



INTERVIEW

Mark D Pegram, MD

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Tracks 1-9

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| Track 1 | NSABP-B-50-I (KATHERINE): A Phase III trial of T-DM1 versus trastuzumab as adjuvant therapy for patients with HER2-positive breast cancer (BC) who have residual tumor in the breast or axillary nodes after neoadjuvant treatment | Track 5 | Second-line endocrine therapy options for ER-positive metastatic BC (mBC) |
| Track 2 | Results of BETH: A Phase III study of adjuvant chemotherapy/trastuzumab with or without bevacizumab for patients with HER2-positive, node-positive or high-risk node-negative BC | Track 6 | Results of a Phase II trial of letrozole with or without the CDK4/6 inhibitor palbociclib (PD-0332991) as first-line therapy for ER-positive, HER2-negative mBC |
| Track 3 | Efficacy of anthracycline- versus nonanthracycline-containing adjuvant regimens for HER2-positive BC | Track 7 | Case discussion: A 34-year-old woman with locally advanced ER/PR-negative, HER2-positive IDC receives neoadjuvant FEC followed by weekly paclitaxel in combination with trastuzumab and pertuzumab |
| Track 4 | Case discussion: A postmenopausal woman in her early fifties presents with recurrent ER/PR-positive, HER2-negative IDC | Track 8 | Perspective on the recent FDA approval of neoadjuvant pertuzumab |
| | | Track 9 | Choice of chemotherapy to combine with pertuzumab/trastuzumab |

Select Excerpts from the Interview

Track 1

- ▶ **DR LOVE:** What are your thoughts on the NSABP-B-50-I trial evaluating T-DM1 versus trastuzumab for patients with HER2-positive breast cancer who have residual disease after preoperative systemic treatment (1.1)?
- ▶ **DR PEGRAM:** That study is open and accruing well. It's an interesting and innovative study design for patients who do not achieve a pathologic complete response (pCR) after neoadjuvant trastuzumab and chemotherapy. Patients are randomly assigned to continue a year of adjuvant trastuzumab, which is the current standard, or to complete the year with T-DM1.

It's a promising study that will quickly answer questions in early breast cancer. The study population is unique because it includes only patients who didn't achieve a pCR. If the trial is positive, our enthusiasm for further developing T-DM1 in the adjuvant and neoadjuvant settings will be heightened.

1.1

NSABP-B-50-I (KATHERINE): A Phase III Trial of T-DM1 versus Trastuzumab as Adjuvant Therapy for Patients with HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Nodes After Neoadjuvant Treatment

Protocol ID: NCT01772472

Target Accrual: n = 1,484

Eligibility

- HER2-positive invasive breast cancer
- Clinical Stage T1-4/N0-3/M0 at presentation
- No Stage T1a/bN0 or Stage IV breast cancer allowed

R

T-DM1

3.6 mg/kg every 3 weeks for 14 cycles

Trastuzumab

6 mg/kg every 3 weeks for 14 cycles

www.clinicaltrials.gov. Accessed June 2014.

Tracks 2-3

► **DR LOVE:** Would you discuss the results of the Phase III BETH trial evaluating adjuvant therapy in patients with HER2-positive breast cancer with trastuzumab and chemotherapy with or without bevacizumab (Slamon 2013; [1.2])?

► **DR PEGRAM:** The most important aspect of the BETH trial was whether bevacizumab would add therapeutic benefit. The results were disappointing in that they showed no efficacy signal. This was not entirely surprising because of the results of the NSABP-C-08 trial in the adjuvant colorectal cancer setting (Allegra 2011). As soon as I saw those results, my enthusiasm for adjuvant bevacizumab for human solid tumors was diminished. That said, testing clinical hypotheses in randomized trials, even if the results are negative, provides important findings about the biology of HER2-positive

1.2

Efficacy and Safety Results from the Phase III BETH Trial of Adjuvant Therapy with Trastuzumab (T) and Chemotherapy* with or without Bevacizumab (Bev) for Patients with HER2-Positive Early Breast Cancer

