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Adjuvant Cytotoxic and Targeted Therapy

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- **Versionen 2002 – 2020:**
  Dall / Fehm / Harbeck / Jackisch /Janni / Loibl / Lux/ von Minckwitz / Möbus / Müller / Nitz / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2021:**
  Albert / Kümmel

Subtype-specific Strategies for Systemic Treatment

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	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred	
HR+/HER2- and „low-risk"	
▪ Endocrine therapy without chemotherapy	++
HR+/HER2- and „high-risk"	
▪ Conventionally dosed AT- based chemotherapy (q3w)	+
▪ Dose dense chemotherapy (including weekly schedule)	++
▪ Followed by endocrine therapy	++
HER2+	
▪ Trastuzumab (plus Pertuzumab in N+ or NACT)	++
▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy	++
▪ Anthracycline-free chemotherapy + anti-HER2 therapy	++
Triple-negative (TNBC)	
▪ Conventionally-dosed AT-based chemotherapy	+
▪ Dose-dense chemotherapy (AT-based including weekly schedule)	++
▪ Neoadjuvant platinum-containing chemotherapy	+
▪ Neoadjuvant chemotherapy + ICPi (immune checkpoint-inhibitors)	+/-*

* Study participation recommended

Adjuvant Chemotherapy: TNBC

- **Indication for chemotherapy in <u>node-negative disease</u>**
  - **> 10 mm**
  - **> 5–10 mm**
  - **≤ 5 mm**

Oxford		
LoE	GR	AGO
2b	B	++
2b	B	+
2b	B	-

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Adjuvant Chemotherapy without Trastuzumab: Overview

	Oxford		
	LoE	GR	AGO
▪ Dose-dense anthracycline / taxane based (incl. weekly) chemotherapy	1a	A	++
▪ Conventional anthracycline-/taxane-based (q3w)	1a	A	+
▪ „Tailored“ anthracycline-/taxane-based	1b	B	+/-
▪ If anthracyclines cannot be given			
▪ Docetaxel plus cyclophosphamide	1b	B	+
▪ Paclitaxel mono weekly	1b	B	+/-
▪ CMF	1a	A	+/-
▪ Low-dose maintenance chemo	1b	B	-

Gray R et al., Lancet 2019

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

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

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

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

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Recommended Dose-dense and / or Dose-escalated, Sequential Adjuvant Chemotherapy

	Oxford LoE	Oxford GR	AGO
Dose-dense regimen			
▪ A_{60} X4 → Pac_{175} x4 → C_{600} x4 q2w	1b	A	++
▪ A_{60}C q2w x4→ Pac_{175} q2w x 4	1b	B	++
▪ E_{90}C q2w x4→ Pac_{175} q2w x 4	1b	A	++
▪ E_{90}C q2w x4 → Pac_{80} q1w x 12	1b	B	++
▪ $NabPac_{125}$ x8-12→ E_{90}C q2(3)w x4	1b	B	+
Dose-dense and dose-escalated regimen (N ≥ 4+)			
▪ E_{150}→Pac_{225}→C_{2000} q2w	1b	A	++

Recommended Conventional Regimens for Adjuvant Chemotherapy

* Extrapolation from doxorubicin trials

		Oxford		
		LoE	GR	AGO
Anthrazycline-/ taxane-based regimen				
▪ *EC q3w x 4 → Pac q1w x 12		2b	B	++
▪ AC q3w x 4 → Pac q1w x 12		1b	A	++
▪ AC → D qw3	$A_{60}C$ q3w x 4 → D_{100} x 4	1b	A	+
▪ *EC → D qw3	$E_{90}C$ q3w x 4 → D_{100} x 4	1b	B	+
▪ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	+
Anthrazycline-free regimen				
▪ DC similar efficacy as EC → D	D_{75} C_{600} x 6	1b	B	+
▪ DC >> 4 x AC	D_{75} C_{600} x 4	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxane-free regimen (if pN0)				
▪ $FE_{100}C$ x 6	$F_{500}E_{100}C_{500}$ x 6	2b[(a)]	B	+

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Adjuvant Chemotherapy
Other Drugs

