

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Guidelines Breast
Version 2010.1.1 D

Adjuvante Chemotherapie + Trastuzumab

(Optimale Substanzen / Dosierung /
Trastuzumab)

Adjuvante Chemotherapie (Optimale Substanzen / Dosierung / Trastuzumab)

- **Version 2002:**
Möbus / Nitz
- **Version 2003 - 2009:**
**Harbeck / Jackisch / Janni /
von Minckwitz / Möbus / Müller /
Schneeweiss / Simon / Solomeyer /
Stickeler / Thomssen**
- **Version 2010:**
Jackisch / Harbeck

Adjuvante Chemotherapie ohne Trastuzumab: Übersicht

Oxford / AGO
LoE / GR

➤ Anthrazykline (anstatt CMF)	1a	A	++
➤ Taxane (nodal-positiv)	1a	A	++
➤ Taxane (nodal-negativ)	2b	B	+/-*
➤ Taxane können für N0-Pat. mit hohem Rezidivrisiko von Vorteil sein	2b	B	+
➤ Dosisdichte Therapie (N+)	1b	B	+*
➤ CMF (anstatt keiner Therapie)	1a	A	++

* Studienteilnahme empfohlen

FEC / FAC

Optimale Kombinationen und Dosierungen

Oxford / AGO
LoE / GR

Dosierung

- | | | | |
|---|----|---|----|
| ➤ Epirubicin ≥ 30 mg/m ² /Woche | 1b | A | ++ |
| ➤ Doxorubicin = 20 mg/m ² /Woche | 1b | A | ++ |

Kombinationen

- | | | | |
|--|----|---|----|
| ➤ French: FE ₁₀₀ C q3w x 6 | 1b | B | ++ |
| ➤ Canadian: C _{p.o.} E ₆₀ F d1 + 8 q4w x 6 | 1b | B | + |
| ➤ UK: E ₁₀₀ q3w x 4 - CMF x 4 | 1b | B | + |
| ➤ US: FA ₆₀ C q3w x 6 | 1b | B | + |

Phase III Anthrazyklin-Studien

Trial	Source	Ind	Treatment	N	F/U mo	DFS/EFS/RFS/TTR	OS	Remarks
NCIC CTG MA5	Levine 2005	N+	6 x FE _{ad} C vs. 6 x CMF classic	710	120	RFS 52% vs 45% p = 0.05	62% vs. 58%, p=0.047	No endocrine treatment
Mouridsen	Mouridsen 1999	N-/N+	6 x FE _{ad} C vs. 6 x CMF classic	1195	ND	ND	FEC > CMF statistically significant	Significance only in premenopausal pts. Published as abstract
GEICAM	Martin 2003	N+	6 x FA _{ad} C vs. 6 x CMF i.v.	570	90	ND	ND	Specific data only node negatives
FASG01	Fumoleau 1999	N+	6 x FE _{ad} C vs. 3 x FE _{ad} C or 3 x FE _{7d} C	602	96	DFS: 6 x FEC better than 3 x FE _{ad} C, p=0.018 3 x FE _{7d} C, p = 0.04	6 x FEC vs. 3 x FE _{ad} 67.4% vs. 60.8% p = 0.04	Published as abstract
FASG05	Bonneterre 2001	N+	6 x FE _{10d} C vs. 6 x FE _{ad} C	565	67	DFS 66.3% vs. 54.8% p=0.03	77.4% vs. 65.3% p=0.007	Postmenop. pts. treated with Tam 30 mg/d for 3 years at beginning of CHT.
FASG09		N+	6 x FE _{10d} C vs. 6 x E ₅₀ V ₂₅	482	ND	ND	ND	Equi-effective
Piccart	Piccart 2001	N+	6 x E _{ad} C vs. 6 x CMF	522	48	EFS: HR 0.96; p=0.8	HR 0.97; p=0.87	
Piccart	Piccart 2001	N+	8 x E _{10d} C ₃₃₀ vs. 6 x E _{ad} C	510	48	EFS: HR 0.73; p=0.04	HR 0.69; p=0.05	Proof of dose response curve for epirubicine
Paradiso	Paradiso 2001	N-	6 x FE _{ad} C vs. nil	248	70	DFS: 81% vs. 69%; p < 0.02	ND	N-, fast proliferating BC, determined by [3H]-thymidine incorporation assay
INT-0102	Hutchins 2005	N-	6 x FA _{ad} C vs. 6 x CMF classic	2690	120	DFS: 77% vs. 75%; HR = 1.09; p=0.26	85% v 82%, HR = 1.19; p=0.03	Tam randomly assigned: Benefit for HR Pos. pts: DFS, HR = 1.32; p = .003; OS, HR = 1.26; p = .03
GEICAM	Martin 2003	N-	6 x FA _{ad} C vs. 6 x CMF	415	77	DFS 73% vs. 62%, p= 0.046	FAC > CMF p=0.037	DFS and OS not different betw. FAC and CMF in N+ pts.
NEAT/BR9601	Poole 2006	N-/N+	4 x E _{10d} ? 4 x CMF classic vs. 6(8) x CMF	2391	48	RFS 76% vs. 69% P < 0.001	82% vs. 75% p < 0.001	HR+ pts. Received in 46% Tam concurrently with CHT

