

Case #2
**Locally Advanced Primary Breast
Cancer: Multidisciplinary
Management**

Part II

Christos Markopoulos
Athens University Medical School
Athens, Greece

Definitions of pathologic complete response are inconsistent: **false** or **true**?

1. referral

- Breast only
- Breast and Lymph nodes

2. residual accepted

- foci of invasive tumor only
- tumor cells only
- in situ tumor only

Definitions of pathologic complete response are inconsistent: **true !**

- **Near pCR** Near total disappearance of invasive tumor (only focal invasive tumor)
- **Quasi pCR (QpCR)** Total or near total disappearance of invasive tumor in the removed breast
- **Comprehensive pCR (CpCR)** No evidence of residual invasive tumor
- **Strict pCR (SpCR)** Disappearance of all tumor cells
- **pCRinv** Only in situ tumor residuals
- **Comprehensive pCRbr+n** No evidence of residual invasive tumor in the removed breast and axillary nodes
- **Strict pCRbr+n** No malignant tumor cells in the removed breast and axillary nodes

Definitions of pathologic complete response
are inconsistent: **true !**

Significance of pCR

- residual pathological nodal involvement seems to be an important predictor of outcome
- presence of residual ductal carcinoma in situ does not influence long- term disease-free or overall survival
- **preferred definition of pCR:**
‘the absence of residual invasive cancer within both the breast and lymph nodes’

pCR rates following neoadjuvant chemotherapy are

3%-30%: **true !**

Authors	Trial	Patients	T >5 cm (%) / S (%)	Type of chemo	c CR (%)	pCR (%)
Tan et al., 2001 ⁸	RCT	56	79	MMM	9	
		52	64	Endocrine treatment		
Heys et al., 2002 ¹²	RCT	50	59, N2-13	CVAP+CVAP	34	16
		47	60, N2-6	CVAP+T	62	34
Thomas et al., 2004 ¹³	RCT	200	84	CVAP	18	12
				Randomisation post op		
Therasse et al., 2003 ¹⁴	RCT	217	100	CEF	31	14
		220	100	EC+Fulgrastin	27	10
Semiglazov et al., 2007 ¹⁵	RCT	118	>70	D+P		
		121	>70	Endocrine treatment		
Ezzat et al., 2004 ¹⁶	Phase 2	126	88	PC	28	16
Matteis et al., 2002 ¹⁷	Phase 2	q	80	ET	20	13
Lebowitz et al., 2004 ¹⁸	Phase 2	29	70	T+Cap±AC	31	7
Espinosa et al., 2004 ¹⁹	Phase 2	50	100	ET	20	18
Kao et al., 2005 ²⁰	Phase 2	16	100	P±Vino	NR	46
Tham, 2005 ²¹	Phase 2	51	73	Taxane	27	11
Gradishar et al., 2005 ²²	Phase 2	45	100	Taxane	7	7
Kuerer, 1999 ²³	Pros	372	89	FAC	NR	12
Clark et al., 1998 ²⁴	Pros	34	100	A	NR	21
Shen et al., 2004 ²⁵	Pros	33	100	A/CMF/other	30	12
Huang et al., 2005 ²⁶	Retro	542	84	FAC/VACP/AT	14	NR
Baldini et al., 2004 ²⁷	Retro	68	100	FAC/FEC	NR	3
Erol et al., 2005 ²⁸	Retro	74	100	CMF	15	19
Kim et al., 2004 ²⁹	Retro	25	100	FAC/FEC/AC/Vino/T/CF	4	NR
McIntosh et al., 2003 ³⁰	Retro	166	73	CVAP	21	15
Favret et al., 2001 ³¹	Retro	64	100	FAC	45	NR
Agoglu et al., 2005 ³²	Retro	28	100 (TNM-LAPC)	FAC	11	3
Colozza M et al 1996 ³³	Retro	30	100	CisAC	7	7
Gajdos et al., 2002 ³⁴	Retro	139	76	Cytosan MF/ A	8	13

• 24 trials & series

• 70% of patients with tumors >5cm

• Surgery after Chemotherapy

• pCR 3%-34% (46%)

