



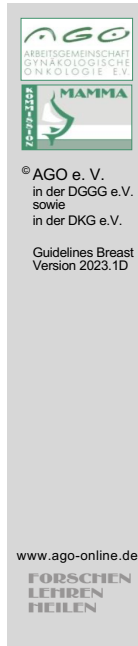
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Guidelines Breast  
Version 2023.1D

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LEHREN  
HEILEN

# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Neoadjuvante (Primäre) systemische Therapie



## Neoadjuvante systemische Therapie

### ■ Versionen 2002–2022:

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 / Thill / Thomssen

### ■ Version 2023:

Fasching / Friedrich

### Systematic review of published evidence

PUBMED 1999-2021

ASCO 1999-2021

SABCS 1999-2021

ECCO/ESMO 1999-2021

## Strategien der differenzierten Systemtherapie in der kurativen Situation

Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugen; Studienteilnahme empfohlen.

AGO

■ HR+ / HER2- mit „niedrigem Rückfallrisiko“	
■ Endokrine Therapie ohne Chemotherapie	++
■ HR+ / HER2- mit „erhöhtem Rückfallrisiko“	
■ endokrine / endokrin-basierte Therapie (Abemaciclib <sup>1</sup> )	++
■ 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-basierte Chemotherapie (inkl. weekly Schemata)	++
■ Neoadjuvante platinhaltige Chemotherapie	+
■ Neoadjuvante platinhaltige Chemotherapie mit ICPI (Pembrolizumab)	+
■ gBRCA1/2 <sup>MUT</sup> (HR+/HER- o. TNBC)	
■ Olaparib <sup>1</sup>	++
■ 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	++

<sup>1</sup>Gemäß Zulassung bzw. Studienpopulation (falls noch nicht zugelassen), \* s. Prognosekapitel

### Systematic review of published evidence

PUBMED 1999-2023

ASCO 1999-2023

SABCS 1999-2023

ECCO/ESMO 1999-2023

### Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010: 375; 377
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011: 29; 3351
3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014: 15; 640
4. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-

3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): in print
4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)
5. Loibl S, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2017;28:497-504
6. Schneeweiss A et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer 89:27-35, 2017
7. Hurvitz SA, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2017. pii: S1470-2045(17)30716-7 [Epub ahead of print]
8. Swain SM, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2017. doi: 10.1093/annonc/mdx773. [Epub ahead of print]
9. Von Minckwitz G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 13;377(2):122-131.

#### Her2+ Antrazyklin-freie Chemotherapie:

1. Ramphorstet MS, van der Voort A, Workhoven ED al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Dec;19(12):1630-1640. doi: 10.1016/S1470-2045(18)30570-9.
2. Anna van der Voort, Mette S. van Ramshorst, Erik D. van Werkhoven et al. J Clin Oncol 38: 2020 (suppl; abstr 501)

#### TNBC neoadjuvant chemotherapy with ICP

1. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.

2. Schmid P, Cortes J, Puztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549.
3. Schmid P, Cortes J, Dent R et al. KEYNOTE-522: Phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment for early triple-negative breast cancer (TNBC). ESMO 2021 Abstract #VP7\_2021

#### Abemaciclib:


1. Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14. PMID: 34656740.
2. Johnston SRD, Toi M, O'Shaughnessy J et al.; monarchE Committee Members. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023 Jan;24(1):77-90.

#### Olaparib

1. Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848.
2. Geyer CE Jr, Garber JE, Gelber RD et al.; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer. Ann Oncol 2022;33(12):1250-1268

#### Platin salts:

1. Geyer CE, Sikov WM, Huober J et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384-394.
2. van Mackelenbergh MT, Seither F, Möbus V et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy - A meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. Eur J Cancer 2022; 166: 185-201
3. Gupta S, Nair NS, Hawaldar RW et al., Addition of platinum to sequential taxan-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: a phase III randomized controlled trial SABCS 2022, GS5-01



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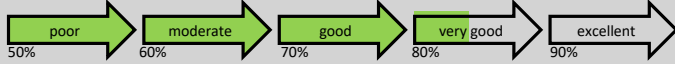
## Lee-Schonberg Index

<https://eprognosis.ucsf.edu/leeschonberg-result.php>

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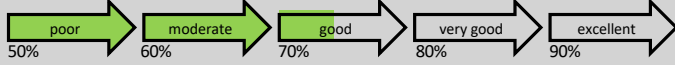
**Lee Index**

- 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.



1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
2. Schonberg MA, Davis RB, McCarthy EP, and Marcantonio ER. Index to predict 5-year mortality of community dwelling adults aged 65 and older using data from the National Health Interview Survey. J Gen Intern Med. 2009;24(10):1115-1022.
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.



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## Lee-Schonberg Index


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**Risk Calculator questions**

1. How old is your patient?
2. What is the sex of your patient?
3. What is your patient's ?
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?

1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
2. Schonberg MA, Davis RB, McCarthy EP, and Marcantonio ER. Index to predict 5-year mortality of community dwelling adults aged 65 and older using data from the National Health Interview Survey. J Gen Intern Med. 2009;24(10):1115-1022.
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.