A, doxorubicin; C, cyclophosphamide; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; F, fluorouracil; FFP, freedom from progression; F/U, follow-up; HR, hazard ratio; M, methotrexate; ND, no data; ns, not significant; OS, overall survival; pts, patients; RFS, relapse-free survival; TTR, time to recurrence; vs, versus.

Anthrazyklin-freie Regime ohne Trastuzumab*

Oxford / AGO
LoE / GR

Äquivalente OS Effektivität zu ≥ 4 x A / EC:

- 6 x CMF 1a A +/-

Verbesserte OS Effektivität zu 4 x AC :

- 4 x DC 1b B +

*Studienteilnahme für anthrazyklin-freie Regime empfohlen

D = Docetaxel; C = Cyclophosphamid

OS = Gesamtüberleben

Taxane

Optimale Kombinationen und Dosierungen

Oxford / AGO
LoE / GR

Regimen

- | | | | | | |
|---|----------------------------|--|-----------------------|----------|-----------|
| ➤ | DAC | D₇₅A₅₀C q3w x 6 | 1b | B | ++ |
| ➤ | FEC → D | FE₁₀₀C q3w x 3 → D₁₀₀ q3w x 3 | 1b | B | ++ |
| ➤ | AC → P_w* | A₆₀C q3w x 4 → P₈₀ qw1 x 12 | 1b | B | ++ |
| ➤ | AC → D | A₆₀C q3w x 4 → D₁₀₀ qw3 x 4 | 1b^a | B | ++ |
| ➤ | EC → D | E₉₀C q3w x 4 → D₁₀₀ qw3 x 4 | 1b^a | B | ++ |

* E₉₀C → P_w dürfte äquieffektiv sein

Empfohlene Taxan-haltige Regime Standarddosierungen

Nodal-positiv

Kombinationsregime

- DAC (BCIRG 001, anstatt FAC)
- DC (US Oncol., anstatt AC)
- AD (E2179, anstatt AC)

Sequentielle Regime (gleiche Dauer)

- FEC → D (PACS 01, anstatt FEC)
- AC → Pw (E1199, anstatt AC → P3w)
- FE₆₀C → D (TACT, anstatt FE₆₀C)
- AP → CMF (TACT, anstatt E → CMF)
- AP → CMF (ECTO, anstatt A → CMF)

Sequentielle Regime (ungleiche Dauer)

