The relationship between quantitative HER2 gene expression by the 21-gene RT-PCR assay and adjuvant trastuzumab (H) benefit in NCCTG (Alliance) N9831.

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Background: There is considerable interest in developing HER2 testing criteria for adjuvant H. We used the 21-gene assay to examine the relationship of HER2 mRNA to benefit from H. **Methods:** N9831 compared adjuvant chemotherapy AC-T to concurrent chemotherapy-trastuzumab AC-TH in stage I-III HER2+ breast cancer. Recurrence Score (RS) and HER2 mRNA expression were determined by Onco*type* DX (neg<10.7, equiv 10.7 to <11.5, and pos ≥11.5 $\log_2$ expression units). Cox regression was used to assess the association of HER2 expression with H benefit for distant recurrence. **Results:** Median follow-up: 7.4 yrs. Of 1,940 total pts, 901 had consent and sufficient tissue. HER2 by RT-PCR was neg in 130 (14%), equiv in 85 (9%), and pos in 686 (76%) pts. Concordance between HER2 assessments was 95% for RT-PCR vs central IHC (>10% + cells = +), 91% for RT-PCR vs central FISH (≥2.0 = pos) and 94% for central IHC vs central FISH. In the primary analysis, the association of HER2 expression with H benefit was marginally non-significant (P=0.057). In hormone receptor pos pts (local IHC) the association was significant (P=0.002). The association was nonlinear with the greatest estimated benefit at lower and higher HER2 mRNA expression levels. The observed treatment benefit in low HER2 pts was not due to imbalance between arms in RS and individual gene expression values. **Conclusions:** Concordance among HER2 assessments by central IHC, FISH, and RT-PCR was high. Association of HER2 mRNA expression with H benefit was marginally non-significant. A consistent benefit of trastuzumab irrespective of mHER2 levels was observed in the pts with either IHC+ or FISH+ tumors. Benefit was observed in pts with high HER2 by RT-PCR but also observed for the small groups of pts with negative results by quantitative RT-PCR or FISH (Table). Plausible mechanisms for this observation will be discussed.

H benefit Cox hazard ratios (95% CI) by central HER2 status (adjusted for nodes).

	Neg	**Equivocal**	**Pos**
IHC	0.31 (0.05, 1.37) P=0.127	0.85 (0.27, 2.31) P=0.763	0.49 (0.33, 0.71) P<0.001
FISH	0.33 (0.09,0.93) P=0.034		0.54 (0.37,0.78) P<0.001
RT-PCR	0.31 (0.09,0.83) P=0.017	0.44 (0.09,1.59) P=0.217	0.55 (0.37,0.81) P=0.002