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Adjuvant Cytotoxic and Targeted Therapy

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Adjuvant Cytotoxic and Targeted Therapy

- **Versions 2002 – 2022:**
  Albert / Dall / Fasching / Fehm / Harbeck / Jackisch /Janni / Kümmel / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Rody / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2023:**
  Gluz / Thill

Strategies for Differentiated Systemic Treatment in the Curative Situation

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If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended	AGO
▪ HR+ / HER2- and „low recurrence-risk”	
▪ Endocrine therapy without chemotherapy	++
▪ HR+ / HER2- and „high recurrence-risk”	
▪ Endocrine / endocrine-based therapy (abemaciclib)	++
▪ Patients with indication for chemo-endocrine therapy*	
▪ Conventionally dosed AT-based chemotherapy (q3w)	+
▪ Dose dense chemotherapy (including weekly schedule)	++
▪ Triple-negative (TNBC)	
▪ Conventional dosed AT-based chemotherapy (q3w)	+
▪ Sequential AT-based chemotherapy (incl. weekly schedule)	++
▪ Neoadjuvant platinum-containing chemotherapy	+
▪ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)	+
▪ gBRCA1/2mut (HR+/HER- or TNBC respectively[1])	
▪ Olaparib[1] 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), *see prognosis chapter

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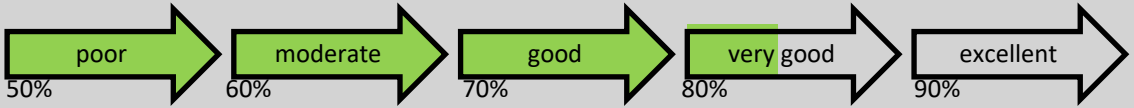
Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

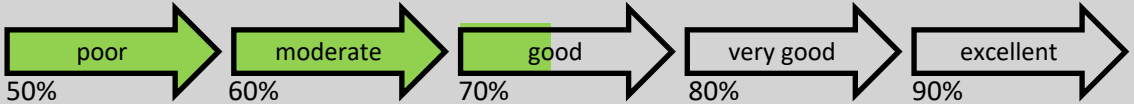
Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality).
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 82% of the time (c-statistic). The life expectancy calculator sorts patients who lived longer from patients who lived shorter correctly 78-80% of the time in the validation studies
- Calibration: The model was well calibrated across all risk levels with less than 3% difference between estimated and actual mortality rates.



Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).
- Discrimination: This risk calculator sorts patients who died within 5 years from patients who lived correctly 75% of the time (c-statistic). The discrimination was the same in the independent validation study. For 10 year and 14 year mortality the calculator sorts patients correctly 73% and 72% of the time.
- Calibration: The model was well calibrated across all risk levels with less than 10% difference between estimated and actual mortality.



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Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

Risk Calculator questions

1. How old is your patient?
2. What is the sex of your patient?
3. What is your patient's ?
4. Which best describes your patient's health in general?
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis?
6. Has your patient ever had cancer (excluding minor skin cancers)?
7. Does your patient have congestive heart failure?
8. Does your patient have diabetes or high blood sugar?
9. Which best describes your patient's cigarette use?
10. Does your patient have difficulty walking 1/4 mile (several city blocks) without help from other people or special equipment?
11. During the past 12 months, how many times was your patient hospitalized overnight?
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?
13. Because of a health or memory problem, does your patient have difficulty managing money - such as paying bills and keeping track of expenses?
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering?
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?

Adjuvant Chemotherapy: in Small, Node-Negative Tumors (T1)

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	Oxford		
	LoE	GR	AGO
▪ **Indication for chemotherapy in**			
▪ **TNBC**			
▪ **> 10 mm**	2b	B	++
▪ **> 5–10 mm**	2b	B	+
▪ **≤ 5 mm**	2b	B	+/-
▪ **HER2+ in combination with trastuzumab**			
▪ **> 10 mm**	1a	A	++
▪ **6–10 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	-

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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)

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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	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 or 3 x (F)EC-> 3 x Doc	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				
▪ EC (q3-2w) x 4-6	$E_{90}C_{600}$ x 4-6	2b[(a)]	B	+

* Extrapolation from doxorubicin trials

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Adjuvant Chemotherapy
Other Drugs

	Oxford LoE	Oxford GR	AGO
▪ **Capecitabine-containing regimen in TNBC***			
▪ adjuvant / neoadjuvant	1a	A	+/-
▪ postneoadjuvant in non-pCR patients**			
▪ With non-pCR after A-T-containing chemotherapy	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ 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

** in stage II-III without platinum/pembrolizumab-based pretreatment

Van Mackelenbergh M et al., 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%-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 HER2-directed Treatment

	Oxford LoE	Oxford GR	Oxford AGO
Trastuzumab + Pertuzumab			
pN+	1b[a]	B	++
pN-	1b[a]	B	+/-
Neratinib			
1 year after 1 year trastuzumab (HR-positive, stage II-III)	1b	B	+
1 year after trastuzumab/pertuzumab/T-DM1 at high risk and HR-positive	5	D	+/-

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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	+
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	1a	A	++

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	+
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	A	++
▪ Capecitabine (non-pCR)	1b	A	+/-

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

How to calculate CPS+EG Score?

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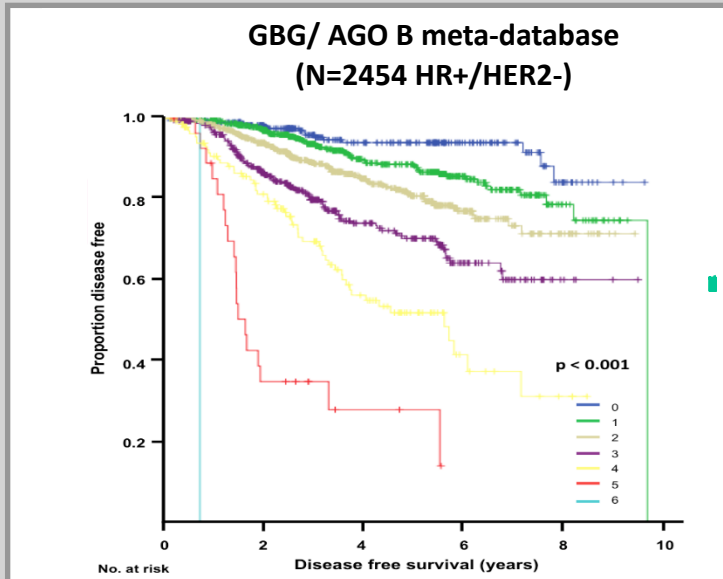
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
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
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

	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	42.0 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) 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. 89.9%	n.r.	88% vs. 78%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*			
▪ With non-pCR after A-T-containing chemotherapy*	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	+/-
▪ Olaparib (*gBRCA^{MUT}*)[1]	1b	A	++
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+

[1] according inclusion criteria of OlympiA trial, advantage especially with platinum-free NACT
* in stage II-III without platinum/pembrolizumab-based pretreatment

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Postneoadjuvant 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, high-risk, for example stage II-III)*	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, high risk , for example stage II-III)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive, high risk (stage II-III)*)	5	D	+/-

* In combination with standard endocrine treatment