	Oxford LoE	Oxford GR	Oxford AGO
▪ Capecitabine-containing regimen in TNBC	1a	B	+/-
▪ adjuvant/neoadjuvant	1a[a]	A	+/-
▪ postneoadjuvant in non-pCR patients*	1a[a]	A	+
▪ Platinum-containing regimen			
▪ Anthracycline-free adjuvant therapy in TNBC	1b	B	+
▪ Anthracycline-based adjuvant therapy in TNBC	5	D	+/-
▪ 5- fluorouracile added to EC/AC	1b	A	--

*no platinum pretreatment

Van Mackelenbergh M et al., SABCS 2019, abstr. GS1-07

Effects of capecitabine as part of neo-/adjuvant chemotherapy

Meta-analysis of individual patient data from 12 randomized trials (n=15,457)

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

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

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

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Adjuvant Treatment with Trastuzumab +/- Pertuzumab

	Oxford LoE	Oxford GR	AGO
Trastuzumab + Pertuzumab			
pN+	1b[a]	B	+
pN-	1b[a]	B	+/-
Trastuzumab in node-negative disease (if chemotherapy is indicated)			
> 10 mm	1a	A	++
> 5–10 mm	2b	B	+
≤ 5 mm	2b	B	+/-

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Adjuvant treatment with Trastuzumab/Pertuzumab

	Oxford		
	LoE	GR	AGO
Start of treatment			
▪ Simultaneously with taxanes	1a	A	++
▪ Sequentially up to 3 months after chemotherapy	1b	B	+
▪ s.c. = i.v.	1a	A	++
Duration			
▪ For 1 year	1a	A	++
▪ For 0.5 years (Trastuzumab)	1a	A	+
▪ For 2 years	1b	A	-

Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

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	Oxford		
	LoE	GR	AGO
Trastuzumab simultaneously with			
▪ paclitaxel / docetaxel after AC / EC	1a	A	++
▪ P q1w 12 x in pT < 2 cm, pN0	2b	B	+
▪ docetaxel and carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultaneously with			
▪ paclitaxel q1w (or docetaxel q3w) after EC/AC	1b	B	++
▪ docetaxel+ carboplatin	1b	B	+
▪ taxanes dose-dense	2b	B	+
Radiotherapy concurrently with Trastuzumab/Pertuzumab	2b	B	+

Adjuvant Therapy With Other Targeted Agents

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	Oxford		
	LoE	GR	AGO
▪ Lapatinib	1b[a]	B	-
▪ (delayed adjuvant treatment)	1b	B	-
▪ Lapatinib + Trastuzumab	1b[a]	B	-
▪ Neratinib* (one year) after completing a year of adjuvant trastuzumab (if HR-positive)	1b	B	+
▪ Bevacizumab	1b	B	--

*** In addition to standard endocrine treatment**

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Post-neoadjuvant therapy: HER2-negative

	Oxford LoE	Oxford GR	AGO
HR positiv (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal status (s. chap. 10)	1a	A	++
▪ Capecitabine (in case of non-pCR)	3b	C	+/-
▪ Endocrine therapy + Abemaciclib	2b	B	+/-*
▪ Endocrine therapy + Palbociclib	1b[a]	B	-*
Triple negative (TNBC) (in case of non-pCR)			
▪ Capecitabine (up to 8 cycles)**	1b	B	+
▪ Experimental post-neoadjuvant therapies within clinical trials	5	D	+*

* Study participation recommended

** without prior platinum-based therapy

Post-neoadjuvant therapy: HER2-positive

	Oxford		
	LoE	GR	AGO
pCR			
▪ Low risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive)*	2b	B	-
non-pCR			
▪ T-DM1	1b	B	+
▪ Neratinib after 1 year* Trastuzumab (HR-positive)*	2b	B	+/-
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+/-

* In combination with standard endocrine treatment

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Biosimilars
Genaral Considerations

Biosimilars that are used for treatment (i.e. trastuzumab) and supportive care of breast cancer (i.e G-CSF) must be approved by the respective regulatory authorities (EMA, FDA) after passing the stringent development and validation processes required before being used in daily practise.*

* Thill M et al. Einführung und Verwendung von biosimilaren Antikörpern in der Therapie des Mammakarzinoms. Geburtshilfe Frauenheilkd 2018; DOI: 10.1055/s-0043-118761