Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2023.1E

Neoadjuvant
(Primary) Systemic Therapy

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Neoadjuvant Systemic Therapy

- **Versions 2002–2022:**
  Bauerfeind / Blohmer / Costa / Dall / Fehm / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Stickeler / Untch / Thill / Thomssen

- **Version 2023:**
  Fasching / Friedrich

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]**	++
▪ **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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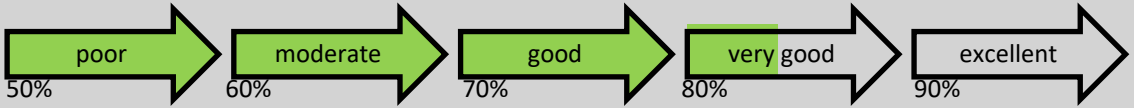
Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

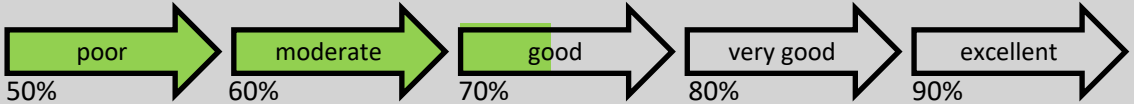
Lee Index

- 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?

Anthracycline-free Taxan / Carboplatin based Regimen for HER2+

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Regimen	Ppts. (n)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.5%

T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab

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Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford	
	LoE	GR
▪ Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy (data most consistent for HER2pos and TNBC)	1b	A
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response	1a	A
▪ Pathological complete response is associated with improved survival	1b	A
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymphadenectomies lymphonodectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B

Neoadjuvant Systemic Chemotherapy - Indications

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	Oxford		
	LoE	GR	AGO
▪ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++
▪ To allow a risk adapted postoperative therapy (data most consistent for HER2pos and TNBC)	1b	A	++
▪ Inflammatory breast cancer	2b	B	++
▪ Inoperable breast cancer	1c	A	++
▪ Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	++

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

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Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low(↓↓) probability to reach pCR; See aso chapter „Prognostic and predictive factors“

Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

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Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ gBRCA-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ gBRCA-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50 % of stroma area)

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Neoadjuvant Systemic Chemotherapy Recommended Regimens

	Oxford		
	LoE	GR	AGO
▪ Use of adjuvant standard regimens for NACT*	1a	A	++
▪ Taxane mono followed by anthracycline (reverse order)	4	D	+/-
▪ Platinum in TNBC (cT1 / cN+ or cT2) (irrespective of BRCA status)	1b	A	+
▪ Platinum in TNBC (from cT1 / cN+ or cT2) (irrespective of BRCA status)	1a	A	+
▪ Nab-paclitaxel weekly instead of paclitaxel qw1 (in TNBC)	1a	A	+
▪ Pembrolizumab in combination with carbo / paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

* See chapter Adjuvant Chemotherapy;
** > 2 cm or cN+, PD-L1 independent

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Recommended Regimen in Triple Negative Breast Cancer

	Oxford LoE	Oxford GR	AGO
Non-platinum-containing regimen			
ddEC x 4 → $pacli_{80}$ q1w x 12	1b	B	++
$NabPac_{125}$ q1w x 12 → $E_{90}C$ q(2)3w x 4	1b	B	+/-
Platinum-containing regimen			
$NabPac_{125}$ / $carbo_{AUC\ 2}$ q1w x 8 → ddEC x 4	1b	B	+
$Pacli_{80}$ q1w x 12 / $carbo_{AUC\ 6}$ q3w x 4 → ddAC / ddEC x 4	1b	B	+
Docetaxel / $carbo_{AUC6}$ q3w x 6 or paclitaxel/$carbo_{AUC1,5}$ q1w x18	2b	B	+
$NabPac_{100}$ / $carbo_{AUC\ 6}$ q4w x 4	2b	C	+
Checkpoint inhibitors			
$Pembro_{200}$ q3w + Pac_{80} / $carbo_{AUC\ 1,5}$ q1w x 12 → $E_{90}C$ q3w x 4	1b	B	+
$Pembro_{200}$ q3w + Pac_{80} q1w x 12 / $carbo_{AUC\ 5}$ q3w → $E_{90}C$ q3w x 4	1b	B	+

ICPi plus Neoadjuvant Chemotherapy for Triple Negative Breast Cancer Patients

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	GeparNuevo	IMpassion031	Keynote 522	neoTRIP
Phase	II	III	III	II
N	174	333	602 (pCR) 1174 (EFS)	280
Prim. endpoint	pCR	pCR	pCR + EFS	EFS
CPi	Durvalumab (24-26 weeks)	Atezolizumab (1 y)	Pembrolizumab (1 y)	Atezolizumab (24 weeks)
Chemo	$NabPac_{125}$ q1w x12 → EC q2w x4	$NabPac_{125}$q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 → AC/EC q3w x4	$NabPac_{125}$ + carbo AUC 2 q1w d1 and d8
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0
PD-L1 positive	87%	46%	83%	56%
pCR ITT	53.4% vs. 44.2% Δ 10.8% (n.s.)	57.6% vs. 41.2% Δ 16.5% (p < 0.01)	64.8% vs. 51.2% Δ 13.6% (p < 0.00055)	43.5% vs. 40.8% Δ 2.6% (n.s.)
pCR PD-L1 positive	58% vs. 50%	69% vs. 49%	69% vs. 55%	52% 48%
pCR PD-L1 negative	44% vs. 18%	48% vs. 34%	45% vs. 30%	32% vs. 32%
Follow up/EFS/iDFS (months)/HR EFS/iDFS	43.7 months iDFS: 0.48 (p = 0.0389)	20 months EFS: 0.76 (n.s.)	39.1 months EFS: 15.7 vs. 23.8 m 0.63 (p = 0.00031)	---
EFS/iDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% npCR 76.3% vs. 69.7%	---	pCR 94.4% vs. 92.5% npCR 67.4% vs. 56.8%	---

