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Biomarker Analysis Identified Women Most Likely to Benefit From T-DM1

- Patients with the highest tumor HER2 levels benefited most.
- The EMILIA phase III clinical trial led to FDA approval of T-DM1.
- Presence of tumor PIK3CA mutations did not diminish treatment response.

WASHINGTON, D.C. — For women with metastatic, HER2-positive breast cancer, the amount of HER2 on their tumor might determine how much they benefit from a drug called trastuzumab emtansine (T-DM1), according to data from a subanalysis of the phase III clinical trial that led the U.S. Food and Drug Administration to approve the drug on Feb. 22, 2013. These findings were presented by José Baselga, M.D., Ph.D., physician-in-chief at Memorial Sloan-Kettering Cancer Center in New York, N.Y., at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

"EMILIA was a landmark phase III clinical trial," said Baselga. "It showed that T-DM1 prolonged progression-free and overall survival for patients with HER2-positive metastatic breast cancer that had been previously treated with trastuzumab and a taxane chemotherapy compared with lapatinib plus capecitabine. Also, it provided proof-of-concept that a new class of drugs called antibody-drug conjugates can benefit patients."

Antibody-drug conjugates consist of an antibody attached to a toxic chemotherapy, according to Baselga. In the case of T-DM1, the antibody is trastuzumab and the toxic chemotherapy is emtansine. Trastuzumab recognizes the protein HER2, which is found at high levels in HER2-positive breast cancers, and targets the emtansine to the HER2-positive cancer cells, which are killed by the toxic chemotherapy.

In this subanalysis, Baselga and colleagues analyzed tissue samples from patients enrolled in EMILIA to examine whether tumor levels of HER2, as assessed by the amount of HER2 messenger ribonucleic acid (mRNA), affected treatment response. Patients with tumor samples expressing greater than the median amount of tumor HER2 mRNA were considered to have high levels of HER2. Those with tumor samples expressing the median amount of tumor HER2 mRNA or less were considered to have low levels of HER2.

"Even though everyone enrolled in the clinical trial had breast cancer expressing elevated levels of HER2, we know that each person's tumor has different molecular features," said Baselga. "Even the degree to which HER2 expression is elevated differs from patient to patient."

Consistent with the prior analysis, he and his colleagues found that all patients treated with T-DM1 had significantly longer progression-free and overall survival compared with those treated with lapatinib and capecitabine (9.6 months progression-free survival versus 6.4 months; and 30.9 months for overall survival versus 25.1 months).

Patients with tumors expressing higher levels of HER2 derived greater benefit from treatment with T-DM1 compared with patients with tumors expressing lower levels of HER2: Overall survival was 34.1 months for those with high levels of HER2 versus 26.5 months. For patients with tumors expressing higher levels of HER2, those receiving T-DM1 had a 47 percent decreased risk for death compared with those receiving lapatinib and capecitabine.

The researchers also investigated whether tumor mutations in the PIK3CA gene affected treatment response. According to Baselga, patients with PIK3CA-mutated, HER2-positive breast cancer normally do not respond as well to treatment with conventional HER2-targeted therapies such as trastuzumab compared with patients without PIK3CA mutations in their tumors.

However, for patients treated with T-DM1, PIK3CA mutation status did not significantly decrease progression-free survival.

"Our findings are an important step toward identifying the best therapy for individual patients with HER2-positive breast cancer," said Baselga. "HER2-positive breast cancer is not a uniform disease; each patient is different. These data help us as we look to identify a panel of molecular features that we can use to make informed treatment decisions."

Kadcyla (ado-trastuzumab emtansine or T-DM1) is a trademark of Genentech, a member of the Roche Group.

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Abstract Number: LB-63

Presenter: José Baselga, M.D., Ph.D.

Title: Relationship between tumor biomarkers (BM) and efficacy in EMILIA, a phase 3 study of trastuzumab emtansine (T-DM1) in HER2-postitive metastatic breast cancer (MBC)

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Background: The antibody-drug conjugate T-DM1 retains the mechanisms of action of trastuzumab, including HER2 targeting and interruption of HER2 signaling, and provides a means of delivering the cytotoxic agent DM1 directly to HER2-positive tumors. In the EMILIA study, T-DM1 demonstrated a statistically significant progression-free and overall survival (PFS, OS) benefit with less toxicity vs capecitabine plus lapatinib (XL) in patients (pts) with previously treated HER2-positive MBC. Activating mutations of PIK3CA may lead to resistance to currently available HER2-directed therapies. The relationship between treatment efficacy and tumor HER2 mRNA expression or PIK3CA mutation status was examined in pts from EMILIA.

Methods: Tumor tissue collected for HER2 testing was also used for HER2 mRNA analysis by qRT-PCR and for PIK3CA assessment (with additional consent), using a PIK3CA Mutation Detection Kit. PFS and OS were analyzed for each BM subgroup using the Kaplan-Meier method and a Cox regression model.

Results: Median mRNA concentration ratios and PIK3CA mutation frequency were similar across treatment arms and consistent with data previously reported. T-DM1 demonstrated superior PFS and OS vs XL in all BM subgroups. The hazard ratio of OS was less for pts with high (>median) vs low tumor HER2 mRNA levels. For XL-treated pts, PIK3CA mutations were associated with shorter median PFS and OS; PIK3CA mutations did not significantly affect T-DM1 treatment outcomes.

Conclusions: Pts in all BM subgroups analyzed to date had longer PFS and OS with T-DM1 vs XL. Pts with tumors expressing high HER2 mRNA levels derived even greater OS benefit from T-DM1. XL-treated pts with PIK3CA mutations had worse outcomes than those with wild type PIK3CA. T-DM1-treated pts with PIK3CA mutations had a similar treatment benefit as those without, suggesting that the unique mechanism of action of T-DM1 may overcome PIK3CA mutation resistance

Table. Efficacy by BM Subgroup in EMILIA

PFS

	T-DM1		XL		Hazard ratio[a]	95% CI
	n	Median PFS (months)	n	Median PFS (months)		
All patients	495	9.6	496	6.4	0.66	(0.56, 0.78)
HER2 mRNA concentration ratio						
≤Median	230	8.2	204	6.4	0.64	(0.50, 0.82)
>Median	197	10.6	235	6.9	0.65	(0.50, 0.85)
PIK3CA mutation status						
Mutated	40	10.9	39	4.3	0.45	(0.25, 0.82)
Wild type	93	9.8	87	6.4	0.74	(0.50, 1.10)

OS

	T-DM1		XL		Hazard ratio[a]	95% CI
	n	Median OS (months)	n	Median OS (months)		
All patients	495	30.9	496	25.1	0.70	(0.56, 0.87)
HER2 mRNA concentration ratio						
≤Median	230	26.5	204	23.7	0.80	(0.59, 1.09)
>Median	197	34.1	235	24.8	0.53	(0.37, 0.76)
PIK3CA mutation status						
Mutated	40	NE	39	17.3	0.26	(0.12, 0.57)
Wild type	93	NE	87	27.8	0.68	(0.40, 1.15)

[a]Hazard ratios are based on unstratified analyses.
CI, confidence interval; HER, human epidermal growth factor receptor; NE, not estimable; OS, overall survival; PIK3CA, phosphatidylinositide 3-kinase catalytic subunit alpha; PFS; progression-free survival; T-DM1, trastuzumab emtansine; XL, capecitabine + lapatinib