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Adjuvant Cytotoxic and Targeted Therapy

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- **Versions 2002 – 2021:**
  Albert / Dall / Fehm / Harbeck / Jackisch /Janni / Kümmel / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2022:**
  Fasching / Rody

Strategies for Differentiated Systemic Treatment in the Curative Situation

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	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended	
„Low absolute risk implies low absolute benefit“	
▪ **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 endocrine-based therapy**	++
▪ **Triple-negative (TNBC)**	
▪ **Conventional dosed AT-based chemotherapy (q3w)**	+
▪ **Sequential AT-based chemotherapy (incl. weekly schedule)**	++
▪ **Neoadjuvant Neo-/adjuvant platinum-containing chemotherapy**	+
▪ **Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)**	+
▪ **HER2 negative, gBRCA1/2mut (ER pos. and TNBC respectively[1])**	
▪ **Olaparib postneoadjuvant**	+
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab in N+ or NACT)**	++
▪ **Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy**	+
▪ **Anthracycline-free, chemotherapy + anti-HER2 therapy**	++

[1] **According to approval or study population (if not approved)**

Adjuvant Chemotherapy: TNBC

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	Oxford		
	LoE	GR	AGO
▪ **Indication for chemotherapy in <u>node-negative disease</u>**			
▪ **> 10 mm**	**2b**	**B**	**++**
▪ **> 5–10 mm**	**2b**	**B**	**+**
▪ **≤ 5 mm**	**2b**	**B**	**-**

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 are not a preferred option			
▪ 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	GR	AGO
Dose-dense regimen			
▪ A_{60} x 4 → Pac_{175} x 4 → C_{600} x 4 q2w	1b	A	++
▪ A_{60}C q2w x 4 → Pac_{175} q2w x 4	1b	B	++
▪ E_{90}C q2w x 4 → Pac_{175} q2w x 4	1b	A	++
▪ E_{90}C q2w x 4 → Pac_{80} q1w x 12	1b	B	++
▪ $NabPac_{125}$ x 8-12 → E_{90}C q2(3)w x 4	1b	B	+
Dose-dense and dose-escalated regimen (N ≥ 4+)			
▪ E_{150} → Pac_{225} → C2000 q2w	1b	A	++

Recommended Conventional Regimens for Adjuvant Chemotherapy

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		Oxford LoE	Oxford GR	AGO
Anthrazyklin-/ taxan-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	+[a]
Anthrazyklin-free regimen				
▪ 6 x DC corresponds to EC → D	D_{75} C_{600} x 6	1b	B	+
▪ 4 x DC >> 4 x AC	D_{75} C_{600} x 4	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxan-free regimen (if pN0)				
▪ $FE_{100}C$ x 6	$F_{500}E_{100}C_{500}$ x 6	2b[(a)]	B	+

* Extrapolation from doxorubicin trials

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Adjuvant Chemotherapy
Other Drugs

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

* DPYD genotyping for the identification of a DPD Deficiency
** 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)

Adjuvant Treatment with Trastuzumab +/- Pertuzumab

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	Oxford		
	LoE	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	-

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Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

	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	+

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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

Postneoadjuvant Therapy HR+ / HER2-

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	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence[1]	1b	B	+
▪ Palbociclib for 1-2 yrs + endocrine therapy	1b	B	-
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	B	+
▪ Capecitabine (non-pCR)	3b	C	+/-

1 According inclusion criteria monarchE-study,
2 According inclusion criteria OlympiA-study

How to calculate CPS+EG Score?

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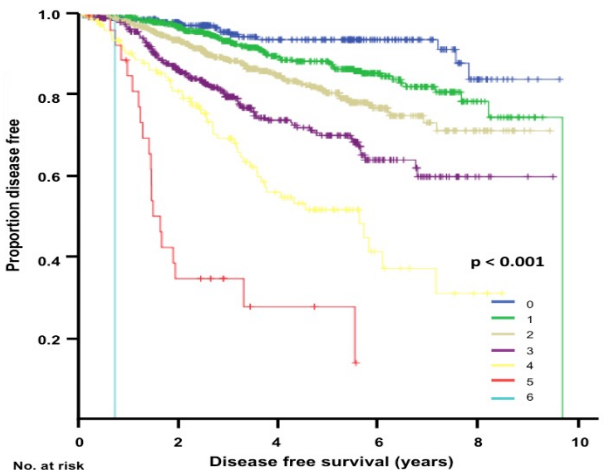
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

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	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.59-0.82) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*	1a	A	+
▪ Olaparib (*gBRCAm^{MUT}*)[1]	1b	B	+
▪ Continuation of Pembrolizumab, if started with neoadj. therapy (q3w up to 9 courses)	1b	B	++

[1] according inclusion criteria of OlympiA trial
* without platin based previous therapy

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Postneoadjuvant Therapy: HER2-positive

	Oxford LoE	Oxford 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	+
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+/-
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive*)	5	D	+/-

* In combination with standard endocrine treatment