Title: A Venezuelan Study of Breast Cancer ER PR and HER2 Expression by the Standard Method, Immunohistochemistry (IHC), Compared to a New Method, Quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR)

Authors:

Background: Assessment of ER, PR and HER2 is of significant importance in breast cancer diagnosis and treatment. We have performed the first large assessment of central IHC for ER, PR and HER2 by a South American central lab IHC to central lab RT-PCR by Oncotype DX®.

Design: Breast cancer specimens from the Fundación BADAN were evaluated by IHC for ER (1D5), PR (636) using ≥1% staining for positivity and HER2 (A0485) using ASCO/CAP guidelines of 3+ in ≥30%. Standardized quantitative RT-PCR analysis for ER and PR used Oncotype DX with the pre-defined cutoffs of 6.5 and 5.5 for positivity. For HER2 the standard pre-defined cutoffs were used: positive ≥11.5 units, equivocal >10.7-<11.5 units, and negative ≤10.7 units (each unit represents a 2-fold change in expression). Concordance analysis excluded the equivocal range from both assays according to ASCO/CAP Guidelines (Wolff et al, 2006). Reference normalized expression measurements ranged from 0 to 15, where each 1-unit increase reflects about a 2-fold increase in RNA.

Result: Evaluable data was obtained in 96 pts for ER, 95 pts for PR (1 pt assessment unavailable) and 89 pts for HER2 (7 pt assessments unavailable). Two-by-two tables (below) compare IHC versus RT-PCR for ER, PR and HER2. The overall concordance for ER between IHC and RT-PCR was 94% (Kappa 0.467; 95% CI 0.107, 0.828); for PR between IHC and RT-PCR was 92% (Kappa 0.668; 95% CI 0.457, 0.878); and for HER2 between IHC and RT-PCR was 97% (Kappa = 0.649; 95% CI 0.280, 1.000). 3 IHC 2+ cases and 4 equivocal cases by Oncotype DX were excluded from Concordance and Kappa statistics

Conclusion: RT-PCR by Oncotype DX for ER, PR and HER2 status is useful for active monitoring of IHC assays as mandated by ASCO/CAP and shows a high degree of overall concordance between central IHC performed in South America and central RT-PCR for ER, PR and HER2 status.

Table 1

ER		Oncotype DX		
		-	+	All
IHC	-	3	4	7
	+	2	87	89
	All	5	91	96

Concordance = 90/96 = 0.938
Kappa = 0.467 (95% CI 0.107, 0.828)

Table 2

PR		Oncotype DX		
		-	+	All
IHC	-	10	1	11
	+	7	77	84
	All	17	78	95

Concordance = 87/95 = 0.916
Kappa = 0.668 (95% CI 0.457, 0.878)
Note: 1 IHC assessment was not evaluable

Table 3

HER2, Excluding Equivocal per CAP/ASCO guidelines		Oncotype DX			
		-	Equivocal	+	All
IHC	-	83	4	1	84
	2+	3	0	0	
	3+	2	0	3	5
	All	85		4	89

Concordance = 86/89 = 0.966
Kappa = 0.649 (95% CI 0.280, 1.000)
Note: 3 IHC 2+ and 4 Equivocal by Oncotype DX were excluded from Concordance and Kappa statistics