National Cancer Institute

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(%)	*P*
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 (%)	*P*
Overall	399	63 (16)	
Absent (0%)	129 (32)	43 (33)	<.0001
Low (1-9%)	94 (23)	7 (7)	
Positive (≥ 10%)	171 (42)	13 (8)	
Unknown	5 (2)	0 (0)	

Colleoni M, Clin Cancer Res 10; 6622–6628, 2004

DFS by HR status

Author	Pts	**HR+**	HR-	*P*
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)	*P*
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%**	*P*
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**	

Guarneri V, J Clin Oncol 24:1037-1044, 2006

Late OS by HR

HR	Pts	5-yrs%	**10-yrs%**	*P*
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**	

Guarneri V, J Clin Oncol 24:1037-1044, 2006

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 - (%)	*P*
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%	*P*
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 (%)	*P*
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%	*P*	5-yr OS%	*P*
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 - (%)	*P*
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%	*P*	5-yr OS%	*P*
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%	*P*	5-yr OS%	*P*
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