Cytostatic Therapy In Metastatic Breast Cancer

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- Version 2002: von Minckwitz
- Version 2003: Schneeweiß/Friedrichs
- Version 2004: Harbeck
- Version 2005: Untch
- Version 2006: Möbus, Stickeler

Cytostatic Therapy

Disease Free And Overall Survival

Oxford / AGO
LOE / GR

- A survival benefit has been shown in recent single prospective randomised studies — 1b
- An increase in survival during time in clinical studies has been shown in retrospective analyses — 2a

Impact Of Cross-Over

To Investigational Regimen In MBC Trials

Study	Regimen Std vs Invest		Crossover Agent	Crossover Frequency	Survival Benefit
Sledge 2003	single A or T	AT combin	single agent	57%	NO
Paridaens 2000	DOX	T	T	47%	NO
Nabholtz 1999	MV	T	T	24%	YES
O'Shaughnessy 2002	T	XT	X	17%	YES
Albain 2004	T	GT	G	14%	Strong trend
Bishop 1999	CMFP	T	T	6%	YES

Treatment Of Metastatic Breast Cancer

Predictive Factors

Therapy	Factor	Oxford LOE	/ GR	AGO
Hormontherapy	Receptor status (primary tumor, metastasis)	1a	A	++
	previous response	1b	A	++
Chemotherapy	previous response	1b	A	++
Trastuzumab	HER2 (primary tumor, better metastasis)	1a	A	++
Bisphosphonates	bone metastasis	1a	A	++

Cytostatic Therapy Goals

Oxford LOE 1b GR A AGO ++

Monotherapy:

- **Favourable therapeutic index (- effect, -toxicity, - life quality)**
- **Indicated when**
  - **Slow, not life threatening progression**
  - **Uneffective or progression under endocrine therapy**

Polychemotherapy:

- **Unfavourable therapeutic index (- effect, -toxicity, - life quality)**
- **Indicated to achieve fast remission**

Mono –Vs Polychemotherapy (Randomised, (A)= Abstract)

n	Line	Mon	Pol	ORR (%)	TTP(F)	OS (HR, CI)	QoL Mon	Source (1975-91)
2442	³ 1st	Mon	Pol	34 vs 48	ND	0,82, 0,75-0,9	ND	Fossati 1998 (15 Studien)
n	Line	Mon	Pol	ORR (%)	TTP(F) (Mo)	OS (Mo)	QoL Mon	Quelle (ab 1991)
40	1st	E	CMF	29 vs 58	2 vs 5 (F)	ns	®	Fraser 1993
91	2nd	D	VF	54 vs 44	7 vs 5	ND	ND	Bonneterre 1997 (a)
739	1st	P(® A)	AP	33 vs 46	6 vs 8 (F)	ns	®	Sledge 2003
		A(® P)	AP	34 vs 46	6 vs 8 (F)	ns	®	
294	1st-2nd	E(® Mc)	CEF(® McVb)	ns	ns	ns	-	Joensuu 1998
209	1st	P	CMFPd	ns	ns	17 vs 14	®	Bishop 1999
387	1st-2nd	D	McVb	30 vs 12	4 vs 2	11 vs 9	®	Nabholtz 1999
267	1st-2nd	D	MF	42 vs 21	6 vs 3	ns	®	Sjostrom 1999, Hakamies-Blomqvist 2000
300	1st-2nd	A	AV	ns	ns (P/F)	ns	®	Norris 2000
65	³ 2nd	V	MxF	ns	2 vs 5 (F)	ns	®	Venturino 2000
65	³ 2nd	F	MxF	ns	3 vs 5 (F)	ns	®	
511	1st-4th	D	DCa	30 vs 42	4 vs 6	12 vs 15	®	O´Shaughnessy 2002
260	1st	Mx	FEC	ns	ns	ns	-	Heidemann 2002
182	1st	E ® P	EP	ns	ND	ND	ND	Baldini 2002 (a)
48	1st	A ® D	AD	ns	ND	ND	ND	Ramos 2002 (a)

M, Methotrexat; Mc, Mitomycin; Mo, Monate; Mon, Monochemotherapie; Mx, Mitoxantrone; n, Anzahl auswertbare Pat.; ND, keine Angaben; ns, nicht signifikant; ORR, overall response rate; OS, overall survival; P, Paclitaxel; Pd, Prednison; Pol, Polychemotherapie; QoL, quality of life; TTP(F), time to progression(treatment failure); V, Vinorelbin;Vb, Vinblastin. A, Doxorubicin; C, Cyclophosphamid; Ca, Capecitabin; D, Docetaxel; E, Epirubicin; F, Fluorouracil;

