. Arm two, carbo, pac and bev. Bev you got for the six cycles you got your chemo and then the third arm was carbo/pac for six cycles with bevacizumab in more of a maintenance point of view for 15 months. This gets a little bit complicated because this has been chopped up on multiple different manuscripts and most

recently presented at ASCO over the summer looking at the two groups, and this gets a little confusing is the investigator-related investigator responses and the independent research council responses. So, if you look at the blue lines, the blue lines are really the combination of chemotherapy plus bev plus maintenance, at the top there, compared to the standard of care. The blue and the gray, so if you look at bev, bev is always the blue regimen. Regardless of how you chop this, there is a benefit for bevacizumab with maintenance therapy. If you're looking at the investigator-related outcomes, the median PFS is 18 months versus 12 months. If you're looking at the independent review council, it's 19 months versus 13 months, so they're pretty spot on. This wasn't the only trial that has led to the FDA approval. The Feds took a few of the trials into context. This is probably just coming up with the bulk of the data, as well as the most photogenic that I could put up on the slide for you, to be honest.

Updates from ASCO over the summer, the hazard ratio for stage IV patients, 0.774, and median overall survival with the updates for bev, 34.5 months versus the control. So it looks like there is potentially a 3- to 4-month overall survival benefit for stage IV disease for the subgroups, so this is unique to the subgroup, okay? Keep that in mind.

So summary, and I think I maybe a minute early. There's a lot of agents that have pretty much been moved up in first-line therapy. We're seeing the explosion of CDK4/6 inhibitors with AIs for hormone receptor–positive breast cancer, PARP inhibitors for breast cancer, this will expand as most of the talks have discussed with somatic mutations, BRCAness. Myriad has panels for

homologous recombination deficiency that will probably expend other cancers, as well, looking at BRCA reversions as a mediation of resistance. There are updates to TKIs, which is a good thing because those drugs are very well tolerated. I always tell patients when they come in the room and we're going to put them on an EGFR inhibitor, they're lucky – I don't say lucky, to a patient – but you're lucky you're going to look like you're 16 years old again. You're going to have acne on your face and your back and your chest.

New approvals for BRAF. There's new iterations of drugs coming out, prostate cancer is becoming more complex, I think we'll see more PARP inhibitors in the future, and bevacizumab has – it's an oldie but a goodie, it's not going anywhere.

So, at this point, I will go ahead and entertain any questions. Seventy-two slides.

FEMALE I do have one question. When using the CDK4/6 drugs in metastatic breast cancer as first line, what is the time to onset for this drug?

DR. KIEL The question is what's the time to onset? Do you mean when you start to see initial response or –

FEMALE Correct. Correct. When I get a metastatic breast, many times we need – they're pretty far progressed.

DR. KIEL Yeah, you should start to see some response, at least clinically on your exam, within the first month, month-and-a-half. This is also complicated exceedingly by the fact that these drugs are used in combination. So

in a rare minority of patients, they might have *ESR1* mutations, which could promote resistance to hormonal therapy, except for fulvestrant. But for the most part, you should start to see a little bit of clinical response in the first month or two. The exception is there is some data with abemaciclib, for phase 1/phase 2 data with monotherapy across multiple disease states, showing you should see something with monotherapy activity in I think about 2 to 3 months. Does that help?

FEMALE I have a question about the BRCA reversions that you're doing the research on.

DR. KIEL Yes.

QUESTION Does that mean that since most germline *BRCA* positive or triple negative that there might be a possibility that estrogen could be in play in the future for them, as well?

DR. KIEL So with BRCA reversions, even if the *BRCA* mutation is corrected in the cancer cell, it really would not at this point, have no pathologic consequences for hormonal receptor expression for ER/PR, there would be two independent pathways. That's not to say that over time, breast cancer can change to where patients can be ER/PR HER2 negative and then come back as positive and vice versa, that still can happen but it's exceedingly rare and independent of the *BRCA* mutations.

FEMALE I was wondering if you could comment on the prostate drug approvals in nonmetastatic. There the ADT is compared to ADT plus either the abi or the enzalutamide. We would always use bicalutamide in that situation,

but that was not the comparator arm. And in stage III lung cancer, the immunotherapy for a year is compared to nothing and we always would give additional consolidative chemotherapy after the chemo-radiation was finished. Could you comment on those two points?

DR. KIEL Sure. So, the first one was ADT and using anti-testosterone agents like bicalutamide or potentially, some institutions use degarelix for their drug of choice. To be honest, that's the way, in consultation the Feds with the drug company wanted it done. It's not unreasonable, and a lot of clinical practices still do what you do. A purist would probably say that looking at overall survival advantage, there isn't going to be one. But I think the way that these trials are smart in taking things into account was looking at the PSA doubling time and most of those patients if their doubling quickly you could get around with ADT monotherapy. And then the second question was related to durvalumab? Oh, so giving chemotherapy past chemo rads. So, that wasn't necessarily a standard of care everywhere, that's why they didn't do it in the trial because there's not enough data to show that that leads to an overall survival advantage.

FEMALE We have a patient, 50-year-old-gentleman with stage IV colon who has Lynch. And we've had him on pembrolizumab, almost going on two years. We're afraid to take him off –

DR. KIEL Yeah.

FEMALE I'm wondering if there's any data on long-term PD-L1.

DR. KIEL So, the *New England Journal of Medicine* trial that was published, I think 2 years ago for treatment agnostic, which was mostly colorectal cancer, some of those patients I know from experience are around like 30 or 40 months. So, the short answer is we don't know what to do if you stop it. We don't, I don't, nobody does. I don't think anybody is going to give you a clear answer. I think we're still teasing that out of how much immunotherapy is enough. We're kind of getting into the problems that lymphomas used to have with maintenance rituximab where they would be on it long term. The short answer is we don't know. The potential concern is if you have these patients on long-term and they start to develop *JAK* mutations, which regulate STAT pathways, those decrease the probability of immunotherapy going forward, but those are also rare patient populations. I think what is being looked at, is potentially giving patients trials of 12 months and then stopping and restarting at the time of relapse, but none of that data has been published yet. Those patients are still recruiting at trials.

Okay. If you need anything, I will hide out in the back. Please come up and talk to me.

[END]