- AC → P (NSABP B-28, anstatt AC)
- FEC → P (GEICAM 9906, anstatt FEC)
- AC → D (BCIRG 005, AC-D, anstatt DAC)
- EC → D (WSG/AGO, EC-D, anstatt FEC)
- A → D → CMF > AD → CMF (BIG 2-98, anstatt A ± C → CMF)
- E → D → CMF (TAXIT 216, anstatt E → CMF)

➤ Nodal-negativ*

- DAC (GEICAM 9805, anstatt FAC)
- AP → CMF (ECTO, anstatt A → CMF)
- AD (E2197, anstatt AC)
- DC (US Oncol., anstatt AC)

Oxford / AGO LoE / GR

	Oxford	AGO
1b	B	++
1b	B	+
2b	B	+/-
1b	B	++
1b	B	++
2b	B	-
2b	B	+
1b	B	+
2b	B	+
1b ^a	B	++
1b ^a	B	++
2b	B	+
2b	B	+/-
2b ^a	B	+/-
2b	B	+/-
2b	B	-
2b	B	+/-

Nur 1 Studie (PACS 01) zeigte einen Vorteil für OS verglichen zu adäquat dosierten, anthrazyklin-haltigen Regimen (FEC-D vs FEC; LoE 1b, B). In der Sequenz AC-Taxane, gibt es aktuell keine Evidenz für einen Vorteil eines der beiden Taxane. Neben den substanz-spezifischen Nebenwirkungen war die wöchentliche Gabe generell weniger toxisch. (LoE 2b^a, B)

A = Doxorubicin, D = Docetaxel; E = Epirubicin; P = Paclitaxel *Studienteilnahme empfohlen

Taxane in der adjuvanten Therapie: Overview over Phase III Trials with N>900 (1)

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Trial	Source	Ind	Treatment	N	F/U mo	DFS/EFS/RFS/TTR	OS	Remarks
PACS 01	Roche 2006	N+	3xFE ₁₀₀ C → 3xD ₁₀₀ vs 6 xFE ₁₀₀ C	1999	60	DFS HR 0.82, p=0.012	HR 0.73, p=0.017	age ≥ 50 DFS HR 0.67, p<0.01 age < 50 DFS HR 0.98, p=0.69
TACT	Ellis 2007	N+/N-	4xFE _{ad} C → 4xD ₁₀₀ vs. 8xF _{ad} C vs. 4xE ₁₀₀ → 4xCMF classic	4162	52	DFS HR 0,97 P= 0,62	HR 0,98 P= 0,76	4xFE _{ad} C → 4xD ₁₀₀ vs. control
BCIRG 001	Martin 2005	N+	6xD _{ad} C vs 6xF _{ad} C	1491	55	DFS HR 0.72, p<0.01	HR 0.7, p<0.01	doxorubicin dose below 20mg/m ² /week
GEICAM 9906	Martin 2005	N+	4xFE _{ad} C → 8xP ₁₀₀ qw vs 6 xFE _{ad} C	1248	46	DFS HR 0.63, p<0.01	HR 0.74, p=0.14	concurrent use of tamoxifen
CALGB 9344	Henderson 2003	N+	4xA _{ad} C vs A ₇₅ C vs A _{ad} C → 4xP ₁₇₅ vs nil	3121	68	TTR HR 0.83, p<0.01	HR 0.82, p<0.01	no doxorubicin dose effect
NSABP B-28	Mamounas 2005	N+	4xA _{ad} C → 4xP ₂₂₅ vs 4xA _{ad} C	3060	65	DFS HR 0.83, p<0.01	HR 0.93, p=0.46	concurrent use of tamoxifen
BIG 02-98	Crown 2006	N+	4xA ₇₅ → 3xCMF vs 4xA _{ad} C → 3xCMF vs 3xA ₇₅ → 3xD ₁₀₀ → 3xCMF vs 4xA _{ad} D ₇₅ → 3xCMF	2887	57	D vs no D EFS HR 0.86, p=0.051	ns	A → D vs AD HR 0.83, p=0.047
US Oncology	Jones 2007	N+/N-	4xD ₇₅ C vs 4xA _{ad} C	1016	84	DFS HR 0.74, p=0.033	HR 0.69, p=0.032	N- DFS HR 0.73, ns N+ DFS HR 0.67, p<0.05
Taxit216	Bianco 2006	N+	4xE ₁₂₀ → 4xD ₁₀₀ → 4xCMF vs 4xE ₁₂₀ → 4xCMF	972	53	DFS HR 0.8, p=0.079	HR 0.74, p=0.10	
E21 97	Goldstein 2005	N+/N-	4xA _{ad} D _{ad} vs 4xA _{ad} C	2885	59	DFS HR 1.03, p=0.70	HR 1.09, p=0.49	
ECTO†	Gianni 2005	N+/N-	4xA _{ad} P ₂₂₀ → 4xCMF vs 4xA ₇₅ → 4xCMF	904	43	FFP HR 0.66, p=0.01	HR 0.71, p=0.16	concurrent use of tamoxifen; N+ vs N- HR 2.55, p<0.01
NCIC CTG MA21	Bumell 2006	N+/N-	6xCE _{ad} F vs 6xE ₁₂₀ C q2w → 4xP q3w vs 4xA _{ad} C q3w → 4xP q3w	2104	30	CEF vs EC-T ns; CEF or EC-T vs AC-T, p<0.01	ND	no difference in ER+ pts

