

Tim Hunt, and Paul Nurse was associated with identifying this biology in normal cells. For some time now, it's also been identified that dysregulation of the cell cycle is a hallmark of cancer, and this concept has been pursued aggressively as a new treatment modality in different malignancies. In breast cancer specifically, a disease that is driven by growth factors such as estrogen, it has been identified that these growth factors signal through the cyclin-D1, CDK-retinoblastoma (Rb) pathway. It is the interaction between cyclin-D and CDK4/6 that's responsible for driving the hyperphosphorylation of Rb and then allowing for the transition from G1 to S phase and further cell cycle progression.

In the context of breast cancer, there's been interest in targeting this pathway, ie, the CDK-Rb pathway, as not only estrogen receptor but other growth factor/pathway such as the epidermal growth factor (EGF) pathway, the HER2 pathway, and other receptor tyrosine kinases, as well as intracellular kinases such as phosphoinositide 3-(PI3)-kinase and mitogen-activated protein (MAP) kinase, signal through it.

One of the big moves toward [their] clinical development in breast cancer came from laboratory work that was done at UCLA in collaboration with Pfizer.<sup>9</sup> Dennis Slamon and myself and others, collaborating with Pfizer, did a preclinical evaluation with a compound, which at the time was known as PD-0332991, which was an early compound designed to specifically inhibit just CDK4/6. In preclinical evaluation without any specific preconceived notion of what subtype of breast cancer this drug might work in, we showed that this compound really had preferential activity in ER-positive breast cancer cell lines and also in HER2-positive cells lines. This was in contrast to those that would be of the non-luminal or basal/triple-negative

When you look back, there are certain observations in ER-positive breast cancer, molecularly, that are underpinnings for this observation. They appear to have an intact CDK-RB pathway, and therefore blocking that pathway has a growth inhibitory effect in these models. Then, we showed that this compound performed synergistically with the anti-estrogen tamoxifen *in vitro*. Based on that synergy, we designed a phase I/II clinical study that eventually became known as PALOMA-1.<sup>8,10</sup> There are now other CDK4/6 inhibitors in development, ribociclib and abemaciclib, which are also following along in the development plan of palbociclib based on these early observations.

**Moderator:** Clinical trials utilizing CDK4/6 inhibitors in breast cancer are focused on HR/ER-positive breast cancer. What is the reason for focusing on this population?

**Dr Finn:** Breast cancer is not one disease; molecularly, it's a very diverse disease. However, in the clinic, we still approach it as three diseases, which are HER2-positive, ER-positive, or triple-negative. The backbone of treatment for each of those subtypes is HER2-directed therapy, endocrine therapy, or chemotherapy, respectively. The preclinical data pointed us toward

this ER-positive subset and also demonstrated the synergy with anti-estrogens, which really set the stage to test this laboratory hypothesis in the clinic. I said before, in retrospect maybe, you could have hypothesized that ER-positive breast cancer would be a group that might benefit because the incidence of RB loss, a likely resistance marker to CDK4/6 targeted agents, for example, is very uncommon. Also, Rb loss is more common in triple negative breast cancer which explains why these drugs are not likely to be very effective there.

In addition, we know that estrogen signaling and several of the hypothesized mechanisms of resistance to estrogen signaling—such as increased peptide growth factor signaling or receptor tyrosine kinase activation, which could mediate estrogen resistance, also commonly converge on the CDK4/6 pathway. So, [there were] several pieces of evidence that suggested that this would be a group of patients that may benefit from this approach. And put together, ultimately, these pieces of evidence paved the path for clinical testing of CDK4/6 inhibitors in this specific population.

**Moderator:** What, in your opinion, were some of the reasons that the first-generation CDK inhibitors never took off despite acceptable preclinical study data?

