Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2019.1

Adjuvant Cytotoxic and Targeted Therapy

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- **Versions 2002 – 2018:**
  Harbeck / Jackisch /Janni / Loibl / Lux/ von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Schütz / Solomeyer / Stickeler / Thill / Thomssen / Untch

- **Version 2019:**
  Schmidt / Thomssen

Subtype-specific Strategies for Systemic Treatment

	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 neoadjuvant at high risk)	++
▪ Sequential A/T-based regimen with concurrent T + anti Her 2 therapy	++
▪ Anthracycline-free, platinum-containing regimen	+
▪ Anthracycline-free, taxane-containing regimen	+
Triple-negativ (TNBC)	
▪ Conventionally dosed AT-based chemotherapy	+
▪ Dose dense chemotherapy (AT - based including weekly schedule)	++
▪ Neoadjuvant platinum-containing chemotherapy	+

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Dose-Density of Paclitaxel

Regimen	ED [mg/m²]	Courses	cumulative	mg/m²/week
<u>Conventional dose-density</u>				
EC-Pac q3w	175	4	700	58,33
<u>Dose-dense regimen</u>				
ddEC-ddPac q2w	175	4	700	87,5
ddEC-Pw q1w	80	12	960	80

Adjuvant Chemotherapy without Trastuzumab: Overview

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	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., SABCS 2017, abstr. GS1-01

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; 2p=0.0004)
Overall survival: 10-y Gain 2.8% (95%-C.I. 0.8 – 4.8)
(RR = 0.86; 95%-C.I. 0.77 – 0.95; 2p=0.004)

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)

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

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	Oxford LoE	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	++
Dose-dense and dose-escalated regimen (N ≥ 4+)			
▪ E_{150}→Pac_{225}→C_{2500} q2w	1b	A	++

* G-CSF obligatory

Recommended Conventional Regimens for Adjuvant Chemotherapy

* Extrapolated from doxorubicin trials

		Oxford LoE	Oxford GR	AGO
Anthracycline / taxane based regimen				
▪ *EC q3w x 4 → P_{ac} q1w x 12		2b	B	++
▪ AC q3w x 4 → Pac q1w y 12		1b	A	++
▪ AC → D	$A_{60}C$ q3w x 4 → D_{100} x 4	1b	A	+
▪ *EC → D	$E_{90}C$ q3w x 4 → D_{100} x 4	1b	B	+
▪ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	+
Anthracycline-free regimen				
▪ DC corresponds to EC → D	D_{75} C_{600} x 6	1b	B	+
▪ DC >> 4 x AC	$D_{75}C_{600}$ x 6	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxane-freie 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	GR	AGO
▪ Capecitabine containing regimen in TNBC	1a	B	+/-
- generally	1b[a]	B	-
- postneoadjuvant in non-pCR patients	2b	C	+
▪ Platinum containing regimen in TNBC	5	D	+
▪ 5- Fluorouracile added to EC/AC	1b	A	--

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Adjuvant Treatment with Trastuzumab +/- Pertuzumab

	Oxford LoE	GR	AGO
Trastuzumab	1a	A	++
▪ **Trastuzumab + Pertuzumab**			
▪ **N+ and / or HR-**	1b	B	+
▪ **N- and HR+**	1b	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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Adjuvante Therapie mit Trastuzumab

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

Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

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	Oxford LoE	Oxford GR	AGO
Trastuzumab simultaneously with			
▪ With paclitaxel / docetaxel after AC / EC	1b	A	++
▪ With P q1w 12 x without A in pT < 2 cm, pN0	2b	B	+
▪ With docetaxel and carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultaneously with			
▪ With paclitaxel q1w (or docetaxel q3w) after EC/AC	1b	B	++
▪ With docetaxel+ carboplatin	1b	B	+
▪ With taxanes dose-dense	2b	B	+*
Radiotherapy concurrent with Trastuzumab	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	-
▪ Bevacizumab	1b	B	--

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Postneoadjuvant Therapy

	Oxford LoE	Oxford GR	AGO
HR positive (pCR and non-pCR)*			
▪ Endocrine Therapy according to Menopausal Status (see. Ch. 10)	1a	A	++
▪ Capecitabine (if non-pCR)	3b	C	+/-
HER2 positive(after pCR)			
▪ Low risk: Trastuzumab (to complete 12 months)	2a	C	++
▪ High risk (eg HR-/N+): Trastuzumab + Pertuzumab (to complete 12 months)	2b	C	+
HER2 positive (if non-pCR)			
▪ T-DM1 (to complete 14 doses of anti-HER2-Therapy)	1b	B	+
▪ Neratinib after 1 year Trastuzumab (only if HR-positive)	4	C	+/-
▪ Trastuzumab + Pertuzumab (to complete 12 months)	2b	C	+/-
Tripelnegative (TNBC) (if non-pCR)			
▪ Capecitabine (up to 8 courses)	1b	B	+

*Study participation recommended

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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 after passing the stringent development and validation processes required by the authorities in charge (EMA, FDA) before 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