A, doxorubicin; C, cyclophosphamide; D, docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; F, fluorouracil; FFP, freedom from progression; F/U, follow-up; HR, hazard ratio; M, methotrexate; ND, no data; ns, not significant; OS, overall survival; P, paclitaxel; qw, weekly; q3w, three weekly; RFS, relapse-free survival; T, taxane; TTR, time to recurrence; vs, versus.

† adjuvant part of trial

Taxane in der adjuvanten Therapie: Overview over Phase III Trials with N>900 (2)

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Trial	Source	Ind	Treatment	N	F/U mo	DFS/EFS/RFS/ TTR	OS	Remarks
GEICAM 9805	Martin 2008	N-	6xDA _{ad} C vs 6xFA _{ad} C	1059	67	DFS HR 0.7, p=0.012	HR 0.7, p=0.21	doxorubicin dose below 20mg/m ² /week
EC-DOC	Nitz 2008	N+ (1-3 LN)	6xFE ₁₀₀ C vs 4xE _{ad} C → 4xD _{ad}	826 (1026 total)		EFS HR 1.514, p=0.009	HR 0.91, p=0.04	
BCIRG 005	Eiemann 2008	N+	6xDA _{ad} C vs 4xAC 4xD _{ad}	3298	65	DFS HR 1.0, p=0.98	HR 0.91, p=0.7	
FinXX trial	Joensuu 2008	N-/N+	3xD _{ad} X ₁₀₀ → 3xFX _{ad} C vs 3xD _{ad} → 3xFE ₇₅ C	1500	36	RFS HR 0.66, p=0.02	HR 0.66, p=0.089	epirubicine below 30mg/m ² /week
NSABP 30	Ganz 2008	N+	4xA _{ad} C → 4xD ₁₀₀ vs A _{ad} D ₇₅ x 4 vs D ₇₅ A _{ad} C x 4	5351	73	DFS HR 0.83, p=0.006 AC → D vs DAC HR 0.80, p=0.001 AC → D vs AD HR 0.96 p=0.96 DAC vs AD	HR 0.86, p=0.086 AC → D vs DAC HR 0.83, p=0.034 AC → D vs AD HR 0.96 p=0.67 DAC vs AD	Dose modifications during study for AD and DAC, part of patients received Tam simultaneously with chemo
ECOC 1199	Sparano 2008	N+	4xA _{ad} C → 4xP ₇₅ 3wvs 4xA _{ad} C → 12 xP _{ad} w 4xA _{ad} C → 4xD ₁₀₀ 3wvs 4xA _{ad} C → 12xD ₇₅ wvs	4950		DFS (compared to AC → P 3w) PwHR 1.27, p=0.006 D 3w HR 1.23, p=0.02 Dw HR 1.09, p=0.29	compared to AC → P 3w PwHR 1.32, p=0.01 D 3w HR 1.13, p=0.25 Dw HR 1.02, p=0.80	

