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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Systemische Therapie des primären, frühen Mammakarzinoms – Triple-negativ



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Systemische Therapie des primären, frühen Mammakarzinoms – Triple-negativ

■ Versionen 2002–2024:

Bauerfeind / Blohmer / Costa / Dall / Fasching / Fehm / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Hober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Stickeler / Untch / Thill / Thomssen

■ Version 2025:

Banys-Paluchowski / Loibl

Strategien der differenzierten Systemtherapie in der kurativen Situation		AGO
Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugen; Studienteilnahme empfohlen.		
<ul style="list-style-type: none"> ▪ HR+ / HER2- mit „niedrigem Rückfallrisiko“ <ul style="list-style-type: none"> ▪ Endokrine Therapie ohne Chemotherapie ▪ HR+ / HER2- mit „erhöhtem Rückfallrisiko“ <ul style="list-style-type: none"> ▪ Endokrine Therapie ▪ Endokrin-basierte Therapie (Abemaciclib oder Ribociclib) ▪ Bei Patientinnen mit Indikation zur chemo-endokrinen Therapie*: <ul style="list-style-type: none"> ▪ Konventionell dosierte AT-basierte Chemotherapie (q3w) ▪ Dosisdichte Chemotherapie (inkl. weekly-Regime) 	 	
<ul style="list-style-type: none"> ▪ gBRCA1/2^{MUT} (HR+ / HER2- o. TNBC) <ul style="list-style-type: none"> ▪ Olaparib +/- endokrine Therapie ▪ Triple-negative (TNBC) <ul style="list-style-type: none"> ▪ Konventionell dosierte AT-basierte Chemotherapie (q3w) ▪ Dosisdichte sequentielle AT-basierte Chemotherapie (inkl. weekly Schemata) ▪ Neoadjuvante platinhaltige Chemotherapie ▪ Neoadjuvante platinhaltige Chemotherapie mit ICPI (Pembrolizumab) ▪ HER2+ <ul style="list-style-type: none"> ▪ 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 	 	

* s. Prognosekapitel

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Systematic review of published evidence

PUBMED 1999-2024

ASCO 1999-2024

SABCS 1999-2024

ECCO/ESMO 1999-2024

General Statements:

Loibl S, André F, Bachelot T et al.(2024) Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol : 35:159–182.

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):

2. Schneeweiss A, 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 randomized phase II cardiac safety study (TRYPHAENA). *Annals Oncol* 2013; 24; 2278-84
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]
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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, 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. 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. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS, Goetz MP, Hamilton EP, Huang CS, Senkus E, Tryakin A, Cicin I, Testa L, Neven P, Huober J, Shao Z, Wei R, André V, Munoz M, San Antonio B, Shahir A, Harbeck N, Johnston S. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *J Clin Oncol*. 2024 Jan 9;JCO2301994.
2. Goetz MP, Cicin I, Testa L, et al. (2024) Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study. *NPJ Breast Cancer* 10:34.
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Ribociclib:

1. Fasching PA, Stroyakovskiy D, Yardley D et al. (2024) LBA13 Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2- early breast cancer (EBC): 4-year outcomes from the NATALEE trial. *Annals of Oncology* 35:S1207.
2. Hortobagyi GN, Lacko A, Sohn Jet al. (2024) A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. *Ann Oncol*.

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. III randomized controlled trial SABCS 2022, GS5-01
4. MasonSRE, WillsonML, EggerSJ, BeithJ, DearRF, GoodwinA. Platinum-based chemotherapy for early triple-negative breast cancer. *Cochrane Database of Systematic Reviews* 2023, Issue 9. Art. No.: CD014805.

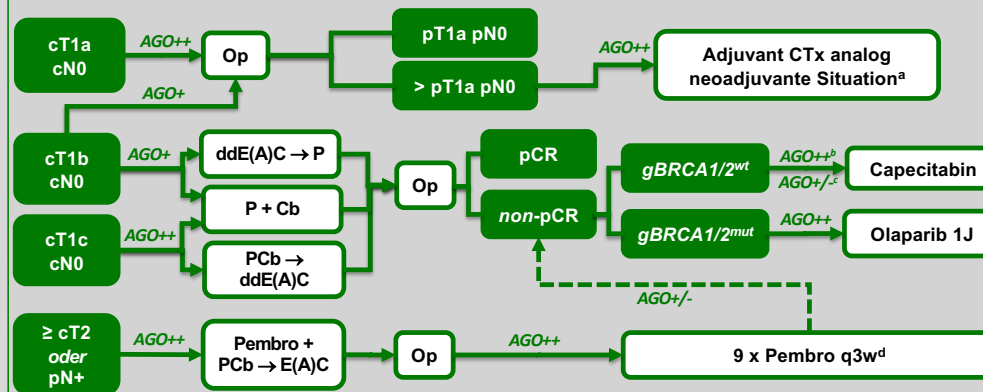
Therapie beim frühen triple-negativen Mammakarzinom

