INTERVIEW

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CD 1, Tracks 1-15

Track 1 NEOSPHERE: Efficacy of neoadjuvant pertuzumab, trastuzumab and the combination with chemotherapy for locally advanced, inflammatory or early HER2-positive early breast cancer (BC)

Track 2 Long-term survival in patients with advanced HER2-positive BC treated with trastuzumab

Track 3 Results of CLEOPATRA: A Phase III study of first-line docetaxel/trastuzumab with or without pertuzumab for HER2-positive metastatic BC (mBC)

Track 4 Next-generation adjuvant studies in HER2-positive early BC

Track 5 The ALTTO study and the feasibility of adjuvant trastuzumab/lapatinib/chemotherapy

Track 6 POETIC trial of perioperative endocrine therapy in postmenopausal patients with ER-positive BC

Track 7 Impact of Onco*type* DX® Recurrence Score® on selection of adjuvant therapy for ER-positive, HER2-negative BC

Track 8 BOLERO-2 results: Exemestane with or without everolimus in ER-positive locally advanced or metastatic BC refractory to nonsteroidal aromatase inhibitors (AIs)

Track 9 **Case discussion:** A 43-year-old woman with a 0.6-cm, Grade II, strongly ER/PR-positive, HER2-positive, node-negative BC with a Ki-67 of 8% and an Onco*type* DX Recurrence Score of 12

Track 10 Treatment of ER-positive, HER2-positive, subcentimeter, node-negative BC

Track 11 **Case discussion:** A 58-year-old woman with a 4-cm, strongly ER/PR-positive, HER2-negative BC with a Ki-67 of 8% who refuses neoadjuvant chemotherapy and has a gradual, significant response to neoadjuvant letrozole

Track 12 Duration of adjuvant AI therapy

Track 13 Viewpoint on the antitumor effect of adjuvant bisphosphonate treatment

Track 14 **Case discussion:** A 63-year-old woman with a 2.5-cm, Grade III, strongly ER-positive, PR-negative, HER2-negative invasive ductal carcinoma with 2 positive nodes who undergoes radiation therapy, adjuvant chemotherapy and letrozole and whose disease recurs 4 years later with multiple vertebral metastases

Track 15 Perspective on data with fulvestrant in postmenopausal patients with ER-positive mBC

Select Excerpts from the Interview

CD 1, Tracks 1, 3

DR LOVE: Would you discuss the NEOSPHERE trial of neoadjuvant pertuzumab and trastuzumab for patients with locally advanced, inflammatory or early HER2-positive breast cancer, which was recently published in *Lancet Oncology*?

DR SMITH: The NEOSPHERE trial randomly assigned patients to 4 arms: trastuzumab/docetaxel, pertuzumab/docetaxel, trastuzumab/pertuzumab/docetaxel and trastuzumab/pertuzumab (Gianni 2012; [1.1]). The arm with the best efficacy was trastuzumab/pertu-

1.1 **NEOSPHERE Study: Pathologic Complete Response (pCR) in the Breast and Lymph Node Status of Patients Receiving Neoadjuvant Trastuzumab and/or Pertuzumab**

	TH (n = 107)	THP (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node-negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node-positive at surgery	7.5%	6.5%	5.6%	6.3%

T = docetaxel; H = trastuzumab; P = pertuzumab

Gianni L et al. *Lancet Oncol* 2012;13(1):25-32.

zumab/docetaxel, with about double the pathologic complete responses (pCR). What is interesting is that in the trastuzumab/pertuzumab arm, 27% of the patients with ER-negative disease experienced pCR and were probably cured with no chemotherapy.

A pCR in a patient with HER2-positive disease is usually indicative of a favorable outcome. It is unclear how predictive pCRs are in the long term, but most patients with pCRs generally fare well. In this trial, they all received chemotherapy after surgery, so we'll never really know.

This raises the question of whether we can identify markers that indicate which patients don't need chemotherapy. I believe a currently unidentifiable subgroup of patients with HER2-positive disease can be cured with combination anti-HER2 therapy alone. The trick is, can we find out who they are? A biomarker analysis of patients in the NEOSPHERE trial was presented at SABCS 2011. Unfortunately, the results were not promising (Gianni 2011).

DR LOVE: Would you also talk about the CLEOPATRA data and whether you would use pertuzumab outside of a research setting if it were available?

DR SMITH: The CLEOPATRA trial evaluated trastuzumab/docetaxel with or without the addition of pertuzumab for patients with HER2-positive metastatic breast cancer (Baselga 2012b; [1.2]). Pertuzumab made a huge difference — it extended progression-free survival by about 50%. The hazard ratio was spectacular. To put it in perspective, the benefit from adding pertuzumab to trastuzumab was as large as the original benefit of adding trastuzumab to chemotherapy. This is like another quantum leap, which is exciting.

I foresee using pertuzumab as first-line therapy in metastatic disease. I would also consider administering the combination of pertuzumab and trastuzumab for patients who experience relapse after completing adjuvant trastuzumab.

CD 1, Track 8

DR LOVE: Would you comment on the recently published BOLERO-2 trial, which evaluated exemestane and everolimus in patients with ER-positive metastatic breast cancer refractory to nonsteroidal aromatase inhibitors?

