

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Correlation between preoperative chemotherapy response and ER, PgR, HER-1, HER-2 expression

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Definitions

- **Predictive factors:** characteristics of tumor which predict the **magnitude of response** to a given treatment
- **Prognostic factors:** characteristics of tumor which predict inherent **disease outcome**

Why ER, PgR, HER-1 and HER-2?

- Tumors completely lacking ER/PgR particularly sensitive to preoperative chemotherapy (CT)
- HER-1 and HER-2 linked with resistance to CT and worse prognosis
- ER+/PgR- breast cancers overexpress HER-1 and HER-2

Can we use these markers to tailor therapy?

pCR* by Hormone Receptor (HR) status*

Author	Pts	HR+ pCR (%)	HR- pCR(%)	<i>P</i>
Bear	2411	8.3	16.7	<.001
Gianni	438	10	45	<.001
Ring	435	8.1	21.6	<.001
Guarneri	1731	8	24	<.001
Von Minckwitz	913	6.2	22.8	<.001
Colleoni	399	7.6	33.3	<.001

*definitions of both pCR and HR+ varied between studies

ER/PgR and pCR: IBCSG-IEO preoperative study

ER/PgR	Pts (%)	pCR (%)	<i>P</i>
Overall	399	63 (16)	
Absent (0%)	129 (32)	43 (33)	<.0001
Low (1-9%)	94 (23)	7 (7)	
Positive ($\geq 10\%$)	171 (42)	13 (8)	
Unknown	5 (2)	0 (0)	

DFS by HR status

Author	Pts	HR+	HR-	<i>P</i>
Amat *°	710	65	57	NS°°°
Hennessy **	403	68	46	<.001
Guarneri **	1731	67	56	<.001
Ring **	435	80	60	.0001
Colleoni ***	399	74	41	<.001
Gianni**	438	NA°°	NA°°	<.001

* 10-year DFS

** 5-year DFS

*** 4-year DFS

°at final surgery

°°data not available

°°°not significant

Residual axillary disease

	ER positive (N°= 163)	ER negative (N°=128)	<i>P</i>
5-year RFS%	68	46	<.001
5-year OS%	84	53	<.001

Hennessy B, J Clin Oncol 23: 9304-9311, 2005

Late DFS by HR

HR	Pts	5-yrs%	10-yrs%	<i>P</i>
Negative	555	56.1	49.0	<.0001
Positive	1163	67.2	39.6	
HR negative				
no pCR	423	50.0	42.9	<.0001
pCR	132	83.4	73.0	
HR positive				
no pCR	1072	65.3	38.2	<.0001
pCR	91	93.1	75.9	

Late OS by HR

HR	Pts	5-yrs%	10-yrs%	<i>P</i>
Negative	555	70.8	63.7	<.0001
Positive	1163	85.4	42.7	
HR negative				
no pCR	423	67.4	58.8	.003
pCR	132	83.9	83.9	
HR positive				
no pCR	1072	84.5	41.3	.04
pCR	91	96.4	96.4	

HER-2 evaluation

Author	Pts	Positive
Gregory	710	Positive
Guarneri	1371	3+ or A
Falo	300	Positive or A
Geisler	79	3+ or 2+
Zhang	97	3+ or A
Loibl	648	A
Petit	79	Positive
Vincent-Salomon	54	3+ or 2+
Burcombe	118	3+

A= Amplified

pCR by HER-2

Author	Pts	HER-2+ (%)	HER-2 - (%)	<i>P</i>
Zhang	97	18	13	
Burcombe	118	44	36	
Penault-Llorca	115	39	9	
Vincent-Salomon	54	13.3	34	
Petit	79	16.6	13	
Learn	104	22	24	
Guarneri ER-	455	29	22.4	<.001
Guarneri ER+	916	15.3	6	
Loibl	648	24.5	19.2	

DFS by HER-2

Author	Pts	HER-2+ 5-yrs%	HER-2- 5-yrs%	<i>P</i>
Gregory [°]	710	NA ^{°°}	NA ^{°°}	.008
Guarneri ER+	916	60.2	66.3	<.001
Guarneri ER-	455	43.7	53.3	
Falo ^{*°}	300	53.3	61	.29
Geisler	79	NA ^{°°}	NA ^{°°}	.06
Zhang ^{**}	97	NA ^{°°}	NA ^{°°}	NS ^{°°°}

*8-yrs

°at final surgery

°°°not significant

**4-yrs

°°data not available

IBCSG-IEO study: updated results

Baseline Feature	Pts (%)	pCR (%)	<i>P</i>
Overall	488	85 (17)	-
ER and PgR Absent	178 (36)	59 (33)	<0.0001
ER and/or PgR Low/Positive	305 (63)	26 (9)	
HER-2 Positive	70 (14)	16 (23)	0.38
HER-2 Negative	224 (46)	40 (18)	

IBCSG-IEO study: updated results

Baseline Feature	Pts (%)	5-yr DFS%	<i>P</i>	5-yr OS%	<i>P</i>
Overall	488	60±2	-	78±2	-
ER and/or PgR Low/Positive	305 (63)	71±3	<.0001*	87±2	<.0001*
ER and PgR Absent	178 (36)	41±4		61±4	
HER-2 Negative	224 (46)	62±3	.02	80±3	.04
HER-2 Positive	70 (14)	45±6		66±6	

*Multivariate analysis

IBCSG-IEO study: exploratory biomarker analyses

Baseline Feature	Pts (%)	pCR (%)	5-yr DFS%	5-yr OS%
Overall	488	85 (17)	60±2	78±2
ER & PgR Pos. (any)	222 (45)	19 (9)	74±3	90±2
ER Pos. (any) & PgR absent	81 (17)	7 (9)	65±6	81±4
ER & PgR Absent & HER-2 Negative	85 (17)	29 (34)	50±6	69±6
ER & PgR Absent & HER-2 positive	44 (9)	14 (32)	24±7	46±8

pCR by HER-1

Author	Pts	HER-1 + (%)	HER-1 - (%)	<i>P</i>
Guarneri	115	5.5	6.3	0.9
Bucholz	82	21	12	0.3

Guarneri V, Breast Cancer Res Treat 99: 152, 2006

Bucholz TA, Cancer 104: 676-81, 2005

DFS and OS by HER-1

HER-1	Pts	5-yr DFS%	<i>P</i>	5-yr OS%	<i>P</i>
Negative	98	66	.62	78	.19
Positive	17	65		45	

Guarneri V, Breast Cancer Res Treat 99: 152, 2006

DFS and OS by HER-1

HER-1	Pts	5-yr DFS%	<i>P</i>	5-yr OS%	<i>P</i>
Negative	68	76	.02	76	.03
Positive	14	46		46	

Bucholz TA, Cancer 104: 676-81, 2005

Steroid hormone receptor status

Summary

- Negative hormone receptor status is one of the strongest predictive markers for preoperative CT in general
- Steroid hormone receptor status is also prognostic, though the time course may be complex

HER-2 status Summary

- HER-2 positive status is not a consistent predictor of response to preoperative CT
- Trend to worse outcome
- Standardized criteria to define HER-2 positive tumors are warranted for cross study comparison

HER-1 status Summary

- Limited data available
 - Need for further studies
- HER-1 positive status is not a consistent predictor of response but may have prognostic significance

Conclusions

- Limited information on **tailoring treatment** for an individual patient
- Patterns of treatment outcome vary in different subpopulations. Major contrast between endocrine responsive and endocrine non-responsive
- Definition of specific **niches** for tailored research is key for future trials