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	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%
<p>T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab</p>				

1. Hurvitz SA, Miller JM, Dichmann R et al. Final analysis of a phase II 3 arm randomized trial of neoadjuvant trastuzumab or lapatinib or th combination of trastuzumab and lapatinib, followed by six cycles of docetaxel and carboplatin with trastuzumab and/or lapatinib in patients with Her2+ breast cancer (TRIO-US B07). Cancer Res 2013, 73(24 suppl). S1-02.
2. Schneeweiss A, Chia S, Hickish T et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with Her2-positive early breast cancer: a randomised phase II Cardiac safety study (TRYPHAENA) Ann Oncol. 2013 Sep;24(9):2278-84. doi:10.1093/annonc/mdt182.
3. Hurvitz SA, Martin M, Symmans WF et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with Her2-positive breast cancer (KRISTINE): a randomized, open-label, multicentre, phase 3 trial. Lancet oncol, 2018 Jan;19(1):115-126. doi:10.1016/S1470-2045(17)30716-7.
4. Rimawi MF, Cecchini RS, Rastogi P et al. A phase II trial evaluating pCR in patients with HR+ Her-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, pertuzumab (TCHP) +/- estrogen deprivation: NRG Oncology/NSABP B-52 Cancer Res 2017;77(4 suppl):S3-06.
5. Van Ramshorst MS, van der Voort A, van Werkhoven ED et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual Her2 blockade for Her2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. Dec;19(12):1630-1640; doi:10.1016/S1470-2045(18)30570-9.



## Neoadjuvante systemische Chemotherapie – Klinischer Benefit

	Oxford	
	LoE	GR
▪ Ermöglicht eine Prognoseverbesserung durch Individualisierung der neoadjuvanten und post-neoadjuvanten Behandlung (insb. bei HER2 pos und TNBC)	1b	A
▪ Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie (bei gleichem Regime und gleicher Zyklenzahl, wenn die postneoadjuvante Therapie nicht anhand des pathologischen Ansprechens stratifiziert wird)	1a	A
▪ Pathologische Komplettremission ist mit einem besseren Überleben assoziiert	1b	A
▪ Kann Operabilität bei primär inoperablen Tumoren erreichen	1b	A
▪ Verbessert die Optionen für eine brusterhaltende Operation	1b	A
▪ Senkt die Rate an axillären Lymphonodektomien	2b	B
▪ Erlaubt Individualisierung der Therapie nach dem Interims-Ansprechen	1b	B

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)

1. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16; 2672
2. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19; 4224
3. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26; 778
4. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol Lancet Oncol. 2018 Jan;19(1):27-39.

Pathological complete response is associated with improved survival in all subgroups

1. von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796
2. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16; 2672
3. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for

Research and Treatment of Cancer trial 10902. J Clin Oncol 2001: 19; 4224

4. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008: 26; 778
5. EBCTCG. Long-term outcomes for neoad
6. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
7. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32; 3883
8. Yee D, et al. Pathological complete response predicts event-free and distant disease free survival in the I-SPY 2 Trial. SABCS 2017 (abs GS3-08)

#### Can achieve operability in primary inoperable tumors

1. Makhoul I, et al. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011: 103; 348
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

#### Improved options for breast conserving surgery

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

#### Reduces the rate of lymphadenectomies

1. Fernandez-Gonzalez S, et al. The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures. Clin Breast Cancer 2018 Feb;18(1):71-77.
2. Reimer T et al. Avoiding axillary sentinel node biopsy after neoadjuvant systemic therapy in breast cancer: rationale for the prospective, multicentric EUBREAST-01 trial. Cancers 2020;3698; doi:10.3390/cancers12123698

#### Allows individualization of therapy according to mid-course treatment effect

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in

various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796

Allows individualization of post-neoadjuvant treatment

1. von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796
2. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014; 32, 3883
3. Marmé F, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 53:65-74, 2016
4. Symmans WF, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol 35(10):1049-1060, 2017
5. Loibl S, et al. Risk Assessment after Neoadjuvant Chemotherapy in Luminal Breast Cancer Using a Clinicomolecular Predictor. Clin Cancer Res. 2018;24(14):3358-3365.
6. Masuda N, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 376, 2147–2159, 2017
7. von Minckwitz G, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-628.

## Neoadjuvante systemische Chemotherapie – Indikationen

	Oxford		
	LoE	GR	AGO
▪ Wenn die gleiche postoperative adjuvante Chemotherapie indiziert ist	1b	A	++
▪ Um eine risikoadaptierte postoperative Therapie durchzuführen (insbesondere bei HER2 pos und TNBC)	1b	A	++
▪ Inflammatorisches Mammakarzinom	2b	B	++
▪ Inoperables Mammakarzinom	1c	A	++
▪ Große operable Mammakarzinome, die primär eine Mastektomie und adjuvante Chemotherapie erfordern, mit dem Ziel der Brusterhaltung	1b	B	++

### Inflammatory breast cancer

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

### Inoperable breast cancer

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

### Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant

systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

3. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018 Jan;19(1):27-39.