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A, Doxorubicin; C, Cyclophosphamid; Cb, Carboplatin; CTx, Chemotherapie; dd, dosisdicht (alle 2 Wochen); E, Epirubicin; *gBRCA1/2^{mut}*, Keimbahn *BRCA1/2* Mutation; *gBRCA1/2^{wt}*, Keimbahn *BRCA1/2* Wildtyp; J, Jahr; Op, Operation; P, Paclitaxel; pCR, pathologische Komplettremission; Pembro, Pembrolizumab; q3w, alle 3 Wochen; ^asofern postoperativ keine Änderung in Prognosefaktoren; ^bnach A/T-haltiger Chemotherapie; ^cnach Chemotherapie mit Platin ± Pembrolizumab; ^dsofern Pembrolizumab neoadjuvant begonnen wurde.

Indikation zur Chemotherapie +/- Checkpointinhibitortherapie (TNBC)

	Oxford		
	LoE	GR	AGO
▪ Klinisch nodal-positiv			
▪ Neoadjuvante Chemotherapie in Kombination mit Pembrolizumab	1b	A	++
▪ Klinisch nodal-negativ			
▪ ≥ T2 → Neoadjuvante Chemotherapie in Kombination mit Pembrolizumab	1b	A	++
▪ T1c → Neoadjuvante Chemotherapie bevorzugt	2b	B	++
▪ T1b → Neoadjuvante oder adjuvante Chemotherapie	2b	B	+
▪ T1a → Adjuvante Chemotherapie	2b	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
- Tarantino P, Leone J, Vallejo CT et al. Prognosis and treatment outcomes for patients with stage IA triple-negative breast cancer. NPJ Breast Cancer. 2024 Apr 4;10(1):26. doi: 10.1038/s41523-024-00634-6
- Pfob A, Surovtsova I, Kokh DB; Baden-Württemberg Cancer Registry (BWCR); Heil J, Banys-Paluchowski M, Morakis P. Use of chemotherapy and loco-regional therapy in stage IA triple-negative breast cancer and their association with oncologic outcomes: A cancer registry study. Int J Cancer. 2025 Feb 1;156(3):587-597. doi: 10.1002/ijc.35189. Epub 2024 Sep 18.
- Nonneville A, Goncalves C, Zemmour M et al. Adjuvant chemotherapy in pT1ab node-negative triple-negative breast carcinomas: Results of a national multi-institutional retrospective study. European J Cancer. 2017; (84):34-43.
- Oladeru OT, Singh AK, Ma SJ. Association of Adjuvant Chemotherapy With Overall Survival Among Women With Small, Node-Negative, Triple-Negative Breast Cancer. JAMA Netw Open. 2020 Sep 1;3(9):e2016247.
- Steenbruggen TG, van Werkhoven E, van Ramshorst MS, et al.. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. Eur J Cancer. 2020 Aug;135:66-74. doi: 10.1016/j.ejca.2020.04.033. Epub 2020 Jun 14. PMID: 32554215.

Allgemeine Grundsätze

	Oxford		
	LoE	GR	AGO
▪ Chemotherapieregime können sowohl adjuvant als auch neoadjuvant verwendet werden	1a	A	++
▪ Dosisdichte Schemata sollten bevorzugt eingesetzt werden (wenn Pembrolizumab nicht indiziert)	1a	A	++
▪ Hinzunahme Platinsalze zur anthrazyklin-/taxanhaltigen Chemotherapie (cT1 cN0) (unabh. vom gBRCA-Status)	1b	B	+
▪ Hinzunahme Platinsalze zur anthrazyklin-/taxanhaltigen Chemotherapie (≥ cT2 oder cN+) (unabh. vom gBRCA-Status)	1a	A	++
▪ Pembrolizumab in Kombination mit Carboplatin / Paclitaxel → 4 x EC q3w neoadjuvant und postoperativ (ab cT2 oder cN+)	1b	A	++
▪ Olaparib bei gBRCA ^m <ul style="list-style-type: none"> ▪ Adjuvant: Tumorgroße ≥ 2 cm oder pN+ ▪ Post-neoadjuvant: non-pCR 	1b	A	++

Keine rein adjuvante ICPI-Therapie außerhalb von Studien.

