INTERVIEW

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Tracks 1-13

Track 1 Lead study author's insight on the initial results from EMILIA, a Phase III study of trastuzumab emtansine (T-DM1) versus capecitabine/lapatinib in HER2-positive locally advanced or metastatic breast cancer (mBC) previously treated with trastuzumab and a taxane

Track 2 Improvement in progression-free survival with T-DM1 versus capecitabine/lapatinib

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Track 11 Current therapeutic algorithm for patients with ER-positive, HER2-positive BC

Track 12 Perspective on the dosing schedules and toxicities observed in the CALGB-40502 study of weekly paclitaxel, nanoparticle albumin-bound (*nab*) paclitaxel or ixabepilone with or without bevacizumab as first-line therapy for locally recurrent or metastatic BC

Track 13 Perspective on the current status of bevacizumab in BC

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you discuss the results of the Phase III EMILIA study, which you recently presented in the ASCO 2012 plenary session?

DR BLACKWELL: The EMILIA study evaluated T-DM1 versus lapatinib/capecitabine in 980 patients with HER2-positive locally advanced or metastatic breast cancer (mBC) previously treated with trastuzumab and a taxane. The study had 2 coprimary endpoints — progression-free survival (PFS) determined by an independent review and overall survival (OS).

We paid close attention to median dose intensity — which measures how much drug was successfully administered — on both study arms. The dose intensity for lapatinib on the control arm was 94%. On the T-DM1 arm, it was 100%. So, as much as we have

concerns regarding dose adjustments with lapatinib and capecitabine, we were able to administer the combination to these patients and we still observed a benefit for the T-DM1 arm.

Specifically, the study met its first coprimary endpoint — PFS was improved in absolute terms by 3.2 months in favor of T-DM1 with a hazard ratio of 0.65 and a *p*-value of less than 0.0001, so a 35% proportional improvement in PFS was observed (Verma 2012; [1.1]). The other coprimary endpoint was OS, and at the time the PFS event rate was met, a planned interim survival analysis was prompted.

The median OS at the time of the first analysis was 23.3 months for lapatinib/capecitabine but had not been reached for T-DM1. When you evaluate the hazard ratio for survival, it was 0.621 with a *p*-value of 0.0005. It seems as if that should be statistically significant, but because this was a planned interim analysis the preset efficacy stopping boundary was a *p*-value of 0.0003 (Editor's note: Subsequent to this interview the second interim OS analysis results for EMILIA were published; see figure 1.1).

T-DM1 was well tolerated. Patients on the T-DM1 arm experienced primarily as Grade 3/4 adverse events laboratory abnormalities such as elevations in AST/ALT and transient thrombocytopenia. The latter generally occurs somewhere between days 8 and 10, so if you don't specifically look for it between the 21-day cycles you might not see it. Grade 3/4 thrombocytopenia — platelet counts less than 100,000 and something that historically could put patients at an increased risk for bleeding — was reported in approximately 14% of patients. Patients should be aware of it just as with standard chemotherapy. Increased bleeding or excessive nosebleeds should be checked.

1.1

EMILIA: Results of a Phase III Trial of T-DM1 versus Capecitabine (Cape) with Lapatinib (Lap) for HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated with Trastuzumab and a Taxane

Response	**T-DM1** (n = 495)	**Cape/lap** (n = 496)	Hazard ratio	*p*-value
Median progression-free survival	9.6 mo	6.4 mo	0.65	<0.001
Median overall survival (second interim analysis)*	30.9 mo	25.1 mo	0.68	<0.001
Two-year overall survival	64.7%	51.8%	—	—
Select adverse events (Grade ≥3)	**T-DM1** (n = 490)		**Cape/lap** (n = 488)	
Diarrhea	1.6%		20.7%	
Hand-foot syndrome	0%		16.4%	
Vomiting	0.8%		4.5%	
Nausea	0.8%		2.5%	
Mucosal inflammation	0.2%		2.3%	
Elevated AST	4.3%		0.8%	
Elevated ALT	2.9%		1.4%	
Thrombocytopenia	12.8%		0.2%	

* Conducted on the basis of 331 deaths; met the predefined O'Brien-Fleming stopping boundary (efficacy stopping boundary, $p = 0.0037$ or hazard ratio = 0.73)

Verma S et al. *N Engl J Med* 2012;[Epub ahead of print].

We noted increased liver enzymes on both arms of the study but more frequently on the T-DM1 arm. We've seen elevations in AST and ALT with capecitabine and in ALT with lapatinib. AST/ALT levels must be monitored when patients are receiving both of those agents. The same will apply with T-DM1. Approximately 1 out of 4 patients experienced an increase in AST, but severe increases were observed only in 3% to 4% of patients.

No Grade 3/4 hemorrhage-related deaths occurred on the T-DM1 arm. No difference in the transfusion rate and small differences in anemia rates were observed. No Grade 4 anemia was observed on either arm of the study. We reported considerable diarrhea and hand-foot syndrome with capecitabine/lapatinib — approximately 1 out of 4 women experienced Grade 3/4 diarrhea and about 15% of patients experienced Grade 3/4 hand-foot syndrome.

