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Neoadjuvant
(Primary) Systemic Therapy

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Neoadjuvant Systemic Therapy

- **Versions 2002–2020:**
  Bauerfeind / Blohmer / Costa / Dall / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Untch

- **Version 2021:**
  Fehm / Stickeler

Subtype-specific Strategies for Systemic Treatment

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	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred	
HR+/HER2- and „low-risk"	
▪ Endocrine therapy without chemotherapy	++
HR+/HER2- and „high-risk"	
▪ Conventionally dosed AT-based chemotherapy (q3w)	+
▪ Dose dense chemotherapy (including weekly schedule)	++
▪ Followed by endocrine therapy	++
HER2+	
▪ Trastuzumab (plus Pertuzumab in N+ or NACT)	++
▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy	++
▪ Anthracycline-free chemotherapy + anti-HER2 therapy	++
Triple-negative (TNBC)	
▪ Conventionally-dosed AT-based chemotherapy	+
▪ Dose-dense chemotherapy (AT-based including weekly schedule)	++
▪ Neoadjuvant platinum-containing chemotherapy	+
▪ Neoadjuvant chemotherapy + ICPi (immune checkpoint-inhibitors)	+/-*

*study paticipation recommended

Anthracycline-free Taxan/Carboplatin based regimen for Her2+

Regimen	Pts. (n=)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.5%

T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab

HER2+ Early Breast Cancer
Neo-/adjuvant and postneoadjuvant Therapy

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Adjuvant Therapy:
low risk of recurrence
Rezidivrisiko
Paclitaxel$_{weekly\ x\ 12}$ + Trastuzumab[1]

- elderly or fragile patients

  or

- pT1, pN0

Adjuvant Therapy:
high risk of recurrence
CHT + Trastuzumab + Pertuzumab[2]

- Node-positive (pN+)
- Irrespective of ER-status[5]

Neoadjuvant Therapy[3]
Trastuzumab + Pertuzumab

- Node-positive (cN+/pN+)

  or

- cT $\geq$ 2

Postneoadjuvant Therapy[4]
Trastuzumab +/- Pertuzumab
or T-DM1

In case of pCR:

- Trastuzumab
- Trastuzumab + Pertuzumab
  - Node-positive prior NACT
  - Irrespective of ER-status

In case of non-pCR:

- T-DM1

Total duration of anti-HER2-therapy: 1 year

1.Tolaney SM, *et al*. J Clin Oncol April 2019; 2. von Minckwitz G, *et al.* N Engl J Med 2017; 377:122–131 (inkl. Suppl.); 3. Gianni L, *et al.* Lancet Oncol 2012;13:25-32; 4. von Minckwitz G, *et al*. N Engl J Med 2019; 380:617-628, 5. Piccart M, et al. SABCS 2019 (abs GS1-04)

Neoadjuvant (Primary) systemic Therapy

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Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford LoE	Oxford GR
▪ Leads to improvement of prognosis by individualization of post-neoadjuvant therapy	1b	A
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the post-neoadjuvant therapy is not individualized according to pathological response	1a	A
▪ Pathological complete response is associated with improved survival	1b	A
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymphadenectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B

Neoadjuvant Systemic Chemotherapy - Indications

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	Oxford		
	LoE	GR	AGO
▪ Inflammatory breast cancer	2b	B	++
▪ Inoperable breast cancer	1c	A	++
▪ Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	++
▪ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++
▪ To allow a risk-adapted postoperative therapy	1b	A	++

Neoadjuvant Systemic Chemotherapy
Response Prediction I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

*High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low(↓↓) probability to reach pCR
See aso chapter „Prognostic and predictive factors“

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Neoadjuvant Systemic Therapy
Response Prediction II

Factor	LoE_{2009}	CTS	GR	AGO
▪ Multigene signatures	II	B	B	+/-
▪ Ki-67	I	B	A	+
▪ Tumor infiltrating lymphocytes*	I	B	B	+
▪ *PIK3CA* mutation in HER2 positive BC	I	B	B	+/-
▪ g*BRCA*	II	B	B	+
▪ Homologous recombination deficiency	IV	C	C	+/-
▪ PD-L1 status (TNBC)	II	B	B	+/-

*** LPBC is defined as dense lymphocytic infiltration of inner peritumoral stroma outside of invasion front (> 50% of stromal area are covered by lymphocytes)**

