

Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Systemic Therapy of Primary Early Breast Cancer - Hormone Receptor-positive, HER2-negative

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Systemic Therapy of Primary Early Breast Cancer - Hormone Receptor-positive, HER2-negative

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■ Version 2025:

Park-Simon / Schmidt

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

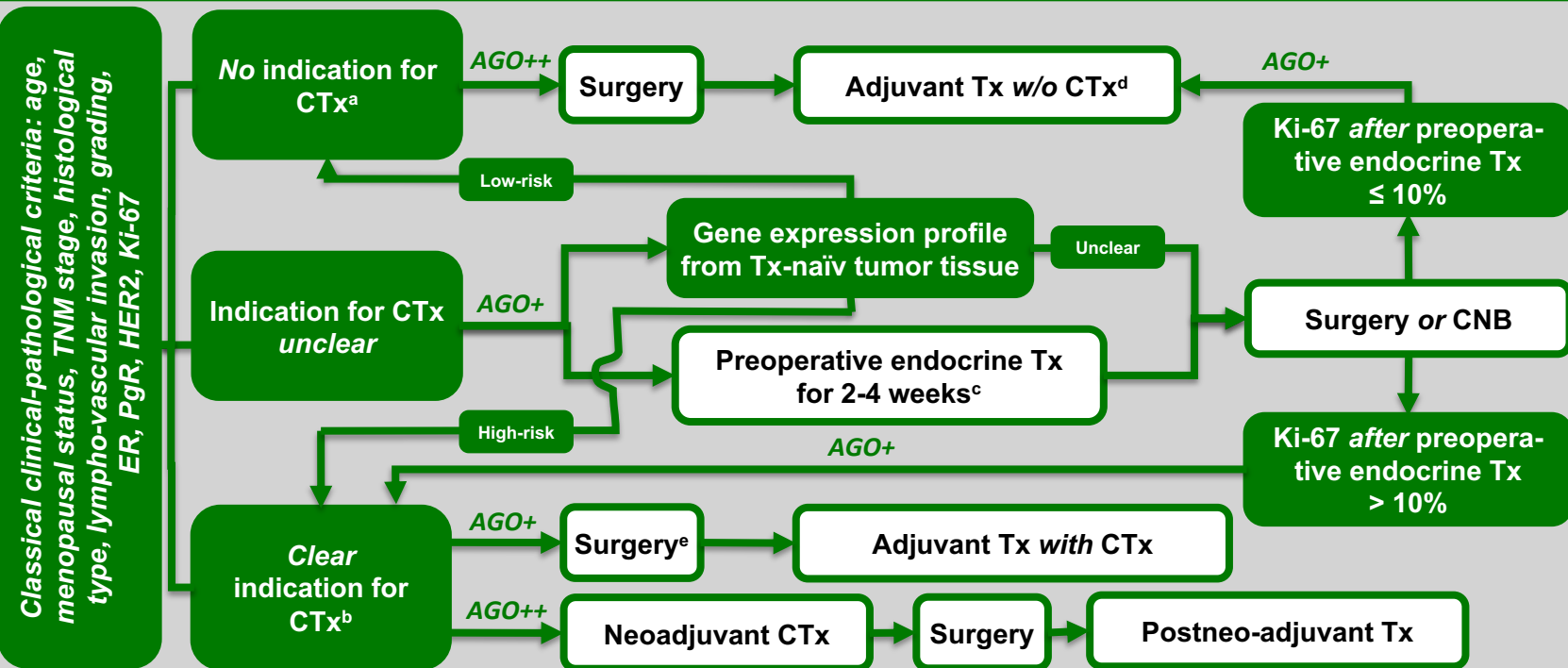
- | | |
|---|--------------------|
| <ul style="list-style-type: none"> ▪ HR+ / HER2- and „low recurrence-risk“ <ul style="list-style-type: none"> ▪ Endocrine therapy without chemotherapy | ++ |
| <ul style="list-style-type: none"> ▪ HR+ / HER2- and „high recurrence-risk“ <ul style="list-style-type: none"> ▪ endocrine therapy ▪ endocrine-based therapy (abemaciclib or ribociclib) ▪ Patients with indication for chemo-endocrine therapy* <ul style="list-style-type: none"> ▪ Conventionally dosed AT-based chemotherapy (q3w) ▪ Dose dense chemotherapy (including weekly schedule) | ++
+
+
++ |
| <ul style="list-style-type: none"> ▪ gBRCA1/2mut (HR+ / HER2- or TNBC respectively) <ul style="list-style-type: none"> ▪ Olaparib +/- endocrine therapy | ++ |
| <ul style="list-style-type: none"> ▪ Triple-negative (TNBC) <ul style="list-style-type: none"> ▪ Conventional dosed AT-based chemotherapy (q3w) ▪ Sequential AT-based chemotherapy (incl. weekly schedule) ▪ Neoadjuvant platinum-containing chemotherapy ▪ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab) | +
++
+
++ |
| <ul style="list-style-type: none"> ▪ HER2+ <ul style="list-style-type: none"> ▪ Trastuzumab (plus Pertuzumab in N+ or NACT) <ul style="list-style-type: none"> ▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy ▪ Anthracycline-free, chemotherapy + anti-HER2 therapy | ++
++
++ |

