Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2022.1E

Neoadjuvant
(Primary) Systemic Therapy

Guidelines Breast
Version 2022.1E

Neoadjuvant Systemic Therapy

- **Versions 2002–2021:**
  Bauerfeind / Blohmer / Costa / Dall / Fehm / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Stickeler / Untch

- **Version 2022:**
  Thill / Thomssen

Strategies for Differentiated Systemic Treatment in the Curative Situation

Guidelines Breast
Version 2022.1E

	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended	
„Low absolute risk implies low absolute benefit“	
▪ **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 endocrine-based therapy**	++
▪ **Triple-negative (TNBC)**	
▪ **Conventional dosed AT-based chemotherapy (q3w)**	+
▪ **Sequential AT-based chemotherapy (incl. weekly schedule)**	++
▪ **Neoadjuvant Neo-/adjuvant platinum-containing chemotherapy**	+
▪ **Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)**	+
▪ **HER2 negative, gBRCA1/2mut (ER pos. and TNBC respectively[1])**	
▪ **Olaparib postneoadjuvant**	+
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab in N+ or NACT)**	++
▪ **Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy**	+
▪ **Anthracycline-free, chemotherapy + anti-HER2 therapy**	++

[1] **According to approval or study population (if not approved)**

Anthracycline-free Taxan / Carboplatin based Regimen for HER2+

Guidelines Breast
Version 2022.1E

Regimen	Ppts. (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

Guidelines Breast
Version 2022.1E

Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford	
	LoE	GR
▪ Leads to improvement of prognosis by individualization of neoadjuvant and 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 postneoadjuvant therapy is not stratified according to pathologic 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 lymphonodectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B

Guidelines Breast
Version 2022.1E

Neoadjuvant Systemic Chemotherapy - Indications

	Oxford		
	LoE	GR	AGO
▪ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++
▪ To allow a risk adapted postoperative therapy	1b	A	++
▪ 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	++

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Guidelines Breast
Version 2022.1E

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ 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“

Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

Guidelines Breast
Version 2022.1E

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ gBRCA-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ gBRCA-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50 % of stroma area)

Neoadjuvant Systemic Chemotherapy Recommended Regimens

Guidelines Breast
Version 2022.1E

	Oxford		
	LoE	GR	AGO
▪ Use of adjuvant standard regimens for NACT*	1a	A	++
▪ Taxane mono followed by anthracycline (reverse order)	4	D	+/-
▪ Platinum in TNBC (cT1 / cN+ or cT2) (irrespective of BRCA status)	1b	A	+
▪ Platinum in TNBC (from cT1 / cN+ or cT2) (irrespective of BRCA status)	1a	A	+
▪ Nab-paclitaxel weekly instead of paclitaxel qw1 (in TNBC)	1a	A	+
▪ Pembrolizumab in combination with carbo / paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

* See chapter Adjuvant Chemotherapy;
** ≥ 2 cm or cN+, PD-L1 independent

Recommended Regimen in Triple Negative Breast Cancer

Guidelines Breast
Version 2022.1E

	Oxford LoE	Oxford GR	AGO
Non-platinum-containing regimen			
ddEC x 4 → $pacli_{80}$ q1w x 12	1b	B	++
$NabPac_{125}$ q1w x 12 → $E_{90}C$ q(2)3w x 4	1b	B	+/-
Platinum-containing regimen			
$NabPac_{125}$ / $carbo_{AUC\ 2}$ q1w x 8 → ddEC x 4	1b	B	+
$Pacli_{80}$ q1w x 12 / $carbo_{AUC\ 6}$ q3w x 4 → ddAC / ddEC x 4	1b	B	+
Docetaxel / $carbo_{AUC6}$ q3w x 6 or paclitaxel/$carbo_{AUC1,5}$ q1w x18	2b	B	+
$NabPac_{1oo}$ / $carbo_{AUC\ 6}$ q4w x 4	2b	C	+
Checkpoint inhibitors			
$Pembro_{200}$ q3w + Pac_{80} / $carbo_{AUC\ 1,5}$ q1w x 12 → $E_{90}C$ q3w x 4	1b	B	+
$Pembro_{200}$ q3w + Pac_{80} q1w x 12 / $carbo_{AUC\ 5}$ q3w → $E_{90}C$ q3w x 4	1b	B	+

