INTERVIEW

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Tracks 1-15

Track 1 **Case discussion:** A 40-year-old woman presents with breast enlargement, nipple inversion and slight erythema and is diagnosed with ER/PR-negative, HER2-positive inflammatory breast cancer (IBC)

Track 2 Treatment of HER2-positive IBC

Track 3 Biology of HER2-positive IBC

Track 4 Role of JAK-STAT pathway inhibitors in IBC

Track 5 Prognosis of patients with IBC

Track 6 Management of ER/PR-positive, HER2-negative IBC

Track 7 Activity and tolerability of eribulin in metastatic disease

Track 8 Brain metastases in patients with IBC

Track 9 Treatment approach for patients with IBC who present with metastatic disease

Track 10 Effect of locoregional therapy on outcomes for patients with metastatic breast cancer (mBC)

Track 11 **Case discussion:** A 60-year-old woman with a 1.8-cm, ER-positive, PR-negative, HER2-negative invasive ductal carcinoma and a 21-gene Recurrence Score® (RS) of 35

Track 12 Efficacy and tolerability of the investigational CDK4/6 inhibitor abemaciclib in ER-positive, HER2-negative mBC

Track 13 Activity of CDK4/6 inhibitors in ER/PR-positive, HER2-negative mBC

Track 14 Therapeutic options for patients who experience disease progression while receiving adjuvant endocrine therapy

Track 15 Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive BC

Select Excerpts from the Interview

Tracks 2-4, 6-7

DR LOVE: Would you discuss the management of HER2-positive inflammatory breast cancer (IBC)?

DR OVERMOYER: About 30% to 40% of patients with IBC have HER2-positive tumors. These patients most often have ER/PR-negative disease and are typically exquisitely sensitive to HER2-targeted therapy. We now have a study under way in which patients undergo a biopsy and then receive a preoperative loading dose of pertuzumab and trastuzumab (1.1). Then they have another biopsy, start weekly trastuzumab/paclitaxel and continue with that combination and add pertuzumab every 3 weeks to complete 16 doses before surgery. The primary endpoint is pathologic complete response (pCR) rate, and we're opening the study to other institutions now.

We're trying to minimize chemotherapy and maximize HER2-directed therapy in this population. How much chemotherapy patients with HER2-positive disease need

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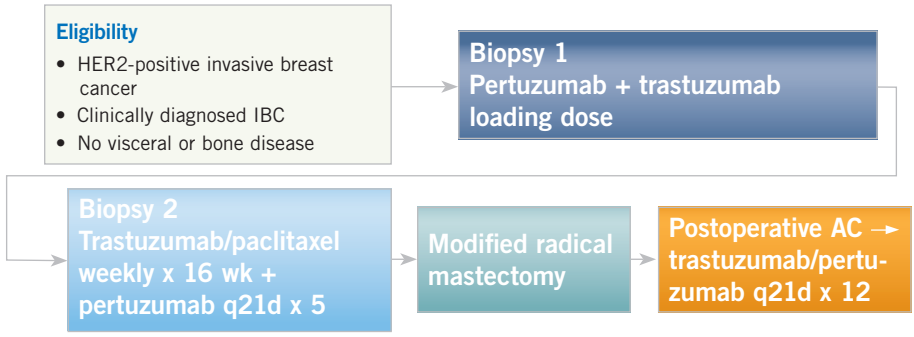
Phase II Trial of Paclitaxel/Trastuzumab/Pertuzumab as Preoperative Therapy for HER2-Positive Inflammatory Breast Cancer (IBC)

Protocol ID: NCT01796197 **Target Accrual:** 30



www.clinicaltrials.gov. Accessed December 2015.

is unclear, but we have seen clinically that these individuals experience dramatic responses with only pertuzumab and trastuzumab.

DR LOVE: What interesting novel regimens and/or concepts are being investigated for patients with triple-negative IBC or ER-positive, HER2-negative IBC?

DR OVERMOYER: Some retrospective studies have shown that 40% to 50% of IBC is triple-negative. Unfortunately for these patients, outcomes are poor. Interestingly, nearly 100% of our patients with triple-negative IBC exhibit overexpression of STAT3, and thus we are evaluating agents that target the JAK2/STAT3 pathway.

We are initiating a Phase II study evaluating the JAK1/2 inhibitor ruxolitinib with paclitaxel followed by dose-dense AC as preoperative therapy for triple-negative IBC (NCT02041429). We also recently closed a Phase I study at our institution evaluating ruxolitinib/paclitaxel until response then ruxolitinib alone for patients with metastatic breast cancer (mBC). Several individuals on that trial had IBC, and one who initially presented with metastatic triple-negative IBC is still on the study. She has been receiving single-agent ruxolitinib for about a year and has no evidence of disease. So some disease subtypes clearly respond to this agent.