If similar postoperative adjuvant chemotherapy is indicated

1. Untch M, et al. Neoadjuvant chemotherapy: early response as a guide for further treatment: clinical, radiological, and biological. J Natl Cancer Inst Monogr 2011: 43; 138
2. Loibl S, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012: 13 ; 887

## Neoadjuvante Chemotherapie (NACT)

### Prädiktive Faktoren für pCR I

Faktor	pCR* Wahrscheinlichkeit	LoE	Oxford GR	AGO
▪ Junges Alter	↑	1a	A	+
▪ Adipositas	↓	2a	B	+
▪ cT1 / cT2-Tumoren o. N0 o. G3	↑↑	1a	A	++
▪ Negativer ER- und PR-Status	↑↑	1a	A	++
▪ Triple negative (TNBC)	↑↑	1a	A	++
▪ Positiver HER2-Status	↑↑	1a	A	++
▪ Frühes klinisches Ansprechen	↑	1b	A	+
▪ Invasives lobuläres Karzinom	↓	1a	A	+
▪ Metaplastisches Karzinom	↓↓	4	C	+

\* Hohe (↑) oder sehr hohe (↑↑) Wahrscheinlichkeit einer pCR, niedrigere (↓) oder sehr niedrige (↓↓) Wahrscheinlichkeit einer pCR  
 Siehe auch Kapitel „Prognostische und prädiktive Faktoren“

#### General evidence

1. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384: 164-72.
2. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol 2013;24: 2978-84.
3. van Mackelenbergh MT, Denkert C, Nekljudova V, et al. Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. Breast Cancer Res Treat 2017.
4. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366: 299-309.
5. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30: 1796-804.

#### Body mass index

1. Wang H, Zhang S, Yee D, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a meta analysis. Breast Cancer 2021;28(3):616-629

#### Lobular cancer

1. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. *Breast Cancer Res Treat* 2014;144: 153-62.

#### Metaplastic breast cancer

1. McMullen ER, Zoumberos NA, Kleer CG. Metaplastic Breast Carcinoma: Update on Histopathology and Molecular Alterations. *Arch Pathol Lab Med*. 2019 Dec;143(12):1492-1496.
2. Tzanninis IG, Kotteas EA, Ntanasis-Stathopoulos I et al. Management and Outcomes in Metaplastic Breast Cancer. *Clin Breast Cancer*. 2016 Dec;16(6):437-443.
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## Neoadjuvante Chemotherapie (NACT) Prädiktive Faktoren für pCR II

Faktor	pCR* Wahrscheinlichkeit	Oxford		
		LoE	GR	AGO
■ <b>Genexpressions-Profil (Gensignaturen)</b> (Mammaprint®, Endopredict®, Oncotype DX®, Prosigna®, Breast Cancer Index <sup>SM</sup> )	↑	2b	B	+/-
■ <b>Ki-67</b>	↑	2b	B	+
■ <b>Tumor-infiltrierende Lymphozyten**</b>	↑	2a	B	+
■ <b>PIK3CA Mutation (für HER2-positives MaCa)</b>	↑	2a	B	+/-
■ <b>gBRCA Mutation (für Effekt der Chemotherapie)</b>	↑	2b	B	+
■ <b>gBRCA Mutation (für Platin-Effekt)</b>	↔	2b	B	+/-

\* Hohe (↑) oder sehr hohe (↑↑) Wahrscheinlichkeit einer pCR, niedrigere (↓) oder sehr niedrige (↓↓) Wahrscheinlichkeit einer pCR  
 \*\* Definiert als dichte lymphozytäre Infiltration des inneren peritumoralen Stromas außerhalb der Invasionsfront  
 (Stroma besteht mit > 50 % aus Lymphozyten)

### TIL

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## Neoadjuvante systemische Chemotherapie

### Empfohlene Schemata

	Oxford		
	LoE	GR	AGO
▪ Analog zu adjuvanten Standardschemata*	1a	A	++
▪ Taxan mono gefolgt von Anthrazyklin (umgekehrte Reihenfolge)	4	D	+/-
▪ Platinsalze beim TNBC (cT1 / cN0) (unabh. des BRCA-Status)	1b	A	+
▪ Platinsalze beim TNBC (ab cT1 / cN+ o. cT2) (unabh. des BRCA-Status)	1a	A	+
▪ Nab-Paclitaxel qw anstatt Paclitaxel q1w (bei TNBC)	1a	A	+
▪ Pembrolizumab in Kombination mit Carbo / Paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

\* Siehe Kapitel adjuvante Chemotherapie  
 \*\* > 2 cm oder cN+, PD-L1 unabhängig

#### Use of adjuvant standard regimens for NACT

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## Empfohlene Schemata beim triple-negativen Mammakarzinom

