INTERVIEW

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Tracks 1-16

Track 1 NSABP-B-48: A proposed Phase III neoadjuvant trial of TC → carboplatin/gemcitabine or paclitaxel → AC with or without the PARP1 inhibitor iniparib (BSI-201) in triple-negative breast cancer (TNBC)

Track 2 Rationale for investigating iniparib in the proposed NSABP-B-48 trial

Track 3 NSABP-B-41 trial: Neoadjuvant AC followed by paclitaxel and trastuzumab, lapatinib or the combination for patients with operable HER2-positive breast cancer (BC)

Track 4 Survival benefit with lapatinib/trastuzumab for patients with HER2-positive metastatic BC (mBC) progressing on trastuzumab

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Track 7 Novel anti-HER2 investigational agents: trastuzumab-DM1 (T-DM1) and pertuzumab

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Track 11 Ongoing and proposed clinical trials using randomization based on the Onco*type* DX® assay Recurrence Score® (RS) in node-negative and node-positive BC

Track 12 Perspective on the clinical use of the MammaPrint® assay

Track 13 **Case discussion:** A 40-year-old woman with TNBC and one of 27 positive nodes receives TAC and is diagnosed with pulmonary and brain metastases three years later

Track 14 Tolerability of nanoparticle albumin-bound (*nab*) paclitaxel compared to standard-formulation taxanes in mBC

Track 15 Pathologic complete response rates from a Phase II neoadjuvant trial of weekly *nab* paclitaxel followed by AC in locally advanced BC

Track 16 Use of bevacizumab in metastatic TNBC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you describe the NSABP study investigating PARP inhibition in the neoadjuvant setting for triple-negative breast cancer (TNBC)?

DR GEYER: NSABP-B-48 will be a randomized Phase III trial evaluating the addition of iniparib (BSI-201) to neoadjuvant chemotherapy in palpable and operable TNBC, and the primary endpoint will be pathologic complete response (pCR). The regimens being evaluated include the standard control regimen of weekly paclitaxel x 12 followed by AC for four cycles compared to TC x 4 followed by carboplatin/gemcitabine. Both chemotherapy options are with or without the PARP inhibitor iniparib. The total sample size will be 540 patients, and if the effect with iniparib is large — with a hazard ratio of 0.65 or lower — then longer-term endpoints could also be affected.

DR LOVE: Where are we in terms of the clinical development of iniparib or PARP inhibitors in general?

DR GEYER: Among the clinical studies, the Phase II study with iniparib has shown the most striking results (O'Shaughnessy 2010; [1.1]).

One of the issues that has slowed down the development of other PARP inhibitors is synergistic toxicity with chemotherapy (Dent 2010; Isakoff 2010), which, for some reason, is not present with iniparib (O'Shaughnessy 2009b; [1.2]). Our perspective has been that the Phase II trial results with iniparib, though not definitive, are strong enough to conduct Phase III trials and also to move the agent into the neoadjuvant setting, in which efficacy could be quickly determined based on pCR. We believe that concurrent chemotherapy/iniparib is so well tolerated that it makes sense to evaluate it quickly in the neoadjuvant setting rather than wait for the recurrence events, which could take years, in the adjuvant setting.

1.1

Final Efficacy Results of a Randomized Phase II Study of Iniparib in Combination with Carboplatin/Gemcitabine (C/G) in Metastatic Triple-Negative Breast Cancer

	C/G (n = 62)	C/G + iniparib (n = 61)	Hazard ratio	*p*-value
Overall response rate (ORR)	32.3%	52.5%	—	0.023
Clinical benefit rate (CBR)*	33.9%	55.7%	—	0.015
Median progression-free survival	3.6 months	5.9 months	0.59	0.012
Median overall survival	7.7 months	12.3 months	0.57	0.014

* CBR = ORR + stable disease ≥ 6 months

O'Shaughnessy J et al. *Proc ESMO* 2010;**Abstract LBA11**.

1.2

Frequently Observed Grade III/IV Adverse Events in a Randomized Phase II Study of Iniparib in Combination with Carboplatin/ Gemcitabine (C/G) in Metastatic Triple-Negative Breast Cancer

	C/G (n = 59)		C/G + iniparib (n = 57)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	14%	2%	21%	0%
Thrombocytopenia	17%	10%	14%	16%
Neutropenia	32%	24%	37%	21%
Febrile neutropenia	5%	2%	0%	0%
Fatigue	22%	2%	7%	0%

O'Shaughnessy J et al. Poster. San Antonio Breast Cancer Symposium 2009b;**Abstract 3122**.

Tracks 4-5

DR LOVE: What are your thoughts on the combination of anti-HER2 agents in the metastatic setting?

DR GEYER: A study recently reported on women who had disease refractory to trastuzumab who were randomly assigned to full-dose lapatinib versus an attenuated dose of lapatinib with continued trastuzumab (Blackwell 2009; [1.3]). When you examine the design of that study, it appears as if the deck is stacked in favor of lapatinib.

What's remarkable, however, is that in this population with heavily pretreated advanced breast cancer, the combination resulted in an improvement in progression-free survival and a strong trend toward a survival advantage with the combination. This has greatly affected how I practice. I find myself using trastuzumab/ lapatinib to give patients some time off chemotherapy.

DR LOVE: What about capecitabine/trastuzumab in the metastatic setting?