Outcome	Chemo/T (n = 1,757)	Chemo/T/bev (n = 1,752)	Hazard ratio	p-value
38-month IDFS	92%	92%	1.00	0.9789
38-month OS	96%	97%	0.87	0.4387
Select Grade 3 or 4 adverse events	Chemo/T (n = 1,750)	Chemo/T/bev (n = 1,722)		p-value
Hypertension	4%	19%		<0.0001
Thromboembolic event	2%	3%		NR
Bleeding	<1%	2%		<0.0001
Heart failure	<1%	2.1%		0.0621
Proteinuria	<1%	1%		<0.0001

* TCH or TH → FEC

IDFS = invasive disease-free survival; OS = overall survival; NR = not reported

Slamon DJ et al. San Antonio Breast Cancer Symposium 2013; **Abstract S1-03.**

early breast cancer and tells us if we need to redirect our research focus. Although making cross-trial comparisons is problematic, it is reassuring that patients on the control arm of the BETH trial appeared to fare remarkably well with the backbone of docetaxel/carboplatin/trastuzumab (TCH) in the adjuvant setting. This result further bolsters the notion that nonanthracycline-containing regimens are safe and effective in HER2-positive early breast cancer.

Whether anthracyclines are superior or not remains an open question. In my view the BCIRG 006 trial did not answer that question satisfactorily. Although the difference in efficacy between the AC → TH and the TCH arms was statistically insignificant, a visual trend in the graphic analysis favored the anthracycline regimen (Slamon 2011). I always discuss the merits of AC → TH compared to TCH with my patients with lymph node-positive, HER2-positive early breast cancer. I present these results in a balanced and fair way and allow my patients to make as informed a decision as possible after seeing the data.

Tracks 8-9

▶ **DR LOVE:** What is your view on the recent FDA approval of neoadjuvant pertuzumab?

▶ **DR PEGRAM:** I applaud the FDA for coming up with new guidelines for accelerated approval that are perhaps paradigm shifting. Pertuzumab is the first drug approved for neoadjuvant breast cancer. The FDA guidance demands, in addition to the use of pCR as an endpoint, commitment to time-to-event Phase III trials in the neoadjuvant and adjuvant settings. The adjuvant APHINITY Phase III trial will compare chemotherapy/trastuzumab to chemotherapy/trastuzumab/pertuzumab head to head (NCT01358877).

Pertuzumab adds little toxicity but increases diarrhea and cutaneous rash. Fortunately it has no effect on left ventricular ejection fraction. The only factor of concern with this accelerated approval is whether the pCR results will hold up in the long term without further adjuvant pertuzumab. We will not have that answer until we obtain the APHINITY trial results.

▶ **DR LOVE:** In terms of chemotherapeutic backbones for pertuzumab/trastuzumab combinations, what are the options you tend to use?

▶ **DR PEGRAM:** The FDA label indication and the NCCN guidelines differ in the use of neoadjuvant pertuzumab regimens. On the basis of the NEOSPHERE study the FDA label approves neoadjuvant pertuzumab in combination with docetaxel and trastuzumab. It also mentions that neoadjuvant FEC followed by neoadjuvant docetaxel/trastuzumab/pertuzumab, based on the TRYPHAENA study, may be an option to consider. Additionally, the label indicates that TCH with pertuzumab is a possibility. It specifically states that no safety data exist with doxorubicin-containing regimens. The NCCN guidelines prefer neoadjuvant regimens for HER2-positive disease to include AC → paclitaxel/trastuzumab/pertuzumab. They also suggest that TCH with pertuzumab is a reasonable treatment option. ■

SELECT PUBLICATIONS

Allegra C et al. **Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: Results of NSABP protocol C-08.** *J Clin Oncol* 2011;29(1):11.

Slamon D et al. **Adjuvant trastuzumab in HER2-positive breast cancer.** *N Engl J Med* 2011;365(14):1273-83.