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Transcript and References

Slide 1

Hi, I'm Dr. Richard Finn from the Division of Hematology/Oncology at the Geffen School of Medicine at UCLA. Thank you for joining me today for this educational activity reviewing the role of cyclin-dependent kinase (CDK) 4 and 6 inhibitors in the management of breast cancer.

Slide 2

When we're talking about CDKs, we're focusing on a target that plays a critical role in controlling cell division. If we step back and just think about the cell cycle, which we all learn about in our training, we remember that the cell cycle under normal conditions is very tightly controlled and is divided into several distinct phases, and the role and goal of each phase is to prepare for the next phase and ultimately mitosis and cell division.

During each transition point from each phase to the next, there are key regulatory components and proteins and genes involved that regulate cell division so that daughter cells do not contain genetic errors. We know the four phases are G1, S, G2, and then eventually mitosis.

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CDKs are a large family of serine/threonine kinases that play a role in regulating these transitions from one phase of a cell cycle to the next. As their name implies, they do not function by themselves but interact with regulatory subunits called the cyclin proteins. Together, cyclins and their corresponding CDK function to regulate cell division.

There are several known CDKs and cyclins. In general, they play specific roles during specific parts of the cell cycle. In addition, specific CDKs interact with specific cyclin proteins.

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For example, CDKs 4 and 6, which play a key role in regulating their transition from G1 to S, typically associate with D-type cyclins; CDK2 proteins interact with the E- and A-type and again regulate cell cycle progression at various stages. There are also some CDKs that function as transcription factors and not as catalytic enzymes.

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In breast cancer, alterations in the cyclin D/CDK 4/6 pathway have been described. Throughout the years of basic science, we've understood that amplification of cyclin D1 occurs in a subset of breast cancers. Overexpression also occurs. There can be alterations in CDK 4, both amplification and overexpression. Ultimately, retinoblastoma (Rb) loss—the loss of the *RB* gene product that is critical in regulating G1 to S and is the target for CDK 4/6—is lost in a subset of breast cancers.

There can also be loss of negative regulators of the pathway, such as p16 and p27, which when lost cause this pathway to become hyperactive. When correlating all these genetic alterations with various clinical findings, such as response to antiestrogens and prognosis, we see that in some studies, the alterations appear to be favorable, and in others they are negative prognostic factors.

But ultimately in breast cancer, when we think of the various molecular subtypes of this disease, we know that breast cancer can be driven by growth factor signaling, which in some cases involves peptide growth factors such as the human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor pathways, among others, or steroid growth factors such as estrogen. Regardless of whether these breast cancers are driven by peptide growth factors or steroid growth factors, the common denominator is that these pathways feed into the cyclin D1/CDK 4/6 pathway.

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On this slide, we see a diagram of how CDK 4/6, cyclin D, and Rb play a role in cell cycle progression. As you can see on the outside of the cell, there are various mitogenic factors, such as estrogen binding to the estrogen receptor, and other peptide growth factors such as the HER family driving increased expression of cyclin D1, which then interacts with CDK 4/6.

Together, cyclin D1 and CDK 4/6 are responsible for adding phosphates, or hyperphosphorylating, the Rb protein in the nucleus. Once Rb is hyperphosphorylated, it

releases the E2F transcription factor to allow preparation and transition into S phase, and this hyperphosphorylation of Rb is a critical point in this G1 to S progression.

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There are various CDK 4/6 inhibitors in development—palbociclib, ribociclib (previously known as LEE011), and abemaciclib—the LY compound on the diagram. All are designed to block the CDK 4/6 kinase and therefore block hyperphosphorylation of Rb, and therefore induce a G1 arrest and prevent cell cycle progression.

One of the first selective CDK 4/6 inhibitors to go to clinical development is this compound, palbociclib. As you can see from its kinase profile, it is very selective for CDK 4 and 6 with the low IC_{50} (50% inhibitory concentration). This is different from early generation CDK inhibitors, which were very nonselective and had activity against a broad spectrum of CDKs, and as a result did not function very well in the clinic.

