INTERVIEW

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Tracks 1-15

Track 1 **Case discussion:** A 43-year-old woman with ER/PR-negative, HER2-positive mBC who has a complete response to docetaxel/trastuzumab on a clinical trial and crosses over to T-DM1 upon disease progression

Track 2 Results of a Phase II study of T-DM1 versus trastuzumab/docetaxel in previously untreated HER2-positive mBC

Track 3 Adverse events with T-DM1 compared to docetaxel/trastuzumab

Track 4 Mechanism of action of the antibody-drug conjugate T-DM1

Track 5 Relationship of tolerability, duration of treatment and efficacy of T-DM1

Track 6 Applicability of the CLEOPATRA data to patients who received prior adjuvant trastuzumab

Track 7 Redefining the treatment approach to HER2-positive BC in the era of novel agents

Track 8 Targeting the PI3K/AKT/mTOR pathway with everolimus to overcome resistance to trastuzumab and endocrine therapy

Track 9 Results of a Phase I study of everolimus in combination with weekly paclitaxel and trastuzumab for patients with HER2-positive mBC pretreated with trastuzumab

Track 10 BOLERO-1: A Phase III study of everolimus in combination with trastuzumab and paclitaxel as first-line therapy for HER2-positive locally advanced or metastatic BC

Track 11 Everolimus-associated mucositis and pneumonitis

Track 12 Penetration of the blood-brain barrier with everolimus

Track 13 Integrating everolimus into the treatment of endocrine-resistant mBC

Track 14 Progression-free survival as an endpoint in clinical trials

Track 15 Perspective on the current status of bevacizumab in BC

Select Excerpts from the Interview

Tracks 2-5

DR LOVE: Would you discuss your Phase II study comparing T-DM1 to trastuzumab/docetaxel as first-line therapy for patients with mBC?

DR HURVITZ: On this study 137 patients with HER2-positive, untreated mBC were randomly assigned to trastuzumab/docetaxel or T-DM1. Notably, only 27% of patients on the control arm received trastuzumab in the adjuvant setting compared to 18% on the study arm. PFS, the primary endpoint in the study, was 14.2 months with T-DM1 — 5 months more than with trastuzumab/docetaxel. This was associated with a 41% relative risk reduction for PFS, which was statistically significant. The objective

response rates and clinical benefit rates were similar between the 2 groups (Hurvitz 2011; [4.1]).

Of note, the median duration of docetaxel treatment on the control arm was 5.5 months versus 10 months with T-DM1 alone. This suggests that the tolerability of trastuzumab/docetaxel is different than T-DM1. Patients were able to receive T-DM1 much longer than the full trastuzumab/docetaxel combination because of the targeted delivery of T-DM1 to cancer cells.

Also of profound importance on this study was the difference in adverse events (AEs) between the 2 arms (4.1). Grade 3 or higher AEs were observed in 89% of the patients on the trastuzumab/docetaxel arm compared to only 46% on the T-DM1 arm. That is a huge difference. Serious AEs were also higher for patients on the control arm. Rates of AEs leading to treatment discontinuation were 7% with T-DM1 versus 29% with trastuzumab/docetaxel. The vast majority of patients — approximately 96% — on the T-DM1 arm did not lose their hair, which is an important clinical endpoint from a patient's perspective. Overall, T-DM1 was a much better tolerated therapy.

The most common side effects of T-DM1 are fatigue and nausea. Some patients experience an elevation in their AST or ALT. The all-grade thrombocytopenia was higher with T-DM1, and the incidence of Grade 3/4 thrombocytopenia was approximately 9% on the T-DM1 arm and 3% on the trastuzumab/docetaxel arm.

DR LOVE: In your opinion, what is the reason for the improved efficacy of T-DM1?

DR HURVITZ: I believe the duration of treatment is an important reason why T-DM1 yields more efficacy because the response rates between the 2 treatment arms are similar.

