Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Version 2020.1

Adjuvant Cytotoxic and Targeted Therapy

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- **Versionen 2002 – 2019:**
  Dall / Harbeck / Jackisch /Janni / Loibl / Lux/ von Minckwitz / Möbus / Müller / Nitz / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2020:**
  Fehm / Stickeler

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 A/T-based regimen with concurrent T + anti-HER2 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	+

Adjuvant Chemotherapy: TNBC

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- **Indication for chemotherapy in <u>node-negative disease</u>**

	Oxford		
	LoE	GR	AGO
> 10 mm	2b	B	++
> 5–10 mm	2b	B	+
≤ 5 mm	2b	B	-

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Adjuvant Chemotherapy without Trastuzumab: Overview

	Oxford LoE	Oxford GR	Oxford 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	-

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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%-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)

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

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	Oxford LoE	Oxford GR	Oxford 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

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* Extrapolation 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-free regimen (if pN0)				
▪ $FE_{100}C$ x 6	$F_{500}E_{100}C_{500}$ x 6	2b[(a)]	B	+

Adjuvant Chemotherapy
Other Drugs

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	Oxford		
	LoE	GR	AGO
▪ Capecitabine-containing regimen in TNBC	1a	B	+/-
▪ in general	1a[a]	A	-
▪ postneoadjuvant in non-pCR patients*	1a[a]	A	+
▪ Platinum-containing regimen 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

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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	+/-

Aphinity-Trial - Update

Clinical benefit of the dual blockade with trastuzumab / pertuzumab

HR (95%-CI) for IDFS			6-yr-IDFS rate		
Group	Primary analysis (2017) *	Update (2019)**	Pertuzumab arm	Placebo arm	Absolute benefit 95%-CI
ITT	0,81 (0,66-1,00)	0,76 (0,64 -0,91)	90,6%	87,8%	2,8% (1,0-4,6)
N+	0,77 (0,62-0,96)	0,72 (0,59-0,87)	87,9%	83,4%	4,5% (1,9-7,1)
N0	1,13 (0,58-1,86)	1,02 (0,69-1,53)	95,0%	94,9%	0,1% (-2,0 -2,2)
HR pos	0,86 (0,56-1,13)	0,73 (0,59 – 0,92)	91,2%	88,2%	3,0% (0,8-5,2)
HR neg	0,76 (0,56-1,04)	0,83 (0,63-1,10)	89,5%	87,0%	2,5% (-0,7-5,6)

** FU: 45,5 mths; ** FU: 74,1 mths*

OS difference after 74.1 mths of median follow-up did not reach statistical significance

Mod. Nach Piccart M et al. SABCS 2019; abstr. GS1-04

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Adjuvant treatment with trastuzumab

	Oxford LoE	Oxford GR	Oxford 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	1a	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			
▪ 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	2b	B	+

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Adjuvant Therapy With Other Targeted Agents

	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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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 (in case of non-pCR)	3b	C	+/-
HER2-positive (in case of pCR)			
▪ Low-risk: Trastuzumab (to complete 12 months)	2a	C	++
▪ High-risk (N+): Trastuzumab + Pertuzumab (to complete 12 months)	2b	C	+
HER2-positive (in case of non-pCR)			
▪ T-DM1	1b	B	+
▪ Neratinib after 1 year* Trastuzumab (HR-positive)	3b	B	+/-
▪ Trastuzumab + Pertuzumab (to complete 12 months)	2b	C	+/-
Triple negative (TNBC) (if non-pCR)			
▪ Capecitabine (up to 8 courses)**	1b	B	+

* in combination with standard endocrine therapy
** without platin based previous therapy

Biosimilars
Genaral Considerations

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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