INTERVIEW

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Tracks 21-31

Track 1 Improvement in progression-free survival with the addition of pertuzumab to docetaxel/trastuzumab as first-line therapy for patients with mBC

Track 2 Minimal pertuzumab-related toxicities in the CLEOPATRA study

Track 3 APHINITY: An ongoing Phase III trial evaluating the addition of pertuzumab to chemotherapy/trastuzumab as adjuvant therapy for HER2-positive early-stage BC

Track 4 Relative lack of toxicity with T-DM1 compared to chemotherapy/trastuzumab

Track 5 HER2 discordance between primary BC and paired nodal and distant metastases

Track 6 Importance of performing biopsy/rebiopsy in patients with mBC

Track 7 Update on status of the irreversible EGFR/HER2 tyrosine kinase inhibitors neratinib and afatinib for HER2-positive mBC

Track 8 Use of the Onco*type* DX DCIS Score for the identification of patients with DCIS who may forgo radiation therapy

Track 9 Lessons learned from a Phase III colorectal cancer trial: Revisiting the duration of bevacizumab administration

Track 10 Viewpoint on the initial results with the addition of bevacizumab to trastuzumab/docetaxel in the AVEREL trial

Track 11 Investigation of long-term anti-angiogenic strategies in the treatment of BC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on pertuzumab and the results of the CLEOPATRA study, which was presented at the 2011 San Antonio Breast Cancer Symposium (SABCS)?

DR PEGRAM: Originally, pertuzumab was thought to be effective in diseases without HER2 amplification or overexpression because of its ability to block HER2/HER3 heterodimerization, which is a potent signaling force. It was thought that pertuzumab would have efficacy in HER2-negative diseases such as prostate cancer, non-small cell lung cancer, ovarian cancer and HER2-negative breast cancer. However, in Phase I/II trials this was not the case (Gianni 2010). As such pertuzumab had a "dark horse, latecomer" aspect for many clinical oncologists.

I was pleasantly surprised by the magnitude of the treatment effect of adding pertuzumab to trastuzumab and docetaxel for patients with mBC (Baselga 2012; [2.1]). Pertuzumab extended PFS by 6.1 months. The hazard ratio was 0.62, and the difference was

2.1

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 = 808)	**18.5 months**	**12.4 months**	**0.62**	**<0.001**
(Neo)adjuvant chemotherapy				
With trastuzumab (n = 88)	16.9 months	10.4 months	0.62	NR
No trastuzumab (n = 288)	21.6 months	12.6 months	0.60	NR
Interim OS* (n = 402, 406)	82.8%	76.4%	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* 2012;366(2):109-19.

statistically significant. These impressive results will be practice changing. Because this was a planned interim analysis, the investigators reported few events for the OS analysis. The *p*-value for the OS benefit in the pertuzumab group was 0.005, but it did not meet the O'Brien-Fleming stopping boundary of 0.001. However, it will be interesting to follow up with patients over time because a trend was seen toward a survival benefit. One of the most impressive properties of pertuzumab is that it does not significantly increase toxicity. The study reported a slight increase in neutropenia, mucositis and some low-grade gastrointestinal toxicity, probably because of longer treatment times.

It's important to note that in the CLEOPATRA study few patients received prior adjuvant trastuzumab therapy similar to many of the original pivotal clinical trials of trastuzumab (Eiermann 2001). It is unclear whether the results from these trials can be translated into the modern era and whether pertuzumab will have similar benefits in patients with prior trastuzumab treatment. Clearly, more studies are required with a focus on the patient cohort of the current era who are survivors of adjuvant trastuzumab therapy but with relapsed disease.

Track 8

DR LOVE: Would you discuss the results with the Oncotype DX DCIS genomic analysis score that were presented at SABCS 2011?

DR PEGRAM: I have no doubt that many patients with DCIS are overtreated because, in the historical era, many patients who underwent lumpectomy alone without radiation therapy never experienced relapse. Therefore, Dr Melvin Silverstein hypothesized that a specific group of patients with DCIS could be considered for surgical excision only without radiation therapy (Silverstein 2003). The recent report from the ECOG-E5194 study in a unique nonradiated cohort supports the Silverstein hypothesis. The median age of patients enrolled on the study was 61 years, and all had ER-positive disease (Solin 2011; [2.2]). Most of the patients had low-/intermediate-grade DCIS.

