INTERVIEW

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Dr Geyer is Associate Director of the Clinical Trials Office at Massey Cancer Center in Richmond, Virginia.

Tracks 1-11

Select Excerpts from the Interview

Tracks 1-2, 5

DR LOVE: Could you review some of the ongoing trial concepts evaluating PARP inhibitors in the management of BRCA-mutated HER2-negative breast cancer?

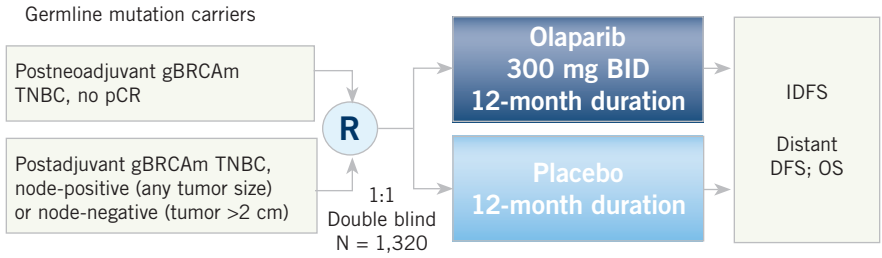
DR GEYER: Studies have demonstrated that with the monotherapy PARP inhibitor approach, the presence of germline BRCA mutation underlying the breast cancer is necessary for good activity to be observed. In a Phase II study of 2 dose levels of olaparib for women with confirmed BRCA1- or BRCA2-mutant, advanced, heavily pretreated breast cancer, the objective response rate was 41% (Tutt 2010).

PARP inhibitors have also been evaluated as monotherapy for patients with TNBC with or without germline BRCA mutations. An interesting study that I am involved with called the OlympiA trial is currently evaluating adjuvant olaparib monotherapy (Tutt 2015; [4.1]).

The eligibility criteria for this study are broad. Patients with germline BRCA1 or BRCA2 mutations who have completed definitive local treatment and at least 6 cycles of neoadjuvant or adjuvant chemotherapy are eligible. Patients with TNBC must have node-positive disease or node-negative disease with tumors larger than 2 centimeters.

4.1

OlympiA: A Phase III Trial of Olaparib as Adjuvant Therapy for Germline BRCA-Mutated (gBRCAm), High-Risk HER2-Negative Primary Breast Cancer



TNBC = triple-negative breast cancer; pCR = pathologic complete response; IDFS = invasive disease-free survival; OS = overall survival

Tutt A et al. *Proc ASCO* 2015;**Abstract TPS1109**.

If they have received neoadjuvant chemotherapy, they must have residual disease in the breast or lymph nodes. Patients with ER-positive disease in the adjuvant setting should have 4 or more positive nodes, making the disease high risk in nature.

Other studies are investigating augmenting the activity of DNA-targeting agents, such as carboplatin, by adding a PARP inhibitor (NCT02163694) for patients with locally advanced or metastatic disease.

Another study the NSABP is participating in is the Phase III neoadjuvant BRIGHTNESS study of veliparib and carboplatin/paclitaxel in TNBC (NCT02032277). The study was launched after the results of the Phase II I-SPY 2 trial demonstrated a jump in pathologic complete response rate from 26% in the control arm to 52% in the veliparib/carboplatin/paclitaxel arm for patients with hormone receptor–negative and HER2-negative breast cancer and a 90% probability of success in a Phase III trial (Rugo 2013).

Track 8

DR LOVE: What is your approach to the use of genomic testing in the adjuvant ER-positive, HER2-negative setting? Which assays, if any, do you use, and in what situations?

DR GEYER: I routinely use the Onco*type* DX assay for patients with node-negative disease who have T1c tumors. I tend not to order it for clear high-grade cancer because I have found that in that situation I usually wind up treating the cancer anyway. I have started using the Onco*type* DX assay occasionally for patients with larger tumors in the neoadjuvant setting. In my opinion the Onco*type* DX assay is the best test we have to determine whether chemotherapy can benefit the patient.

DR LOVE: Have you used any of these assays to help make a decision whether to extend or end endocrine therapy at 5 years?

DR GEYER: For patients with node-positive disease I tend to continue therapy. And if the patient is experiencing a lot of side effects, that usually drives the duration of

therapy. But I do use genomic testing when the additional information will help the patient and me to determine the best next step in terms of therapy.

I find the data on the Breast Cancer Index interesting in this setting (Sgroi 2013; [4.2]). That's the assay that I'm ordering right now if I'm considering stopping endocrine therapy at 5 years, but I want something to support that.

4.2

Prediction of Late Distant Recurrence (DR) in Patients with ER-Positive, Node-Negative Breast Cancer Using the Breast Cancer Index (BCI)

BCI linear (BCI-L) model	10-year DR	Hazard ratio (adjusted for CTS*)
BCI-L low (n = 390)	4.8%	Reference
BCI-L intermediate (n = 166)	18.3%	2.89
BCI-L high (n = 109)	29.0%	4.86

* Clinical Treatment Scores (CTS) is a prognostic model using the classical variables of tumor size and grade, lymph node status, age and treatment.

