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Abstract title: LATE BREAKING ABSTRACT: T-DM1 for HER2-positive metastatic breast cancer (MBC): Primary result from TH3RESA, a phase 3 study of T-DM1 vs treatment of physician's choice

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Background: T-DM1, an antibody-drug conjugate comprising the cytotoxic agent DM1 linked to trastuzumab, is approved in the US for patients (pts) with MBC previously treated with trastuzumab and a taxane. There is no clear standard of care for pts with progressive disease (PD) after ≥2 HER2-directed regimens for MBC. TH3RESA is an ongoing phase 3 study evaluating T-DM1 vs treatment of physician's choice (TPC) in this pt population (NCT01419197; Genentech, a member of the Roche Group).

Methods: Pts with centrally confirmed HER2-positive unresectable locally advanced BC or MBC with PD after ≥2 HER2-directed regimens, including trastuzumab and lapatinib, in the unresectable recurrent/metastatic setting and a taxane (any setting) were randomized 2:1 to T-DM1 (3.6 mg/kg IV q3w or TPC. Co-primary endpoints were progression-free survival (PFS) by investigator and overall survival (OS). After EMILIA data were reported, crossover from TPC to T-DM1 was allowed post-progression.

Results: At the 11 Feb 2013 cutoff, 602 pts were randomized; 44 pts in the TPC arm had crossed over to T-DM1. TPC comprised HER2-directed regimens (83.2%) and single-agent chemotherapy (16.8%). Pts had received a median of 4 prior regimens (excluding hormonal therapy) in the recurrent/metastatic setting, and the majority (75.1%) had visceral disease. PFS and objective response rate (ORR) were significantly improved with T-DM1; the interim OS analysis showed a similar trend, but the stopping boundary was not crossed (Table). PFS benefit was consistent across subgroups, including age, visceral involvement, number of prior regimens, and TPC type. The T-DM1 safety profile was consistent with prior studies. Fewer grade ≥3 adverse events (AEs) overall were reported for T-DM1 vs TPC (32.3% vs 43.5%). More grade ≥3 thrombocytopenia (4.7% vs 1.6%) was reported with T-DM1. More grade ≥3 neutropenia (2.5% vs 15.8%), febrile neutropenia (0.2% vs 3.8%), and diarrhea (0.7% vs 4.3%) were reported with TPC.

	T-DM1 n=404	**TPC n=198**
PFS, median mos	6.2	3.3
HR (95% CI)	0.528 (0.422, 0.661)	

Interim OS, median mos	Not reached	14.9
HR (95% CI)	0.552 (0.369, 0.826)	
P value	.0034	
	Stopping boundary: HR=0.363	
	T-DM1 n=345	**TPC n=163**
ORR, % (95% CI)	31.3 (26.5, 36.5)	8.6 (5.1, 13.8)
Difference, % (95% CI)	22.7 (16.2, 29.2)	
P value	<.0001	

Conclusions: T-DM1 resulted in a statistically significant improvement in PFS, with fewer grade ≥3 AEs than TPC in pts previously treated with ≥2 HER2-directed regimens for HER2-positive MBC.