* see prognosis chapter

Therapy of HR-positive, HER2-negative Early Breast Cancer

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CNB, core needle biopsy; CTx, chemotherapy; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Tx, therapy; w/o, without; ^ae.g. \leq cT1c cN0-1 G1-2 Ki-67 \leq 5% or -if situation unclear- low-risk gene expression profile; ^be.g. inoperable tumor or \geq 4 clinically involved axillary nodes or G3 and Ki-67 \geq 35% or -if situation unclear- high-risk gene expression profile; ^cstandard endocrine Tx; ^dif no change of prognostic factors after surgery; ^eif not done already.

Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1

GR: A

AGO: ++

Endocrine responsive – hormone receptor positive Immunohistology (ER and/or PgR)

0%	pos. cells:	endocrine resistant
1–10%	pos. cells:	possibly endocrine sensitive
> 10%	pos. cells:	endocrine sensitive
Unknown hormone receptor status:		endocrine sensitive

If ER negative / PR positive (> 10% positive cells): reassess IHC status

If ER low (1-10%): Implications for therapy should be recommended in the pathology report

Adjuvant Endocrine Therapy

Assessment of Menopausal Status

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Assessment of menopausal status:

- Menstruation history
- FSH, E2

Oxford		
LoE	GR	AGO

++

++

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

Oxford

LoE GR

- Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy **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**
- The RCB Score and the class of RCB are subtype independent prognostic factors **2a B**
- 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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- **If similar postoperative adjuvant chemotherapy is indicated**
- **To allow a risk adapted postoperative therapy**
- **Inflammatory breast cancer**
- **Primary inoperable breast cancer**
- **Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation**

Oxford

LoE GR AGO

1b A ++

1b A ++

2b B ++

1c A ++

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

Oxford

LoE	GR	AGO
-----	----	-----

2a	B	++
----	---	----

2b	B	++
----	---	----

(Neo-)adjuvant Chemotherapy without Trastuzumab: Overview

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- **Dose-dense anthracycline / taxane based (incl. weekly) chemotherapy**
- **Conventional anthracycline / taxane based (q3w)**
- **„Tailored“ anthracycline-/ taxane based**
- **If anthracyclines are not a preferred option**
 - **Docetaxel plus cyclophosphamide**
 - **Paclitaxel mono weekly**
 - **CMF**

Oxford

LoE	GR	AGO
-----	----	-----

1a	A	++
----	---	----

1a	A	+
----	---	---

1b	B	+/-
----	---	-----

1b	B	++
----	---	----

1b	B	+/-
----	---	-----

1a	A	+/-
----	---	-----

Recommended Dose-dense and / or Dose-escalated, Sequential (Neo-)adjuvant Chemotherapy

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Dose-dense regimen

- $A_{60} \times 4 \rightarrow Pac_{175} \times 4 \rightarrow C_{600} \times 4$ q2w
- $A_{60}C$ q2w $\times 4 \rightarrow Pac_{175}$ q2w $\times 4$
- $E_{90}C$ q2w $\times 4 \rightarrow Pac_{175}$ q2w $\times 4$
- $E_{90}C$ q2w $\times 4 \rightarrow Pac_{80}$ q1w $\times 12$
- $NabPac_{125} \times 8-12 \rightarrow E_{90}C$ q2(3)w $\times 4$

Dose-dense and dose-escalated regimen (N $\geq 4+$)

- $E_{150} \rightarrow Pac_{225} \rightarrow C2000$ q2w

Oxford

LoE	GR	AGO
-----	----	-----

1b	A	++
1b	B	++
1b	A	++
1b	B	++
1b	B	+
1b	A	++

Recommended Conventional Regimens for (Neo-)adjuvant Chemotherapy

Oxford

LoE GR AGO

Anthrazyklin-/ taxan-based regimen

- *EC q3w x 4 → Pac q1w x 12
- AC q3w x 4 → Pac q1w x 12
- AC → D qw3 A₆₀C q3w x 4 → D₁₀₀ x 4
- *EC → D qw3 E₉₀C q3w x 4 → D₁₀₀ x 4
- DAC D₇₅A₅₀C q3w x 6

2b	B	++
1b	A	++
1b	A	+
1b	B	+
1b	A	+ ^a

Anthrazyklin-free regimen

- 6 x DC corresponds to EC → D or 3 x (F)EC-
3 x Doc D₇₅ C₆₀₀ x 6
- 4 x DC >> 4 x AC D₇₅ C₆₀₀ x 4
- Pac mono P₈₀ q1w x 12
- CMF

1b	B	+
1b	B	+
1b	B	+/-
1a	A	+/-

Taxan-free regimen

- EC (q3-2w) x 4-6 E₉₀C₆₀₀ x 4-6

2b ^(a)	B	+
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* Extrapolation from doxorubicin trials