A, doxorubicin; C, cyclophosphamide; D, docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; F, fluorouracil; FFP, freedom from progression; F/U, follow-up; HR, hazard ratio; M, methotrexate; ND, no data; ns, not significant; OS, overall survival; P, paclitaxel; qw, weekly; q3w, three weekly; RFS, relapse-free survival; T, taxane; TTR, time to recurrence; vs, versus.

† adjuvant part of trial

Taxane in der adjuvanten Therapie: Meta-Analyses of Phase III Trials with N>900



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Trial	Source	Ind	Treatment	N	F/U mo	DFS/EFS/RFS/ TTR	OS	Remarks
(9 trials)	Bria 2006	N+/N-	T vs no T	15598		DFS HR 0.86, p<0.01 N+ DFS HR 0.84, p<0.01	HR 0.87, p<0.01 N+ HR 0.84, p<0.01	no heterogeneity
(13 trials)	De Laurentiis 2008	N+/N-	T vs no T	22903		DFS HR 0,83, p<0,00001	HR 0,85, p<0,00001	no heterogeneity
(12 trials)	Ferguson 2007	N+/N-	T vs no T	19943	60	DFS HR 0,81, p<0,00001	HR 0,81, p<0,00001	no heterogeneity
(21 trial)	Bedard PL 2010	N+/N-	T vs no T	36.000				

A, doxorubicin; C, cyclophosphamide; D, docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; F, fluorouracil; FFP, freedom from progression; F/U, follow-up; HR, hazard ratio; M, methotrexate; ND, no data; ns, not significant; OS, overall survival; P, paclitaxel; qw, weekly; q3w, three weekly; RFS, relapse-free survival; T, taxane; TTR, time to recurrence; vs, versus.

† adjuvant part of trial

Adjuvante Chemotherapie (dosisdicht und/oder dosiseskaliert) bei nodal-positivem Mammakarzinom*

Oxford / AGO
LoE / GR

Dosisdichte Schemata (N +)

➤ **dd ACP / AC-P q2w (statt q3w)**
(CALGB 9741)

1b B +°

➤ **AC / ddP q1w x 12 (statt p q3w)**

1b B ++

Dosisdichtes und dosiseskaliertes Schema (N ≥ 4+)

➤ **dd E-P-C q2w (statt) EC-P q3w)**
(AGO)

1b B ++°

Hochdosisschemata (N ≥ 10+)

