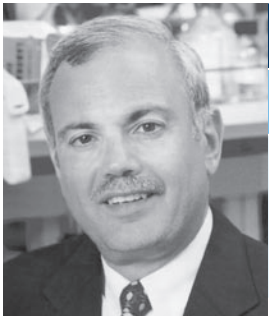


INTERVIEW

Dennis J Slamon, MD, PhD

Dr Slamon is Professor of Medicine, Chief of the Division of Hematology/Oncology and Director of Clinical and Translational Research at UCLA's David Geffen School of Medicine in Los Angeles, California.

CD 2, Tracks 17-32

Track 17 BOLERO-2 results and clinical research on pathways involved in hormone resistance

Track 18 Rationale for the BOLERO-1 trial of everolimus in combination with trastuzumab and paclitaxel in the treatment of HER2-positive locally advanced or metastatic BC

Track 19 Everolimus-associated mucositis and pneumonitis

Track 20 Trials of everolimus/hormonal therapy in the adjuvant setting

Track 21 BCIRG 006 study: Lead investigator's insight on a nonanthracycline regimen (TCH) as an acceptable standard for HER2-positive BC

Track 22 Rationale for investigation of combined blockade of the HER2 and ER pathways

Track 23 Differential response rates to chemotherapy/trastuzumab among patients with ER-positive, HER2-positive versus ER-negative, HER2-positive BC

Track 24 Antibody-drug conjugate strategy in cancer research

Track 25 Results of a Phase II study of T-DM1 versus trastuzumab/docetaxel for previously untreated HER2-positive mBC

Track 26 Perspective on the efficacy and tolerability of trastuzumab/lapatinib in HER2-positive early BC

Track 27 Lessons learned and remaining questions from the Neo-ALTTO and ALTTO studies of dual HER2 blockade

Track 28 Current status of BETH: A Phase III randomized trial of adjuvant chemotherapy/trastuzumab with or without bevacizumab for HER2-positive BC

Track 29 BEATRICE: A Phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for TNBC

Track 30 Duration of anti-angiogenic treatment

Track 31 Investigation of irreversible tyrosine kinase inhibitors — afatinib and neratinib — in BC

Track 32 Perspective on the role of PARP inhibition in BC

Select Excerpts from the Interview

CD 2, Track 18

DR LOVE: What are your thoughts on the potential role of everolimus in ER-positive and also HER2-positive breast cancer?

DR SLAMON: We have a large preclinical laboratory that is linked to many of our clinical trials and are therefore largely involved with translational studies. Early preclinical studies of everolimus in a panel of breast cancer cell lines revealed that it was most effective in ER-positive and HER2-positive breast cancer. The strategy behind the BOLERO-2 trial of everolimus in ER-positive breast cancer was developed after earlier Phase I trials showed that everolimus was also effective in other cancer types

(Baselga 2012a; [1.3, page 6]). The BOLERO-1 trial is similar in size to BOLERO-2 but studies the use of everolimus in the first line for HER2-positive disease (4.1). Data from the BOLERO-1 trial should be reported soon.

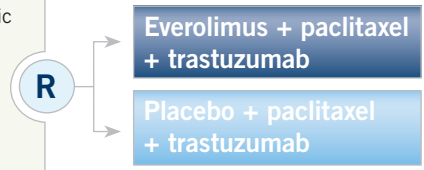
4.1

BOLERO-1: A Randomized Phase III Trial of Everolimus in Combination with Trastuzumab and Paclitaxel as First-Line Therapy for Women with HER2-Positive Locally Advanced or Metastatic Breast Cancer

Protocol ID: NCT00876395 **Target Accrual:** 717

Eligibility

- HER2-positive, locally advanced or metastatic breast cancer with ≥1 measurable lesions or bone metastasis
- Prior endocrine therapy allowed but should be discontinued at randomization
- Prior (neo)adjuvant trastuzumab and/or chemotherapy allowed but discontinued for >1 year prior to randomization



Primary endpoint: Progression-free survival

www.clinicaltrials.gov, May 2012.

