Guidelines Breast
Version 2024.1D

Adjuvante zytostatische und zielgerichtete Therapien

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Guidelines Breast
Version 2024.1D

- **Versionen 2002 – 2023:**
  Albert / Dall / Fasching / Fehm / Gluz / Harbeck / Jackisch / Janni / Kümmel / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Rody / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2024:**
  Loibl / Lüftner

Strategien der differenzierten Systemtherapie in der kurativen Situation

Guidelines Breast
Version 2024.1D

	AGO
Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugen; Studienteilnahme empfohlen.	
▪ **HR+ / HER2- mit „niedrigem Rückfallrisiko”**	
▪ **Endokrine Therapie ohne Chemotherapie**	++
▪ **HR+ / HER2- mit „erhöhtem Rückfallrisiko”**	
▪ **endokrine / endokrin-basierte Therapie (Abemaciclib [1])**	++
▪ **Bei Patientinnen mit Indikation zur chemo-endokrinen Therapie*:**	
▪ **Konventionell dosierte AT-basierte Chemotherapie (q3w)**	+
▪ **Dosisdichte Chemotherapie (inkl. weekly-Regime)**	++
▪ **Triple-negative (TNBC)**	
▪ **Konventionell dosierte AT-basierte Chemotherapie (q3w)**	+
▪ **Dosisdichte sequentielle AT-basirte Chemotherapie (inkl. weekly Schemata)**	++
▪ **Neoadjuvante platinhaltige Chemotherapie**	+
▪ **Neoadjuvante platinhaltige Chemotherapie mit ICPi (Pembrolizumab)**	+
▪ **gBRCA1/2^{MUT} (HR+/HER- o. TNBC)**	
▪ **Olaparib[1]**	++
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab bei N+ oder NACT)**	++
▪ **Sequentielle AT-basierte Chemotherapie mit simultaner Gabe von T + anti-HER2-Therapie**	++
▪ **Anthrazyklin-freie Chemotherapie + anti-HER2-Therapie**	++

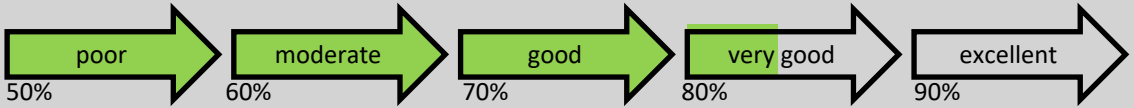
[1] **gemäß Zulassung bzw. Studienpopulation (falls noch nicht zugelassen), * s. Prognosekapitel**

Guidelines Breast
Version 2024.1D

Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

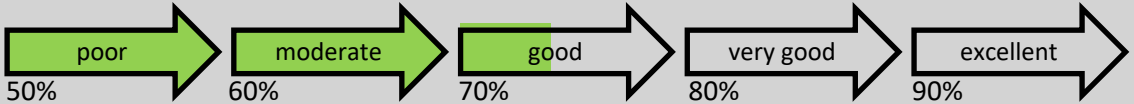
Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality).
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 82% of the time (c-statistic). The life expectancy calculator sorts patients who lived longer from patients who lived shorter correctly 78-80% of the time in the validation studies
- Calibration: The model was well calibrated across all risk levels with less than 3% difference between estimated and actual mortality rates.



Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).
- Discrimination: This risk calculator sorts patients who died within 5 years from patients who lived correctly 75% of the time (c-statistic). The discrimination was the same in the independent validation study. For 10 year and 14 year mortality the calculator sorts patients correctly 73% and 72% of the time.
- Calibration: The model was well calibrated across all risk levels with less than 10% difference between estimated and actual mortality.



Guidelines Breast
Version 2024.1D

Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

Risk Calculator questions

1. How old is your patient?
2. What is the sex of your patient?
3. What is your patient‘s BMI?
4. Which best describes your patient's health in general?
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis?
6. Has your patient ever had cancer (excluding minor skin cancers)?
7. Does your patient have congestive heart failure?
8. Does your patient have diabetes or high blood sugar?
9. Which best describes your patient's cigarette use?
10. Does your patient have difficulty walking 1/4 mile (several city blocks) without help from other people or special equipment?
11. During the past 12 months, how many times was your patient hospitalized overnight?
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?
13. Because of a health or memory problem, does your patient have difficulty managing money - such as paying bills and keeping track of expenses?
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering?
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?