**Dr Finn:** As I mentioned earlier, the biology behind cell cycle regulation control has been known for some time, and it is not a very big step to say, in cancer, [that] this pathway is dysregulated. Therefore, if we target the proteins that regulate the cell cycle or loss of cell cycle control, then maybe that would be an appropriate way to treat cancer. This is what led to the development of the first-generation CDK inhibitors. The first generation or earlier CDK inhibitors tended to be pan-CDK; they were not very specific. And, in doing so, they were also associated with what looked to be cytotoxicity, meaning they did not differentiate themselves much from a chemotherapy effect and had broad preclinical activity. They were non-selective against cancer cells versus normal cells, and that became very apparent in clinical development in that dose-escalation studies were difficult because of toxicity.

In addition, the earlier compounds did not have the best pharmacokinetic properties and were somewhat disappointing. They never really demonstrated significant clinical activity and really had no specific direction of where to go in the clinic with respect to patient selection. These factors drove the interest in identifying compounds that target specific CDKs in hopes that these would be more effective and less toxic and have more on-target tumor effects than off-target toxic effects or effects on the normal tissue.

**Moderator:** Recent approval of palbociclib in Europe was based on data from the landmark PALOMA-1<sup>10</sup>, PALOMA-2<sup>5</sup>, and PALOMA-3<sup>11</sup> trials. Would you be able to share with us a brief overview of the findings from these studies that led to its approval in HR-positive/HER2-negative locally advanced or metastatic

breast cancer?

**Dr Finn:** The success of palbociclib and other CDK4/6 inhibitors in ER-positive/HER2-negative breast cancer is really the result of a rational clinical development program. They grew out of the preclinical findings we discussed earlier that identified that targeting CDK4/6 with palbociclib looked to be an effective approach to targeting ER-positive/HER2-negative breast cancer. There was synergy and blocking cell growth in the laboratory when palbociclib was combined with anti-estrogen. We showed that blocking CDK4/6 with palbociclib also had some ability to reverse resistance in models of acquired endocrine resistance.

With these data, the PALOMA-1/TRIO-18 study was launched, as a phase I/II study, around 2009, with the idea that we could test this laboratory hypothesis. That study accrued 165 patients after a small phase I study of 12 patients. This 165-patient phase II study randomized patients between letrozole alone and palbociclib and letrozole in an open-label, randomized phase II study. The results of that study were quite phenomenal in regards to the magnitude of benefit we saw with the combination. That is to say, the progression-free survival (PFS) went from about 10 months in the control arm to just over 20 months with the combination.

Certainly, this improvement in PFS always needs to be balanced against side effects. And, in reality, the side effect profile was very predictable. The most common adverse events (AEs) seen were neutropenia or leukopenia, with a fairly high incidence of grade 3, some grade 4 events. Typically, this neutropenia could be managed with dose delays, dose reductions, or interruptions. In this trial, there were no reported cases of neutropenic fever (febrile neutropenia). Palbociclib was dosed 3 weeks on, 1 week off, whereas letrozole was dosed continuously. The drug appears to be otherwise well tolerated. Other side effects tend to be fairly-low grade, grade 1 or grade 2 at the most.

What was also remarkable [was] that this degree of benefit with palbociclib and letrozole was pretty consistent across various clinical subgroups irrespective of age, performance status, number of visceral sites, and whether or not they had prior adjuvant therapy, chemotherapy, or endocrine therapy. I should mention the PALOMA-1 study was in the frontline setting and enrolled advanced breast cancer patients that had not received any therapy for their advanced disease, though prior adjuvant therapy was allowed.

Based on the results of PALOMA-1 trial, 2 large phase III studies were launched, one being PALOMA-2 which was essentially the same population; first-line, ER-positive, HER2-negative advanced breast cancer. The other being PALOMA 3, in pre-treated patients in combination with fulvestrant.

PALOMA-2 had a similar study design except it was powered as a large phase III study (ie, enrolled 666 patients). Patients were randomized 2:1 to receive letrozole and palbociclib or letrozole and placebo with a primary endpoint of PFS and secondary endpoints [that included] overall survival, objective response, dura-

tion of response, and side effects. PALOMA-2 was a global study that was really designed to confirm the findings in PALOMA-1.