See also chapter „Prognostic and predictive factors“

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Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

	Oxford		
	LoE	GR	AGO
▪ Use of adjuvant standard regimens for NACT*	1a	A	++
▪ Taxane followed by anthracycline (reverse order)	1a	A	+
▪ Platinum in TNBC (irrespective of BRCA status)	1a	A	+
▪ Nab-Paclitaxel weekly instead of Paclitaxel weekly	1a	A	+
▪ Checkpoint inhibitors in combination with chemotherapy (TNBC)	1b	B	+/-**

* See chapter Adjuvant Chemotherapy; ** Study participation recommended

ICPi plus neoadjuvant chemotherapy for triple negative breast cancer patients

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	GeparNuevo	IMpassion031	Keynote 522	NeoTRIP
Phase	II	III	III	II
n	174	333	602	280
Prim. Endpunkt	pCR	pCR	pCR + EFS	EFS
CP*i*	Durvalumab (24-26 Wo)	Atezolizumab (1J)	Pembrolizumab (1 J)	Atezolizumab (24 Wo)
Chemo	Nab-P -> EC	Nab-P _> ddAC	Pac+Carbo -> AC oder EC	Nab-P + Carbo
PDL-1 positiv	87%	46%	83%	56%
pCR ITT	53% vs. 44 % Δ 9% (n.s.)	58% vs. 41% Δ 17% (p<0.01)	65% vs. 51% Δ 14% (p<0.001)	44% vs. 41% Δ 3% (n.s.)
pCR PDL-1 positiv	58 % vs. 50%	69% vs. 49%	69% vs. 55%	52% vs. 48%
pCR PDL-1 negativ	44 % vs. 18%	48% vs. 34%	45% vs. 30%	32% vs. 32%
Follow-uo (Mths) / HR EFS	-	20 mths 0,76 (ns)	15 mths 0,63 (ns)	-

Modifiziert nach Carey L et al. SABCS 2020, ES4

Neoadjuvant Systemic Therapy
Recommended Methods of Monitoring of Response

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound	2b	B	++
▪ Palpation	2b	B	++
▪ Mammography	2b	B	++
▪ MRI	2b	B	+
▪ PET(-CT)	2b	B	+/-
▪ Pretherapeutic marking of tumor region	5	D	++
▪ Pretherapeutic marking of pN+	2a	B	+*

*study participation recommended (AXSANA /Eubreast 3 Trial)

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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	Oxford		
	LoE	GR	AGO
▪ Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)	2b	B	++
▪ Trastuzumab in combination with standard polychemotherapy (low-risk)*	1b	A	+
▪ Anti-HER2 agents without chemotherapy	2b	B	+/-**

* Monochemotherapy and trastuzumab should preferably be used in the adjuvant setting

** Study participation recommended

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Neoadjuvant Chemotherapy
Treatment strategies based on clinical response

	Oxford		
	LoE	GR	AGO
In case of early response			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
In case of no change:			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
In case of disease progression			
▪ Re-evaluation of tumorbiological factors	5	D	+/-
▪ Stop NACT and proceed to surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-

Axillary Surgery and NACT

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						Oxford		
						LoE	GR	AGO
SLNE after NACT						2b	B	++
SLNE before NACT						2b	B	-
cN-Status (before NACT)	**pN-Status (before NACT)**	**cN-Status (after NACT)**	**Surgical procedure (after NACT)**	**pN-Status (after NACT and Surgery)**	**Surgical consequence from histology****			
cN0	—	ycN0	SLNE alone	ypN0 (sn)	—	2b	B	++***
				ypN0 (i+) ypN1$_{mic}$ (sn)	ALND	2b	C	+ (+/- at i+)
					none **	5	D	+/-
				ypN1 (sn)	ALND	2b	C	++
					none **	5	D	+/-
cN+	pN+$_{CNB}$	ycN0	SLNE alone* TAD (TLNE + SLNE)* ALND*	ypN0 ypN0 ypN0	—	2b 2b 2b	B B B	+/-*** +*** +***
			SLNE alone* TAD (TLNE + SLNE)*	ypN+ incl. ypN0 (i+)	ALND	2b	B	+ (+/- at i+)
			ALND	ypN+	—	2b	B	++
			none	n.d.	none**	5	D	-
cN+	pN+$_{CNB}$	ycN+	ALND	ypN+ incl. ypN0 (i+)	—	2b	B	++
			none	n.d.	none**	5	D	-