O'Shaughnessy ASCO 2003: Phase III Pac + Gemcitabine vs Pac first line (n= 529)
TTP (5.4 vs. 3.6 Mo) und Ansprechrate (39.3 vs 25.6%) signifikant besser bei Kombination. Verträglichkeit vergleichbar.
Albain, ASCO 2004: median OS 18,5 vs 15, 8 months (p=0,018)
Cochrane (2005): 37 trials (5707 women) of which 28 had published time-to-event data.
Statistically significant advantage for ORR and TTP, modest improvement in overall survival and signicantly worse toxicities.

Cytostatic Therapy

LOE 1c GR A AGO ++

- **Evaluate compliance before therapy (especially in older patients, reduced KI, comorbidities)**
- **Assess toxicites (subjectively and objectively)**
- **Doses according to published protocols**
- **Evaluation of representative parameters (Lead metastases, Tumor markers, Symptoms) before therapy and about two monthly under therapy**

Cytostatic Therapy Duration

	Oxford LOE	AGO GR	
As long as the therapeutic index is favorable			
➢ **Intermittent therapy if progress**	**2b**	**B**	**++**
➢ **Cytostatic maintenance until progress**	**2b**	**B**	**-**
➢ **Monotherapy** (depending on pretreatment and side effects)			**+/-**
➢ **Stop therapy if**	**1c**	**A**	**++**
➢ **Progress**			
➢ **toxicity**			

Intermittendly Vs Continously Chemotherapy (Randomised, (A)= Abstract)

n	Line	Induktion	Status	Therapy	Kontrollarm	TTP (Mo)	OS (Mo)	Tox.	Source
Intermittierende vs kontinuierliche Therapie									
43	1st	Mx x 4	³ NC	Mx	nil	ns	ns	-	Harris 1990
100	1st	VA(E)C MxMMc x 6	³ NC	VA(E)C MxMMc x 6	nil	10 vs 7	ns	-	Gregory 1997
Zytostatische Erhaltung vs keine Erhaltung									
145	1st	CAF x 6	³ NC	CMF	nil	9 vs 3	ns	-	Muss 1991
141	1st	A based x 6	CR†	CMFPTH	nil	19 vs 8	ns	-	Falkson 1998
184	1st	CA(M)F x 4-6	³ PR	CMF x 24	HD-CaCTh x 1	ns	ns	¯®	Stadtmauer 2000, 2002 (a)

A, Doxorubicin; C, Cyclophosphamid; Ca, Carboplatin; CR, complete remission; E, Epirubicin; F, Fluorouracil; H, Halotestin; HD, Hochdosis mit Stammzelltransplantation; M, Methotrexat; Mx, Mitoxantron; Mc, Mitomycin; Mo, Monate; n, Anzahl auswertbare Pat.; NC, no change/stable disease; ND, keine Angaben; ns, nicht signifikant; OS, overall survival; P, Prednison; PR, partial remission; QoL, quality of life; T, Tamoxifen; Th, Thiotepa; TTP, time to progression; V, Vincristin.
† bez. Knochenmetastasen Response ausreichend

Cytostatic Therapy Choices

Oxford LOE 1c GR A AGO: ++

The choice of drugs to be used depends on:

- Patients expectations
- Health condition and age
- Aggressiveness of the disease and localisation of metastases
- Previous therapy

Cytostatic Therapy
1st line Therapy

	Oxford LOE	/ AGO GR	
Monotherapy:			
➢ Doxo, Epi, Mitox (A), Liposomal (A_{lip})	1b	A	++
➢ Taxanes (T)	1b	A	++
➢ Vinorelbin	3b	B	+
Polychemotherapy:			
➢ A + T	1b	A	++
➢ Doc + Cap after adj. A	1b	A	+
➢ T + Gemcitabine after adj. A	2b	B	++
➢ (F) + A + C or A_{lip} + C	1b	B	++
➢ CMF(1+8)	2b	B	+/-
➢ BMF (Bendamustin)	1b	B	+/-

