INTERVIEW

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Tracks 1-14

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Tracks 1-5

DR LOVE: Palbociclib recently received accelerated approval for use as first-line therapy in combination with letrozole for postmenopausal women with ER-positive, HER2-negative metastatic breast cancer. Would you talk about its mechanism of action and efficacy?

DR TOLANEY: Palbociclib is a CDK4/6 inhibitor, and it works by causing cell cycle arrest that eventually leads to cellular apoptosis. CDK4/6 is thought to be an important target in ER-positive breast cancer because the cyclin D pathway drives a lot of these cancers. Preclinical data suggest that the addition of CDK4/6 inhibitors to hormonal therapy is synergistic.

PALOMA-1 was a Phase II study that randomly assigned patients to up-front letrozole alone or letrozole in combination with palbociclib. The results showed an impressive improvement in progression-free survival (PFS), from 10 to 20 months (Finn 2015; [1.1]). This led to the accelerated approval of palbociclib in combination with letrozole as first-line therapy for ER-positive metastatic breast cancer.

The Phase III PALOMA-3 trial recently presented at ASCO and published in *The New England Journal of Medicine* investigated palbociclib in combination with fulvestrant for women with ER-positive breast cancer who had experienced disease relapse. The results demonstrated an increase in PFS from 3.8 months to 9.2 months with the addition of palbociclib to fulvestrant (Turner 2015; [1.2]). These data suggest that palbociclib is also effective in the second-line setting. I believe that, based on these results, palbociclib will eventually receive full approval.

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PALOMA-1: Results of a Phase II Study of Palbociclib with Letrozole versus Letrozole Alone as First-Line Treatment for Postmenopausal Women with ER-Positive, HER2-Negative Advanced Breast Cancer

Efficacy	Palbociclib + letrozole (n = 84)	Letrozole (n = 81)	Hazard ratio	*p*-value
Overall response rate	43%	33%	NR	0.13
Median PFS	20.2 mo	10.2 mo	0.488	0.0004
Median OS	37.5 mo	33.3 mo	0.813	0.42

NR = not reported; PFS = progression-free survival; OS = overall survival

Finn RS et al. *Lancet Oncol* 2015;16(1):25-35.

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PALOMA-3: Results of a Phase III Study of Palbociclib with Fulvestrant versus Fulvestrant Alone in ER-Positive, HER2-Negative Advanced Breast Cancer After Failure of Endocrine Therapy

Efficacy	Fulvestrant + palbociclib (n = 347)	Fulvestrant + placebo (n = 174)	Hazard ratio	*p*-value
Overall response rate	10.4%	6.3%	NR	0.16
Median PFS	9.2 mo	3.8 mo	0.422	<0.001

At interim analysis, overall survival data were immature, with a total of 28 deaths: Fulvestrant/palbociclib (n = 19), fulvestrant/placebo (n = 9).

	Fulvestrant + palbociclib (n = 345)		Fulvestrant + placebo (n = 172)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Neutropenia	79%	62%	3.5%	0.6%
Fatigue	38%	2%	26.7%	1.2%
Nausea	29%	0%	26.2%	0.6%
Alopecia	14.8%	0%	5.8%	0%

NR = not reported; PFS = progression-free survival

Turner NC et al. *N Engl J Med* 2015;373(3):209-19; Turner NC et al. *Proc ASCO* 2015;**Abstract LBA502**.

These data will change how we treat ER-positive disease. Given the results of these studies, I would now consider administering fulvestrant in combination with palbociclib for patients with metastatic disease who experience disease progression on an adjuvant aromatase inhibitor. It is likely that CDK4/6 inhibition will provide added benefit irrespective of the type of hormonal therapy it is combined with.

DR LOVE: What are some of the typical side effects associated with palbociclib?