Use of adjuvant standard regimens for NACT

1. Early Breast Cancer Trialists' Collaborative Group (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;19(1):27-39. doi: 10.1016/S1470-2045(17)30777-5.

Taxane followed by anthracycline sequence

1. Bines J, et al. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? *Ann Oncol* 2014; 25; 1079
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
3. Wang D, Feng J, Xu B. A meta-analysis of platinum-based neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy for triple-negative breast cancer. *Future Oncol.* 2019; 15(23); 2779-2790

Platinum in TNBC (irrespective of BRCA status)

1. Alba E, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from

- the GEICAM/2006-03, multicenter study. *Breast Cancer Res Treat* 2012; 136; 487
2. Von Minckwitz G , et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; 15; 747
 3. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. *Breast Cancer Res Treat* 2014; 145; 401
 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
 5. Sikov WM, 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* 2015; 33; 13
 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.
 11. Iwase M, Ando M, Aogi K, et al. Long-term survival analysis of addition of carboplatin to neoadjuvant chemotherapy in HER2-negative breast cancer. *Breast Cancer Res Treat*. 2020 Apr;180(3):687-694.
 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.
 13. Saleh RR, Nadler MB, Desnoyers A, et al. Platinum-based chemotherapy in early-stage triple negative breast cancer: A meta-analysis. *Cancer Treat Rev*. 2021 Nov;100:102283.

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15. Li J, Chen L, Tan W, et al. Platinum is essential in neoadjuvant treatment of triple-negative breast cancer: a network meta-analysis. *Cancer Biol Med*. 2022 Feb 16;j.issn.2095-3941.2021.0529. doi: 10.20892/j.issn.2095-3941.2021.0529. Online ahead of print
16. Feng W, He Y, Xu J, et al. A meta-analysis of the effect and safety of platinum-based neoadjuvant chemotherapy in treatment of resectable triple-negative breast cancer. *Anticancer Drugs*. 2022 Jan 1;33(1):e52-e60
17. Shepherd JH, Ballman K, Polley MYC et al. CALGB 40603 (Alliance): Long-Term Outcomes and Genomic Correlates of Response and Survival After Neoadjuvant Chemotherapy With or Without Carboplatin and Bevacizumab in Triple-Negative Breast Cancer. *J Clin Oncol* 2022 Jan 19;40(12):1323–1334
18. Wang D, Feng J, Xu B. A meta-analysis of platinum-based neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy for triple-negative breast cancer. *Future Oncol*. 2019: 15(23); 2779-2790

Immune checkpoint inhibitor therapy:

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2. Schmid P, Cortes J, Dent R, et al.; KEYNOTE-522 Investigators. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *N Engl J Med*. 2022 Feb 10;386(6):556-567
3. 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. doi: 10.1056/NEJMoa1910549.
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5. Geyer CE, Tang G, Nekljudova V et al. GS3-05 NSABP B-59 / GBG-96-GeparDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo followed by adjuvant atezolizumab or placebo in patients with Stage II and III triple-negative breast cancer. *SABCS 2024*
6. Conte P, Dieci MV, Bisagni G et al. A-BRAVE trial: a phase III randomised trial with Avelumab in early triple negative breast cancer with residual disease after neoadjuvant chemotherapy or at high risk after primary surgery and adjuvant chemotherapy. *ASCO 2024*
7. Loibl S, Schneeweiss A, Huober J et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent

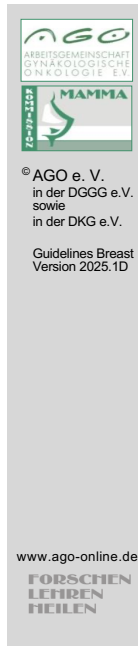
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9. Gianni L, Huang CS, Egle I, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study: *Ann Oncol.* 2022 May;33(5):534-543. doi: 10.1016/j.annonc.2022.02.004. Epub 2022 Feb 17. PMID: 35182721
10. Gianni L, Huang CS, Egle I, et al. Event-free survival (EFS) analysis of neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen in high-risk triple negative breast cancer (TNBC): NeoTRIP Michelangelo randomized study *Ann Oncol.* 2023 October; VOLUME 34, SUPPLEMENT 2, S1258-S1259

