INTERVIEW

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Tracks 1-15

Select Excerpts from the Interview

Tracks 2-3, 5

DR LOVE: Would you provide an update on the status of PARP inhibitor research in breast cancer?

DR GELMON: PARP inhibitors have suffered from long delays in development in breast cancer, but we're starting to see some exciting results again. A number of PARP inhibitors are much like olaparib, and many of these agents are entering Phase II studies on

which patients with BRCA1 or BRCA2 mutations are randomly assigned to a PARP inhibitor or best standard care. I believe these studies will rapidly garner much information about the role of PARP inhibitors in the metastatic setting.

Another exciting trial opening in the adjuvant setting is OlympiA (NCT02032823). On this study patients with germline BRCA1/2 mutations and high-risk HER2-negative primary breast cancer are randomly assigned to olaparib or placebo after definitive local therapy and neoadjuvant or adjuvant chemotherapy.

The goal is to determine whether PARP inhibition decreases recurrence rates in BRCA carriers with breast cancer. It will be a long time before we understand whether PARP inhibition has a role in therapy for patients without the BRCA mutation, but that's part of our dissection of the different breast cancer subtypes.

DR LOVE: A presentation at the 2013 San Antonio Breast Cancer Symposium (SABCS) by Hope Rugo on the I-SPY 2 trial reported that the addition of veliparib and carboplatin to standard neoadjuvant therapy increased pCR rates, particularly for the subset of patients with triple-negative breast cancer (Rugo 2013; [2.1]). What are your thoughts on that data set?

DR GELMON: That's an interesting data set. Platinums are looking better and better in the neoadjuvant setting. Whether veliparib made a difference I don't believe we know yet. For now I'd use the adjectives "hypothesis-generating" and "interesting" to describe this study. To make more of it at this point probably would be a mistake.

2.1

First Efficacy Results from the Phase II I-SPY 2 Trial for Patients with High-Risk Breast Cancer: Addition of Veliparib/Carboplatin (V + Carbo) to Standard Neoadjuvant Therapy*

Signature	Estimated pCR rate		Probability V + carbo is superior to control	Predictive probability of success in Phase III trial
	V + carbo	Control*		
All HER2-negative	**33%**	**22%**	**92%**	**55%**
HR-positive/HER2-negative	14%	19%	28%	9%
HR-negative/HER2-negative	**52%**	**26%**	**99%**	**90%**

* Paclitaxel qwk x 12, doxorubicin and cyclophosphamide q2-3wk x 4
pCR = pathologic complete response; HR = hormone receptor

Conclusions: Adaptive randomization successfully identified a biomarker-drug pair for V + carbo on the basis of a modest number of patients. V + carbo has graduated with a triple-negative breast cancer signature, and that is the subset recommended for this regimen's subsequent development. As expected, toxicity is increased with V + carbo, but this was well managed by dose reduction and delay.

Analyses are currently under way to define additional biomarkers that may be predictive of response. The I-SPY 2 standing trial mechanism efficiently evaluates agents/combinations in biomarker-defined patient subsets.

Rugo HS et al. San Antonio Breast Cancer Symposium 2013;**Abstract S5-02**.

Tracks 7-8

DR LOVE: What are your thoughts on the CDK4/6 inhibitor palbociclib for patients with ER-positive metastatic breast cancer (mBC)?

DR GELMON: We were involved in a Phase II trial that randomly assigned postmenopausal women with ER-positive mBC to receive letrozole or letrozole with palboci-

clib. Initial results of this trial were presented almost 2 years ago and demonstrated a remarkable improvement in progression-free survival with the addition of palbociclib to letrozole (Finn 2012).

Final results were recently reported and continue to show an exciting progression-free survival advantage — about 20 months with palbociclib/letrozole versus about 10 months with letrozole alone. A 4-month difference in overall survival also was observed, although it was not statistically significant (Finn 2014; [2.2]).

The large Phase III PALOMA-2 trial (NCT01740427) is evaluating the same design with a few caveats — the study incorporates more pharmacokinetic and safety endpoints. Another Phase III trial called PENELOPE-B (NCT01864746) is evaluating palbociclib after neoadjuvant chemotherapy for patients with ER-positive, HER2-normal primary breast cancer. Patients who do not experience a pCR will receive endocrine therapy with or without palbociclib. A large international trial called PALLAS is also slated to begin enrollment in about 6 months. That trial will evaluate letrozole with or without palbociclib as adjuvant therapy for ER-positive breast cancer.