DR TOLANEY: Overall, palbociclib is fairly well tolerated. Neutropenia is the most significant toxicity. The data from both the PALOMA-1 and the PALOMA-3 study showed approximately a 60% rate of Grade 3 or 4 neutropenia. However, in both studies the rates of febrile neutropenia were not significant. Blood counts must be closely monitored. Neutropenia sometimes requires dose holds and reductions. Fatigue and mild nausea have also been reported.

DR LOVE: Would you review what is known about other CDK4/6 inhibitors and what strategies are currently under investigation with this class of agents?

DR TOLANEY: Three CDK4/6 inhibitors are currently under investigation — palbociclib, ribociclib and abemaciclib. In early studies, only abemaciclib has demonstrated a high monotherapy response rate. A Phase I study of abemaciclib in patients with ER-positive metastatic breast cancer demonstrated approximately a 25% monotherapy response, which is impressive (Patnaik 2014).

The Phase II MONARCH 1 study investigating abemaciclib monotherapy in patients with ER-positive metastatic breast cancer that has progressed on a minimum of 2 prior lines of chemotherapy and prior hormonal therapy recently completed accrual (NCT02102490). If that trial is positive, abemaciclib could be an exciting option for

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Select Ongoing Phase III Trials Evaluating CDK4/6 Inhibitors for ER-Positive, HER2-Negative Breast Cancer

Trial identifiers	N	Disease setting	Treatment arms
MONARCH 3 (NCT02246621)	450	• Advanced disease, no prior systemic therapy • Postmenopausal	• Abemaciclib + NSAI • Placebo + NSAI
MONARCH 2 (NCT02107703)	630	• Advanced disease, ≤1 prior systemic therapy • Postmenopausal	• Abemaciclib + fulvestrant • Placebo + fulvestrant
PALLAS (NCT02513394)	4,600	• Early disease	• Palbociclib + standard ET • Standard ET
PENELOPE-B (NCT01864746)	1,100	• High-risk disease • After neoadjuvant chemotherapy	• Palbociclib + ET • Placebo + ET
MONALEESA-3 (NCT02422615)	660	• Advanced disease • Postmenopausal	• Ribociclib + fulvestrant • Placebo + fulvestrant
MONALEESA-7 (NCT02278120)	660	• Advanced disease • Premenopausal	• Ribociclib + NSAI/tamoxifen + goserelin • Placebo + NSAI/tamoxifen + goserelin

NSAI = nonsteroidal aromatase inhibitor; ET = endocrine therapy

www.clinicaltrials.gov. Accessed October 2015.

patients in that setting. Ongoing Phase III studies are evaluating abemaciclib with endocrine therapy in both the first- and second-line settings for ER-positive metastatic breast cancer (1.3). Abemaciclib has the added benefit of having CNS penetration, and studies are under way evaluating abemaciclib to treat brain metastases.

Tolerability differs among the CDK4/6 inhibitors. Abemaciclib is associated with lower rates of neutropenia than palbociclib, but it does cause higher rates of diarrhea.

Preclinical data also suggest that adding CDK4/6 inhibitors to either PI3 kinase or mTOR inhibitors may be synergistic. Studies with different triplet combinations are ongoing, including a trial evaluating the addition of ribociclib to exemestane and everolimus (NCT01857193). These triplet combinations are interesting, and we'll have to determine their toxicity profiles.

DR LOVE: Is this strategy being evaluated in the (neo)adjuvant setting?

DR TOLANEY: A Phase II randomized study is currently evaluating the safety of palbociclib in combination with endocrine therapy in the neoadjuvant setting for postmenopausal patients with ER-positive Stage II/III breast cancer (NCT02296801). The Phase III PALLAS trial is investigating the efficacy of palbociclib with adjuvant endocrine therapy for women with hormone receptor-positive breast cancer (1.3).

Track 8

DR LOVE: Moving to HER2-positive breast cancer, would you discuss the ExteNET study investigating the pan-HER tyrosine kinase inhibitor neratinib in early breast cancer?