	Oxford		
	LoE	GR	AGO
<b><u>Nicht-platinhaltige Regime</u></b>			
▪ ddEC x 4 → Pacli <sub>80</sub> q1w x 12	1b	B	++
▪ NabPac <sub>125</sub> q1w x 12 → E <sub>90</sub> C q2(3)w x 4	1b	B	+/-
<b><u>Platinhaltige Regime</u></b>			
▪ NabPac <sub>125</sub> / Carbo <sub>AUC 2</sub> q1w x 8 → ddEC x 4	1b	B	+
▪ Pacli <sub>80</sub> q1w x 12 / Carbo <sub>AUC 6</sub> q3w x 4 → ddAC / ddEC x 4	1b	B	+
▪ Docetaxel / Carbo <sub>AUC 6</sub> q3w x 6 oder Paclitaxel/Carbo <sub>AUC 1,5</sub> q1w x 18	2b	B	+
▪ NabPac <sub>100</sub> / Carbo <sub>AUC 6</sub> q4w x 4	2b	C	+
<b><u>Checkpoint-Inhibitoren</u></b>			
▪ Pembro <sub>200</sub> q3w + Pac <sub>80</sub> / Carbo <sub>AUC 1,5</sub> q1w x 12 → E <sub>90</sub> C q3w x 4	1b	B	+
▪ Pembro <sub>200</sub> q3w + Pac <sub>80</sub> q1w x 12 / Carbo <sub>AUC 5</sub> q3w → E <sub>90</sub> C q3w x 4	1b	B	+

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### ICPi in combination with chemotherapy

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### Statement carboplatin

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ICPi plus Neoadjuvant Chemotherapy for Triple Negative Breast Cancer Patients				
	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 (1 y)	Pembrolizumab (1 y)	Atezolizumab (24 weeks)
Chemo	NabPac <sub>125</sub> q1w x12 → EC q2w x4	NabPac <sub>125</sub> q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 → AC/EC q3w x4	NabPac <sub>125</sub> + 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% vs. 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%	---



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LEHREN  
HEILEN

1. Loibl S, Untch M, Burchardi N et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279-1288. doi: 10.1093/annonc/mdz158.
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negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study: SABCS 2019 GS3-04

## Neoadjuvante systemische Therapie Empfohlene Methoden zur Überprüfung des Ansprechens

- **Mammasonographie**
- **Palpation**
- **Mammographie**
- **MRT**
- **PET(-CT)**
- **Prätherapeutische Markierung der Tumorregion**
- **Prätherapeutische diagnostische Sicherung (core needle biopsy) und Markierung im Falle von cN+ (CNB) (wenn TAD geplant bei ≤ 3 suspekten Lymphknoten)**

Oxford		
LoE	GR	AGO
2b	B	++
2b	B	++
2b	B	++
2b	B	+
2b	B	+/-
5	D	++
2b	B	++*

(CNB: core needle biopsy; TAD: targeted axillary dissection;  
 \*Studienteilnahme empfohlen (AXSANA /Eubrest 3 – Studie)

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#### Mammography

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## Neoadjuvante zielgerichtete Therapie bei HER2-positiven Tumoren

	Oxford		
	LoE	GR	AGO
▪ <b>Pertuzumab + Trastuzumab in Kombination mit Chemotherapie (high-risk bei cT2-4 und / oder cN+)</b>	<b>2b</b>	<b>B</b>	<b>++</b>
▪ <b>Trastuzumab in Kombination mit Standard-Kombinations-Chemotherapie (low-risk)*</b>	<b>1b</b>	<b>A</b>	<b>+</b>
▪ <b>HER2 gerichtete Substanzen ohne Chemotherapie</b>	<b>2b</b>	<b>B</b>	<b>+/-</b>

\* Trastuzumab + Monochemotherapie bevorzugt in der adjuvanten Therapie einzusetzen

### Review

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### Pertuzumab + Trastuzumab in combination with chemotherapy

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## Neoadjuvante Chemotherapie – Vorgehen je nach Ansprechen

	Oxford		
	LoE	GR	AGO
<b>Frühes Therapieansprechen:</b>			
▪ Fortführung der neoadjuvanten Therapie	1b	A	++
<b>Bei keiner Änderung:</b>			
▪ Komplettierung der NACT, anschl. Operation	2b	C	++
▪ Fortsetzen der NACT mit einem nicht-kreuzresistenten Schema	2b	B	+
▪ AC oder EC x 4 → D x 4 oder Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
<b>Bei Progression:</b>			
▪ Reevaluation der Tumorbiologie	5	D	+/-
▪ Abbruch der NACT und Operation oder Bestrahlung	4	D	++
▪ Zusätzliche adj. Chemotherapie mit nicht-kreuzresistenten Schemata	4	D	+/-

### Completion of neoadjuvant chemotherapy

1. Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001; 19; 3506
2. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008; 100; 542
3. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008; 100; 552
4. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

### In case of no change:

### Completion of NACT, followed by surgery

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

2. Smith IC, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002; 20; 1456
3. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008; 100; 542
4. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013; 31; 3623-30

#### Continuation of NST with non-cross-resistant regimen

##### AC or EC x 4->D x 4 or Pw x 12

1. Bear HD, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003; 21; 4165
2. Bear HD, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006; 24; 2019

##### DAC2x -> NX x 4

1. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013; 31; 3623-30

#### In case of progressive disease:

##### Stop of NACT and immediate surgery or radiotherapy

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

Additional adjuvant chemotherapy with non-cross-resistant regimen

1. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 29, 1956, 2011
2. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07
3. Colleoni M, Gray KP, Gelber S et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.