Guidelines Breast
Version 2024.1D

(Neo-)Adjuvante Chemotherapie: bei kleinen, nodal-negativen Tumoren (T1)

	Oxford		
	LoE	GR	AGO
Indikation zur Chemotherapie bei			
TNBC			
> 10 mm neoadjuvant bevorzugt	2b	B	++
> 5–10 mm neoadjuvant oder adjuvant	2b	B	+
≤ 5 mm adjuvant	2b	B	+/-
HER2+ in Kombination mit Trastuzumab			
> 10 mm neoadjuvant oder adjuvant	1a	A	++
> 5–10 mm adjuvant	2b	B	+
≤ 5 mm adjuvant	2b	B	+/-

Adjuvante Chemotherapie ohne Trastuzumab: Überblick

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
▪ Dosis-dicht Anthrazyklin-/ Taxan-basiert (inkl. weekly)	1a	A	++
▪ Konventionell Anthrazyklin-/ Taxan-basiert (q3w)	1a	A	+
▪ „Tailored“ Anthrazyklin-/ Taxan-basiert	1b	B	+/-
▪ Wenn auf Anthrazykline verzichtet werden soll			
▪ Docetaxel plus Cyclophosphamid	1b	B	++
▪ Paclitaxel mono wöchentlich	1b	B	+/-
▪ CMF	1a	A	+/-

Gray R et al., Lancet 2019

Early Breast Cancer Trialists' Cooperative Group (EBCTCG)
Increasing the dose-density of adjuvant chemotherapy: an EBCTCG meta-analysis

Same chemotherapy drugs and doses **(n = 10,004)**

Recurrence-free survival: 10-y Gain 4.3% (95%-C.I. 2.2 – 6.5)
(RR = 0.83; 95%-C.I. 0.76 – 0.91; p < 0.0001)
Overall survival: 10-y Gain 2.8% (95%-C.I. 0.8 – 4.8)
(RR = 0.86; 95%-C.I. 0.77 – 0.96; p = 0.0054)

ER negative: **10-y Gain 4.7%** (95%-C.I. 2.3 – 7.1)
ER positive: **10-y Gain 3.1%** (95%-C.I. 1.5 – 4.7)

Guidelines Breast
Version 2024.1D

Empfohlene dosis-dichte und / oder dosis-eskalierte, sequentielle adjuvante Chemotherapie

	Oxford		
	LoE	GR	AGO
Dosis-dichte Regime			
▪ A_{60} x4 → Pac_{175} x4 → C_{600} x4 q2w	1b	A	++
▪ $A_{60}C$ q2w x 4 → Pac_{175} q2w x 4	1b	B	++
▪ $E_{90}C$ q2w x 4 → Pac_{175} q2w x 4	1b	A	++
▪ $E_{90}C$ q2w x 4 → Pac_{80} q1w x 12	1b	B	++
▪ $NabPac_{125}$ x 8-12 → $E_{90}C$ q2(3)w x 4	1b	B	+
Dosis-dichtes und dosis-eskaliertes Regime (N ≥ 4+)			
▪ E_{150} → Pac_{225} → C_{2000} q2w	1b	A	++

Empfohlene konventionelle Regime für die adjuvante Chemotherapie

Guidelines Breast
Version 2024.1D

		Oxford LoE	Oxford GR	Oxford AGO
Anthrazyklin-/ Taxan-basierte Regime				
▪ *EC q3w x 4 → Pac q1w x 12		2b	B	++
▪ AC q3w x 4 → Pac q1w x 12		1b	A	++
▪ AC → D q3w	$A_{60}C$ q3w x 4 → D_{100} x 4	1b	A	+
▪ *EC → D q3w	$E_{90}C$ q3w x 4 → D_{100} x 4	1b	B	+
▪ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	+[a]
Anthrazyklin-freie Regime				
▪ 6 x DC entspricht EC → D oder 3 x (F)EC-3 x Doc	D_{75} C_{600} x 6	1b	B	+
▪ 4 x DC >> 4 x AC	D_{75} C_{600} x 4	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxan-freie Schemata				
▪ EC (q3-2w) x 4-6	$E_{90}C_{600}$ x 4-6	2b[(a)]	B	+

