Relationship between Tumor Biomarkers and Efficacy in EMILIA, a Phase III Study of Trastuzumab Emtansine in HER2-Positive Metastatic Breast Cancer

José Baselga,Gail D Lewis Phillips,Sunil Verma,Jungsil Ro,Jens Huober,Alice E Guardino,Meghna K Samant,Steve Olsen,Sanne L De Haas & Mark D Pegram

PURPOSE
HER2-positive breast cancer is heterogeneous. Some tumors express mutations, like activating PIK3CA mutations or reduced PTEN expression, that negatively correlate with response to HER2-targeted therapies. In this exploratory analysis, we investigated whether the efficacy of trastuzumab emtansine (T-DM1), an antibody-drug conjugate comprised of the cytotoxic agent DM1 linked to the HER2-targeted antibody trastuzumab, was correlated with the expression of specific biomarkers in the phase III EMILIA study.

EXPERIMENTAL DESIGN
Tumors were evaluated for HER2 (n = 866), EGFR (n = 832), and HER3 (n = 860) mRNA expression by quantitative reverse transcriptase PCR; for PTEN protein expression (n = 271) by IHC; and for PIK3CA mutations (n = 259) using a mutation detection kit. Survival outcomes were analyzed by biomarker subgroups. T-DM1 was also tested on cell lines and in breast cancer xenograft models containing PIK3CA mutations.

RESULTS
Longer progression-free survival (PFS) and overall survival (OS) were observed with T-DM1 compared with capecitabine plus lapatinib in all biomarker subgroups. PIK3CA mutations were associated with shorter median PFS (mutant vs. wild type: 4.3 vs. 6.4 months) and OS (17.3 vs. 27.8 months) in capecitabine plus lapatinib-treated patients, but not in T-DM1-treated patients (PFS, 10.9 vs. 9.8 months; OS, not reached in mutant or wild type). T-DM1 showed potent activity in cell lines and xenograft models with PIK3CA mutations.

CONCLUSIONS
Although other standard HER2-directed therapies are less effective in tumors with PI3KCA mutations, T-DM1 appears to be effective in both PI3KCA-mutated and wild-type tumors. Clin Cancer Res; 22(15); 3755-63. ©2016 AACR.

Kantonsspital St.Gallen

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