It should be noted that the FDA [and] other regulatory agencies approved the combination of palbociclib and letrozole based on the PALOMA-1 data. On February 3, 2015, the drug got accelerated FDA approval. PALOMA-2 was meant to confirm that finding and also serve for further global registration.

At the same time, PALOMA-3 was launched, and this was a study again based on the hypotheses from the laboratory that targeting CDK4/6 would reverse endocrine resistance and act synergistically with anti-endocrine approaches in ER-positive breast cancer. This study randomized women to fulvestrant and placebo versus fulvestrant and palbociclib. Similar to PALOMA-2, PALOMA-3 was also a large study that enrolled 574 women with HR positive/HER2 negative advanced metastatic BC who had had progression on an aromatase inhibitor, such as letrozole or anastrozole. Some of them also had chemotherapy in the frontline setting. The patients were randomized 2:1 to palbociclib and fulvestrant or placebo and fulvestrant. The primary endpoint was PFS, and the secondary endpoints included overall survival, side effects, and response.

So, what's played out over the course of the last year or so has been 2 positive phase III studies with palbociclib and letrozole, [the] PALOMA-2 and PALOMA-3 studies, both positive studies meeting their endpoints. All 3 PALOMA studies had a very similar side-effect profile. It was very predictable again in regards to neutropenia and leukopenia. In PALOMA-2, there was a small rate of neutropenic fever of about 1.8%, so under 2%. Taken together, all these data support the importance of targeting CDK4/6 in ER-positive breast cancer and support the global registration for palbociclib with both letrozole and fulvestrant in the given indications.

**Moderator:** [The] MONALEESA-2 trial<sup>16</sup> showed significant slowing of disease progression with [the] addition of ribociclib to endocrine therapy. Would you share with us key findings from this study and its likely clinical implications?

**Dr Finn:** The MONALEESA-2 study evaluated another CDK4/6 inhibitor, ribociclib. This molecule, like palbociclib, is very potent and selective for cyclin-dependent kinases 4 and 6 versus other CDKs and other kinases. MONALEESA-2 was a very similar study, in design, to PALOMA-1 and PALOMA-2, more specifically, as it was a large phase III study, randomizing women 1:1 with ribociclib and letrozole versus ribociclib and placebo. Ribociclib was dosed similarly to palbociclib in that it [was] given once daily 3 weeks on, 1 week off. I think everybody was very gratified, but maybe not so surprised, to see the results of MONALEESA-2 in that it mimics very well the results of PALOMA-2.

MONALEESA-2 arguably was based on the early data with palbociclib from PALOMA-1 and accrued 668 women to a prospective study in the frontline setting of postmenopausal ER-positive,

TABLE. Key Efficacy Data From Select CDK4/6 Clinical Trials<sup>5,10,11,16,50</sup>

