

Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Systemic therapy of primary early breast cancer - HER2+

Neoadjuvant Systemic Therapy

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- **Versions 2002–2024:**

Bauerfeind / Blohmer / Costa / Dall / Fasching / 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 2025:**

Blohmer / Huober

Strategies for Differentiated Systemic Treatment in the Curative Situation

AGO

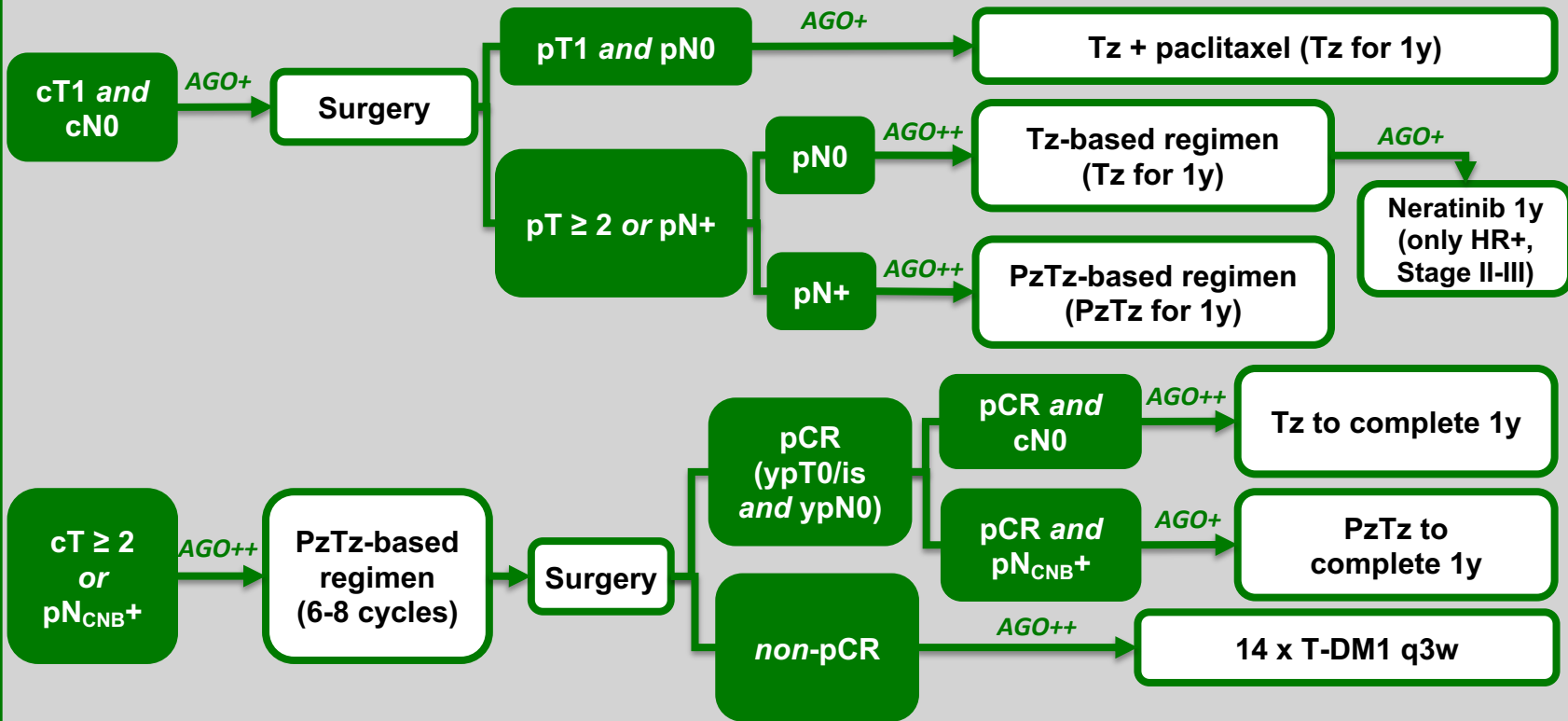
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended

- **HR+ / HER2- and „low recurrence-risk“**
 - Endocrine therapy without chemotherapy ++
- **HR+ / HER2- and „high recurrence-risk“**
 - endocrine therapy ++
 - endocrine-based therapy (abemaciclib or ribociclib) +
 - Patients with indication for chemo-endocrine therapy*
 - Conventionally dosed AT-based chemotherapy (q3w) +
 - Dose dense chemotherapy (including weekly schedule) ++
- **gBRCA1/2mut (HR+ / HER2- or TNBC respectively)**
 - Olaparib +/- endocrine therapy ++
- **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) ++
- **HER2+**
 - Trastuzumab (plus Pertuzumab in N+ or NACT) ++
 - Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy ++
 - Anthracycline-free, chemotherapy + anti-HER2 therapy ++

*see prognosis chapter

Therapy of HER2-positive Early Breast Cancer

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CNB, core needle biopsy; HR, hormone receptor; pCR, pathological complete response; Pz, Pertuzumab; q3w, every 3 weeks; T-DM1, Trastuzumab emtansine; Tz, Trastuzumab; y, year; if HR+ additional adjuvant endocrine therapy.