➤ **High-dose / PBSCS (statt Cx ohne PBSCS)**

1a A -

*Studienteilnahme empfohlen

P = Paclitaxel; °Behandlung in erfahrenen Zentren

Dose Density: Overview over Published Phase III Trials with N > 1000

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Trial	Source	Ind	Treatment	N	F/U mo	DFS/EFS	OS	Remarks
CALGB 9741	Citron 2003	N+	4x A_{100} → 4x P_{175} → 4xC vs 4x A_{100} C → 4x P_{175} q2w vs q3w	2005	36	q2 vs q3w HR 0.74, p=0.010 seq vs con HR 0.93, p=0.58	q2 vs q2w HR 0.69, p=0.013 seq vs con HR 0.89, p=0.48	ER+ vs ER- HR 0.18, p<0.01;
CALGB 9741	Hudis 2005	N+	4x A_{100} → 4x P_{175} → 4xC vs 4x A_{100} C → 4x P_{175} q2w vs q3w	1938	36	q2 vs q2w ER+ ns ER- p=0.014	q2 vs q2w ER+ ns ER- p=0.039	restrospective analysis
AGO	Moebus 2006	N≥4+	3xE ₁₂₀ → 3xP ₂₂₅ → 3xC ₂₀₀₀ q2w vs 4xE ₂₀₀ C ₈₀₀ → 4xP ₁₇₅ q3w	1284	62	HR 0.72, p<0.01	HR 0.76, p=0.029	
GONO-MIG	Venturini 2005	N+/N-	6x $FE_{100}C$ q3w vs 6x $FE_{100}C$ q2w	1214	125	EFS HR 0.88, p=0.31	HR 0.87, p=0.35	
ECOC 1199	Sparano 2008	N+	4x $A_{100}C$ → 4x P_{175} 3w vs 4x $A_{100}C$ → 12x P_{30} w 4x $A_{100}C$ → 4xD ₁₀₀ 3w vs 4x $A_{100}C$ → 12xD _{20}} w vs	4950		DFS (compared to AC→P 3w): Pw HR 1.27, p=0.006 D 3w: HR 1.23, p=0.02 Dw: HR 1.09, p=0.29	compared to AC→P 3w: Pw HR 1.32, p=0.01 D 3w: HR 1.13, p=0.25 Dw: HR 1.02, p=0.80	
NCIC CTG MA21	Burnell 2006	N+/N-	6x $CE120F$ vs 6xE ₁₂₀ C q2w → 4xP q3w vs 4x $AB0C$ q3w → 4xP q3w	2104	30	CEF vs EC-T ns; CEF or EC-T vs AC-T, p<0.01	ND	no difference in ER+ pts

A, doxorubicin; C, cyclophosphamide; con, concurrent; D, Docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; ER, estrogen receptor; F/U, follow-up; HR, hazard ratio; ns, not significant; OS, overall survival; P, paclitaxel; q2w, two weekly; q3w, three weekly; seq, sequential; vs, versus.

High-dose Cx/ABST: Overview over Published Phase III Trials with N > 100

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Trial	Source	Indication	Control	HD-Cx	N	F/U	DFS	OS	Remarks
Dutch Trial	Rodenhuis 2003	N ≥ 4+	5xFE ₅₀ C	4xFE ₅₀ C → 1xHD-CTCb	885	57Mo	p=0.057	ns	
CALGB 9082	Peters 2005	N ≥ 10+	4xFA ₆₀ C → 1xCPB	4xFA ₆₀ C → 1xHD-CPB	785	7.3Y	ns	ns	
Anglo-Celtic I	Leonard 2004	N ≥ 4+	4xA ₇₅ → 8xCMF	4xA ₇₅ → 1xC → 1xHD-CT	605	6Y	ns	ns	
ECOG	Tallman 2003	N ≥ 10+	6xC AF	6xC AF → 1xHD-CT	540	6.1Y	ns	ns	
Scandinavian Trial	Bergh 2000	N > 5-8+	9xFEC (tailored)	3xFEC → 1xHD-CTCb	525	34Mo	(P=0.04)	ns	better DFS in control arm
WSG	Nitz 2005	N ≥ 9+	4xE ₉₀ C → 3xCMF	2xE ₉₀ C → 2xHD-ECT	403	49Mo	p < 0.001	p=0.02	
Michelangelo	Gianni 2007	N ≥ 4+	3xE ₁₂₀ → 6xCMF	1xHD-C → 1xHD-M → 2xHD-E → 1xHD-TMe	382	136Mo	ns	ns	
IBCSG 15-95	Basser 2006	N ≥ 10+ ≥ 5+ R- or T3	4xA ₆₀ (E ₉₀)C → 3xCMF	3xHD-E ₂₀₀ C ₄₀₀ → 3xCMF	344	68Mo	ns	ns	
PEGASE 01	Roche 2001	N ≥ 8+	4xFE ₁₀₀ C	4xFE ₁₀₀ C → 1xHD-NMeC	314	33Mo	p=0.002	ns	
GABG	Zander 2004	N ≥ 10+	4xE ₉₀ C → 3xCMF	4xE ₉₀ C → 1xHD-CTN	307	3.8Y	p=0.095	ns	
UK ICCG	Coombes 2006	N ≥ 4+	6xFE ₅₀ C	3xFE ₅₀ C → 1xHD-CTCb	281	68Mo	ns	ns	
Meta-analysis									
(13 trials)	Farquhar 2005	high-risk N+	w/o ABST	with ABST	5064	3-4Y	p < 0.01	ns	
(13 trials)	Farquhar 2005	high-risk N+	w/o ABST	with ABST	5064	5-6Y	ns	ns	
(15 trials)	Berry 2007	high-risk N+	w/o ABST	with ABST	6210	4-8Y	p < 0.01	ns	