To answer the second part of your question, 20% to 40% of patients with IBC have ER/PR-positive, HER2-negative disease. We're planning a trial evaluating eribulin because in preclinical mouse models, targeting angiogenesis can change the vascular flow and change EMT (epithelial-to-mesenchymal transition)-directed genes. Our study is trying to mimic that by using eribulin followed by dose-dense AC.

We also have a study of eribulin in the first- and second-line settings for metastatic disease. I've administered first-line eribulin to many patients, and it's well tolerated. The major toxicity is neuropathy, which can be severe. You can work around the neutropenia using growth factors. Alopecia occurs more than I'd like to say, but eribulin is more favorable than paclitaxel in this regard, and patients can receive therapy for a considerable amount of time before we see significant hair loss.

Another study is evaluating eribulin in 2 cohorts of patients with mBC, those with triple-negative breast cancer (TNBC) and those with ER-positive disease (NCT01827787).

Tracks 12-14

DR LOVE: What is your experience with the CDK4/6 inhibitors palbociclib and abemaciclib for patients with ER-positive mBC?

DR OVERMOYER: Palbociclib in combination with letrozole for up-front therapy doubles progression-free survival (PFS) from about 10 to 20 months (Finn 2015), and the PALOMA-3 data indicate that this agent is active when administered with fulvestrant to patients with disease progression after hormone therapy (Turner 2015a; [1.2]). We would expect it also to enhance therapy in TNBC, so we're evaluating it with chemotherapy in that setting.

DR LOVE: The situation people ask us about most is that of relapse during adjuvant hormone therapy, particularly aromatase inhibitors (AIs). How do you evaluate those patients? Do they all receive palbociclib, or do some receive hormone therapy alone?

DR OVERMOYER: In newly relapsed or first- or second-line recurrent disease after a patient's exposure to hormone therapy, I try to administer palbociclib in addition to the AI. If they've already received an AI, I use fulvestrant and palbociclib. I haven't had much pushback from insurance companies, so for patients who develop relapse on an adjuvant AI fulvestrant and palbociclib would be my off-study choice.

With regard to abemaciclib, one study suggested a response rate of approximately 30% with that drug as monotherapy in ER-positive disease before chemotherapy, although in terms of toxicity neutrophil counts are a problem (Tolaney 2014; [1.3]). We routinely reduce the dose due to neutropenia.

Abemaciclib is also being evaluated in combination with hormonal therapy. We have a study under way at our institution using abemaciclib and anastrozole. I recently

1.2

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* 2015a;373(3):209-19; Turner NC et al. *Proc ASCO* 2015b;**Abstract LBA502**.

1.3

Efficacy and Safety of Abemaciclib (LY2835219) Monotherapy for Patients with Metastatic Breast Cancer

Efficacy	All patients (N = 47)	HR-positive (N = 36)
Objective response rate (CR + PR)	12 (25.5%)	12 (33.3%)
Clinical benefit rate (CR + PR + SD ≥24 wk)	23 (48.9%)	22 (61.1%)
Disease control rate (CR + PR + SD)	33 (70.2%)	29 (80.6%)
Select adverse events (N = 47)	**Grade 3 or 4**	**All grades**
Diarrhea	4 (8.5%)	32 (68.1%)
Nausea	2 (4.3%)	28 (59.6%)
Fatigue	1 (2.1%)	21 (44.7%)
Vomiting	1 (2.1%)	21 (44.7%)
Decreased neutrophil count	10 (21.2%)	19 (40.4%)
Decreased platelet count	5 (10.6%)	15 (31.9%)

CR = complete response; PR = partial response; SD = stable disease

Tolaney S et al. San Antonio Breast Cancer Symposium 2014;**Abstract P5-19-13**.

placed a 70-year-old woman on this trial. She presented with ER/PR-positive, HER2-negative locally advanced disease with involvement of the ovaries and bone, and although initially we had to hold therapy and then reduce the dose because of diarrhea, she has now been receiving this combination for a year and is faring beautifully.

DR LOVE: Where does everolimus fit in?

DR OVERMOYER: Because everolimus is approved with exemestane as second-line therapy, I use an AI and palbociclib followed by exemestane and everolimus. Some of my colleagues' experiences with everolimus have been more favorable than mine, however. My patients have had a hard time with mucositis and fatigue, and I have dose reduced every time I've used it. It's difficult to keep patients on therapy. The maximum duration I've administered was 6 months, and then I had to stop the everolimus and continue the exemestane alone. ■

SELECT PUBLICATIONS

Baselga J et al. **Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2012;366(6):520-9.

Finn RS 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(1):25-35.

Tolaney SM et al. **Clinical activity of abemaciclib, an oral cell cycle inhibitor, in metastatic breast cancer.** San Antonio Breast Cancer Symposium 2014;**Abstract P5-19-13**.

Turner NC et al. **Palbociclib in hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2015a;373(3):209-19.

Turner NC 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.** *Proc ASCO* 2015b;**Abstract LBA502**.