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Critical to the development of any new drug in cancer medicine is to identify a patient population that we think is most likely to benefit. This slide demonstrates some of the pivotal preclinical data that identified a role for CDK 4/6 inhibitors in estrogen receptor (ER)–positive breast cancer. As you can see along the x axis, there's a large panel of breast cancer cell lines color-coded according to their molecular subtype. Their sensitivity to palbociclib is on the y axis—the lower number meaning the cell lines that are more sensitive.

As you can see, the cell lines that were most sensitive to palbociclib represented the luminal ER-positive breast cancer subtypes as well as some of the HER2 amplified cell lines, whereas those that were most resistant tended to be the non-luminal or ER-negative lines. This led to a hypothesis that perhaps if we were to move a drug like palbociclib or other CDK 4/6 inhibitors into the clinic, we would focus on the ER-positive subgroup.

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As a pathway to clinical development, I, Dr. Slamon, and other colleagues at UCLA looked preclinically at the role of palbociclib in combination with tamoxifen in vitro in several ER-positive cell lines. As you can see, there was a synergistic interaction between antiestrogens and CDK 4/6 inhibition in increasing the amount of cell cycle arrest and growth inhibition.

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This led to an open-label, randomized, phase 2 study, the PALOMA-1 study, to test the idea of whether this laboratory observation would hold up in the clinic. This study was designed in two parts. Both parts of the study enrolled women that were ER-positive/HER2-negative, postmenopausal, with advanced breast cancer and were not treated for metastatic disease. They could have treatment for adjuvant disease, but had not received therapy yet for their advanced disease and were randomized between the combination of palbociclib and letrozole versus letrozole alone.

Palbociclib was given 125 mg daily, 3 weeks on/1 week off, and these cohorts were accrued sequentially, initially just based on ER-positive/HER2-negative, then another cohort, ER-positive/HER2-negative, but also evaluating patients who have molecular alterations in the cyclin D1 pathway, such as cyclin D1 amplification or loss of p16, the negative regulator, the idea being to try to select a finer group of patients other than ER-positive alone.

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The patients were well balanced for various prognostic factors. There were some slight imbalances, perhaps a little more visceral disease in the letrozole-alone arm. However, I would like to point out that about half the patients in each arm had a new diagnosis or had never had prior systemic treatment in the adjuvant setting, but approximately one-third of patients had prior anti-hormonal treatment such as tamoxifen or even aromatase inhibitors.

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This was a positive study. This was an open-label study, but there was a significant improvement in progression-free survival (PFS)—the primary endpoint—with the addition of palbociclib to letrozole. Here you see the hazard ratio is 0.488 for PFS, or approximately a 51% decrease in the risk for progression with the addition of palbociclib. Median PFS was improved by about 10 months, from about 10.2 months with letrozole alone to just over 20 months with the addition of palbociclib.

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Here on this forest plot, you can see that across many clinically important subgroups, there was a consistent benefit with the addition of palbociclib to the letrozole. That includes cohorts 1 or 2, whether you considered just ER-positive or had the additional markers of cyclin D1 and p16 loss. Both groups had a significant improvement in PFS.

There was also a significant improvement whether they had visceral disease or bone-only disease, prior chemotherapy, prior antiestrogen therapy, or prior systemic therapy. There was significant improvement for patients who had de novo disease or those who had prior adjuvant chemotherapy or any adjuvant therapy.

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Secondary endpoints include response rate; there was a significant improvement in response rate. If we look at all randomized patients, not just those with measurable disease, the improvement in response was from 33% to 43%. If we look at patients who just had measurable disease, the improvement was from 39% to 55%, so there was a consistent benefit in improving response.

Arguably, response rates of 55% with the combination of CDK 4/6 inhibition and letrozole rival any combination chemotherapy regimen. If you include the stable disease rate for more than 6 months of 32% in all patients, we're approaching a disease control rate of 80% or higher.

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Certainly, we need to consider side effects when evaluating a new agent in cancer medicine. As we see on this slide of the side-effect profile of the combination of palbociclib and letrozole, the most common adverse events that were observed were leukopenia and neutropenia. This was an expected finding—given the mechanism of action of a CDK 4/6 inhibitor—that it would affect the bone marrow, which is proliferating. In the dosing regimen, palbociclib was dosed 3 weeks on/1 week off to allow for bone marrow recovery. Remarkably, even though we had neutropenia, no cases of febrile neutropenia were seen.