2.2

PALOMA-1: Final Results of a Phase II Study of Letrozole (L) with or without the CDK4/6 Inhibitor Palbociclib (P) as First-Line Therapy for ER-Positive, HER2-Negative Metastatic Breast Cancer (mBC)

	P + L	L alone	Hazard ratio	*p*-value
Median PFS	20.2 mo	10.2 mo	0.488	0.0004
Median OS	37.5 mo	33.3 mo	0.813	0.2105

PFS = progression-free survival; OS = overall survival

- The most common adverse events on the P + L arm were neutropenia, leukopenia, fatigue and anemia.

Conclusions: "P + L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P + L in this same mBC population is ongoing."

Finn RS et al. *Proc AACR* 2014;**Abstract CT101**.

Tracks 11-13

DR LOVE: What options do you typically discuss with patients with ER-positive mBC who develop resistance to aromatase inhibitor (AI) therapy?

DR GELMON: We see a number of patients who have experienced long responses on hormonal agents but who have now experienced disease progression, and the question is, what's the next treatment? Outside a clinical trial, the major options I would discuss include fulvestrant or the combination of exemestane and everolimus. Benefits for fulvestrant include that it is well tolerated and is administered by intramuscular injection once a month. Most patients fare well with this agent.

However, we have the option of exemestane and everolimus, which is an exciting combination. We know from the BOLERO-2 trial that a significant benefit of about 4 months was seen in progression-free survival with everolimus/exemestane versus exemestane/placebo for patients with advanced breast cancer whose disease recurred or progressed during or after treatment with nonsteroidal AIs (2.3).

At the recent European Breast Cancer Meeting in Glasgow, Martine Piccart presented the overall survival results for BOLERO-2 and, although everolimus/exemestane also had about a 4-month advantage, the difference was not statistically significant (2.3).

We know that patient tolerance to this combination is variable. Some women tolerate it beautifully, whereas others may experience fatigue or mouth sores. I have many patients who sail through it. I have other patients who start at 10 mg but need to be reduced to 5 mg, and then they feel fine. So I believe the toxicity is there, but it's not extensive. I have observed some pulmonary toxicity, however.

We previously performed a randomized Phase II study of everolimus weekly versus daily and observed this pulmonary toxicity to be schedule dependent (Ellard 2009). I have since observed 2 patients with early toxicity with the daily dosing. We have to see these patients at 4 weeks and then again every 6 weeks or so. We can't use our usual algorithm for endocrine therapy. ■

2.3

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

	Exemestane + everolimus (n = 485)	Exemestane + placebo (n = 239)	Hazard ratio	*p*-value
Median PFS (by central assessment)	11.0 mo	4.1 mo	0.38	<0.0001
Median PFS (by investigator assessment)	7.8 mo	3.2 mo	0.45	<0.0001
ORR (by central assessment)	12.6%	2.1%	—	—
Median OS*	31.0 mo	26.6 mo	0.89	0.14

PFS = progression-free survival; ORR = objective response rate; OS = overall survival

Baselga J et al. *N Engl J Med* 2012;366(6):520-9; Yardley DA et al. *Adv Ther* 2013;30(10):870-84; * Piccart M et al. *Proc European Breast Cancer Conference* 2014;**Abstract LBA1**.

SELECT PUBLICATIONS

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

Ellard SL et al. **Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163.** *J Clin Oncol* 2009;27(27):4536-41.

Finn RS et al. **Results of a randomized Phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC).** San Antonio Breast Cancer Symposium 2012;**Abstract S1-6**.

O'Shaughnessy J et al. **A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ASCO* 2011;**Abstract 1007**.

Piccart M et al. **Everolimus plus exemestane for hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (BC): Overall survival results from BOLERO-2.** *Proc European Breast Cancer Conference (EBCC-9)* 2014;**Abstract LBA1**.

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**.

Yardley DA et al. **Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis.** *Adv Ther* 2013;30(10):870-84.