1st-line A Oder Alip Vs Control (Randomised, (A)= Abstract)

n	Line	An	Kontrolle	ORR (%)	TTP(F) (Mo)	OS (Mo)	QoL An	Quelle
Doxorubicin, liposomales Doxorubicin								
739	1st	P(→A)	AP	33 vs 46	6 vs 8 (F)	ns	→	Sledge 2003
		A(→P)	AP	34 vs 46	6 vs 8 (F)	ns	→	
509	1st	A	PLD	ns	ns	ns	ND	O´Brien 2004
331	1st	A	P	41 vs 25	8 vs 4	ns	→	Paridaens, Kramer 2000
154	1st	A	nPLD	ns	ND	ND	ND	Harris 1998 (a)
141	1st	A	E	ns	ns	ns	ND	Perez 1991
300 (225†)	1st-2nd	A	AV	ns	ns (F)	ns	→	Norris 2000
322 (152†)	1st-2nd	A	D	33 vs 48	ns	ns	→	Chan 1999
71 (37†)	1st-2nd	A	I	46 vs21	ns	ns	ND	Lopez 1989
Epirubicin								
294	1st	E (→Mc)	CEF (→McVb)	ns	ns	ns	↑	Joensuu 1998
40	1st	E	CMF	29 vs 58	2 vs 5 (F)	ns	→	Fraser 1993
410	1st	E	G	40 vs.16	6,1 vs. 3,4	19,1 vs. 11,8	?	Feher 2005
Mitoxantron								
260	1st	Mx	FEC	ns	ns	ns	↑	Heidemann 2002

A, Doxorubicin; An, Anthrazykline; C, Cyclophosphamid; D, Docetaxel; E, Epirubicin; F, Fluorouracil; G, Gemcitabin; I, Idarubicin; M Methotrexat; Mo, Monate; Mc, Mitomycin; Mx, Mitoxantron; n, Anzahl auswertbare Pat.; ND, keine Angaben; ns, nicht signifikant; nPLD, nicht-pegyliertes liposomales Doxorubicin; ORR, overall response rate; OS, overall survival; P, Paclitaxel; PLD, pegyliertes liposomales Doxorubicin; QoL, quality of life; TTP(F), time to progression(treatment failure); V, Vinorelbin; Vb, Vinorelbin.
† = 1st-line

1st-line T Vs Control (Randomised, (A)= Abstract)

n	Line	T	Kontrolle	ORR (%)	TTP(F) (Mo)	OS (Mo)	QoL T	Quelle
3663	1st-4th	T	kein T	↑	↑	↑	→	Gershi 2003 (Cochrane Meta)
Paclitaxel								
739	1st	P(→A)	AP	33 vs 46	6 vs 8 (F)	ns	→	Sledge 2003
		A(→P)	AP	34 vs 46	6 vs 8 (F)	ns	→	
331	1st	P	A	25 vs 41	4 vs 8	ns	→	Paridaens, Kramer 2000
209	1st	P	CMFPd	ns	ns (P)	17 vs 14	→	Bishop 1999
41 (?†)	1st-3rd Avb	P	Ca	ns	ns	ns	ND	Talbot 2002
Docetaxel								
511 (171†)	1st-4th Avb	D	DCa	30 vs 42	4 vs 6	12 vs 15	→	O´Shaughnessy 2002
322 (152†)	1st-2nd	D	A	48 vs 33	ns	ns	→	Chan 1999
267 (132†)	1st-2nd Avb	D	MF	42 vs 21	6 vs 3	ns	→	Sjostrom 1999, Hakamies-Blomqvist 2000
387 (74†)	1st-2nd Avb	D	McVb	30 vs 12	4 vs 2	11 vs 9	→	Nabholtz 1999
Docetaxel vs Paclitaxel								
449	1st	D	P	32 vs.25 (n.s.)	5,7 vs. 3,6 (s)	15,4 vs. 12,7 (s)	n.s.	Jones 2005
ABI 007 vs. Paclitaxel								
457	1st-3rd	ABI 007	P	33 vs. 19 (s)	23 vs. 17 weeks (s)	65 vs. 55,7 weeks (n.s.)	→	Gradishar 2005

A, Doxorubicin; Avb, Anthrazyklin-vorbehandelt; C, Cyclophosphamid; Ca, Capecitabin; D, Docetaxel; F, Fluorouracil; M, Methotrexat; Mc, Mitomycin; Mo, Monate; n, Anzahl auswertbare Pat.; ND, keine Angaben; ns, nicht signifikant; ORR, overall response rate; OS, overall survival;
P, Paclitaxel; Pd, Prednison; QoL, quality of life; T, Taxane; TTP(F), time to progression(treatment failure); Vb, Vinblastin. † = 1st-line