A, doxorubicin; ABST, autologous blood stem cell transplantation; C, cyclophosphamide; Cb, carboplatin; DFS, disease-free survival; E, Epirubicin; F, fluorouracil; F/U, follow-up; HD, high-dose plus ABST; M, methotrexate; Mo, months; Me, melphalan; N, mitoxantrone; na, not available; ns, not significant; OS, overall survival; P, cisplatin; R, receptor; T, thiotepa; w/o, without; Y, years.

Bestimmung des HER2-Status

Oxford LoE: 1b

GR: A

AGO: ++

- **Der Nachweis der HER2-Überexpression ist Voraussetzung für eine Behandlung mit Trastuzumab**
- **Qualitätskontrollierte Pathologie mit interner und externer (Ringversuche) Qualitätskontrolle notwendig**

Adjuvante Therapie mit Trastuzumab (1)

	Oxford	/	AGO
	LoE	/	GR
➤ Nodal-positive Erkrankung	2b	B	++
➤ Nodal-negative Erkrankung mit zusätzlichen Risikofaktoren (z.B. ≥ 1 cm)	2b	B	++
➤ Nodal-negative Erkrankung mit Tumoren ≥ 5 mm und zusätzlichen Risikofaktoren (falls Chemotherapie indiziert)	4	C	+

***Studienteilnahme empfohlen**

Zunehmende Evidenz läßt vermuten, dass HER2-Positivität ein negativer prognostischer Faktor bei Patientinnen mit kleinen (≤ 1 cm) nodal-negativen Mammakarzinomen darstellt

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Study	n	Tumour size	Endpoint	HER2+ vs HER2- %	p value
Joensuu et al 2003	239	T1a,b	9-year DDFS	67 vs 95	0.003
Rakshit et al 2008	965	T1a,b	5-year RFS	77.1 vs 93.7	<0.0001
Amar et al 2007	401	T1a,b	RFS	92.6 vs 98.7	0.007
Tovey et al 2008	362	T1a,b,c	5-year BCSS	68 vs 96	<0.001
Pagani et al 2008	340	T1a,b	RFS	87.1 vs 96.8	NR
Norris et al 2006	326	T1a,b,c	10-year RFS	75.6 vs 82.4	0.66
Chia et al 2008	225	T1b	10-year RFS	68.4 vs 81.8	0.312
Park et al 2009*	466	T1a,b	10-year DRFS/OS	HR: 8.8 (DRFS) 5.0 (OS)	0.003 0.067

BCSS = breast cancer specific survival; DDFS = distant disease-free survival, DRFS = distant relapse free survival estimated, 61 month follow-up

RFS = relapse-free survival; NR = not reported

* Park et al, Abstract 564 ASCO 09

Adjuvante Therapie mit Trastuzumab (2)

Oxford / AGO
LoE / GR

Beginn der Therapie

- **Simultan mit Taxanen**
- **Bis zu 3 Monaten nach Chemotherapie**

2b	B	++
2b	B	+

Dauer der Therapie

- **Ein Jahr**
- **Zwei Jahre**

2b	B	++
2b	B	--

Dosierung der Therapie

- **2 (4*) mg/ kg wöchentlich**
- **6 (8*) mg/ kg alle drei Wochen**

2b	B	++
2b	B	++

* "Loading dose"

