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Guidelines Breast  
Version 2025.1E

FORSCHEN  
LEHREN  
HEILEN

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Systemic Therapy of Primary Early Breast Cancer – Triple-negative



## Systemic Therapy of Primary Early Breast Cancer – Triple-negative

### ■ Versions 2002–2024:

Bauerfeind / Blohmer / Costa / Dall / Fasching / 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 2025:

Banys-Paluchowski / Loibl

Systematic review of published evidence

PUBMED 1999-2024

ASCO 1999-2024

SABCS 1999-2024

ECCO/ESMO 1999-2024

## Strategies for Differentiated Systemic Treatment in the Curative Situation

	AGO
<b>If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended</b>	
<ul style="list-style-type: none"> <li>▪ HR+ / HER2- and „low recurrence-risk“               <ul style="list-style-type: none"> <li>▪ Endocrine therapy without chemotherapy</li> </ul> </li> </ul>	++
<ul style="list-style-type: none"> <li>▪ HR+ / HER2- and „high recurrence-risk“               <ul style="list-style-type: none"> <li>▪ endocrine therapy</li> <li>▪ endocrine-based therapy (abemaciclib or ribociclib)</li> <li>▪ Patients with indication for chemo-endocrine therapy*                   <ul style="list-style-type: none"> <li>▪ Conventionally dosed AT-based chemotherapy (q3w)</li> <li>▪ Dose dense chemotherapy (including weekly schedule)</li> </ul> </li> </ul> </li> </ul>	++ + + ++
<ul style="list-style-type: none"> <li>▪ gBRCA1/2mut (HR+ / HER2- or TNBC respectively)               <ul style="list-style-type: none"> <li>▪ Olaparib +/- endocrine therapy</li> </ul> </li> </ul>	++
<ul style="list-style-type: none"> <li>▪ Triple-negative (TNBC)               <ul style="list-style-type: none"> <li>▪ Conventional dosed AT-based chemotherapy (q3w)</li> <li>▪ Sequential AT-based chemotherapy (incl. weekly schedule)</li> <li>▪ Neoadjuvant platinum-containing chemotherapy</li> <li>▪ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)</li> </ul> </li> </ul>	+ ++ + ++
<ul style="list-style-type: none"> <li>▪ HER2+               <ul style="list-style-type: none"> <li>▪ Trastuzumab (plus Pertuzumab in N+ or NACT)                   <ul style="list-style-type: none"> <li>▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy</li> <li>▪ Anthracycline-free, chemotherapy + anti-HER2 therapy</li> </ul> </li> </ul> </li> </ul>	++ ++ ++

\* see prognosis chapter

### Systematic review of published evidence

PUBMED 1999-2024

ASCO 1999-2024

SABCS 1999-2024

ECCO/ESMO 1999-2024

### Trastuzumab in combination with chemotherapy

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1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012; 13; 25-32
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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.
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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.
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Platin salts:

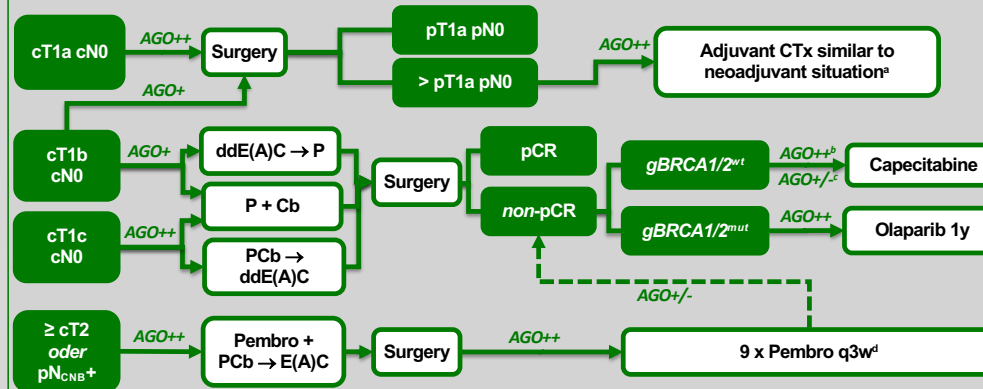
1. Geyer CE, Sikov WM, Huober J et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384-394.
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3. 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
4. III randomized controlled trial SABCS 2022, GS5-01

# Therapy of Triple-negative Early Breast Cancer

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A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; CNB, core needle biopsy; CTx, chemotherapy; dd, dose dense (every 2 weeks); E, epirubicin; gBRCA1/2<sup>wt</sup>, germline BRCA1/2 mutated; gBRCA1/2<sup>wt</sup>, germline BRCA1/2 wild type; pCR, pathological complete response; Pembro, pembrolizumab; P, paclitaxel; y, year; <sup>a</sup>if no change of prognostic factors after surgery; <sup>b</sup>after A/T-containing chemotherapy; <sup>c</sup>after chemotherapy with platinum and/or pembrolizumab; <sup>d</sup>if Pembrolizumab was started before surgery.