ICPi plus Neoadjuvant Chemotherapy for Triple Negative Breast Cancer Patients

Guidelines Breast
Version 2022.1E

	GeparNuevo	IMpassion031	Keynote 522	neoTRIP
Phase	II	III	III	II
N	174	333	602 (pCR) 1174 (EFS)	280
Prim. endpoint	pCR	pCR	pCR + EFS	EFS
CPi	Durvalumab (24-26 weeks)	Atezolizumab (1y)	Pembrolizumab (1y)	Atezolizumab (24 weeks)
Chemo	$NabPac_{125}$ q1w x12 → EC q2w x4	$NabPac_{125}$q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 -> AC/EC q3w x4	$NabPac_{125}$ + carbo AUC 2 q1w d1 and d8
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0
PD-L1 positive	87%	46%	83%	56%
pCR ITT	53.4% vs. 44.2% Δ 10.8% (n.s.)	57.6% vs. 41.2% Δ 16.5% (p < 0.01)	64.8% vs. 51.2% Δ 13.6% (p < 0.00055)	43.5% vs. 40.8% Δ 2.6% (n.s.)
pCR PD-L1 positive	58% vs. 50%	69% vs. 49%	69% vs. 55%	52% 48%
pCR PD-L1 negative	44% vs. 18%	48% vs. 34%	45% vs. 30%	32% vs. 32%
Follow up/EFS/iDFS (months)/HR EFS/iDFS	43.7 months iDFS: 0.48 (p = 0.0389)	20 months EFS: 0.76 (n.s.)	39.1 months EFS: 15.7 vs. 23.8 m 0.63 (p = 0.00031)	---
EFS/iDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% npCR 76.3% vs. 69.7%	---	pCR 94.4% vs. 92.5% npCR 67.4% vs. 56.8%	---

Neoadjuvant Systemic Therapy
Recommended Methods of Monitoring of Response

Guidelines Breast
Version 2022.1E

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

*study participation recommended (AXSANA /Eubreast 3 Trial)

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

Guidelines Breast
Version 2022.1E

	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 stand polychemotherapy (low-risk)*	1b	A	+
▪ Anti-HER2 agents without chemotherapy	2b	B	+/-

* Single agent chemotherapy combined with trastuzumub should preferably be used in the adjuvant setting

Guidelines Breast
Version 2022.1E

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

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0 *	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++
cN+ **	$pN+_{CNB}$	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
		ycN+	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in EUBREAST-01 recommended; ** Study participation in AXSANA recommended

Guidelines Breast
Version 2022.1E

Neoadjuvant Systemic Therapy
Loco-regional Surgery (Breast)

Guidelines Breast
Version 2022.1E

	Oxford		
	LoE	GR	AGO
▪ Pretherapeutic discussion in a multidisciplinary tumor board (e.g. to define the surgical procedure)	1a	B	++
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excicion of posttherapeutic, marked tumorareal	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

Neoadjuvant Systemic Therapy
Indications for Mastectomy

Guidelines Breast
Version 2022.1E

	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	+/-

Guidelines Breast
Version 2022.1E

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	2a	B	++
Radiotherapy within 2 months after surgery	2b	B	++

Neoadjuvant endocrine Therapy (NET)
- Good clinical practice -

Guidelines Breast
Version 2022.1E

- **Suitable for patients who are**
  - **inoperable**
  - **not able or willing to undergo chemotherapy**
- **Data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimale duration of NET is at least 4-6 months or until best repsonse or progression**
- **Choice of endocrine therapy is based on the menopausal status**
- **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks may predict response to endocrine treatment (prognostic / predictive evaluation)**

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

Guidelines Breast
Version 2022.1E

	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	-
Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)	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)

Postneoadjuvant Therapy HR+ / HER2-

Guidelines Breast
Version 2022.1E

	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence[1]	1b	B	+
▪ Palbociclib for 1-2 yrs + endocrine therapy	1b	B	-
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	B	+
▪ Capecitabine (non-pCR)	3b	C	+/-

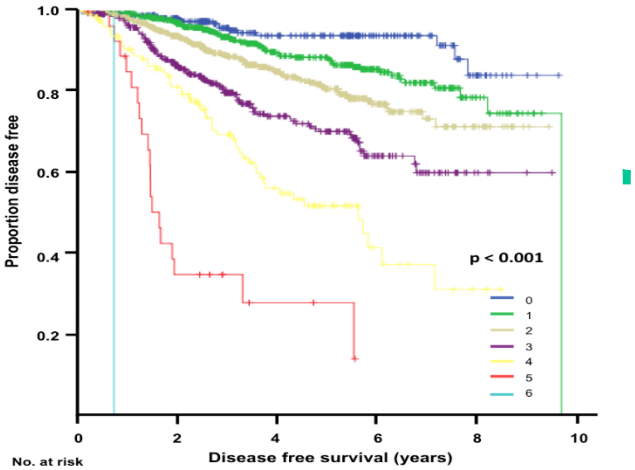
1 According inclusion criteria monarchE-study
2 According inclusion criteria OlympiA-study

How to Calculate CPS+EG Score?

Guidelines Breast
Version 2022.1E

Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

Guidelines Breast
Version 2022.1E

	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.59-0.82) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

Postneoadjuvant Therapy TNBC

Guidelines Breast
Version 2022.1E

	Oxford		
	LoE	GR	AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*	1a	A	+
▪ Olaparib (*gBRCAm^{MUT}*)[1]	1b	B	+
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w up to 9 courses)	1b	B	++

[1] According inclusion criteria of OlympiA trial
* without platin based previous therapy

Guidelines Breast
Version 2022.1E

Postneoadjuvant 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	+
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+/-
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive*)	5	D	+/-

* In combination with standard endocrine treatment