Trastuzumab in Early Breast Cancer: Overview over Published Phase III Trials

Trial	Source	Ind	Treatment	N	F/U mo	DFS	OS	Remarks
NSABP B31/ NCCTG 9831	Perez 2007	IHC 3+ or FISH+	4xA ₆₀ C→4xP ₁₇₅ Tras→Tras 1y vs 4xA ₆₀ C→4xP ₁₇₅	3968	34	HR 0.49, p<0.0001	HR 0.63, p=0.0004	pooled analysis
HERA	Smith 2006	Her2 IHC 3+ or FISH+	any Cx→Tras 1y vs no Tras	3401	24	HR 0.64, p<0.01	HR 0.66, p=0.012	
BCIRG 006	Slamon 2006	Her2 FISH+	4xA ₆₀ C→4xD ₁₀₀ Tras→Tras 1y vs 6xCb(Cis)D ₇₅ Tras→Tras 1y vs 4xA ₆₀ C→4xD ₁₀₀	3222	36	Tras vs no Tras p<0.01; A vs no A ns	Tras vs no Tras p<0.01; A vs no A ns	fewer CHF with CbDTras than AC- DTras
FinHer	Joensuu 2006	Her2 FISH+	3xD ₁₀₀ Tras or 8xVTras→3xFEC vs 3xD ₁₀₀ or 8xV→3xFEC	2nd R 232	36	HR 0.42, p=0.01	HR 0.43, p=0.08	subgroup
PACS-04	Spielmann 2007	IHC 3+ or FISH+	6 X FE ₁₀₀ C vs 6 x Epi ₇₅ /D 75 → Tras 1y vs. no Tras	2ndR 528	48	HR 0.86, p=0,41	HR 1,27	subgroup
Metaanalysi s 5 trials	Viani 2007	IHC 3+ or FISH+	see above	9117		p<0.00001	p<0.00001	30% of pts. Trastuzumab treatment < 1y

A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; CHF, congestive heart failure; Cis, cisplatin; Cx, chemotherapy; D, docetaxel; DFS, disease-free survival; E, epirubicin; F, fluorouracil; FISH, fluorescent in situ hybridization; F/U, follow-up; HR, hazard ratio; IHC, immunohistochemistry; ns, not significant; OS, overall survival; P, paclitaxel; Tras, trastuzumab; V, vinorelbine; vs, versus.

Trastuzumab Adjuvant

Überwachung hinsichtlich CHF

Oxford LoE: 5

GR: D

AGO: ++

Vor Beginn der Trastuzumab-Therapie

- Klinische Untersuchung (Ödeme, Hepatomegalie)
- Echokardiographie (Alternative zu MUGA)

} Bestimmung
LVEF

Während und nach der Trastuzumab-Therapie

Regelmäßige Dokumentation von

- Herzfrequenz; bei Anstieg > 15 % über das individuelle Ausgangsniveau
- Körpergewicht; bei Anstieg ≥ 2 kg/Woche



LVEF alle 3 Monate

Adjuvante Therapie mit Trastuzumab: Regime

Oxford / AGO
LoE / GR

Simultan mit

- | | | | |
|---------------------------------------|-----------------|---|-----|
| ➤ Paclitaxel / Docetaxel nach AC / EC | 1b | B | ++ |
| ➤ Docetaxel und Carboplatin | 1b ^a | B | + |
| ➤ Anthrazyklinen | 2b | B | +/- |
| ➤ mit Taxanen dosisdicht | 2b | B | +/- |
| ➤ mit Taxanen in anderen Regimen | 3b ^a | B | +/- |

Strahlentherapie simultan mit Trastuzumab	2b	B	+
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