What is meaningful about these differences in toxicity is that the side effects that we observed in the study on the T-DM1 arm didn't affect patient quality of life. T-DM1 seems to be what we've been searching for, which is cancer treatment without chemotherapy side effects.

DR LOVE: What was your approach to T-DM1 dosing during the trial when patients experienced Grade 3/4 toxicities?

DR BLACKWELL: We followed well-described dose adjustments in this study for T-DM1. The agent is dosed based on milligrams-per-kilogram dosing. On the first dose reduction you decrease from 3.6 mg/kg to 3 mg/kg, and then the second dose adjustment is to 2.4 mg/kg. If you run into any other Grade 3/4 toxicity after those 2 dose reductions, it is recommended that treatment with the drug be stopped. Because of its long half-life, it won't be like dosing weekly chemotherapy. With every 3-week paclitaxel you can dose adjust it and administer it weekly. You can't do that with T-DM1, given its long half-life.

Tracks 5, 7, 11

DR LOVE: An important issue if and when T-DM1 becomes available is how it might fit in the HER2-positive metastatic algorithm, and in this regard can you discuss how you are approaching the use of pertuzumab now in your practice given its recent FDA approval?

DR BLACKWELL: The pertuzumab approval was based on the CLEOPATRA study, which was a first-line trial of docetaxel/trastuzumab with or without pertuzumab for HER2-positive mBC. Results reported earlier this year indicated an improvement in PFS of approximately 6 months with the addition of pertuzumab, and a recent press release after pertuzumab was approved by the FDA reported that an updated survival analysis showed a significant advantage with the addition of pertuzumab to trastuzumab and docetaxel (Baselga 2012; [1.2]).

I believe the standard first-line therapy will be pertuzumab/trastuzumab and docetaxel, considering this survival advantage. What we're all grappling with is, will we be able to use the combination outside of the first-line setting, outside of the actual eligibility criteria for the CLEOPATRA trial, and will it be covered? The other issue is that docetaxel is a particularly difficult regimen for patients with mBC to complete.

1.2

CLEOPATRA: A Phase III Trial of the Addition of Pertuzumab versus Placebo to Docetaxel/Trastuzumab as First-Line Therapy for Patients with HER2-Positive Metastatic Breast Cancer

	Pertuzumab (n = 402)	Placebo (n = 406)	Hazard ratio	*p*-value
Median progression-free survival[1]	18.5 mo	12.4 mo	0.62	<0.001
Interim overall survival analysis (deaths)*[1]	17.2%	23.6%	0.64	0.005

* Not significant because analysis did not meet O'Brien-Fleming stopping boundary; a trend was evident toward overall survival benefit with pertuzumab

Press release (June 22, 2012): Patients with HER2-positive metastatic breast cancer lived significantly longer (overall survival) when treated with the combination of pertuzumab, trastuzumab and docetaxel chemotherapy compared to trastuzumab and docetaxel chemotherapy alone in the Phase III CLEOPATRA study. These data will be submitted for presentation at an upcoming medical meeting.[2]

[1] Baselga J et al. *N Engl J Med* 2012;366(2):109-19.
[2] **www.roche.com/media/media_releases/med-cor-2012-06-22.html**.

When I administer the combination of docetaxel/pertuzumab/trastuzumab, I will almost certainly set a limit to the amount of docetaxel. I'll set an expectation with the patient that if we run into toxicity, we'll dose reduce. I'll likely drop docetaxel soon after the sixth cycle and administer the dual antibody combination and restage after about 9 weeks to ascertain that the chemotherapy backbone wasn't necessary.

DR LOVE: What are your thoughts on substituting either paclitaxel or nanoparticle albumin-bound (*nab*) paclitaxel for docetaxel with pertuzumab and trastuzumab?

DR BLACKWELL: I wouldn't have a problem, if it was covered, administering *nab* paclitaxel or paclitaxel in place of docetaxel. In my practice about once or twice a week we administer an initial dose of docetaxel, and as the first few drops are going in, the patient starts having trouble breathing and then we have to administer corticosteroids. I believe after such experiences we'd consider switching to *nab* paclitaxel or paclitaxel. I believe *nab* paclitaxel has some advantages, including the fact that it doesn't have the allergic reaction rate that we see with paclitaxel. I think the *nab* paclitaxel weekly dosing schedule needs some tweaking. With some better understanding of what the appropriate dosing schedule is, *nab* paclitaxel can be a useful agent.

DR LOVE: And how might T-DM1 fit in?

DR BLACKWELL: My bias will likely be toward using T-DM1 before I use pertuzumab strictly because of the chemotherapy backbone required for pertuzumab. If payers and reimbursement require that pertuzumab be used only in the first chemotherapy-based, HER2-directed combination, then I will probably administer more first-line pertuzumab. If and when T-DM1 is approved, I believe it will be available as first-, second- and third-line therapy because that's how it was evaluated in the EMILIA study. Then the real wild card is getting pertuzumab available to patients beyond the first-line setting. ■

SELECT PUBLICATIONS

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

Verma S et al. **Trastuzumab emtansine for HER2-positive advanced breast cancer.** *N Engl J Med* 2012;[Epub ahead of print].