Efficacy Endpoints from Clinical Trials	Study Arm	Comparator Arm	P Value
<b>PALOMA-1</b>			
	<b>Palbociclib-Letrozole</b>	<b>Letrozole</b>	
Median PFS	20.2 months (95% CI, 13.8-27.5)	10.2 months (95% CI, 5.7-12.6)	
	<b>HR, 0.488 (95% CI, 0.319-0.748)</b>		<b>.0004<sup>a</sup></b>
Best ORR	43% (95% CI, 32-54)	33% (95% CI, 23-45)	.13
CBR	81% (95% CI, 71-89)	58% (95% CI, 47-69)	<b>.0009<sup>a</sup></b>
<b>PALOMA-2</b>			
	<b>Palbociclib-Letrozole</b>	<b>Placebo-Letrozole</b>	
Median PFS	24.8 months (95% CI, 22.1-not estimable)	14.5 months (95% CI, 12.9-17.1)	
	<b>HR, 0.58 (95% CI, 0.46-0.72)</b>		<b>&lt;.001<sup>b</sup></b>
ORR	42.1% (37.5-46.9)	34.7% (28.4-41.3)	.06
CBR	84.9% (81.2-88.1)	70.3% (63.8-76.2)	<b>.001</b>
<b>PALOMA-3</b>			
	<b>Palbociclib-Fulvestrant</b>	<b>Placebo-Fulvestrant</b>	
Median PFS	9.2 months (95% CI, 7.5-not estimable)	3.8months (95% CI, 3.5-5.5)	
	<b>HR, 0.42 (95% CI, 3.2-11.0)</b>		<b>.16</b>
ORR	10.4% (95% CI, .4-14.1)	6.3% (95% CI, 3.2-11.0)	<b>.001</b>
CBR <sup>c</sup>	34.0% (95% CI, 29.0-39.3)	19.0% (95% CI, 13.4-25.60)	<b>.001</b>
<b>MONALEESA-2</b>			
	<b>Ribociclib-Letrozole</b>	<b>Placebo-Letrozole</b>	
Median PFS	Not reached in the biociclib group (95% CI, 19.3 -not reached)	14.7 months (95% CI, 13.0-16.5)	
	<b>HR, 0.56 (95% CI, 0.43-0.72)</b>		<b>3.29x 10<sup>-6</sup></b>
ORR	40.7% (95% CI, 35.4-46.0)	27.5% (95% CI, 22.8-32.3)	<b>&lt;.001</b>
CBR	79.6% (95% CI, 75.3-84.0)	72.8% (95% CI, 68.0-77.5)	<b>.02</b>
CBR	CBR	CBR	CBR
<b>MONARCH-1<sup>d</sup></b>			
	<b>Abemaciclib Monotherapy</b>		
Median PFS	6.0 months (95% CI, 4.2-7.5)		
ORR	19.7% (95% CI, 13.3-27.5)		
CBR	42.4%		

CBR indicates clinical benefit rate; CI, confidence interval; HR, hazard ratio; ORR, overall objective response rate; PFS, progression free survival;

<sup>a</sup>On-sided analysis, <sup>b</sup>Two-sided analysis, <sup>c</sup>At interim analysis, <sup>d</sup>Single-arm study

Taken together, the data indicate that these new CDK4/6 inhibitors are a promising class of agents for the treatment of advanced/metastatic HR-positive breast cancer.

HER2-negative breast cancer. The hazard ratio in this study was 0.56, which is remarkably similar to the hazard ratio of 0.58 seen with palbociclib. Study populations were generally similar, with one exception, in that the PALOMA-2 study enrolled women who had relapsed on adjuvant therapy—including prior endocrine therapy, as long as it had not been a nonsteroidal aromatase inhibitor (NSAI). Whereas, MONALEESA-2 excluded patients who relapsed on or within 12 months from completion of adjuvant therapy.

Based on these data, ribociclib was recently granted priority review by the US FDA as first-line treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with letrozole. These positive data clearly support the idea of CDK4/6 inhibitor combination therapy for ER-positive, HER2-negative breast cancer.

**Moderator:** Data from the MONARCH-1 trial<sup>20</sup> showed good efficacy of abemaciclib in refractory HR-positive, HER2-negative breast cancer. What were some of the key takeaways from this study?

**Dr Finn:** The MONARCH-1 study was a large, single arm study looking at single agent abemaciclib in ER-positive, HER2-negative advanced breast cancer. These patients not only had advanced disease by staging but also were heavily pretreated. Abemaciclib, like ribociclib and palbociclib, is a very potent CDK4/6 inhibitor. Other early studies have demonstrated that its activity in breast cancer is consistent with the other compounds in regards to its selectivity for ER-positive, HER2-negative disease. There's a large phase III program ongoing with abemaciclib as well as neoadjuvant studies that are all aimed at confirming its potent activity in blocking CKD 4/6 and inducing cell cycle arrest in this population whether as a single agent or in combination.

MONARCH-1 demonstrated a fair amount of single-agent activity for this class. Smaller studies with palbociclib have shown some activity, but really this is the largest single agent experience that's been presented with a CDK4/6 inhibitor in this population.