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Neoadjuvant Systemic Therapy
Recommended Methods of Monitoring of Response

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound	2b	B	++
▪ Palpation	2b	B	++
▪ Mammography	2b	B	++
▪ MRI	2b	B	+
▪ PET(-CT)	2b	B	+/-
▪ Pretherapeutical marking of tumor region	5	D	++
▪ Pretherapeutical diagnostic core needle biopsy and marking in case of of cN+ (CNB) (in case TAD is planned for ≤ 3 suspect lymph nodes)	2b	B	++*

(CNB: core needle biopsy; TAD: targeted axillary dissection;
*study participation recommended (AXSANA /Eubreast 3 Trial)

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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	Oxford		
	LoE	GR	AGO
▪ Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)	2b	B	++
▪ Trastuzumab in combination with stand polychemotherapy (low-risk)*	1b	A	+
▪ Anti-HER2 agents without chemotherapy	2b	B	+/-

* Single agent chemotherapy combined with trastuzumub should preferably be used in the adjuvant setting

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Neoadjuvant Chemotherapy
Treatment Strategies Based on Clinical Response

	Oxford		
	LoE	GR	AGO
In case of early response			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
In case of no change:			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
In case of disease progression			
▪ Re-evaluation of tumorbiological factors	5	D	+/-
▪ Stop NACT and proceed to surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-

Axillary Surgery and NACT

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

* Study participation in EUBREAST-01 recommended

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Axillary Surgery and NACT (cN+)

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN+*	$pN+_{CNB}$	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in AXSANA recommended, ** Cave: In 30.3% false-positive findings, consider CNB if necessary

Neoadjuvant Systemic Therapy
Loco-regional Surgery (Breast)

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	Oxford		
	LoE	GR	AGO
▪ Pretherapeutic discussion in a multidisciplinary tumor board (e.g. to define the surgical procedure)	1a	B	++
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excicion of posttherapeutic, marked tumorareal	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

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Neoadjuvant Systemic Therapy
Indications for Mastectomy

	Oxford		
	LoE	GR	AGO
▪ Positive margins after repeated excisions	3b	C	++
▪ Radiotherapy not feasible	5	D	++
▪ In case of clinical complete response			
▪ Inflammatory breast cancer (in case of pCR)	2b	C	+/-
▪ Multicentric lesions	2b	C	+/-
▪ cT4a-c breast cancer	2b	B	+/-

Neoadjuvant Systemic Therapy
Timing of Diagnosis, Surgery and Radiotherapy

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	Oxford		
	LoE	GR	AGO
Initiation of therapy Delay of therapy (> 60 days) associated with worse prognosis	2b	B	+
Timing of surgery 4-8 weeks after last course of chemotherapy	2a	B	++
Radiotherapy within 2 months after surgery	2b	B	++

Neoadjuvant endocrine Therapy (NET)
- Good clinical practice -

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- **Suitable for patients who are**
  - **inoperable**
  - **not able or willing to undergo chemotherapy**
- **Data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimale duration of NET is at least 4-6 months or until best repsonse or progression**
- **Choice of endocrine therapy is based on the menopausal status**
- **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks may predict response to endocrine treatment (prognostic / predictive evaluation)**

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ **Postmenopausal patients:**			
▪ **Optimizes the option for breast conserving therapy**	1b	A	+
▪ **Aromatase inhibitors (at least 6 months)**	1a[a]	B	+
▪ **Aromatase inhibitor + lapatinib (HER2+ BC)**	2b	B	+/-
▪ **Premenopausal patients**			
▪ **Tamoxifen**	2b	C	+
▪ **Aromatase inhibitors + LHRHa**	1b	C	+/-
▪ **Concurrent chemo-endocrine therapy**	1b	A	-
▪ **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)**	1b	B	+
▪ **Prognostic score:**	1b	B	+
▪ **PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy**			

[a] **Optimal duration of neoadjuvant endocrine therapy is unknown. No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)**

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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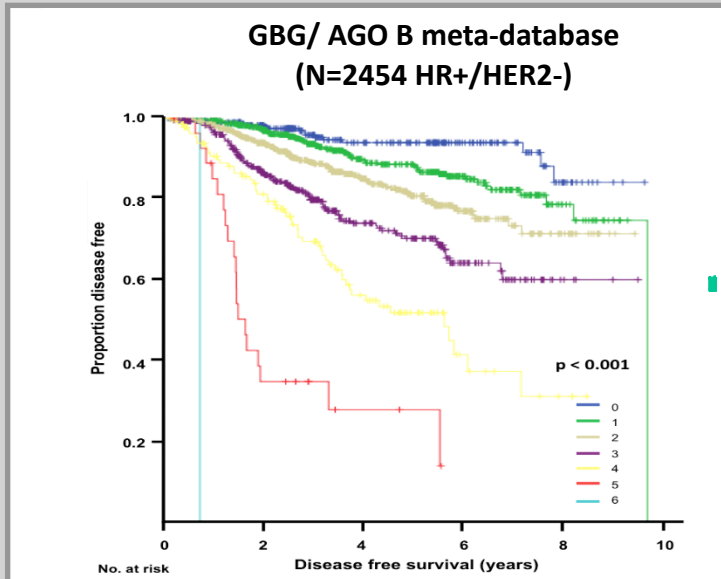
Point assignment for CPS+EG score

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

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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	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	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	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, 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