When we talk about grade 3 neutropenia, we mean an absolute neutrophil count of 500 to 1,000. Even though that happened with a high frequency, it was not complicated by serious infections and typically resolved on its own; growth factors in general were not required for managing patients. Importantly, other significant side effects of chemotherapy were uncommon, such as complete alopecia, diarrhea, nausea, and vomiting. Taken together, the combination had a very manageable side-effect profile that balanced out the impressive results in improving PFS.

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Based on these data, palbociclib was granted accelerated approval by the US Food and Drug Administration (FDA) on February 3, 2015, for the indications studied in the PALOMA-1 clinical trial—that is, in combination with letrozole for the treatment of advanced postmenopausal breast cancer that is ER positive/HER2 negative.

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Given that it was an accelerated approval, a confirmatory study was required. The PALOMA-2 study enrolled 666 women in a 2:1 fashion. It was double-blind, placebo-controlled to letrozole plus palbociclib 125 mg daily, 3 weeks on/1 week off, versus letrozole and placebo, again selecting patients only for ER-positive/HER2-negative status, given the cyclin D1 p16 evaluation in PALOMA-1 did not add any benefit over ER positive alone. The results of this study will be presented at the American Society of Clinical Oncology (ASCO) 2016 meeting. *[Editor's note: The clinical benefit and safety of palbociclib and letrozole in postmenopausal women with ER-positive, HER2-negative advanced breast cancer were confirmed in the randomized phase 3 PALOMA-2 study.*]

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Last year at the ASCO 2015 meeting, results of PALOMA-3 were presented. This study evaluated palbociclib with fulvestrant versus placebo and fulvestrant and, unlike PALOMA-1 and PALOMA-2, it enrolled patients who had endocrine resistance that had progressed either on a prior endocrine regimen or within 12 months of completing adjuvant therapy, and these patients had to have had an aromatase inhibitor. Also, this study included patients who were premenopausal as long as they were on ovarian suppression.

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These are the baseline characteristics for the study. About 20% of patients in each arm were premenopausal or perimenopausal.

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What was reassuring from the PALOMA-3 study is that the side effect profile of palbociclib mimicked the smaller PALOMA-1 study; that is, the most common side effects were neutropenia and leukopenia. But, again, there was no increase in the incidence of neutropenic fever compared with fulvestrant alone. Again, these side effects were managed with dose delays or dose reductions.

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The primary endpoint of this study was PFS. Again, there was significant improvement in PFS with the addition of palbociclib to fulvestrant, improving PFS from 3.8 months to 9.2 months. This correlated to a hazard ratio of 0.422 and was very statistically significant.

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If we look across patient subgroups, as seen in PALOMA-1, a consistent benefit with the addition of palbociclib to fulvestrant based on several important clinical criteria, essentially all of them showing a benefit with the addition of palbociclib.

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There was a quality-of-life assessment included in PALOMA-1, and importantly despite having some increased side effects compared with fulvestrant alone, there was an improvement in quality of life with the addition of palbociclib.

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There are several ongoing studies with palbociclib in breast cancer. Perhaps most important is the movement of palbociclib to the adjuvant setting. This study, the PALLAS study, is currently being conducted through the US cooperative groups and will be evaluating palbociclib for 2 years plus standard endocrine therapy versus endocrine therapy alone to see if this improvement in PFS that we've seen in PALOMA-1 translates into a decrease in recurrence for early breast cancer.

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There are other CDK 4/6 inhibitors in development. This compound abemaciclib is a very potent inhibitor of CDK 4/6, as you can see on this kinase profile.

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It's been evaluated in several single-arm studies. This study looked at a dose-expansion cohort in patients with advanced breast cancer. Unlike palbociclib, abemaciclib is dosed daily without a break on a 28-day cycle.

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Abemaciclib showed impressive single-agent activity. Here on this waterfall plot, you can see a number of patients have had significant decreases in their tumor burden, as well as a number having prolonged stabilized disease. And as we saw from the preclinical data, the patients who are achieving this are those that are hormone receptor-positive.

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As mentioned before, many of these responses were maintained for a long time, and again this was in a cohort of patients who had several prior treatments.