## Indication for Chemotherapy +/- Immune Checkpoint Inhibitor Therapy (TNBC)

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li> <b>Clinical node-positive</b> <ul style="list-style-type: none"> <li>Neoadjuvant chemotherapy in combination with pembrolizumab</li> </ul> </li> </ul>	1b	A	++
<ul style="list-style-type: none"> <li> <b>Clinical node-negative</b> <ul style="list-style-type: none"> <li>≥ T2 → Neoadjuvant chemotherapy in combination with pembrolizumab</li> <li>T1c → Neoadjuvant chemotherapy preferred</li> <li>T1b → Neoadjuvant or adjuvant chemotherapy</li> <li>T1a → Adjuvant chemotherapy</li> </ul> </li> </ul>	1b 2b 2b 2b	A B B B	++ ++ + +/-

- Schmid P, Cortes J, Dent R et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. N Engl J Med. 2024 Nov 28;391(21):1981-1991. doi: 10.1056/NEJMoa2409932
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## General principles

	Oxford		
	LoE	GR	AGO
▪ <b>Chemotherapy regimens can be administered in the neoadjuvant and adjuvant setting</b>	1a	A	++
▪ <b>Dose-dense regimens should be preferentially used (if pembrolizumab is not indicated)</b>	1a	A	++
▪ <b>Addition of platinum salts to anthracycline-/taxane-based chemotherapy (cT1 cN0) (irrespective of <i>gBRCA</i> status)</b>	1b	B	+
▪ <b>Addition of platinum salts to anthracycline-/taxane-based chemotherapy (≥ cT2 or cN+) (irrespective of <i>gBRCA</i> status)</b>	1a	A	++
▪ <b>Pembrolizumab in combination with carboplatin / paclitaxel → 4 x EC q3w neoadjuvant and postoperative (≥ cT2 or cN+)</b>	1b	A	++
▪ <b>Olaparib in case of <i>gBRCA</i><sup>m</sup></b> <ul style="list-style-type: none"> <li>▪ Adjuvant: Tumor size ≥ 2 cm or pN+</li> <li>▪ Post-neoadjuvant: non-pCR</li> </ul>	1b	A	++

ICPi therapy in the adjuvant only setting not recommended outside of clinical studies.

### Use of adjuvant standard regimens for NACT

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### Taxane followed by anthracycline sequence

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2. Earl HM, et al. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2x2 factorial randomised phase 3 trial. *Lancet Oncol* 2014; 15; 201
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### Platinum in TNBC (irrespective of BRCA status)

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  4. Petrelli F, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2014; 144; 223
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  6. Byrski T, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. *Breast Cancer Res Treat* 2014; 147; 401
  7. Sikov WM, Berry DA, Perou CM, et al: Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). *J Clin Oncol*, 2014
  8. Loibl S, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):497-509.
  9. Loibl S et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. *Ann Oncol* 2018;29(12):2341-2347
  10. Li ZY, Zhang Z, Cao XZ, et al. Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer: a systematic review and meta-analysis. *J Int Med Res*. 2020 Oct;48(10):300060520964340.
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  12. Bian L, Yu P, Wen J, et al. Survival benefit of platinum-based regimen in early stage triple negative breast cancer: A meta-analysis of randomized controlled trials. *NPJ Breast Cancer*. 2021 Dec 21;7(1):157.
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#### Immune checkpoint inhibitor therapy:

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## Neoadjuvant Chemotherapy Treatment Strategies Based on Clinical Response

	Oxford		
	LoE	GR	AGO
<b>In case of early response</b>			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
<b>In case of no change:</b>			
▪ 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	+
▪ Paclitaxel / carboplatin → EC (q2w or q3w) x 4	1b	B	+
<b>In case of disease progression</b>			
▪ 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	+/-

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## Preferred Regimens in Triple-negative Breast Cancer

	Oxford		
	LoE	GR	AGO
<b><u>Non-platinum-containing regimens</u></b>			
▪ ddEC x 4 → Paclitaxel <sub>80</sub> q1w x 12 (T1 N0)	1b	B	++
<b><u>Platinum-containing regimens</u></b>			
▪ Paclitaxel <sub>80</sub> / Carbo <sub>AUC 1,5</sub> q1w x 12 → ddEC x 4	1b	B	++
▪ Paclitaxel <sub>80</sub> q1w x 12 / Carbo <sub>AUC 5</sub> q3w x 4 → ddAC / ddEC x 4	1b	B	++
▪ Paclitaxel/Carbo <sub>AUC 1,5</sub> q1w x 18 (T1 N0)	2b	B	++
<b><u>Checkpoint inhibitors</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	++