Lee-Schonberg Index

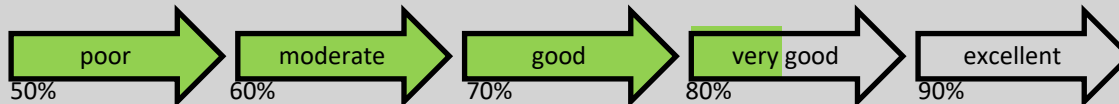
<https://eprognosis.ucsf.edu/leeschonberg-result.php>

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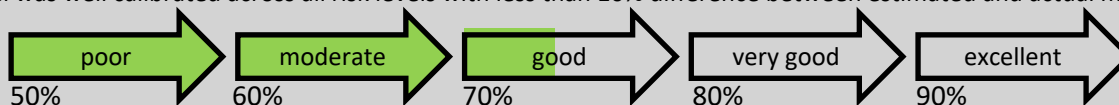
Lee Index

- 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.





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 BMI?
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?

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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: 93.6%

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

Oxford

LoE GR

- Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy
- 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
- Pathological complete response is associated with improved survival
- The RCB Score and the class of RCB are subtype independent prognostic factors
- Can achieve operability in primary inoperable tumors
- Improved options for breast conserving surgery
- Decreases rate of axillary lymphadenectomies lymphonodectomies
- Allows individualization of therapy according to mid-course treatment effect

1b

A

1a

A

1b

A

2a

B

1b

A

1b

A

2b

B

1b

B

Neoadjuvant Systemic Chemotherapy - Indications

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	LoE	GR	AGO
▪ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++
▪ To allow a risk adapted postoperative therapy	1b	A	++
▪ Inflammatory breast cancer	2b	B	++
▪ Primary inoperable breast cancer	1c	A	++
▪ Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	++

Neoadjuvant Systemic Therapy

Timing of Diagnosis, Surgery and Radiotherapy

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Timing of surgery

4-8 weeks after last course of chemotherapy

Radiotherapy within 2 months after surgery

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2a	B	++
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2b	B	++
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Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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	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

Neoadjuvant Chemotherapy

Treatment Strategies Based on Clinical Response

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	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	++
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	+/-

Postneoadjuvant Therapy HER2-positive

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	LoE	GR	AGO
<u>pCR</u>			
▪ 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, stage II-III)*	2b	B	+/-
<u>non-pCR</u>			
▪ 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, stage II-III)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive, stage II-III)*	5	D	+/-

* In combination with standard endocrine treatment

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

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- **HER2+ in combination with trastuzumab**
 - > 10 mm neoadjuvant or adjuvant
 - > 5-10 mm adjuvant
 - ≤ 5 mm adjuvant

Oxford		
LoE	GR	AGO
1a	A	++
2b	B	+
2b	B	+/-

Adjuvant HER2-directed Treatment

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■ Trastuzumab + Pertuzumab

- pN+
- pN-

■ Neratinib

- 1 year after 1 year trastuzumab (HR-positive, stage II-III)
- 1 year after trastuzumab / pertuzumab / T-DM1 (HR-positive, stage II-III)

Oxford		
LoE	GR	AGO

1b ^a	B	++
1b ^a	B	+/-
1b	B	+
5	D	+/-

(Neo)Adjuvant Treatment with Trastuzumab / Pertuzumab

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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	-

(Neo)Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

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Trastuzumab simultaneously with

- paclitaxel / docetaxel after AC / EC
- P q1w 12 x in pT < 2 cm, pN0
- docetaxel and carboplatin

1a A ++

2b B +

1b A +

Trastuzumab + Pertuzumab simultaneously with

- paclitaxel q1w (or docetaxel q3w) after EC / AC
- docetaxel+ carboplatin
- taxanes dose-dense

1b B ++

1b B ++

2b B +

Radiotherapy concurrently with Trastuzumab / Pertuzumab

1a A ++