• pCR rates may be increased with the use of new targeted biological therapies in addition to Chemotherapy

Rates of pCR following neoadjuvant chemotherapy are not related to endocrine responsiveness of the tumor: **false !**

Author/Study	No. of pts	Regimen	% HR neg.	%pCR	
				HR -	HR +
<i>Kemeny</i>	54	FAC	34	20.0	> 7.7
<i>Ring</i>	435	CMF, A/E	29	21.6	> 8.1
<i>Bear</i>	1211	AC	41	13.6	> 5.7
<i>Bear</i>	565	AC+T	43	22.8	> 14.1
<i>GEPARDO</i>	250	ddAC+/-T	44	15.4	> 1.1
<i>GEPARDUO</i>	913	ddAD/CA-D	26	22.8	> 6.2
<i>GEPARTRIO</i>	286	TAC/TAC- NX	32	36.6	> 10.1
<i>Buzdar</i>	1018	FAC+/-P	Na	20.6	> 5.6

Rates of pCR following neoadjuvant chemotherapy are not related to endocrine responsiveness of the tumor: **false !**

Primary Efficacy Results

	4 x ET (n=70)	3 Months Exe/Ana (n=63)	<i>P-value</i>
Clinical Objective Response	64%	64%	NS
pCR	3%	6%	NS
Median time to clinical response	57 days	51 days	NS

Rates of pCR following neoadjuvant chemotherapy are not related to endocrine responsiveness of the tumor: false !

- **Pathologic complete response by chemotherapy is achieved less frequently in ER+ tumors compared to ER- (8% in ER+, 24% in ER-)¹**
- **Endocrine Therapy is a safe alternative to Chemotherapy in hormone-sensitive tumors, with similar response rates but less toxicity²**
- **It is possible that neoadjuvant hormonal therapy offers an advantage over chemotherapy for hormone-sensitive tumors**

¹ Guarneri V et al. *J Clin Oncol*. 2006, Buzdar A et al. *Breast Cancer Res Treat* 2003; 82 (Abstr 302)

² Seminiglazov VF et al. *Proc Am Soc Clin Oncol* 2004; 23:7 (Abstr 519),
Seminiglazov VF et al. *Cancer*. 2007;110:224-54

Patients with pCR have superior OS and DFS: **false** or **true**?

- **Heterogeneity of chemotherapy neoadjuvant trials:**
 - population (*n, age, tumor characteristics*)
 - regimens (*different, old vs new, plus H/T*)
 - evaluation of CR (*imaging*)
 - definition of pCR
 - type of local treatment
- **Generally**, in operable disease, there is no difference in overall survival between neo-adjuvant and adjuvant chemotherapy; the main benefit is down-staging to avoid mastectomy