### Non-platin containing chemotherapy

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2. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347. doi: 10.1093/annonc/mdy460.PMID: 30335131

### ICPi in combination with chemotherapy

1. Schmid P, Cortes J, Dent R et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. N Engl J Med. 2024 Nov 28;391(21):1981-1991. doi: 10.1056/NEJMoa2409932. PMID: 39282906
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### Statement Platin

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## Post-neo/Adjuvant Therapy in Triple-negative Breast Cancer

	Oxford		
	LoE	GR	AGO
<b>pCR</b>			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
<b>Non-pCR</b>			
▪ Capecitabine (q3w up to 8 courses) <sup>1</sup>			
▪ In case of non-pCR after A-T-containing chemotherapy <sup>1</sup>	1a	A	++
▪ In case of non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	-
▪ Olaparib ( <i>gBRCA</i> <sup>MUT</sup> ) <sup>2</sup>	1b	A	++
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	++

<sup>1</sup> in stage II-III without platinum/pembrolizumab-based pretreatment

<sup>2</sup> according to inclusion criteria of OlympiA trial

### Capecitabine

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### Pembrolizumab

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## 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%-CI 2.2-6.5)

(RR = 0.83; 95%-CI 0.76-0.91; p < 0.0001)

**Overall survival: 10-y Gain 2.8%** (95%-CI 0.8-4.8)

(RR = 0.86; 95%-CI 0.77-0.96; p = 0.0054)

ER negative: **10-y Gain 4.7%** (95%-CI 2.3-7.1)

ER positive: **10-y Gain 3.1%** (95%-CI 1.5-4.7)

1. Gray R, Bradley R, Braybrooke J et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019;393(10179):1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8



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## 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%-CI 0.895-1.012, p = 0.115)  
X add. 0.888 (95%-CI 0.817-0.965, p = 0.005)  
X instead 1.035 (95%-CI 0.945-1.134, p = 0.455)

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

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

1. 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.



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## ICPi plus Neoadjuvant Chemotherapy for Patients with Triple Negative Breast Cancer

	GeparNuevo	IMpassion031	Keynote 522	neoTRIP	GeparDOUZE/NSABP-B59
Phase	II	III	III	II	III
n	174	333	602 (pCR) 1174 (EFS)	280	1550
Prim. endpoint	pCR	pCR	pCR + EFS	EFS	EFS
ICPi	Durvalumab (24 weeks)	Atezolizumab (1 y)	Pembrolizumab (1 y)	Atezolizumab (24 weeks)	Atezolizumab (1 y)
Chemo	NabPac125 q1w x 12 → EC q2w x 4	NabPac125q1w x 12 → EC q2w x 4	Pac q1w x 12 + carbo q3w AUC 5 or q1w AUC 1.5 → AC/EC q3w x 4	NabPac125 + carbo AUC 2 q1w d1 and d8	Pac q1w x 12 + carbo q3w AUC 5 or q1w AUC 1.5 → AC/EC q2w/3w x 4
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0	cT1cN1-2 or cT2 cN0-2
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)	48.6% vs. 44.4% Δ 4.2% (n.s.)	63.3% vs. 57.0% Δ 6.3%
Follow up/EFS/IDFS (months)/HR EFS/IDFS	43.7 months 3y IDFS: 85.6% vs. 77.2%, HR 0.48 (p = 0.036)	24 months 2y EFS: 85% vs. 80%, HR 0.76 (n.s.)	75.1 months 5y EFS: 81.2% vs. 72.2%, HR 0.65	54 months 5y EFS: 70.6% vs. 74.9%, HR 1.076 (p = 0.76)	47 months 4y EFS: 85.2% vs. 81.9%, HR 0.8; p = 0.08
EFS/IDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% non-pCR 76.3% vs. 69.7%	n.a.	pCR 92.2% vs. 88.2% non-pCR 62.6% vs. 52.3%	n.a.	pCR: 93% vs. 91% non-pCR: 70.5% vs. 68.9%
OS	3y OS: 95.2% vs. 83.5%; HR 0.24; p = 0.006	2y OS: 95% vs. 90%; HR 0.56	5y OS: 86.6% vs. 81.7%; HR 0.65; p = 0.002	n.a.	4y OS: 90.2% vs. 89.5%; HR: 0.86

### GeparNuevo:

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