## Axilläre operative Interventionen bei NACT (cN0)

							Oxford		
							LoE	GR	AGO
cN-Status (vor NACT)	pN-Status (vor NACT)	ycN-Status (nach NACT)	Axilläre operative Intervention (nach NACT)	AGO	ypN-Status (nach NACT und Operation)	Operative Konsequenz aus Histobefund			
cN0*	Keine OP vor NACT	ycN0	SLNE	++	ypN0 (sn)	Keine	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

\* Studienbeteiligung an EUBREAST-01 empfohlen

1. Giuliano AE, Ballman KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The acosog z0011 (alliance) randomized clinical trial. JAMA 2017, 318, 918-926
2. Reimer TS, Nekljudova V, Loibl, S et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/i t1-2) in the context of breast conserving therapy: First results following commencement of the intergroup-sentinel-mamma (insema) trial. Geburtsh Frauenheilk 2017, 77, 149-157
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Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. *Eur J Cancer* 2020, 130, 92-101.

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Statement: SLNE after NACT

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Axilläre operative Interventionen bei NACT (cN+)							Oxford		
							LoE	GR	AGO
cN-Status (vor NACT)	pN-Status (vor NACT)	ycN-Status (nach NACT)	Axilläre operative Intervention (nach NACT)	AGO	ypN-Status (nach NACT und Operation)	Operative Konsequenz aus Histobefund			
cN+*	pN+ <sup>CNB</sup>	ycN0	ALND	+	ypN0 / ypN+	Keine	2b	B	++
			TAD	+	ypN0	Keine	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	Keine	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	keine	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	Keine	2b	B	++

\* Studienbeteiligung an AXSANA empfohlen; \*\*Cave: In 30,3% falsch-positive Befunde, ggf. CNB

- Giuliano AE, Ballman KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The acosog z0011 (alliance) randomized clinical trial. JAMA 2017, 318, 918-926
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18. Samiei, S.; van Nijnatten, T.J.A.; de Munck, L.; et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. *Ann Surg* 2018.
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for the eubreast-03 axsana study. *Cancers* 2021, 13.

21. Hartmann, S.; Kühn, T.; de Boniface, J.; et al. Carbon tattooing for targeted lymph node biopsy after primary systemic therapy in breast cancer: Prospective multicentre tattoo trial. *Br J Surg* 2021.
22. Barrio, A.V.; Montagna, G.; Mamtani, A.; et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-a rare event. *JAMA oncology* 2021.
23. Wong S.M.; Almana N.; Choi J.; et al. Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer. *Ann Surg Oncol* 2019, 26:3502-3509.
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25. Boughey, J.C.; Ballman, K.V.; Hunt, K.K.; et al. Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: Results from the american college of surgeons oncology group z1071 trial (alliance). *J Clin Oncol* 2015, 33, 3386-3393.
26. Schwentner, L.; Helms, G.; Nekljudova, V.; et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - results from the multi-center sentina trial. *Breast* 2017, 31, 202-207.
27. Le-Petross, H.T.; McCall, L.M.; Hunt, K.K.; et al. Axillary ultrasound identifies residual nodal disease after chemotherapy: Results from the american college of surgeons oncology group z1071 trial (alliance). *AJR Am J Roentgenol* 2018, 210, 669-676.
28. Kim, W.H.; Kim, H.J.; Park, H.Y.; et al. Axillary pathologic complete response to neoadjuvant chemotherapy in clinically node-positive breast cancer patients: A predictive model integrating the imaging characteristics of ultrasound restaging with known clinicopathologic characteristics. *Ultrasound in medicine & biology* 2019, 45, 702-709.
29. Liedtke, C.; Gorlich, D.; Bauerfeind, I.; et al. Validation of a nomogram predicting non-sentinel lymph node metastases among patients with breast cancer after primary systemic therapy - a transsentina substudy. *Breast Care (Basel)* 2018, 13, 440-446.
30. Moo, T.A.; Jochelson, M.S.; Zabor, E.C.; et al. Is clinical exam of the axilla sufficient to select node-positive patients who downstage after nac for slnb? A comparison of the accuracy of clinical exam versus mri. *Ann Surg Oncol* 2019, 26, 4238-4243.
31. Kantor, O.; Sipsy, L.M.; Yao, K.; et al. A predictive model for axillary node pathologic complete response after neoadjuvant chemotherapy for breast cancer. *Ann Surg Oncol* 2018, 25, 1304-1311.

#### Statement: SLNE after NACT

1. El Hage Chehade H, Headon H, El Tokhy O et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving

3,398 patients. Am J Surg. 2016 Nov;212(5):969-981.