* Extrapoliert von Studien mit Doxorubicin

Adjuvante Chemotherapie: Andere Medikamente

Guidelines Breast
Version 2024.1D

	Oxford LoE	Oxford GR	Oxford AGO
Capecitabin-haltige Therapie bei TNBC*			
adjuvant / neoadjuvant (zusätzlich zur Standardtherapie)	1a	A	+/-
postneoadjuvant bei non-pCR**			
Bei non-pCR nach A-T-haltiger Chemotherapie	1a	A	++
Bei non-pCR nach Platin +/- Pembrolizumab-haltiger Therapie	5	D	+/-
Anthrazyklin-freier adjuvanter Therapie bei TNBC (Kombination mit Taxan)	1b	B	+
Anthrazyklin-haltiger adjuvanter Therapie bei TNBC	5	D	+/-
Hinzunahme von 5-Fluorouracil zu EC / AC-Pac	1b	A	--

* DPYD Genotypisierung zum Ausschluss einer DPD Defizienz erforderlich

** Studienlage bei Stadium II-III ohne Platin/Pembrolizumab-basierte Vortherapie

Van Mackelenbergh M et al., Eur J Cancer 2022

Effects of capecitabine as part of neo- / adjuvant chemotherapy
Meta-analysis of individual patient data from 12 randomized trials (n = 15,457)

HR for DFS overall 0.952 (95%-C.I. 0.895-1.012, p = 0.115)
X add. 0.888 (95%-C.I. 0.817-0.965, p = 0.005)
X instead 1.035 (95%-C.I. 0.945-1.134, p = 0.455)

HR for OS overall 0.892 (95%-C.I. 0.824-0.965, p = 0.005)
X add. 0.837 (95%-C.I. 0.751-0.933, p = 0.001)
X instead 0.957 (95%-C.I. 0.853-1.073, p = 0.450)

Significance only for TNBC overall DFS 0.886 (95%-C.I. 0.789-0.994, p = 0.040)
OS 0.828 (95%-C.I. 0.720-0.952, p = 0.008)
X add.: DFS 0.818 (95%-C.I. 0.713-0.938, p = 0.004)
OS 0.778 (95%-C.I. 0.657-0.921, p = 0.004)

Adjuvante HER2-gerichtete Therapie

Guidelines Breast
Version 2024.1D

	Oxford LoE	Oxford GR	Oxford AGO
Trastuzumab + Pertuzumab			
pN+	1b	B	++
pN-	1b	B	+/-
Neratinib			
1 Jahr nach 1 Jahr Trastuzumab (HR-positiv, Stadium II-III)	1b	B	+
1 Jahr nach Trastuzumab / Pertuzumab / T-DM1 (HR-positiv, Stadium II-III)	5	D	+/-

(Neo-)Adjuvante Therapie mit Trastuzumab / Pertuzumab

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
Beginn der Therapie			
▪ Simultan mit Taxanen	1a	A	++
▪ Sequentiell bis zu 3 Monaten nach Chemotherapie	1b	B	+
Dauer			
▪ Für 1 Jahr	1a	A	++
▪ Für 0,5 Jahre (Trastuzumab)	1a	A	+
▪ Für 2 Jahre	1b	A	-

(Neo-)Adjuvante Therapie mit Trastuzumab +/- Pertuzumab: Chemotherapieregime

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
Trastuzumab simultan mit			
▪ Paclitaxel / Docetaxel nach AC / EC	1a	A	++
▪ P q1w 12 x bei pT < 2 cm, pN0	2b	B	+
▪ Docetaxel und Carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultan mit			
▪ Mit Paclitaxel q1w (oder Docetaxel q3w) nach EC / AC	1b	B	++
▪ Mit Docetaxel + Carboplatin	1b	B	++
▪ Mit Taxan dosis-dicht	2b	B	+
Radiotherapie simultan zu Trastuzumab / Pertuzumab	1a	A	++

Postneoadjuvante Therapie HR+ / HER2-

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
HR positiv (pCR und non-pCR)			
▪ Endokrine Therapie nach Menopausenstatus (s. Kap. 10)	1a	A	++
▪ Abemaciclib für 2 Jahre + endokrine Therapie bei hohem Rezidivrisiko[1]	1b	B	+
▪ Olaparib für 1 Jahr + endokrine Therapie (g*BRCA1/2*^{MUT}, bei non-pCR und CPS-EG Score ≥ 3)[2]	1b	A	++
▪ Capecitabin (bei non-pCR)	1b	A	+/-