This study comprised 132 patients who were treated with abemaciclib monotherapy. The results showed a modest overall response rate of 19.7%, and the median PFS in this population was 6.0 months and median OS was 17.7 months. Even though it's a single-arm study, this is very provocative data suggesting that in a population that would otherwise be receiving chemotherapy, that [these are] comparable with those data in this setting, maybe even a little better.

It's always hard to make conclusions on single-arm studies, although it was a large study. The side effect profile of abemaciclib overlapped with those observed with other CDK4/6 inhibitors. It's been argued that abemaciclib has a lower incidence of grade 3 and 4 neutropenia and leukopenia, and perhaps that is because of its differential activity against CDK4 versus CDK6, where CDK6 is more important maybe for bone marrow suppression, whereas CDK4 is more important for tumor suppression. This is a hypothesis that is yet to be proven in the clinic.

Abemaciclib also has a little higher incidence of GI toxicity, specifically diarrhea. Again, all of these observations have been made in single arm phase II studies and we await larger data sets, especially randomized studies with abemaciclib both as single agent and in combination with endocrine therapy.

**Moderator:** What are some of the common AEs seen with CDK4/6 inhibitors in clinical trials? Are the AE profiles of abemaciclib, palbociclib, and ribociclib similar and comparable?

**Dr Finn:** The most common side effects reported with CDK4/6 inhibitors from clinical trials are neutropenia, leukopenia, fatigue. As discussed previously, the most common AEs seen with palbociclib were neutropenia or leukopenia. Typically, neutropenia can be managed with dose delays or dose reductions or interruptions. Growth factors are not required and were used rarely in the clinical trials. The incidences of febrile neutropenia reported with palbociclib are very low (less than 2% reported in PALOMA-2 and 0.6% in PALOMA-3, the same as in the control group in that study) to none (0% reported in PALOMA-1). Other side effects tend to be fairly low grade, grade 1 or grade 2 at the most.

The data from ribociclib in the MONALEESA-2 study showed a small number of patients that had elevated liver enzymes—that is to say, AST and ALT rises during study treatment —[and] a few patients a few patients had prolongation of their QTc interval. But none of these were associated with serious AEs. With abemaciclib, there is higher incidence of GI toxicity that's been reported in the data sets.

**Moderator:** Are there any ongoing trials exploring CDK4/6 inhibitors in early breast cancer in [the] adjuvant or neoadjuvant setting? Why or why not?

**Dr Finn:** There are ongoing studies, certainly that have been launched with palbociclib in the adjuvant setting, adding palbociclib to endocrine therapy, with [a] curative intent. There's the PALLAS study (NCT02513394) which is a large study by the US Cooperative Group as well as the PENELOPE-B study looking at adjuvant palbociclib and endocrine therapy in patients with residual disease after neo-adjuvant chemotherapy (NCT01864746). There are other studies done in early stage settings as well. There was a study presented at the 2015 San Antonio Breast Cancer Symposium that tested the hypothesis [of] whether adding palbociclib to anastrozole as neoadjuvant would enhance [the] complete cell-cycle arrest rate (defined as suppression of Ki67 to  $\leq 2.7\%$ ).

This was a phase II study that enrolled 50 women with clinical stage II/III ER-positive, HER2-negative breast cancer. Patients were started on anastrozole monotherapy for the first cycle. Palbociclib was added for the additional 4 cycles before surgery, which was performed about 2 to 4 weeks after the treatment was stopped. This study met the endpoint: complete cell cycle arrest at cycle 1 was achieved in 87% of the patients. Clinical respons-

es were observed in 67% of the patients who had completed at least 3 cycles of treatment.<sup>21</sup> A similar study (neo-Monarch) was performed with abemaciclib and demonstrated again a significant effect on inducing cell cycle arrest with the addition of CDK4/6 inhibition to endocrine therapy.<sup>22</sup>

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