4.1

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

Efficacy	Trastuzumab + docetaxel	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	NR*	Not reported	

Select adverse events (AE)	Trastuzumab + docetaxel (n = 66)	T-DM1 (n = 69)
Any Grade ≥3 AE	89.4%	46.4%
AE leading to treatment discontinuation (any grade)	28.8%	7.2%
Serious AE (any grade)	25.8%	18.8%
Neutropenia (Grade ≥3)	60.6%	5.8%
Leukopenia (Grade ≥3)	25.8%	0%
Thrombocytopenia (Grade ≥3)	3.0%	8.7%
Alopecia (Grade 1-2)	66.7%	4.3%

PFS = progression-free survival; DOR = duration of response
* NR = not reached; longer follow-up needed to estimate DOR for the T-DM1 arm

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

T-DM1 is trastuzumab that is linked to a derivative of maytansine, which is an incredibly cytotoxic chemotherapy. The "magic" in T-DM1 is that the thioether linker does not release the maytansine until it is inside the tumor cell. So the other possibility is that we're able to deliver highly potent chemotherapy to cancer cells. EMILIA, a Phase III study comparing T-DM1 to capecitabine and lapatinib, completed enrollment at the end of 2011. The results from this study should be available this year and will help us determine the true efficacy of this agent (NCT00829166).

Tracks 8, 13

DR LOVE: Would you discuss the use of the mTOR inhibitor everolimus to overcome resistance to trastuzumab and endocrine therapy?

DR HURVITZ: Everolimus, also known as RAD-001, is an mTOR complex I inhibitor. HER2 activates the PI3-kinase/AKT/mTOR pathway, which is known to be involved in trastuzumab-resistant disease (Nagata 2004). A number of groups have reported data preclinically and through neoadjuvant studies that this appears to be a mechanism of resistance to both trastuzumab and endocrine therapy (Ghayad 2010). It appears that a close interaction exists between the mTOR and ER pathways. Preclinical models suggest that targeting mTOR may overcome trastuzumab resistance in HER2-positive disease and endocrine resistance in ER-positive disease (LoPiccolo 2008). Data from our laboratory indicated that approximately 60% of the HER2-positive cell lines and more than two thirds of the ER-positive or luminal subtypes demonstrated sensitivity to everolimus. These data and similar results from other groups provided support to clinically explore everolimus in these 2 subsets of breast cancer.

DR LOVE: If everolimus is approved for breast cancer, how do you foresee using it in your practice?

DR HURVITZ: I would not administer everolimus in the up-front setting because we do not have data to support its use there. I would administer it for endocrine-resistant disease. Beyond that, will I always administer everolimus in combination with exemestane? Will I use it with tamoxifen, as was done in the TAMRAD study (Bachelot 2010), or with fulvestrant for select patients? I have to say I probably will. If a patient has experienced disease progression on exemestane in the past, then I'm going to pair everolimus with a different agent because the data are interesting and exciting and there's no reason to think that it wouldn't work with another one of these agents. ■

SELECT PUBLICATIONS

Bachelot T et al. **TAMRAD: A GINECO randomized Phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast cancer (MBC) with prior exposure to aromatase inhibitors (AI).** San Antonio Breast Cancer Symposium 2010;**Abstract S1-6**.

Ghayad SE et al. **Endocrine resistance associated with activated ErbB system in breast cancer cells is reversed by inhibiting MAPK or PI3K/Akt signaling pathways.** *Int J Cancer* 2010;126(2):545-62.

Hurvitz S et al. **Trastuzumab emtansine (T-DM1) versus trastuzumab plus docetaxel (H + T) in previously untreated HER2-positive metastatic breast cancer (MBC): Primary results of a randomized, multicenter, open-label, phase II study (TDM4450g/BO21976).** *Proc EMCC* 2011;**Abstract 5001**.

LoPiccolo J et al. **Targeting the PI3K/Akt/mTOR pathway: Effective combinations and clinical considerations.** *Drug Resist Update* 2008;11(1-2):32-50.

Nagata Y et al. **PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients.** *Cancer Cell* 2004;6(2):117-27.