Statement: False-positives in ALND after ycN+

1. Hartmann S, Kühn T, Hauptmann M et al., Axillary staging after neoadjuvant chemotherapy for initially node-positive breast carcinoma in Germany. Geburtsh Frauenheilk 2022, online

Statement: TLNE alone:

1. Swarnkar PK, Tayeh S, Michell MJ et al., The Evolving Role of Marked Lymph Node Biopsy (MLNB) and Targeted Axillary Dissection (TAD) after Neoadjuvant Chemotherapy (NACT) for Node-Positive Breast Cancer: Systematic Review and Pooled Analysis. Cancers (Basel) 2021; 13(7):1539

## Neoadjuvante systemische Therapie

### Lokoregionäre Operation (Mamma)

	Oxford		
	LoE	GR	AGO
■ Prätherapeutische Vorstellung im Tumorboard (z. B. zur Festlegung des OP-Verfahrens)	1a	B	++
■ Frühzeitige Markierung des Tumors mit exakter topographischer Dokumentation	5	D	++
■ Resektion des Tumors / repräsentative Exzision des posttherapeutischen, markierten Tumorareals	2b	C	++
■ Exzision in neuen Tumorgrenzen	2b	C	++
■ Freie Resektionsränder	2a	B	++

#### Pretherapeutic definition of the definitive surgical procedure

1. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018 Jan;19(1):27-39.
2. Bossuyt V, Symmans WF. Standardizing of Pathology in Patients Receiving Neoadjuvant Chemotherapy. Ann Surg Oncol. 2016 Oct;23(10):3153-61.
3. Zdenkowski N et al. A survey of Australian and New Zealand clinical practice with neoadjuvant systemic therapy for breast cancer. Intern Med J. 2016 Jun;46(6):677-83.

#### Mark previous tumor region

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

#### Surgery

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

#### Microscopically clear margins

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

#### Tumor resection according to imaging result

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer.. Ann Surg Oncol 2012; 19; 1508

## Neoadjuvante systemische Therapie

### Indikationen für Mastektomie

	Oxford		
	LoE	GR	AGO
■ Positive Absetzungsränder trotz mehrfacher Nachresektion	3b	C	++
■ Radiotherapie nicht durchführbar	5	D	++
■ Bei einer klinisch kompletten Remission			
■ Inflammatorisches Mammakarzinom (bei pCR)	2b	C	+/-
■ Multizentrisches Mammakarzinom	2b	C	+/-
■ cT4a-c Mammakarzinom	2b	B	+/-

#### Positive margins after repeated excisions

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22; 515

#### Radiotherapy not feasible

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

#### In case of clinical complete response:

##### Inflammatory breast cancer in case of pCR

1. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22; 515
2. Brzezinska M, Williams LJ, Thomas J et al.: Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. Breast Cancer Res Treat 2016;160(3):387-91.

#### Multicentric lesions

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014 [Epub ahead of print]

#### cT4a-c breast cancer

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014

## Neoadjuvante systemische Therapie Zeitablauf von Diagnosestellung, Operation und Radiotherapie

	Oxford		
	LoE	GR	AGO
<b>Therapiebeginn der NACT</b>	<b>2b</b>	<b>B</b>	<b>+</b>
<ul style="list-style-type: none"> <li>Therapieverzögerungen führen zu einer Prognoseverschlechterung</li> </ul>			
<b>Zeitpunkt der Operation nach NACT</b>			
<ul style="list-style-type: none"> <li>4-8 Wochen nach dem letzten Chemotherapiezyklus</li> </ul>	<b>2a</b>	<b>B</b>	<b>++</b>
<b>Radiotherapie innerhalb von 2 Monaten nach der Operation</b>	<b>2b</b>	<b>B</b>	<b>++</b>

### Initiation of chemotherapy after histologic diagnosis

1. de Melo Gagliato D, Lei X, Giordano SH, et al. Impact of Delayed Neoadjuvant Systemic Chemotherapy on Overall Survival Among Patients with Breast Cancer. *Oncologist*. 2020;25(9):749-757. doi: 10.1634/theoncologist.2019-0744.
2. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. 2020;371:m4087. <http://dx.doi.org/10.1136/bmj.m4087>

### Time between surgery and last chemotherapy

1. Cullinane C, Shrestha A, Al Maksoud A, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: A systematic review and meta-analysis. *J Surg Oncol*. 2021 Jul;47(7):1507-1513.
2. Suleman K, Almalik O, Haque E et al. Does the Timing of Surgery after Neoadjuvant Therapy in Breast Cancer Patients Affect the Outcome? *Oncology*. 2020;98(3):168-173.
3. Grubstein A, Rapson Y, Stemmer SM et al. Timing to imaging and surgery after neoadjuvant therapy for breast cancer. *Clin Imaging*. 2020;71:24-28..
4. Sanford RA, Lei X, Barcenas CH et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. *Ann Surg Oncol* 2016;23(5):1515-21.