DR GEYER: I believe it's a reasonable combination. With the multitude of available treatment options, it is increasingly difficult to describe how I treat advanced HER2-positive breast cancer. Capecitabine combinations have an advantage in offering activity against central nervous system disease, which is a problem for women with metastatic HER2-positive breast cancer.

Track 11

DR LOVE: Where are we with the TAILORx study and other studies incorporating the Onco*type* DX Recurrence Score in clinical decision-making?

DR GEYER: The TAILORx trial will be completing its accrual within a few months. The interest in the trial has been tremendous, and ECOG has done a great job in leading the trial. I know that SWOG has wanted to follow up

on the SWOG-8814 data to conduct a prospective TAILORx-like trial for women with node-positive, ER-positive breast cancer.

Some of the surgeons on our breast committee are interested in developing a trial using the Onco*type* DX Recurrence Score in the decision-making process in the neoadjuvant setting. We are in the early stages of the design and are considering how that trial might be conducted. One would broadly expect that pCR rates would be highest in the patient group for whom the benefits from chemotherapy were the largest in the adjuvant setting — that is, the high/intermediate Recurrence Score group. For me, neoadjuvant endocrine therapy is interesting if I can figure out a way to use it confidently and forego chemotherapy.

1.3

EGF104900: A Randomized Phase III Study of Lapatinib versus Lapatinib/Trastuzumab in Patients with HER2-Positive Trastuzumab-Refractory Metastatic Breast Cancer (mBC)

	Lapatinib (n = 145)	Lapatinib + trastuzumab (n = 146)	Hazard ratio	*p*-value
Median progression-free survival	8.1 wk	12.0 wk	0.73	0.008
Median overall survival	38.0 wk	56.0 wk	0.74	0.026

Median number of prior trastuzumab regimens for mBC: 3

"This study demonstrated that lapatinib in combination with trastuzumab offers a chemotherapy-free option that has an acceptable tolerability profile and, versus lapatinib alone, reduced the risk of disease progression by 26% ($P = 0.026$). The efficacy benefits arose in a treatment setting that lacked many of the well-known chemotherapy-related toxicities."

Blackwell KL et al. San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

Tracks 14-15

DR LOVE: What is your opinion regarding the use of *nab* paclitaxel versus standard-formulation paclitaxel in metastatic breast cancer?

DR GEYER: I like to use *nab* paclitaxel because I am convinced that it offers advantages in terms of neuropathy. I believe neuropathy develops later with *nab* paclitaxel, and it is always an issue when I have to stop the standard paclitaxel formulation earlier because of neuropathy. In such situations, the patient is not receiving as much drug as I would like and the persisting neuropathy can make the administration of subsequent therapies more problematic. So I consistently use *nab* paclitaxel, whenever possible, for metastatic breast cancer. Since I have been using it, my patients have had less trouble and my clinical experience has been consistent with the research data.

I also believe *nab* paclitaxel may be more efficacious than standard-formulation taxanes. We conducted a Phase II neoadjuvant study using weekly *nab*

paclitaxel followed by AC, and what stood out was the remarkable lack of toxicity with 12 weekly doses of *nab* paclitaxel. We did not have many treatment delays, and little neuropathy was observed. The pCR rate was 29 percent in that study, and *nab* paclitaxel seemed to be as active as paclitaxel with better tolerability than weekly paclitaxel (Robidoux 2010).

Track 16

DR LOVE: What is your take on the role of bevacizumab for patients with metastatic TNBC?

DR GEYER: I definitely believe that bevacizumab is an attractive option for metastatic TNBC because these patients have fewer treatment options and often we see nice responses to bevacizumab-containing regimens. Bevacizumab has consistently improved response rates and time to disease progression. In view of this, when I am treating metastatic TNBC I routinely administer bevacizumab because it is particularly important to optimize the chemotherapy and I see bevacizumab as a way of optimizing chemotherapy. ■

SELECT PUBLICATIONS

Baselga J et al. **First results of the NeoALTTO trial (BIG 01-06/EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER 2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Blackwell KL et al. **Updated survival analysis of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy.** San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

Dent RA et al. **Safety and efficacy of the oral PARP inhibitor olaparib (AZD2281) in combination with paclitaxel for the first- or second-line treatment of patients with metastatic triple-negative breast cancer: Results from the safety cohort of a phase I/II multicenter trial.** *Proc ASCO* 2010;**Abstract 1018**.

Isakoff SJ et al. **A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer.** *Proc ASCO* 2010;**Abstract 1019**.

O'Shaughnessy J et al. **Final efficacy and safety results of a randomized phase II study of the PARP inhibitor iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ESMO* 2010;**Abstract LBA11.**

O'Shaughnessy J et al. **Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial.** *Proc ASCO* 2009a;**Abstract 3**.

O'Shaughnessy J et al. **Updated results of a randomized phase II study demonstrating efficacy and safety of BSI-201, a PARP inhibitor, in combination with gemcitabine/carboplatin in metastatic triple-negative breast cancer.** Poster. San Antonio Breast Cancer Symposium 2009b;**Abstract 3122**.

Robidoux A et al. **A phase II neoadjuvant trial of sequential nanoparticle albumin-bound paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide in locally advanced breast cancer.** *Clin Breast Cancer* 2010;10(1):81-6.

Tutt A et al. **Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial.** *Lancet* 2010;376(9737):235-44.