The Onco*type* DX DCIS Score assay evaluated 7 cancer-related and 5 housekeeping genes with most of the genes in the proliferation group and 1 in the steroid group. In the low-risk category, the risk of any ipsilateral breast event was approximately 12% and about 5% for invasive ipsilateral breast events. In the high-risk group, the risk of developing any or invasive ipsilateral breast events was about 27% and 19%, respectively. These results suggested that a study of patients with low-risk DCIS Scores randomly assigned to lumpectomy alone versus lumpectomy with radiation therapy may prove that patients in the low-risk group do not need radiation therapy.

Such a trial is required because it would yield a great clinical effect in a similar manner to the original Onco*type* DX chemotherapy story. Also, the application of the DCIS variant of the Onco*type* DX assay to a modern patient cohort with nonradiation therapy-treated DCIS would be interesting to determine if it holds prognostic significance.

I would consider these to be pilot preliminary data because the ECOG-E5194 parent trial enrolled 670 patients, although tumor samples from only 327 of those patients were subjected to the RT-PCR Onco*type* DX DCIS Score assay. Still these data point strongly toward support of Mel Silverstein's original hypothesis that we're overtreating the vast majority of patients with DCIS.

2.2

ECOG-E5194 Study: 10-Year Outcome of Ipsilateral Breast Events (IBE) by the Onco*type* DX DCIS Score Evaluated by Prespecified Risk Groups

	DCIS Score risk group			
Type of IBE	Low (n = 246)	Intermediate (n = 45)	High (n = 36)	*p*-value*
Any IBE	12.0%	24.5%	27.3%	0.02
Invasive IBE	5.1%	8.9%	19.1%	0.01

* Log-rank *p*-value from a Kaplan-Meier risk curve

"The DCIS Score provides independent information on IBE risk beyond clinical pathologic variables including such important clinical variables as prior tamoxifen use, tumor grade and negative margin width."

Solin LJ et al. San Antonio Breast Cancer Symposium 2011;**Abstract S4-6**.

Track 10

DR LOVE: What is your take on the AVEREL trial, which evaluated the addition of bevacizumab to trastuzumab and docetaxel in patients with HER2-positive locally recurrent or metastatic breast cancer?

DR PEGRAM: It is interesting that the AVEREL trial produced a statistically significant PFS with the addition of bevacizumab by independent review assessments conducted in a blinded fashion. However, the investigator assessments reported a *p*-value of 0.07 (Gianni 2011; [2.3]). Overall, the results suggested that the perturbation of VEGF may possess some potential for efficacy, even in HER2-positive mBC.

A PFS advantage of 2.9 months was evident, but no OS effect was observed with the addition of bevacizumab, as assessed by independent review. Although this is a small-scale study, it "opens the door for dusting off bevacizumab" in future investigations in mBC. ■

2.3

AVEREL Trial: Efficacy of Bevacizumab (BEV) in Combination with Trastuzumab (T) and Docetaxel (DOC) as First-Line Therapy for Patients with HER2-Positive Locally Recurrent or Metastatic Breast Cancer

Survival	T + DOC (n = 208)	T + DOC + BEV (n = 216)	Hazard ratio	*p*-value
Median PFS				
INV*	13.7 months	16.5 months	0.82	0.0775
IRC†	13.9 months	16.8 months	0.72	0.0162
Objective response rate	**T + DOC (n = 176)**	**T + DOC + BEV (n = 183)**	**Hazard ratio**	***p*-value**
INV*	69.9%	74.3%	—	0.3492
IRC†	65.9%	76.5%	—	0.0265

PFS = progression-free survival; INV = investigator assessment; IRC = independent review committee assessment
* Unstratified primary analysis per protocol
† Stratified, censored for nonprotocol therapy

Gianni L et al. San Antonio Breast Cancer Symposium 2011;**Abstract S4-8**.

SELECT PUBLICATIONS

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