Radiotherapy 2 mths after surgery BCS

1. Silva SB, Pereira AAL, Marta GN, et al. Clinical impact of adjuvant radiation therapy delay after neoadjuvant chemotherapy in locally advanced breast cancer. Breast. 2018;38:39-44. doi: 10.1016/j.breast.2017.11.012

## Neoadjuvante endokrine Therapie (NET) - Gute klinische Praxis -

- **Geeignet für Patientinnen, die**
  - inoperabel sind.
  - keine Chemotherapie haben möchten / können.
- **Datenlage in der Prämenopause im Gegensatz zur Postmenopause begrenzt.**
- **Die optimale Dauer der endokrinen Therapie ist mind. 4-6 Monate oder bis best response bzw. Progress.**
- **Die Wahl der endokrinen Therapie richtet sich nach dem Menopausenstatus.**
- **Eine Ki-67 Analyse nach zwei- bis vierwöchiger, präoperativer endokriner Therapie kann das Ansprechen auf eine endokrine Therapie vorhersagen (prognostische / prädiktive Evaluation).**

1. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
2. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. JAMA Oncol. 2021 Nov 1;7(11):1700-1708.
3. Harbeck N. Adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.
4. Harbeck N, Gluz O, Kümmel S et al., Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020 GS4-04.
5. Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial. Lancet Oncol. 2020 Nov;21(11):1443-1454
6. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov;12:1758835920973130
7. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed

guidelines. Breast Cancer Res. 2020 Jul 20;22(1):77.

8. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. PLoS One. 2018;13(8):e0201846.
9. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017;35(10):1061–9
10. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.
11. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339

## NET bei Patienten mit endokrin-sensitivem Mammakarzinom

	Oxford		
	LoE	GR	AGO
■ <b>Postmenopausale Patienten</b>			
■ Verbessert die Optionen für brusterhaltende Operationen	1b	A	+
■ Aromataseinhibitoren (mindestens 6 Monate)	1a <sup>a</sup>	B	+
■ Aromataseinhibitor + Lapatinib (HER2+ Mammakarzinom)	2b	B	+/-
■ <b>Prämenopausale Patientinnen</b>			
■ Tamoxifen	2b	C	+
■ Aromataseinhibitoren + LHRHa	1b	C	+/-
■ <b>Simultane chemo-endokrine Therapie</b>	1b	A	-
■ Ki-67 Analyse nach kurzer (2-4 W.) präoperativer endokriner Therapie (Tam/AI +/-GnRHa) (prognost./prädikt. Information)	1b	B	+
■ <b>Prognostischer Score:</b>	1b	B	+
■ PEPI: pTN-Stadium, ER-Expression und Ki-67 Expression nach neoadjuvanter endokriner Therapie			

<sup>a</sup> Keine Langzeitergebnisse zur neoadjuvanten endokrinen Therapie (vs. adjuvante endokrine Therapie)

### Postmenopausal patients:

#### Aromatase inhibitors (for up to 6 months)

1. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23; 5108
2. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339
3. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011; 29; 2342
4. Spring LM et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.
5. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed guidelines. Breast Cancer Res. 2020 Jul 20;22(1):77. doi: 10.1186/s13058-020-01314-6

### AI and fulvestrant

1. Lerebours F, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer. 2016 Oct;122(19):3032-40.

#### Concurrent chemo-endocrine therapy

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339 Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001; 15; 3506
2. Fontein DB, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. Eur J Cancer 2014; 50; 2190
3. Rimawi M, et al. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG oncology/NSABP B-52. San Antonio Breast Cancer Symposium 2016:Abstract S3-06.
4. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.

#### Preoperative ET and Ki67 measurement:

1. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
2. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. JAMA Oncol. 2021 Nov 1;7(11):1700-1708.
3. Harbeck N. Adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.
4. Harbeck N, Gluz O, Kümmel S et al., Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020 GS4-04.
5. Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial. Lancet Oncol. 2020 Nov;21(11):1443-1454

6. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. *Ther Adv Med Oncol*. 2020 Nov23;12:1758835920973130
7. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed guidelines. *Breast Cancer Res*. 2020 Jul 20;22(1):77.
8. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. *PLoS One*. 2018;13(8):e0201846.
9. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol*. 2017;35(10):1061–9
10. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2016 Nov 1;2(11):1477-1486.
11. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. *Breast* 2009; 18; 339

#### Prognostic scores following NST

1. Ellis MJ et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst*. 2008;100(19):1380–8.
2. Marmé F, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. *Eur J Cancer* 53:65-74, 2015
3. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol*. 2017;35(10):1061–9
4. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. *PLoS One*. 2018;13(8):e0201846.

## Postneoadjuvante Therapie HR+ / HER2-

	Oxford		
	LoE	GR	AGO
<b>HR positiv (pCR und non-pCR)</b>			
▪ Endokrine Therapie nach Menopausenstatus (s. Kap. 10)	1a	A	++
▪ Abemaciclib für 2 Jahre + endokrine Therapie bei hohem Rezidivrisiko <sup>1</sup>	1b	B	+
▪ Olaparib für 1 Jahr + endokrine Therapie (gBRCA1/2 <sup>MUT</sup> , bei non-pCR und CPS-EG Score ≥ 3) <sup>2</sup>	1b	A	++
▪ Capecitabin (bei non-pCR)	1b	A	+/-

<sup>1</sup> entsprechend Einschlusskriterien der monarchE-Studie

<sup>2</sup> entsprechend Einschlusskriterien der OlympiA-Studie

### Statement ER and/or PgR positiv (pCR und non-pCR) Endokrine Therapie nach Menopausenstatus (s. Kap. 10)

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14-20;365(9472):1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-1352.