CD 2, Track 21

DR LOVE: Any comments on the BCIRG 006 adjuvant trial in HER2-positive disease now that the results have been formally published?

DR SLAMON: The study went through a number of challenges based on the fact that we were advocating for a nonanthracycline-based regimen in breast cancer treatment, a concept that was not always well received. However, the data from this trial were publicly available long before formal publication and were the basis for the FDA approval of the TCH regimen (Slamon 2011; [4.2]).

Our results indicated a numeric advantage for disease-free survival with the AC → TH over the TCH regimen. The difference between the 2 regimens in the 5-year survival rate was 1%, and the difference in disease-free survival rate was 3%, in favor of the anthracycline-based regimen. These differences were not statistically significant but came at a cost of a statistically significant increase in congestive heart failure and a sustained subclinical loss of cardiac function.

DR LOVE: Would you still feel confident administering TCH to a patient with higher-risk disease — for example, a 50-year-old, otherwise healthy woman with 3 positive nodes?

DR SLAMON: The concept has always been to administer anthracyclines for higher-risk disease. In fact, with larger tumors and those with multiple nodes, even 4 or more, the treatment regimens were identical in terms of the hazard ratios (Slamon 2011). Because no difference was seen in favor of AC → TH, I am comfortable recommending TCH for a patient in this setting.

4.2

BCIRG 006: A Phase III Trial Evaluating AC → T, AC → TH and TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer

Outcome	AC → T (n = 1,073)	AC → TH (n = 1,074)	TCH (n = 1,075)
Estimated 5-year disease-free survival Hazard ratio, *p*-value	75% —	84% 0.64, <0.001	81% 0.75, 0.04
Estimated 5-year overall survival Hazard ratio, *p*-value	87% —	92% 0.63, <0.001	91% 0.77, 0.04
Cardiac-related adverse events	**AC → T**	**AC → TH**	**TCH**
Cardiac-related death	0%	0%	0%
Grade 3 or 4 congestive heart failure	0.7%	2.0%	0.4%*
>10% relative reduction in LVEF	11.2%	18.6%	9.4%†

*$p < 0.001$ for AC → TH versus TCH; †$p < 0.001$ for the comparison between AC → TH and TCH
A = doxorubicin; C = cyclophosphamide; T = docetaxel; H = trastuzumab; LVEF = left ventricular ejection fraction

Slamon D et al. *N Engl J Med* 2011;365(14):1273–83.

CD 2, Track 25

DR LOVE: What is currently known about the antibody-drug conjugate T-DM1, or trastuzumab maytansine, and in what directions are we headed with this agent?

DR SLAMON: In comparison to the approved trastuzumab/docetaxel regimen in metastatic disease, T-DM1 was numerically superior but not statistically better in terms of response rates. A dramatic improvement in progression-free survival was observed with T-DM1 over the traditional trastuzumab/docetaxel therapy, making T-DM1 a promising agent (Hurvitz 2011; [4.3]). Preclinical studies of T-DM1 and pertuzumab produced favorable results (Honig 2011). Pertuzumab in combination with T-DM1 or trastuzumab is currently being clinically evaluated in the Phase III MARIANNE trial (4.4).

4.3

T-DM1 versus Trastuzumab (T) and Docetaxel (D) for Patients with Untreated HER2-Positive Metastatic Breast Cancer

Efficacy	T + D	T-DM1	Hazard ratio	*p*-value
Objective response rate (n = 69, 67)	58.0%	64.2%	Not reported	
Median PFS (n = 70, 67)	9.2 mo	14.2 mo	0.59	0.035
Median DOR (n = 40, 43)	9.5 mo	Not reached	—	
Select adverse events (AEs)	**T + D** (n = 66)		**T-DM1** (n = 69)	
AE leading to treatment discontinuation*	28.8%		7.2%	
Neutropenia (Grade ≥3)	60.6%		5.8%	
Leukopenia (Grade ≥3)	25.8%		0%	
Thrombocytopenia (Grade ≥3)	3.0%		8.7%	

* Any grade AE
PFS = progression-free survival; DOR = duration of response

Hurvitz S et al. *Proc EMCC* 2011;**Abstract 5001**.