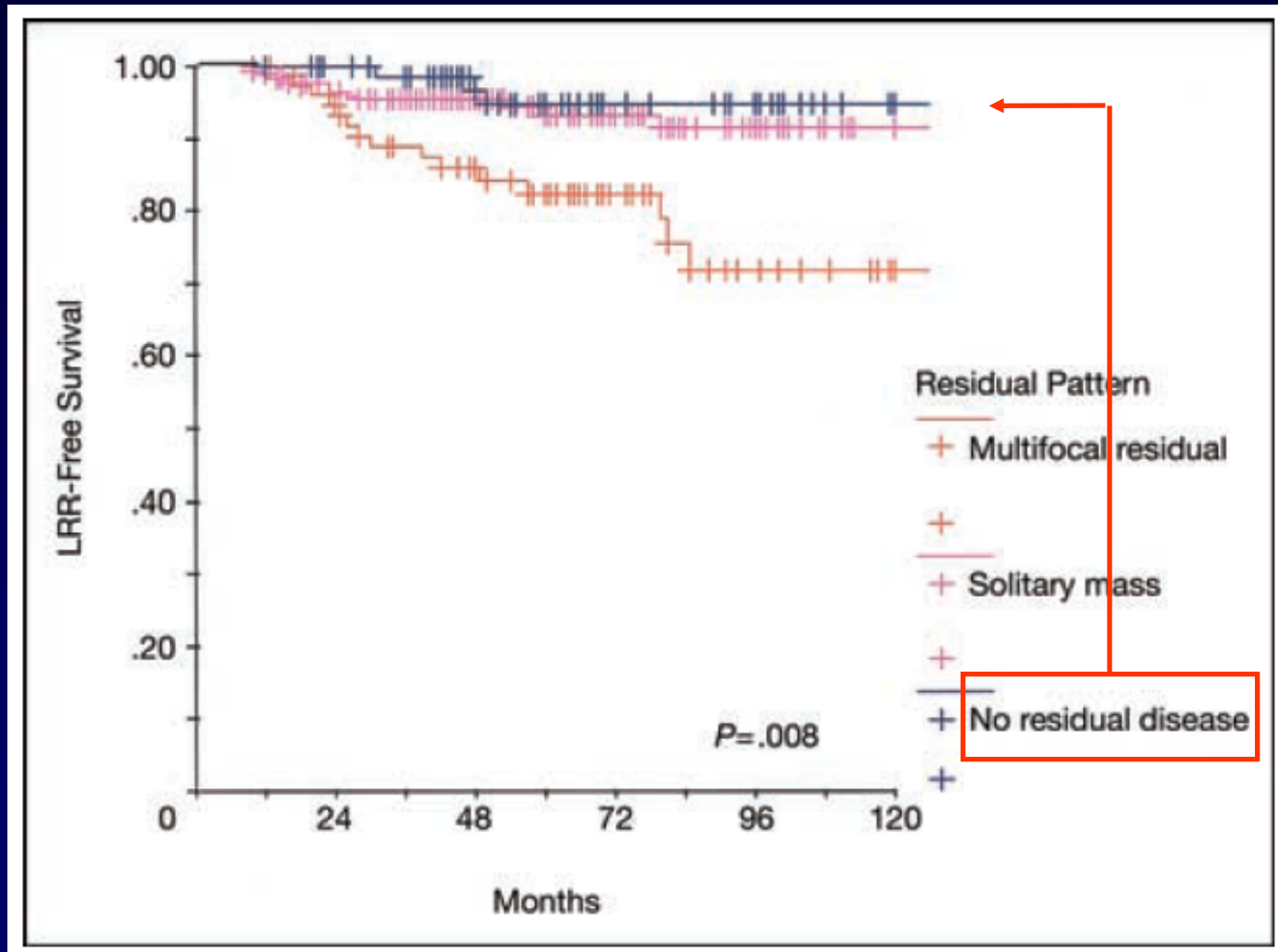
Patients with pCR have superior OS and DFS: false or true?

However:

1. There is an association between the type/category of response and disease-free survival / OS (!)
2. Histological response is a better predictor of outcome
3. pCR of the tumor and the pathological nodal status are independent prognostic indicators of DFS

1. NSABP B-18 and B-27 update. *J Clin Oncol*. 2008;26(16):2793
2. NSABP B-18. *J Natl Cancer Inst Monogr*. 2001; 96–102
3. Heys SD et al. *Clin Breast Cancer Suppl*. 2002; 3(s):69–74
4. Thomas E et al. *J Clin Oncol*. 2004;22:2294–302
5. Hutcheon AW et al. *Breast Cancer Res Treat*. 2003;82(S1):S9
6. Kuerer H et al. *J Clin Oncol*. 1999;17:460–9
7. Rouzier R et al. *J Clin Oncol*. 2002;20:1304–10
8. Cleator SJ et al. *Annals of Oncology*. 2005;16: 267–272