1 entsprechend Einschlußkriterien der monarchE-Studie

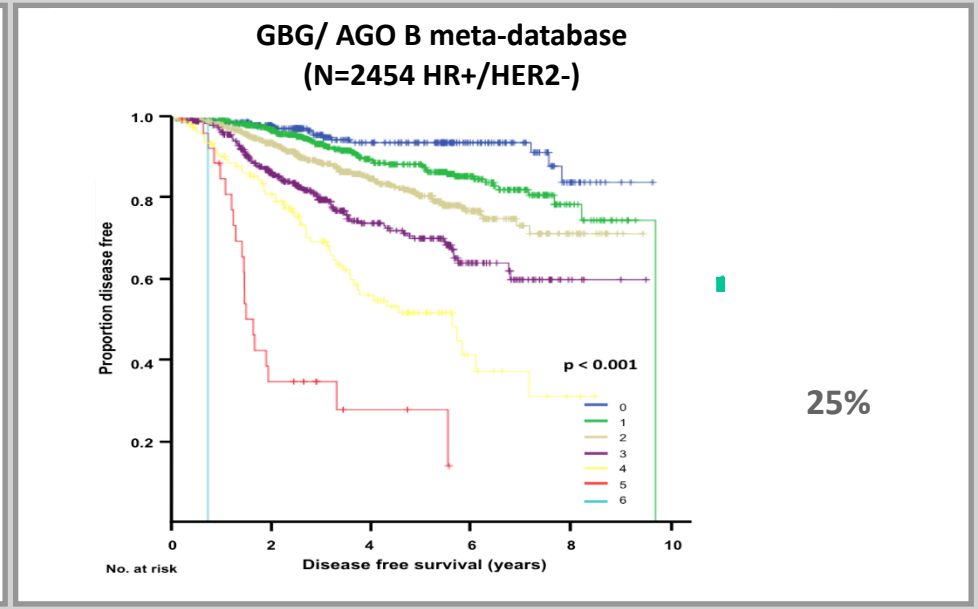
2 entsprechend Einschlußkriterien der OlympiA-Studie

How to calculate CPS+EG Score?

Guidelines Breast
Version 2024.1D

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
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
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



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

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

Guidelines Breast
Version 2024.1D

	monarchE	PALLAS	PENELOPE[B]	NATALLEE
N	5,637	5,600	1,250	5101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	88%
Duration of CDK4/6i treatment	24 months	24 months	12 mths	36 months
Follow-up	42.0 months	24 months	43 months	33.3 months
Discontinuation rate	28%	42%	20%	35.5%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%	19.5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) $p < 0.0001$	0.96 (0.81-1.14) $p = 0.65$	0.93 (0.74-1.16) $p = 0.525$	0.749 (0,628-0.892) $p = 0.0006$
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

Guidelines Breast
Version 2024.1D

Postneoadjuvante Therapie triple-negativ

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	+
Non-pCR			
▪ Capecitabin (q3w bis zu 8 Kurse)*			
▪ Bei non-pCR nach A-T-haltiger Chemotherapie*	1a	A	++
▪ Bei non-pCR nach Platin +/- Pembrolizumab-haltiger Therapie	5	D	+/-
▪ Platinderivate (Carboplatin oder Cisplatin) q3w	1b	B	+/-
▪ Olaparib (*gBRCA^{MUT}*)[1]	1b	A	++
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	++

[1] entsprechend Einschlußkriterien der OlympiA-Studie, Vorteil v.a. bei platin-freier NACT

* Studienlage bei Stadium II-III ohne Platin/Pembrolizumab-basierte Vortherapie

Postneoadjuvante Therapie HER2-positiv

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
pCR			
▪ Low risk: Trastuzumab (bis 12 Mon. komplett)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+
▪ Neratinib nach 1 Jahr* Trastuzumab (HR-positiv, Stadium II-III)*	2b	B	+/-
non-pCR			
▪ T-DM1	1b	B	++
▪ Trastuzumab + Pertuzumab bei cN+ (bis 12 Mon. komplett)	2b	C	+
▪ Zusätzlich nach 1 Jahr (erweiterte adj. Therapie)			
▪ Neratinib nach Trastuzumab (HR-positiv, Stadium II-III)*	2b	B	+
▪ Neratinib nach anderer anti-HER2-Therapie (HR-positiv, Stadium II-III)*	5	D	+/-

* kombiniert mit Standard endokriner Therapie