1st-line V vs Control (randomised)

n	Line	V	Control	ORR (%)	TTP (Mo)	OS (Mo)	QoL V	Source
179 (15†)	1st-3rd	V	Mn	46 vs 28	3 vs 2	8 vs 7	®	Jones 1995
387 1 s		VE	E	50 vs 42	10,1 vs. 8,2	19 vs 18	®	Ejlertsen 2004

Mn, Melphalan; Mo, Monate; n, Anzahl auswertbare Pat.; ORR, overall response rate; OS, overall survival; QoL, quality of life; TTP, time to progression; V, Vinorelbin, E, Epirubicin.

† = 1st-line

Cytostatic Palliative Therapy

After Anthracycline Treatment

	Oxford LOE	/ GR	AGO
➢ Docetaxel	1a	A	++
➢ Paclitaxel	1a	A	++
➢ Capecitabine	2b	B	++
➢ Peg-Liposomal Doxorubicin	2b	B	+
➢ Vinorelbine	2b	B	+
➢ Gemcitabine	3b	B	+/-

Randomised Studies for Salavagetherapy (After Anthrazyklin-Pretreatment) (Randomised, (A) = Abstract

n	Line	T/V/PLD	Kontroll -arm	ORR (%)	TTP (Mo)	OS (Mo)	QoL T/V/PLD	Quelle
511	1st-4th	D	DCa	30 vs 42	4 vs 6	12 vs 15	→	O´Shaughnessy 2002
387	1st-2nd	D	McVb	30 vs 12	4 vs 2	11 vs 9	→	Nabholtz 1999
267	1st-2nd	D	MF	42 vs 21	6 vs 3	ns	→	Sjostrom 1999, Hakamies-Blomqvist 2000
91	2nd	D	VF	54 vs 44	7 vs 5	ND	ND	Bonneterre 1997 (a)
179	1st-3rd	V	Mn	47 vs 28	3 vs 2	8 vs 7	→	Jones 1995
41	1st-3rd	P	Ca	ns	ns	ns	ND	Talbot 2002
153	1st-2nd	DG	D-Ca	32 vs. 32	4,5 vs. 4,5		?	Levy 2005
196	1st	DE	D-Ca	53 vs. 46 (n.s.)	11,8 vs. 10,9 (n.s.)	n.e.	n.d.	Mavroudis 2005 (a)
295	1st-2nd	GD	CaD	27 vs 31 (n.s.)	n.r.	n.r.	n.r.	Chan 2005 (a)

C, Cyclophosphamid; Ca, Capecitabin; D, Docetaxel; F, Fluorouracil; M, Methotrexat; Mc, Mitomycin; Mn, Melphalan; Mo, Monate; n, Anzahl auswertbare Pat.; ND, keine Angaben; ns, nicht signifikant; ORR, overall response rate; OS, overall survival; P, Paclitaxel; PLDD, pegyliertes liposomales Doxorubicin; QoL, quality of life; TTP, time to progression; V, Vinorelbin; Vb, Vinblastin, G, Gemcitabin, E, Epirubicin
† Anthrazyklin-vorbehandelt

Cytostatic Therapy

After Previous Taxane And Anthracycline Treatment

	Oxford LOE	/ GR	AGO
➢ Experimental Therapies in Studies			++
➢ Capecitabine	2b	B	++
➢ Pegliposomal Doxorubicin	2b	B	+
➢ Vinorelbine	2b	B	+

Studys About The Salvage-chemotherapy (After Anthrazyklin- And Taxan-pretreatment (Randomised Or Not-Randomised (A)= Abstract)