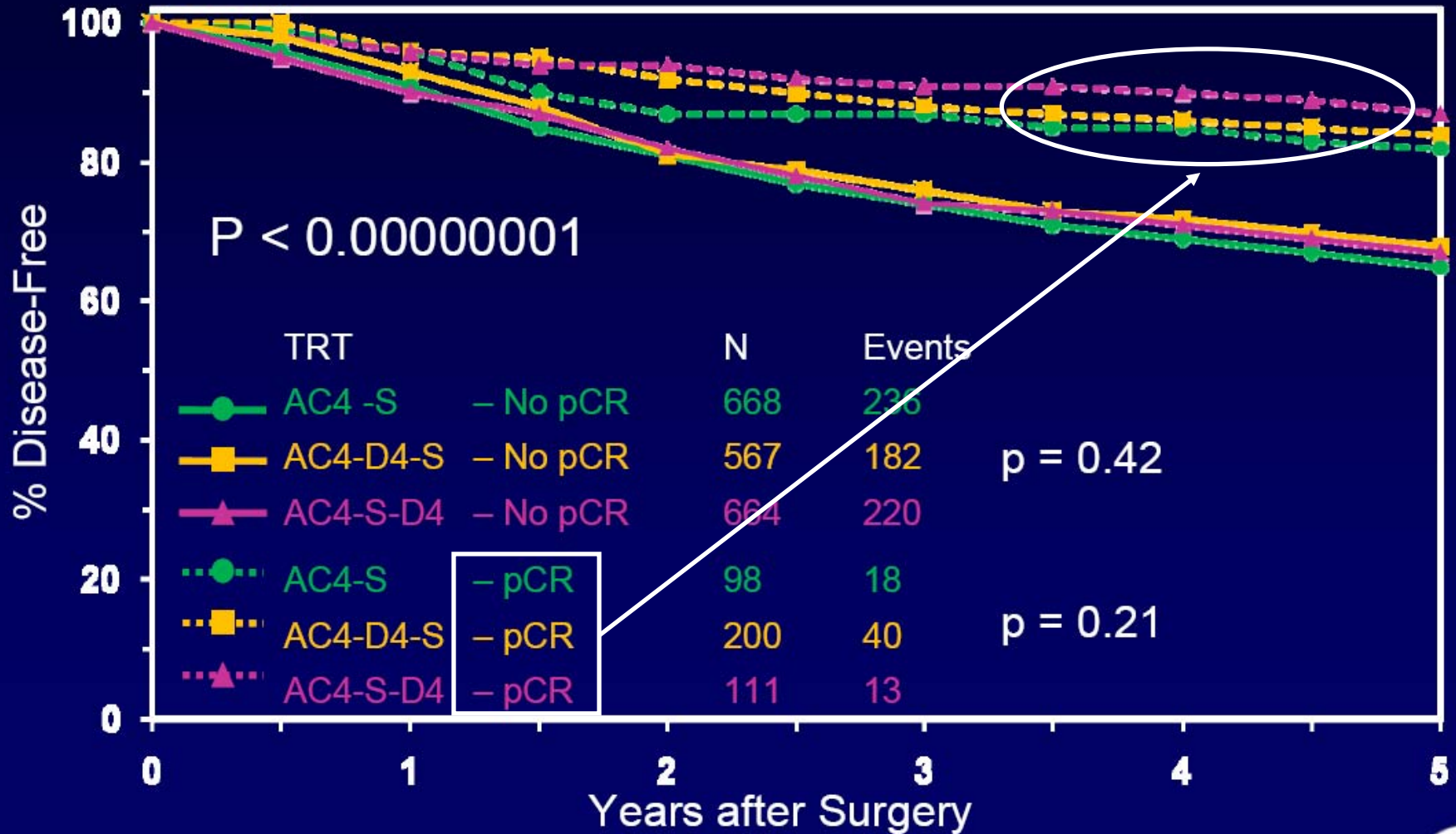
BC after Neoadjuvant Chemotherapy: The M.D. Anderson Cancer Center Experience



Local-regional
Recurrence -
free survival

Type of
residual
primary
tumor

NSABP B-27: Disease-Free Survival Treatment and Pathologic Response



Patients with pCR have superior OS and DFS: **true !**

- Pathologic Complete Response - pCR is the strongest predictor of disease-free and overall survival
- pCR rates may be significantly increased with the combined use of targeted biological therapies (Herceptin, Tyverb) in addition to modern chemotherapy regimens (taxanes and anthracyclines) and that may have a surrogate value on long-term outcome

Part II - Summary

- Which of the following statements regarding neoadjuvant therapy is false?