Conclusion: The 3 BCI-L groups identified 2 risk populations for both early and late DR with 84% (556/665) of patients having a low risk for early DR and a smaller population (39%, 230/596) having a high risk for late DR who may benefit from extended endocrine or other therapy.

Sgroi DC et al. *Lancet Oncol* 2013;14(11):1067-76.

Tracks 9-10

DR LOVE: Would you discuss the results of the Phase III GeparSepto (GBG 69) trial comparing neoadjuvant *nab* paclitaxel to solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (Untch 2014; [4.3])?

DR GEYER: In the final study design, patients received solvent-based paclitaxel at 80 mg/m^2 or *nab* paclitaxel at the reduced dose of 125 mg/m^2. The pathologic complete response rate was 38% with *nab* paclitaxel compared to 29% with solvent-based paclitaxel. The study does raise the question whether these results can translate into a difference in disease-free or overall survival.

I'm a fan of using *nab* paclitaxel. I like to avoid steroid premedication. For a patient with preexisting diabetes, I find *nab* paclitaxel a much easier agent to administer. My own experience and my personal bias is that at the lesser dose of 125 mg/m^2 it doesn't seem to cause neuropathy, which I believe is a serious problem in the adjuvant setting. I'm not sure whether at the higher dose it causes as much neuropathy as solvent-based paclitaxel does.

Track 11

DR LOVE: What are your thoughts on the results of the Phase III NSABP-B-35 trial of tamoxifen versus anastrozole for postmenopausal patients with ductal carcinoma in situ (Margolese 2015)?

DR GEYER: It's not often you see an initial presentation with a median follow-up of 9 years. The primary endpoint was breast cancer-free interval (BCFI), which was partly why the study took so long.

4.3

GeparSepto (GBG 69): Efficacy and Safety Results from the Phase III Trial of Neoadjuvant Chemotherapy with Nanoparticle-Based Paclitaxel (*nab*-P) versus Solvent-Based Paclitaxel (sb-P), Administered Weekly and Followed by Anthracycline/Cyclophosphamide for Patients with Early Breast Cancer

Primary endpoint	**sb-P** (n = 598)	***nab*-P** (n = 606)	Odds ratio	*p*-value
pCR (ypT0 ypN0)	29%	38%	1.5	0.001

Grade 3 or 4 AEs	**sb-P** (n = 598)	***nab*-P** (n = 606)	*p*-value
Neutropenia	61.8%	60.5%	0.636
Fatigue	4.7%	5.9%	0.369
Diarrhea	2.8%	3.3%	0.739
Peripheral sensory neuropathy*	2.7%	10.2%	<0.001
Anemia	1.0%	2.5%	0.076
Hand-foot syndrome	1.0%	2.3%	0.112

pCR = pathologic complete response; AE = adverse event

* Grade 3-4 peripheral sensory neuropathy with *nab*-P 125 mg/m^2: 6 (5.5%)

Four deaths occurred on the study: sb-P, n = 1 due to cardiac decompensation; *nab*-P, n = 3 due to accident at home, multiorgan failure and sepsis.

Conclusion: GeparSepto showed that the pCR rate is significantly higher with *nab*-P than with sb-P when administered weekly before anthracycline-based chemotherapy.

Untch M et al. San Antonio Breast Cancer Symposium 2014;**Abstract PD2-6**.

The Kaplan-Meier curves for BCFI did not show any divergence until about 5 years, with fewer breast cancer recurrences in the anastrozole arm than in the tamoxifen arm. Even though the absolute differences were not great, the hazard ratio was 0.73 and the difference in 10-year BCFI rate was statistically significant with 89.2% for tamoxifen and 93.5% for anastrozole. Interestingly, when the results were broken down by age (younger than 60 versus 60 years or older) the treatment-by-age interaction was statistically significant, suggesting that women younger than age 60 benefitted more from anastrozole compared to tamoxifen. ■

SELECT PUBLICATIONS

Augustovski F et al. **Decision-making impact on adjuvant chemotherapy allocation in early node-negative breast cancer with a 21-gene assay: Systematic review and meta-analysis.** *Breast Cancer Res Treat* 2015;152(3):611-25.

Margolese RG et al. **Primary results, NRG Oncology/NSABP B-35: A clinical trial of anastrozole (A) versus tamoxifen (tam) in postmenopausal patients with DCIS undergoing lumpectomy plus radiotherapy.** *Proc ASCO* 2015;**Abstract LBA500**.

Rugo HS et al. **Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 trial.** San Antonio Breast Cancer Symposium 2013;**Abstract S5-02**.

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.