n	Phase	Substance/Combination	ORR (%)	TTP (Mo)	OS (Mo)	Source
301(253†)	III	PLD vs (V or McVb)	ND	5,8 vs 2,1	11 vs.9 ns	Keller 2004
Monotherapy						
162	II	Capecitabin	20	3	13	Blum 1999
36	II	Capecitabin	26	4,6	18,1	Lee 2004
31	II	Pemetrexed	26	ND	13	Spielmann 2001
23	II	Gemcitabin	0	2	8	Smorenburg 2001
20	II	Irinotecan	5	1	4	Shigeoka 2001
19	II	Vinorelbin	35	3	ND	Udom 2000
Combination						
84	II	FEn	10	2	9	Rivera 2002
60	II	OxF	27	5	12	Zelek 2002
44	II	FEn	16	ND	ND	Skovsgaard 2001
41	II	CF	27	10	13	Kalbakis 2001
33	II	CGF	42	ND	ND	Frasci 2002
29	II	GV	48	ND	ND	Valenza 2000
38	II	CisG	40	6	13,5	Heinemann 2005
39	II	Cis/Capec	35,9	5,2	10,9	Donadio 2005
39	II	G/Capec.	48,7	5	10	Andres 2005

C, Cyclophospamid; En, Eniluracil; F, Fluorouracil; G, Gemcitabin; Mc, Mitomycin; Mo, Monate; n, ANzahl auswertbarer Pat.; ND, keine Angaben; ORR, overall response rate; OS, overall survival; Ox, Oxaliplatin; PLD, pegyliertes liposomales Doxorubicin; TTP, time to progression; V, Vinorelbin; Vb, Vinblastin; C, Cisplatin; Capec, Capecitabin; † Anthrazyklin- und Taxan- vorbehandelt

Randomised And Not Randomised Studys

About The Salvage-Chemotherapy (Mixed Pretreatment)

n	Line	An/V	Kontroll-arm	ORR (%)	TTP (Mo)	OS (Mo)	QoL An/V	Source
272	2nd	A	Mx	29 vs 21	3 vs 2	ns	–	Henderson 1989
322 (174†)	1st2nd	A	D	33 vs 48	ns	ns	®	Chan 1999
294 (126†)	1st2nd	E(® Mc)	CEF(® McVb)	ns†	ND†	ns†	-	Joensuu 1998
300 (75†)	1st2nd	A	AV	ns†	ns†	ns†	®	Norris 2000
51	³ 2nd	A	Cm	30 vs 4	7 vs 2	ns	ND	Van Oosterom 1986
35	2nd	ACc	ACcVc	ns	ND	ns	-	Chlebowski 1983
71 (34†)	1st2nd	A	I	29 vs 12†	ns	ns	ND	Lopez 1989
99	³ 2nd	V	F MxF	ns	ND	ns	®	Venturino 2000
78	≥ 3rd	Irinotecan	entfällt	22%	n.e.	n.e.	n.e.	Vukelja 2005 (a)

A, Doxorubicin; An, Anthrazyklin; C, Cyclophosphamid; Cc, CCNU; D, Docetaxel; E, Epirubicin; F, Fluorouracil; M, Methotrexat; Mc, Mitomycin; Mo, Monate; Mx, Mitoxantrone; n, Anzahl auswertbare Pat.; ND, keine Angaben; ns, nicht signifikant; ORR, overall response rate; OS, overall survival; QoL, quality of life; TTP, time to progression; V, Vinorelbin; Vb, Vinblastin; Vc, Vincristin; † 2 nd -line

Palliative High Dose Therapy

	Oxford LOE	/	AGO GR	
➢ **High Dose-Therapy** **(No treatment outside studies)**	1b		B	- -

HDCT Vs SDCT (Randomised, (A)=abstract)

n	Status bef. HDCT	HDCT	SDCT	FU (Mo)	TTP	OS	Source
					p-Note		
98	CR	1xCPB	-	60	.008	(¯)	Peters 1996 (a)
61	CR/PR	1xCML	A based	24	.04	ns	Lotz 1999 (a)
219	CR/PR	1-2x CaCM	2-4x A o. T based	30	.01	ns	Crump 2001 (a)
180	CR/PR	1xThC	-	48	< .05	ns	Biron 2002 (a)
92	upfront	2xCME	AT	14	.05	ns	Schmid 2002 (a)
184	CR/PR	1xCaCTh	CMF Conservat.	68	ns	ns	Stadtmauer 2000, 2002 (a)

A, Anthrazyklin; B, Carmustin; C, Cyclophosphamid; Ca, Carboplatin; CR, complete remission; E, Etoposid; HDCT, Hochdosischemotherapy; L, L-PAM; M, Mitoxantron; Mo, Months; n, Quantity evaluated Pat.; ns, not significant; OS, overall survival; P, Cisplatin; PR, partial remission; T, Taxan; Th, Thiotepa; TTP, time to progression.