1. Pathologic Complete response - pCR is associated with a favorable prognosis:
 - lower risk of subsequent recurrence, and
 - improved overall survival
2. Reported pCR rates following neoadjuvant chemotherapy range between 3% to 30%
3. Neoadjuvant Chemotherapy is more effective in patients with Hormone Receptor negative tumors
4. Preferred definition of pCR is the absence of residual invasive only cancer within both the breast and axillary lymph nodes

Part III

SLNB in relation to neo-adjuvant systemic therapy.

1. Which is the aim of SLNB in breast cancer patients?
2. Which patients are usually receiving neo-adjuvant?
3. Is there a role of SLNB in patients undergoing neo-adjuvant therapy?
4. Should SLNB be performed before or after neo-adjuvant therapy?
5. Are there sufficient data supporting either approach?

Which is the aim of SLNB in breast cancer patients?

- **Staging of axillary LNs**
- **Avoid complete axillary clearance when LNs are not involved**

- Sentinel node biopsy is accepted as reliable and safe
- Avoidance of axillary dissection reduces morbidity *

* St Gallen 2007, *Annals of Oncology* 18: 1133–1144, 2007

Contraindications for SLNB

- **Absolute**
- **Clinically positive (N1) axillary nodes**
 - Lymph vessels may be infiltrated / blocked by tumor cells
- **Allergy to blue dye and radio-colloid**
- **Relative**
- **Prior biopsy**
- **Previous breast and axillary surgery**
- **Advanced disease**
- **Neo-adjuvant Chemotherapy**
 - Several studies demonstrate SLNB to be feasible and predictive
- **Large tumors**
- **Multicentric and multifocal disease**
- **Pure DCIS**
- **Increased age, obesity, pregnancy**

Which patients are usually receiving neo-adjuvant? The Role of SLNB.

- **Inflammatory breast cancer** ▶ not indicated
 - breast lymphedema, due to occluded lymphatics by metastatic cells
 - inadequate lymphatic drainage
 - mapping agents would also be trapped and not travel to the SLN
 - false-negative rate very high
- **Locally advanced** (*large tumor size*)
 - Palpable lymphadenopathy ▶ FNA-No role for SLNB
 - Non palpable or Clinically negative LNs
 - SLNB is acceptable
 - **Before or after neo-adjuvant chemotherapy?**

Locally advanced with non palpable or clinically negative LNs



- All LNs might have not the same response to chemo as the SLN
- SLNB after neoadjuvant therapy might increase false negative rate
- If SLN positive, complete axillary dissection at definitive surgery
- The presence of nodal disease may alter treatment recommendations
- SLNB during placement of a port or open breast biopsy if needed
- The accuracy is similar to patients with primary surgery (*most studies*)
- SLN identification rate is decreased but, SLNB can accurately predict axillary status
- Neoadjuvant chemo can convert patients to a node-negative status (NSABP B-18)
- Radiotherapy decision to axilla is based on post-therapy residual nodal status
- SLNB performed before chemotherapy may commit patients to more surgery

- **ASCO guidelines** *J Clin Oncol* 23:7703-7720, **2005**
«**SLNB is not acceptable** for T3 or T4 tumors,
inflammatory breast cancer, DCIS without mastectomy,
nodes suspicious for metastasis, pregnancy, prior
breast or axillary surgery, and after preoperative systemic
therapy»
- **Recommendations** from an international expert panel
on the use of neoadjuvant (primary) systemic treatment: new
perspectives, *Annals of Oncology* 18: 1927, **2007** «Sentinel
Lymph Node Biopsy can be offered to women after
neoadjuvant therapy»
- **Further studies** with a larger number of patients, are
required to establish the feasibility & accuracy of SLNB
for BC patients receiving neo-adjuvant chemotherapy

Personal opinion

- **Outside clinical trials, until we have more data:**
 - **only in patients with large tumor size and clinically negative axillary nodes, who undergo neo-adjuvant chemotherapy aiming to breast conserving surgery**
 - **prior** to neo-adjuvant chemotherapy and:
 - if SLNB was negative and there is clinical response of the tumor, then I would omit axillary surgery
 - if SLNB was positive: CAD during definitive surgery.
 - **after neoadjuvant** chemotherapy, I would perform SLNB only in that group of patients, and if there is clinical response of the tumor and LNs are still clinically negative.