INTERVIEW

Kathy D Miller, MD

Dr Miller is Sheila D Ward Scholar of Medicine and Associate Professor of Medicine at the Indiana University Melvin and Bren Simon Cancer Center in Indianapolis, Indiana.

Tracks 1-12

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Tracks 1-5

DR LOVE: Would you discuss some of the newer anti-HER2 agents under investigation in breast cancer and their mechanisms of action?

DR MILLER: Pertuzumab and T-DM1 are two of the novel anti-HER2 agents. Pertuzumab is a monoclonal antibody, like trastuzumab, but it differs from trastuzumab in binding to a different epitope on the extracellular portion of the HER2 receptor. This is considered important because it blocks both homo- and heterodimerization of the HER2 receptor.

Trastuzumab can inhibit signaling, but it doesn't block dimerization. So signaling could still occur through HER3 with trastuzumab on board. Though HER3 does not have an active kinase, it has the most docking sites for the PI3 kinase, and with HER2-HER3 dimerization, activation of the PI3 kinase bound to HER3 may still occur. Because pertuzumab blocks the binding of HER2 and HER3, signaling through HER3 is also expected to be affected.

Pertuzumab was initially studied as monotherapy (Cortes 2009) and then in combination with trastuzumab (Cortes 2010). In both of these studies, enrolled patients had HER2-positive disease that had progressed during trastuzumab-based therapy. The response rates with pertuzumab monotherapy ranged from 10 to 20 percent, with an additional 10 to 15 percent of patients having stable disease. I believe pertuzumab monotherapy in trastuzumab-resistant disease is quite encouraging. The large Phase III CLEOPATRA trial is now evaluating the addition of pertuzumab to docetaxel/trastuzumab in the up-front setting.

DR LOVE: What do we know about T-DM1?

DR MILLER: T-DM1 is another novel anti-HER2 agent that takes a different tactic. It focuses on using the unique expression of the HER2 receptor on breast cancer cells as a way to deliver chemotherapy to the cancer cells. The T-DM1 molecule contains chemotherapy derivatives chemically bound to trastuzumab. The idea is that as the trastuzumab portion of T-DM1 binds to the HER2 receptor, the entire complex will then be internalized and chemotherapy will be released directly into the tumor cell. In theory, that should deliver a much higher concentration of chemotherapy to the tumor cell, which might increase activity. In addition, the side effects should also dramatically decrease because the circulating levels of the chemotherapy should be lower.

Data from Phase II trials in patients with trastuzumab-refractory disease have reported response rates of approximately 30 percent and progression-free survival of six months (Vogel 2009; [2.1]; LoRusso 2010). The toxicity profile is favorable, and thus overall it is encouraging and may challenge the current paradigm of trastuzumab/chemotherapy for patients with HER2-positive breast cancer.

2.1 **Phase II Trial of T-DM1 for Patients with HER2-Positive Metastatic Breast Cancer Who Experienced Disease Progression on Prior HER2-Directed Therapy**

	Investigator		Independent review	
	All (N = 112)	HER2 centrally confirmed (N = 75)	All (N = 112)	HER2 centrally confirmed (N = 75)
Overall response rate	38.4%	48.0%	25.0%	32.0%
Clinical benefit rate (CBR)*	44.6%	54.7%	34.8%	44.0%

* CBR = complete response + partial response + stable disease ≥ 6 months

Vogel CL et al. *Proc ASCO* 2009;**Abstract 1017**.

DR LOVE: Would you discuss your study evaluating the combination of T-DM1 with pertuzumab that was presented at ASCO?

DR MILLER: We presented data for the first 28 patients out of the 44 in the refractory cohort. The toxicity appeared to be similar to T-DM1 alone. Minor systemic issues arose, such as fatigue and thrombocytopenia not associated with bleeding, and no obvious cardiotoxicity was evident. Response rates were between 25 and 30 percent in this refractory population, and we are certainly encouraged by these results and by the lack of an apparent increase in toxicity (Miller 2010; [2.2]).

DR LOVE: What do we know about T-DM1-related thrombocytopenia?

DR MILLER: Thrombocytopenia occurs quite early, often within a couple of days of infusion, and for most patients it is fairly moderate, though some patients might experience significant thrombocytopenia. However, it resolves quickly, within three to four days. I believe thrombocytopenia will garner a lot of attention in the early clinical trials, but as the agent moves into practice and people become accustomed to it, this will not be nearly such a big issue.