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This slide shows the response data between the hormone receptor-positive and hormone receptor-negative patients. This study accrued all patients with metastatic breast cancer, but it was observed that it was the patients who were hormone receptor-positive who had responses and prolonged stabilization of disease, supporting the idea that abemaciclib could play a role in ER-positive breast cancer.

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The side effect profile with abemaciclib is similar to palbociclib and other CDK 4/6 inhibitors. There might be a suggestion that the incidence of leukopenia might be a little lower, whereas the incidence of gastrointestinal toxicity might be a little higher. This will have to be further evaluated in larger studies.

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However, based on this impressive single-agent activity in patients with advanced breast cancer that has been heavily pretreated, abemaciclib was granted a Breakthrough Therapy Designation by the FDA, and further action on that is awaited.

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Meanwhile, abemaciclib has moved into several phase 3 studies. The MONARCH 2 study is evaluating abemaciclib with fulvestrant versus fulvestrant alone in patients with advanced breast cancer that had prior treatment with antiestrogens.

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The MONARCH 3 study is looking at abemaciclib with a nonsteroidal aromatase inhibitor versus placebo and a nonsteroidal aromatase inhibitor. This study is very similar to the PALOMA-1 and PALOMA-2 studies.

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Ribociclib is the other CDK 4/6 inhibitor that is in advanced development. Like the prior two compounds, it is very selective for CDK 4/6 versus other CDKs or other kinases.

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Like the other compounds, this drug has demonstrated single-agent activity. Like palbociclib, it is dosed 3 weeks on/1 week off to help manage the bone marrow suppression that is seen. It's being evaluated as a single agent as well as in combination with other novel agents.

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The MONALEESA program is evaluating ribociclib in various indications. MONALEESA-1 is a presurgical biomarker-driven study, whereas MONALEESA-2 and MONALEESA-3 are phase 3 randomized studies in combination letrozole or fulvestrant, respectively, very similar to the path taken by palbociclib and abemaciclib. Finally, MONALEESA-7 is a phase 3 study in combination with antiestrogens. This appears to be the only study that is exclusively enrolling only premenopausal women.

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This is the schematic for MONALEESA-2, a 1:1 randomization of ribociclib 3 weeks on/1 week off and letrozole, versus letrozole and placebo, the primary endpoint being PFS. Enrollment to this study is completed and results are awaited. *[Editor's note: The phase 3 MONALEESA-2 trial of ribociclib and letrozole in advanced HR-positive, HER2-negative breast cancer was stopped due to positive efficacy results at the interim analysis.]*

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MONALEESA-3, like the PALOMA-3 study, is evaluating ribociclib and fulvestrant versus fulvestrant and placebo. The primary endpoint for this study is PFS.

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And, finally, MONALEESA-7 is looking at the premenopausal cohort with ribociclib either with tamoxifen or an aromatase inhibitor with ovarian suppression, or those agents with placebo. Again, PFS is the primary endpoint.

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At the San Antonio Breast Cancer Symposium in 2015, data were reported on ribociclib in combination with the phosphoinositide-3 kinase inhibitor alpelisib and letrozole. There are data to suggest that there could be synergic interaction between blocking both the CDK 4/6 pathway and the phosphoinositide-3 kinase pathway.

This was a phase 1 study that evaluated a dose and supported the idea that perhaps a triplet combination could further delay and control ER-positive breast cancer, rather than letrozole alone or letrozole and CDK inhibition. It's a very exciting idea and we await further data.

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In addition, there was a study looking at ribociclib with everolimus and exemestane. As we know, everolimus and exemestane is an FDA-approved regimen for hormone-refractory ER-positive breast cancer. They evaluated the triplet combination and are evaluating various doses of everolimus in this phase 1 study to help manage side effects. Further data regarding efficacy are awaited as well.

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Now we will talk about some cases that represent potential indications for CDK 4/6 inhibition in ER-positive breast cancer.

The first case involves a 60-year-old woman who is postmenopausal, initially diagnosed with a stage II ER-positive/HER2-negative breast cancer 3 years ago. This was found during routine healthcare maintenance. She underwent an evaluation and was found to have a well-differentiated tumor. She is treated with breast-conserving surgery, radiation, and then adjuvant letrozole. She is otherwise a healthy and active lady.