DR TOLANEY: I enrolled several patients on this study randomly assigning women who had received trastuzumab-based adjuvant therapy to 1 year of neratinib or placebo. The study reported a small yet statistically significant benefit with the addition of neratinib,

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ExteNET: Results of a Phase III Study of Neratinib After Adjuvant Therapy in HER2-Positive Early Breast Cancer

Efficacy	Neratinib (n = 1,420)	Placebo (n = 1,420)	Hazard ratio	*p*-value
IDFS (2 y)	93.9%	91.6%	0.67	0.009
DFS-DCIS (2 y)	93.9%	91.0%	0.63	0.002
Distant recurrence	3.7%	5.1%	NR	
	Neratinib (n = 1,408)		Placebo (n = 1,408)	
Select adverse events	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Diarrhea	95.4%	39.9%	35.4%	1.6%
Nausea	43.0%	1.8%	21.5%	0.1%
Fatigue	27.1%	1.6%	20.1%	0.4%

IDFS = invasive disease-free survival; DFS-DCIS = disease-free survival including occurrence of ductal carcinoma in situ; NR = not reported

Incidence of cardiac adverse events was similar in both arms.

Chan A et al. *Proc ASCO* 2015;**Abstract 508**.

but the follow-up is not long. A high rate of Grade 3 diarrhea was observed (Chan 2015; [1.4]). I had to dose reduce and hold the drug multiple times, and it does affect quality of life. I believe we need to determine which patients would benefit from this treatment if the longer-term follow-up data look good, because it does have considerable toxicity.

Track 10

DR LOVE: Would you talk about the Phase III MARIANNE study, which was presented at ASCO 2015?

DR TOLANEY: The MARIANNE trial was a 3-arm randomized trial that compared T-DM1 with or without pertuzumab to trastuzumab with a taxane as first-line therapy for HER2-positive metastatic breast cancer. Surprisingly, the 3 arms were not significantly different in terms of PFS (Ellis 2015; [1.5]).

Data from a Phase II trial by Sara Hurvitz comparing trastuzumab/docetaxel to T-DM1 as first-line therapy for metastatic breast cancer showed a significant increase in PFS with T-DM1 compared to the taxane/trastuzumab combination (Hurvitz 2013). So I anticipated that the addition of pertuzumab to T-DM1 would be effective. It is possible that results in different studies may vary with the patients enrolled. The other possibility is that T-DM1 is not as effective as the taxane/trastuzumab/pertuzumab combination. ■

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MARIANNE: Results of a Phase III Study of T-DM1 with or without Pertuzumab versus Trastuzumab with a Taxane as First-Line Therapy for HER2-Positive Metastatic Breast Cancer

Efficacy	HT (n = 365)	T-DM1 (n = 367)	T-DM1 + P (n = 363)
Median progression-free survival	13.7 mo	14.1 mo	15.2 mo
Stratified HR versus HT	—	0.91	0.87
Overall response rate	67.9%	59.7%	64.2%
Median duration of response	12.5 mo	20.7 mo	21.2 mo
Select adverse events	**HT (n = 353)**	**T-DM1 (n = 361)**	**T-DM1 + P (n = 366)**
Alopecia	59.8%	6.6%	9.0%
Diarrhea	48.7%	25.2%	48.1%
Peripheral neuropathy	28.0%	13.3%	17.8%
Neutropenia	22.7%	11.4%	8.7%

HT = trastuzumab/taxane; P = pertuzumab

Median overall survival was not yet reached for any arm.

Ellis P et al. *Proc ASCO* 2015;**Abstract 507**.

SELECT PUBLICATIONS

Hurvitz S et al. **Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer.** *J Clin Oncol* 2013;31(9):1157-63.

Patnaik A et al. **LY2835219, a novel cell cycle inhibitor selective for CDK4/6, in combination with fulvestrant for patients with hormone receptor positive (HR+) metastatic breast cancer.** *Proc ASCO* 2014;**Abstract 534**.