### Statement CDK4/6 inhibitors

1. Harbeck N, Rastogi P, Martin M, et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581.
2. Martin M, Hegg R, Sung-Bae K, et al., Abemaciclib combined with adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC). J Clin Oncol 2021;39(15 suppl): abstract 517
3. Gnant M, Dueck AC, Frantal S, et al.; PALLAS groups and investigators. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7;JCO2102554.
4. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2021 Feb;22(2):212-222.
5. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-

The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518-1530.

6. O'Shaughnessy JA, Johnston S, Harbeck N et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. SABCS 2020:GS1-01.
7. Johnston SRD, Harbeck N, Hegg R et al.; monarchE Committee Members and Investigators Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998.
8. Harbeck N, Rastogi P, Martin M et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581.
9. Johnston SRD, Toi M, O'Shaughnessy J et al.; monarchE Committee Members. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023 Jan;24(1):77-90.
10. Toi M, Boyle F, Im YH et al. Adjuvant Abemaciclib Combined with Endocrine Therapy: Efficacy Results in monarchE Cohort 1. Oncologist. 2023 Jan 18;28(1):e77-e81.

#### Statement Olaparib gBRCAmt

1. Tutt ANJ, Garber JE, Kaufman B, et al.; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.
2. Geyer CE Jr, Garber JE, Gelber RD et al.; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol 2022;33(12):1250-1268

#### Statement Capecitabine (bei non-pCR; 8 Kurse)

1. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R et al. Adjuvant Capecitabine for Early Breast Cancer: 15-Year Overall Survival Results From a Randomized Trial. J Clin Oncol. 2022 Jan 12;JCO2102054.
2. Lluch A et al. Phase III Trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11\_CIBOMA/2004-01). J Clin Oncol. 2020 Jan 20;38(3):203-213.
3. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun

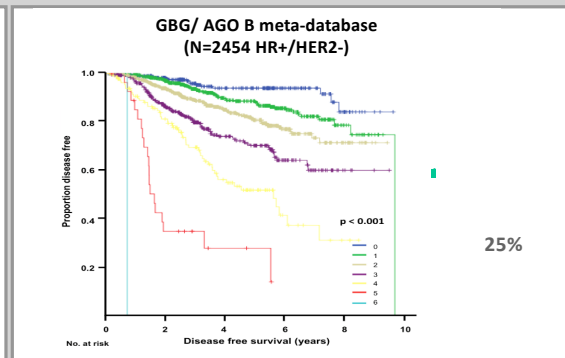


1;376(22):2147-2159.

## How to calculate CPS+EG Score?

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			
	monarchE	PALLAS	PENELOPE <sup>B</sup>
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	42.0 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE <sub>CDKi</sub>	17%	27%	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
2-yr IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%
3-yr IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%
4-yr IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival



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Guidelines Breast  
Version 2023.1D

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FORSCHEN  
LEHREN  
HEILEN

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## Postneoadjuvante Therapie triple-negativ

	Oxford		
	LoE	GR	AGO
<b>pCR</b>			
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	+
<b>Non-pCR</b>			
▪ 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 nach AT-Vorbehandlung	1b	B	+/-
▪ Olaparib ( <i>gBRCA<sup>MUT</sup></i> ) <sup>1</sup>	1b	A	++
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	++

<sup>1</sup> entsprechend Einschlusskriterien der OlympiA-Studie, Vorteil v.a. bei platin-freier NACT  
 \* Studienlage bei Stadium II-III ohne Platin/Pembrolizumab-basierte Vortherapie

### Statement Tripelnegativ (TNBC) (bei non-pCR): Capecitabine (8 Kurse)

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### Pembrolizumab in combination with chemotherapy

1. Schmid P, Cortes J, Pusztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821.

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## Postneoadjuvante Therapie HER2-positiv

### pCR

- Low risk: Trastuzumab (bis 12 Mon. komplett)
- High risk (cN+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)
- Neratinib nach 1 Jahr\* Trastuzumab (HR-positiv, Hochrisiko, z.B. Stadium II-III)\*

### non-pCR

- T-DM1
- Trastuzumab + Pertuzumab bei cN+ (bis 12 Mon. komplett)
- Zusätzlich nach 1 Jahr (erweiterte adj. Therapie)
  - Neratinib nach Trastuzumab (HR+, Hochrisiko, z.B. Stadium II-III)\*
  - Neratinib nach anderer anti-HER2-Therapie (HR-positiv)\*

\* kombiniert mit Standard endokriner Therapie

Oxford		
LoE	GR	AGO
2a	C	++
2b	C	+
2b	B	+/-
1b	B	+
2b	C	+
2b	B	+
5	D	+/-

### Statement HER2 positiv (pCR):

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