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She's been tolerating her letrozole without significant side effects; however, on routine follow-up she's noted to have some abnormalities in her liver enzyme levels. This refers her to a computed tomography evaluation, and she's found to have a 3-cm mass on the liver. Biopsy confirms recurrence of her ER-positive/HER2-negative breast cancer.

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At this time, we'll consider various treatment options. They include chemotherapy, exemestane, everolimus and exemestane, fulvestrant alone, or fulvestrant and palbociclib.

Certainly, there are data to support all of these options. However, based on the PALOMA-3 data, fulvestrant and palbociclib provide a significant improvement in PFS versus fulvestrant alone. This is disease that is progressing with letrozole, a nonsteroidal aromatase inhibitor, and therefore drugs like letrozole or anastrozole are less likely to be active. The patient does have visceral disease, but does not appear to be at risk for immediate death from her tumor, and therefore an endocrine-based approach is reasonable. Certainly, chemotherapy has activity here. However, in an effort to delay the toxicity of chemotherapy, an endocrine-based approach is very appropriate, and we know that fulvestrant plus palbociclib provides a significant improvement in PFS.

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Case 2 is a 54-year-old woman who presents to her doctor complaining of bone pain. During her evaluation, she is noted to have a right-sided breast mass and elevated alkaline phosphatase. Biopsy is performed and pathology is consistent with an ER-positive/HER2-negative breast cancer. Staging studies reveal bone-only disease but no visceral involvement.

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She is started on a bisphosphonate as well as palbociclib 125 mg daily, 3 weeks on/1 week off, and letrozole. Certainly, other options would include letrozole alone or chemotherapy. However, she has newly diagnosed metastatic breast cancer, and we saw that the addition of palbociclib to letrozole provided a 10-month improvement in PFS over letrozole alone. And, in fact, for patients with bone-only disease, this was even greater.

She comes in on cycle 1 day 14, as recommended in the FDA label for the first 2 cycles, to have her white blood cell count closely monitored. Her laboratory results are generally

normal except for a white blood cell count of 2,000 and her absolute neutrophil count (ANC) is 1,200. While her ANC has fallen, it is still grade 2, and no further adjustments in dose are required.

She returns 2 weeks later for cycle 2 day 1. At this time, she finished her 1 week off of palbociclib, and today her white blood cell count is 1,800 with an ANC of 800. Her ANC is less than 1,000. Per the guidelines in the label for palbociclib and as was performed in the clinical studies, patients did not start their next cycle of palbociclib until their ANC was at least 1,000.

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She continues on letrozole but palbociclib is withheld. She returns a few days later and her white blood cell count is now 1,800 and her ANC is 1,100. She resumes palbociclib because her ANC is greater than 1,000 on a 3 week on/1 week off schedule. She continues to have her complete blood cell count checked on day 1 of each cycle. After 3 months on treatment, staging studies show that she has stable disease on imaging and her breast mass is smaller on exam, and she continues on treatment.

Should her white blood cell count and ANC specifically be less than 1,000 on any day 1, then it is recommended that her dose be withheld until her white blood cell count recovers. Dose reductions should be withheld only for patients who have febrile neutropenic or other serious non-hematologic toxicity or prolonged delays in recovering her white blood cell count.

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We are just scratching the surface with the role of CDK inhibitors in breast cancer. There are a lot of unanswered questions. There are ongoing randomized studies evaluating CDK 4/6 inhibitors in the various indications of advanced breast cancer, as well as with various antiestrogen combinations. Ultimately, we're excited to see if the introduction of CDK inhibitors in early breast cancers increases the cure rate for this disease.

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Preclinical data suggest there's a role for CDK inhibition in HER2-amplified breast cancer, and studies of CDK inhibitors in combination with HER2-directed therapy are ongoing.

The mechanisms of acquired resistance to CDK 4/6 inhibition are still largely unknown. These will have to be elucidated so we have a better understanding of how to manage

patients once disease progresses on a CDK 4/6 inhibitor. In addition, while the first approval for these drugs is in breast cancer, I think there's a lot of excitement to see how CDK 4/6 inhibitors will play a role in other malignancies, as well as other types of breast cancer.