*Study participation (Axsana) recommended; ** s. Recommendations chapter Radiotherapy, irradiation alone is not recommended in case of pN1(sn) and pN+ ; ***recommendation grade concerning to staging at cN0 and cN+ ypN0

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Neoadjuvant Systemic Therapy
Loco-regional Surgery (Breast)

	Oxford		
	LoE	GR	AGO
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excision of post-therapeutic, marked tumor area	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

Neoadjuvant Systemic Therapy
Indications for Mastectomy

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	Oxford		
	LoE	GR	AGO
▪ **Positive margins after repeated excisions**	3b	C	++
▪ **Radiotherapy not feasible**	5	D	++
▪ **In case of clinical complete response**			
▪ **Inflammatory breast cancer (in case of pCR)**	2b	C	+/-
▪ **Multicentric lesions**	2b	C	+/-
▪ **cT4a-c breast cancer**	2b	B	+/-

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Neoadjuvant Systemic Therapy
Timing of Diagnosis, Surgery and Radiotherapy

	Oxford		
	LoE	GR	AGO
Initiation of therapy Delay of therapy (> 60 days) associated with worse prognosis	2b	B	
Timing of surgery 4-8 weeks after last course of chemotherapy	2b	B	++
Radiotherapy within 2 months after surgery	2b	B	++

Neoadjuvant endocrine Therapy (NET)
- Good clinical practice -

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- **Suitable for patients who are**
  - **inoperable**
  - **not able or not willing to undergo chemotherapy**
- **Limited data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimal duration of NET is at least 4-6 months or until best response or until progression**
- **Choice of endocrine therapy is based on menopausal status**
- **NET for 2 up to 4 weeks is able to predict response to endocrine treatment by Ki-67 dynamics (prognostic / predictive evaluation)**

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ **Postmenopausal patients:**			
▪ Optimizes the option for breast conserving therapy	1b	A	+
▪ Aromatase inhibitors (at least 6 months)	1a[a]	B	+
▪ Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
▪ **Premenopausal patients**			
▪ Tamoxifen	2b	C	+
▪ Aromatase inhibitors + LHRHa	1b	C	+/-
▪ **Concurrent chemo-endocrine therapy**	1b	A	-
▪ **Preoperative ET (Tam/AI) + Ki-67 after 2-4 weeks (prognostic/predicive evaluation)**	1b	B	+
▪ **Prognostic score:**			
▪ PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy	1b	B	+

[a] **Optimal duration of neoadjuvant endocrine therapy is unknown.**
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

Post-neoadjuvant therapy: HER2-negative

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	Oxford		
	LoE	GR	AGO
HR-positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal status (s. chap. 10)	1a	A	++
▪ Capecitabine (in case of non-pCR)	3b	C	+/-
▪ Endocrine therapy + Abemaciclib	2b	B	+/-*
▪ Endocrine therapy + Palbociclib	1b[a]	B	-*
Triple negative (TNBC) (in case of non-pCR)			
▪ Capecitabine (up to 8 cycles)**	1b	B	+
▪ Experimental post-neoadjuvant therapies within clinical trials	5	D	+*

* Study participation recommended

** without prior platinum-based therapy

Post-neoadjuvant treatment with CDK 4/6i

	MonarchE	PALLAS	Penelope[B]
N	5637	5600	1250
CDKi	Abemaciclib	Palbociclib	Palbociclib
% of pts with NACT	37%	n.r.	100%
Duration of CDK 4/6i treatment	24 mths	24 mths	12 mths
Follow-up	19 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
IDFS-HR (95%-CI)	0.713 (0.583 - 0.871) p = 0.0009	0.93 (0.76-1.15) p = 0.51	0.93 (0.74-1.16) p=0.525
2-yrs IDFS	92% vs. 89%	n.r.	88% vs. 84%
3-yrs IDFS	n.r.	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	n.r.	73% vs. 72%

IDFS: invasive disease-free survival

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Post-neoadjuvant therapy: HER2-positive

	Oxford		
	LoE	GR	AGO
pCR			
▪ Low-risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High-risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive)*	2b	B	-
non-pCR			
▪ T-DM1	1b	B	+
▪ Neratinib after 1 year* Trastuzumab (HR-positive)*	2b	B	+/-
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+/-

* In combination with standard endocrine treatment