2.2

Efficacy Data from a Phase Ib/II Trial of Pertuzumab (P) and T-DM1 for Patients with Previously Treated HER2-Positive Breast Cancer (N = 28)

Partial response	Stable disease	Progressive disease	Missing
35.7%	46.4%	14.3%	3.6%

"Safety, tolerability, and preliminary efficacy of full dose T-DM1 + P are encouraging, with no substantial increase in toxicity over single agent T-DM1, and no new safety signals. Hepatic and Grade 4 thrombocytopenia events were infrequent. T-DM1 dosing was established at 3.6 mg/kg."

Miller K et al. *Proc ASCO* 2010;**Abstract 1012**.

Track 6

DR LOVE: Would you comment on the meta-analysis of studies of bevacizumab-containing first-line therapy in metastatic breast cancer?

DR MILLER: In the individual trials, bevacizumab had no effect on survival, though none of the trials were powered to show a survival advantage. The meta-analysis presented at ASCO revealed no overall survival advantage with bevacizumab (O'Shaughnessy 2010; [2.3]).

Overall survival is an important endpoint, and we obviously want our patients to live longer. However, overall survival is a composite that is driven by the patient's age and comorbidities, the inherent biology of the disease and the efficacy and toxicity of the therapies we administer in multiple lines. So in my view, to a small extent, overall survival might be altered by initial first-line therapy. For an initial therapy to affect overall survival, the effect on other efficacy endpoints must be much greater to see an overall survival difference.

In contrast, progression-free survival is more directly tied to the effect of the therapy being studied. Progression-free survival is also influenced by the inherent biology of the disease, the efficacy and toxicity of the therapy and the ability to deliver the therapy. However, other confounding factors, such as effects from subsequent therapies, can affect overall survival but do not affect progression-free survival. ■

2.3

Meta-Analysis of Three Phase III Studies of Bevacizumab (BV)-Containing First-Line Therapy in HER2-Negative Metastatic Breast Cancer: ECOG-E2100, AVADO and RIBBON-1

	Chemo only (N = 1,008)	Chemo/BV (N = 1,439)	Hazard ratio	*p*-value
Progression-free survival (PFS)	6.7 mo	9.2 mo	0.64	<0.0001
Overall survival (OS)	26.4 mo	26.7 mo	0.97	0.560
One-year survival	77%	82%	—	0.003

"Results from the exploratory analysis of the pooled PFS data show that BV, when combined with first-line chemotherapy (taxane-, anthracycline-, or capecitabine-based regimens), results in clinically meaningful and statistically significant improvements in PFS. Though no statistically significant difference in median OS was seen, the pooled OS data from these trials suggest an early benefit at 1 year."

O'Shaughnessy J et al. *Proc ASCO* 2010;**Abstract 1005**.

SELECT PUBLICATIONS

Baselga J et al. **Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy.** *J Clin Oncol* 2010;28(7):1138-44.

Cortes J et al. **Pertuzumab and trastuzumab: Exploratory biomarker correlations with clinical benefit in patients with metastatic HER2-positive breast cancer.** *Proc ASCO* 2010;**Abstract 1066**.

Cortes J et al. **Pertuzumab monotherapy following trastuzumab-based treatment: Activity and tolerability in patients with advanced HER2-positive breast cancer.** *Proc ASCO* 2009;**Abstract 1022**.

LoRusso P et al. **Quantitative assessment of diagnostic markers and correlations with efficacy in two phase II studies of trastuzumab-DM1 (T-DM1) for patients (pts) with metastatic breast cancer (MBC) who had progressed on prior HER2-directed therapy.** *Proc ASCO* 2010;**Abstract 1016**.

Miller K et al. **A phase Ib/II trial of trastuzumab-DM1 (T-DM1) with pertuzumab (P) for women with HER2-positive, locally advanced or metastatic breast cancer (BC) who were previously treated with trastuzumab (T).** *Proc ASCO* 2010;**Abstract 1012**.

O'Shaughnessy J et al. **A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC).** *Proc ASCO* 2010;**Abstract 1005**.

Vogel CL et al. **A phase II study of trastuzumab-DM1 (T-DM1), a HER2 antibody-drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (MBC): Final results.** *Proc ASCO* 2009;**Abstract 1017**.