4.4

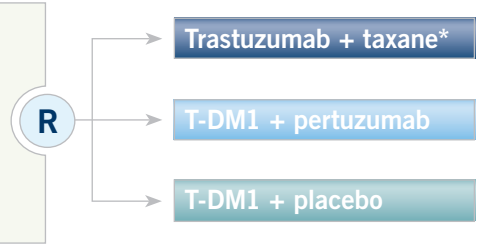
MARIANNE: A Randomized Phase III Trial of T-DM1 in Combination with Pertuzumab versus Trastuzumab in Combination with a Taxane for Patients with Metastatic Breast Cancer

Protocol ID: NCT01120184

Target Accrual: 1,092

Eligibility

- Histologically/cytologically confirmed HER2-positive breast adenocarcinoma
- Locally recurrent or metastatic breast cancer
- Candidate for chemotherapy
- Measurable or nonmeasurable disease per RECIST 1.1



Primary endpoint: Progression-free survival

* Docetaxel or paclitaxel

www.clinicaltrials.gov, May 2012.

CD 2, Track 31

DR LOVE: What are your thoughts on the investigation of irreversible tyrosine kinase inhibitors (TKIs) in breast cancer?

DR SLAMON: Like lapatinib, neratinib is an active anti-HER2 agent associated with gastrointestinal toxicity (Abbas 2012). This characteristic may limit its use in the adjuvant setting. Afatinib is currently undergoing clinical testing, with the assumption that it has equal or better efficacy than lapatinib without a similar significant toxicity profile. I believe afatinib may have some utility (Lin 2012; [4.5]).

4.5

Phase II Study of Afatinib for Patients with HER2-Positive Metastatic Breast Cancer Progressing After Trastuzumab

Response	All treated patients (n = 41)	Evaluable patients (n = 35)
CR + PR + SD	46%	54%
PR	10%	11%
SD	37%	43%
Progressive disease	39%	46%
Median PFS	15.1 weeks	—
Median overall survival	61.0 weeks	—
Select adverse events (n = 41)	**All grades**	**Grade 3**
Diarrhea	90.2%	24.4%
Rash	65.9%	9.8%

CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival

Lin NU et al. *Breast Cancer Res Treat* 2012;[Epub ahead of print].

4.6

Key Ongoing Phase II/III Trials of Irreversible Tyrosine Kinase Inhibitors for Patients with HER2-Positive Breast Cancer

Trial identifier	Phase	N	Setting	Treatment arms
NCT01125566 (LUX-Breast 1)	III	780	Metastatic	• Trastuzumab/vinorelbine • Afatinib/vinorelbine
NCT00878709 (ExteNET)	III	2,842	Early stage	• Neratinib • Placebo
NCT01441596 (LUX-Breast 3)	II	120	Metastatic	• Afatinib • Afatinib/vinorelbine • Investigator's treatment choice
NCT00706030	I/II	80	Metastatic	• Neratinib/vinorelbine

www.clinicaltrials.gov, May 2012.

Some irreversible TKIs may be better than the reversible agents. That is what the early data indicate with neratinib and afatinib.

The ultimate jury is the clinical trial data, and that jury is still out. These trials are accruing, and the results will determine efficacy (4.6). ■

SELECT PUBLICATIONS

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Baselga J et al; CLEOPATRA Study Group. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012b;366(2):109-19.

Honig A et al. **T-DM1 and pertuzumab as new tools for HER2 specific antibody-therapy against breast cancer stem cells in HER2-positive mammary carcinoma.** San Antonio Breast Cancer Symposium 2011;**Abstract P1-04-05**.

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Villarreal-Garza C et al. **mTOR inhibitors in the management of hormone receptor-positive breast cancer: The latest evidence and future directions.** *Ann Oncol* 2012;[Epub ahead of print].