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Thank you very much for your attention, I hope you found this program useful in understanding the preclinical and clinical development of CDK 4/6 inhibitors in breast cancer.

References

Arnold A, Papanikolaou A. Cyclin D in breast cancer pathogenesis. *J Clin Oncol.* 2005;23:4215-4224.

Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Rev Drug Discov.* 2015;14:130-146.

Bardia A, Chavez-MacGregor C, Modi S, et al. Triple blockade with LEE011, everolimus, and exemestane in women with ER+/HER- advanced/metastatic breast cancer: results from a phase 1b clinical trial. *Eur J Cancer* 2014;50:163.

Eli Lilly and Company. NCT02107703. A study of abemaciclib (LY2835219) combined with fulvestrant in women with hormone receptor positive HER2 negative breast cancer (MONARCH 2). https://clinicaltrials.gov/ct2/show/NCT02107703. Accessed June 9, 2016.

Eli Lilly and Company. NCT02246621. A study of nonsteroidal aromatase inhibitors plus abemaciclib (LY2835219) in postmenopausal women with breast cancer (MONARCH 3). https://clinicaltrials.gov/ct2/show/NCT02246621?term=NCT02246621&rank=1. Accessed June 9, 2016.

Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res.* 2016;18:17.

Finn RS, Crown JP, Lang I, et al. The cyclin dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of

oestrogen receptor positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. *Lancet Oncol*. 2015;16:25-35.

Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res*. 2009;11:R77.

Finn RS, Martin M, Rugo HS, et al. PALOMA-2: primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in post-menopausal women with ER+/HER2- advanced breast cancer (ABC). *J Clin Oncol.* 2016;34: abstract 507.

Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther.* 2004;3:1427-1438.

Infant JR, Shapiro G, Wittereen P, et al. A phase 1 study of the single-agent CDK4/6 inhibitor LEE011 in pts with solid tumors and lymphomas. *J Clin Oncol.* 2014;32:5S.

Juric D, Hamilton E, Garcia Esteves L, et al. Phase Ib/II study of LEE011 and BYL719 and letrozole in ER+, HER2-negative breast cancer: safety, preliminary efficacy and molecular analysis. *Cancer Res*. 2015;75:P5-19-24.

Kim S, Loo A, Chopra R, et al. LEE0011: an orally bioavailable, selective small molecule inhibitor of CDK 4/6-reactivating Rb in cancer. *Mol Cancer Ther.* 2013;12:R02.

Malumbres M. Cyclin-dependent kinases. *Genome Biol.* 2014;15:122.

Menu E, Garcia J, Huang X, et al. A novel therapeutic combination using PD 0332991 and bortezomib: study in the 5T33MM myeloma model. *Cancer Res.* 2008;68:5519-5523.

Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol*. 2001;19:2596-2606.

Musgrove EA, Caldon CE, Barraclough J, et al. Cyclin D as a therapeutic target in cancer. *Nat Rev Cancer.* 2011;11:558-572.

Novartis Press Release. May 18, 2016. MONALEESA-2 trial of Novartis' LEE011 (ribociclib) stopped due to positive efficacy results at interim analysis in HR+/HER2- advanced breast cancer. https://www.novartis.com/news/media-releases/monaleesa-2-trial-novartis-lee011-ribociclib-stopped-due-positive-efficacy. Accessed June 28, 2016.

Sutherland RL, Musgrove EA. CDK inhibitors as potential breast cancer therapeutics: new evidence for enhanced efficacy in ER+ disease. *Breast Cancer Res.* 2009;11:112.

Tolaney SM, Rosen LS, Beeram M, et al. Clinical activity of abemaciclib, on oral cell cycle inhibitor, in metastatic breast cancer. *Cancer Res*. 2015;75: P5-19-13.

Turner N, Huang Bartlett C, Cristofanilli M. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2015;373:1672-1673.

Turner NC, Ro, J, Andre F, et al. PALOMA3: A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy. *J Clin Oncol*. 2015;33: abstract LBA502.

Yu Q, Sicinska E, Geng Y, et al. Requirement for CDK4 kinase function in breast cancer. *Cancer Cell* 2006;9:23-32.