Neoadjuvante Chemotherapie Vorgehen je nach Ansprechen

	Oxford		
	LoE	GR	AGO
Frühes Therapieansprechen:			
▪ Fortführung der neoadjuvanten Therapie	1b	A	++
Bei keiner Änderung:			
▪ 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	+
▪ Paclitaxel / Carboplatin → EC (q2w oder q3w) x 4	1b	B	+
Bei Progression:			
▪ Reevaluation der Tumorbiologie	5	D	+/-
▪ Abbruch der NACT und Operation oder Bestrahlung	4	D	++
▪ Zusätzliche adj. Chemotherapie mit nicht-kreuzresistenten Schemata	4	D	+/-

1. Eckert KM, Hoskin TL, Olson CA et al. In-Breast Tumor Progression During Neoadjuvant Chemotherapy: Impact on and Factors Influencing Distant Recurrence-Free Survival. *Ann Surg Oncol* 2024 Dec;31(13):8856-8865. doi: 10.1245/s10434-024-16178-9
2. Elmore LC, Kuerer HM, Barcenas CH et al. Clinical course of breast cancer patients with local-regional progression during neoadjuvant systemic therapy. *Ann Surg Oncol*. 2021;28(10):5477–85
3. Ling YX, Xie YF, Wu HL et al. Prognostic factors and clinical outcomes of breast cancer patients with disease progression during neoadjuvant systemic therapy. *Breast*. 2023;70:63–9



Präferierte Schemata beim triple-negativen Mammakarzinom

	Oxford		
	LoE	GR	AGO
<u>Nicht-platinhaltige Regime</u>			
▪ ddEC x 4 → Paclitaxel ₈₀ q1w x 12 (bei T1 N0)	1b	B	++
<u>Platinhaltige Regime</u>			
▪ Paclitaxel ₈₀ / Carbo _{AUC 1,5} q1w x 12 → ddEC x 4	1b	B	++
▪ Paclitaxel ₈₀ q1w x 12 / Carbo _{AUC 5} q3w x 4 → ddAC / ddEC x 4	1b	B	++
▪ Paclitaxel / Carbo _{AUC 1,5} q1w x 18 (bei T1 N0)	2b	B	++
<u>Checkpoint-Inhibitoren</u>			
▪ Pembro ₂₀₀ q3w + Pac ₈₀ / Carbo _{AUC 1,5} q1w x 12 → E ₉₀ C q3w x 4	1b	B	++
▪ Pembro ₂₀₀ q3w + Pac ₈₀ q1w x 12 / Carbo _{AUC 5} q3w → E ₉₀ C q3w x 4	1b	B	++

Non-platin containing chemotherapy

1. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008 Apr 17;358(16):1663-71. doi: 10.1056/NEJMoa0707056.PMID: 18420499
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
2. 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. doi: 10.1056/NEJMoa1910549.
3. Schmid P, Cortes J, Dent R, et al.; KEYNOTE-522 Investigators. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb 10;386(6):556-567.

Statement Platin

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3. Thomssen C, Schüler K, Bauer M et al.. Efficacy of neoadjuvant systemic carboplatin therapy in triple-negative breast cancer San Antonio Breast Cancer Symposium 2021, Abstr.# P2-12-05
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Docetaxel/Carboplatin

1. Sharma P, Kimler BF, O'Dea A et al. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). *Clin Cancer Res.* 2021 Feb 15;27(4):975-982.

Postneo-/Adjuvante Therapie beim triple-negativen Mammakarzinom

	Oxford		
	LoE	GR	AGO
pCR			
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	+
Non-pCR			
▪ Capecitabin (q3w bis zu 8 Kurse) ¹			
▪ Bei non-pCR nach A-T-haltiger Chemotherapie ¹	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^{MUT}</i>) ²	1b	A	++
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	++

¹ Studienlage bei Stadium II-III ohne Platin / Pembrolizumab-basierte Vortherapie

² entsprechend Einschlusskriterien der OlympiA-Studie

Capecitabine

- 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
- 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
- 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.
- 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

Platinum salts:


- Schneider BP, Jiang G, Ballinger TJ et al. BRE12-158: A Postneoadjuvant, Randomized Phase II Trial of Personalized Therapy Versus Treatment of Physician's Choice for Patients With Residual Triple-Negative Breast Cancer. Journal of Clinical Oncology 2022; 40: 345-355.

Pembrolizumab

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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Olaparib gBRCAmut

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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



Gray R et al., Lancet 2019

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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-BS9
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:

- 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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IMpassion031:

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neoTRIP:

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GeparDOUZE:

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