1.2

CLEOPATRA Study: Efficacy and Safety of the Addition of Pertuzumab versus Placebo to Docetaxel/Trastuzumab as First-Line Therapy for Patients with HER2-Positive Metastatic Breast Cancer

Response	Pertuzumab	Placebo	Hazard ratio	*p*-value
Median PFS				
All patients (n = 402, 406)	**18.5 months**	**12.4 months**	**0.62**	**<0.001**
(Neo)adjuvant chemotherapy				
With trastuzumab (n = 47, 41)	16.9 months	10.4 months	0.62	NR
No trastuzumab (n = 137, 151)	21.6 months	12.6 months	0.60	NR
Interim OS* (n = 402, 406)	17.2%	23.6%	0.64	0.005
Complete response (n = 343, 336)	5.5%	4.2%	NR	
Partial response (n = 343, 336)	74.6%	65.2%		
Progressive disease (n = 343, 336)	3.8%	8.3%		
	Pertuzumab (n = 407)		**Placebo** (n = 397)	
Select adverse events	All grades	≥Grade 3	All grades	≥Grade 3
Febrile neutropenia	13.8%	13.8%	7.6%	7.6%
Mucosal inflammation	27.8%	NR	19.9%	NR
Diarrhea	66.8%	7.9%	46.3%	5.0%
Rash	33.7%	NR	24.2%	NR
LVSD fall; ≥10% <50%	3.8%	NR	6.6%	NR

PFS = progression-free survival; NR = not reported; OS = overall survival; LVSD = left ventricular systolic dysfunction

* Not significant because analysis did not meet O'Brien-Fleming stopping boundary; a trend was evident toward OS benefit with pertuzumab

Hazard ratio <1 favors pertuzumab

Baselga J et al. *N Engl J Med* 2012b;366(2):109-19.

DR SMITH: The addition of everolimus to exemestane had a major effect on time to recurrence compared to exemestane alone. The hazard ratio was 0.36 by central assessment, suggesting a highly significant delay in time to recurrence (Baselga 2012a; [1.3]).

Before we start administering this combination to every patient, however, we need to consider that the addition of everolimus comes with its own toxicities, including diarrhea, mucositis, hyperglycemia and a small incidence of pneumonitis. I have administered everolimus to some patients and have not encountered any serious problems. It's not as harsh as chemotherapy, but it's not as easy as endocrine therapy. The cost is also a concern.

DR LOVE: Would you also comment on the TAMRAD trial, which evaluated the addition of everolimus to tamoxifen for postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer who had previously received aromatase inhibitors?

DR SMITH: I find it interesting that another study reported a similar benefit. The Phase II TAMRAD trial randomly assigned patients with ER-positive, HER2-negative metastatic breast cancer previously treated with aromatase inhibitors to tamoxifen alone or with everolimus (Bachelot 2010).

The addition of everolimus increased the clinical benefit rate and significantly prolonged the time to progression. Analysis of patients who were resistant to original endocrine therapy and who experienced relapse during adjuvant treatment showed a strong trend for a higher benefit in patients who were resistant to treatment, rather than for those who were still sensitive to it.

Everolimus inhibits the mTOR pathway, which is one mechanism whereby estrogen resistance can be overcome. We need to be able to identify patients who are potentially still sensitive to hormone therapy versus those who are resistant. I believe that we may eventually have a marker to do that. ■

1.3

BOLERO-2 Trial: Exemestane and Everolimus in ER/PR-Positive Metastatic Breast Cancer Refractory to Nonsteroidal Aromatase Inhibitors

Efficacy	Everolimus + exemestane (n = 485)	Placebo + exemestane (n = 239)	HR	*p*-value
Median PFS (by central assessment)	10.6 mo	4.1 mo	0.36	<0.001
ORR (by local assessment)	9.5%	0.4%	—	<0.001
	Everolimus + exemestane (n = 482)		Placebo + exemestane (n = 238)	
Select adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis	56%	8%	11%	1%
Fatigue	33%	<4%	26%	1%
Dyspnea	18%	4%	9%	<2%
Anemia	16%	6%	4%	<2%
Hyperglycemia	13%	<5%	2%	<1%
Pneumonitis	12%	3%	0%	0%

HR = hazard ratio; PFS = progression-free survival; ORR = objective response rate

Baselga J et al. *N Engl J Med* 2012a;366(6):520-9.

SELECT PUBLICATIONS

Bachelot T et al. **TAMRAD: A GINECO randomized Phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast cancer (MBC) with prior exposure to aromatase inhibitors (AI).** San Antonio Breast Cancer Symposium 2010;**Abstract S1-6**.

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

Baselga J et al; CLEOPATRA Study Group. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012b;366(2):109-19.

Constantinidou A, Smith I. **Is there a case for anti-HER2 therapy without chemotherapy in early breast cancer?** *Breast* 2011;20(Suppl 3):158-61.

Gianni L et al. **Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial.** *Lancet Oncol* 2012;13(1):25-32.

Gianni L et al. **Neoadjuvant pertuzumab (P) and trastuzumab (H): Biomarker analyses of a 4-arm randomized Phase II study (NeoSphere) in patients (pts) with HER2-positive breast cancer (BC).** San Antonio Breast Cancer Symposium 2011;**Abstract S5-1**.

Lu D et al. **Drug interaction potential of trastuzumab emtansine combined with pertuzumab in patients with HER2-positive metastatic breast cancer.** *Curr Drug Metab* 2012;[Epub ahead of print].