Neoadjuvant endocrine Therapy (NET) - Good clinical practice -

- **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 response 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)**

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Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer



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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Postmenopausal patients: <ul style="list-style-type: none"> ■ Optimizes the option for breast conserving therapy ■ Aromatase inhibitors (at least 6 months) 	1b	A	+
	1a*	B	+
<ul style="list-style-type: none"> ■ Premenopausal patients <ul style="list-style-type: none"> ■ Tamoxifen ■ Aromatase inhibitors + LHRHa 	2b	C	+
	1b	C	+/-
<ul style="list-style-type: none"> ■ Concurrent chemo-endocrine therapy 	1b	A	-
<ul style="list-style-type: none"> ■ Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information) 	1b	B	+
<ul style="list-style-type: none"> ■ Prognostic score: <ul style="list-style-type: none"> ■ PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy 	1b	B	+

* No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

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
- Continuation of NACT with non cross-resistant regimen
 - AC or EC x 4 → D x 4 or Pw x 12
 - DAC x 2 → NX x 4

2b C ++

2b B +

2b B +

1b B +

In case of disease progression

- Re-evaluation of tumorbiological factors
- Stop NACT and proceed to surgery or radiotherapy
- Additional adjuvant chemotherapy with non cross-resistant regimen

5 D +/-

4 D ++

4 D +/-

How to Calculate CPS+EG Score?

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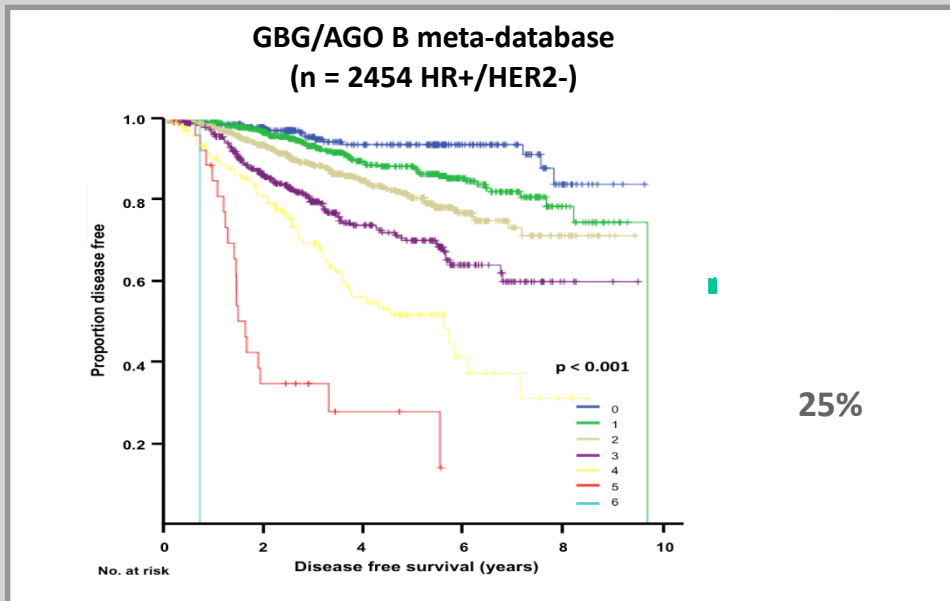
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Point assignment for CPS+EG score

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	



Postneo-/Adjuvant Therapy HR+ / HER2-

Oxford

LoE	GR	AGO
1a	A	++
1b	B	+
1b	B	+
1b	A	++
1b	A	++
5	D	+
1b	A	+/-

- Endocrine therapy according to menopausal state
- Abemaciclib for 2 y + endokrine therapy¹
- Ribociclib (400 mg) for 3 y + AI +/- GnRHa²

- Olaparib for 1 y + endokrine therapy (gBRCA1/2^{MUT})³
 - Adjuvant: ≥ 4 involved lymph nodes
 - Postneoadjuvant: non-pCR and CPS-EG Score ≥ 3
 - CDK4/6i in sequence, starting with olaparib
- Capecitabin (bei non-pCR)

1 Corresponding to monarchE-study

2 Corresponding to Natalee-study

3 Corresponding to OlympiA-study

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

	monarchE	PALLAS	PENELOPE ^B	NATALLEE
n	5,637	5,600	1,250	5101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	95%	n.r.	100%	88%
Duration of CDK4/6i treatment	24 months	24 months	12 mths	36 months
Follow-up	54.0 months	24 months	43 months	44.2 months
Discontinuation rate	28%	42%	20%	36.2%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%	20%
IDFS-HR (95%-CI)	0.680 (0.599-0.720) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.715 (0.609-0.840) P<0.0001
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88.2% vs. 88.5%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	88.5% vs. 83.6%
5-yrs IDFS	83.6% vs. 76%			

IDFS: invasive disease-free survival

Adjuvant Endocrine Therapy

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	Oxford		
	LoE	GR	AGO
■ Endocrine responsive	1a	A	++
■ Endocrine doubtful responsiveness (1-10%)	2b	D	+
■ Endocrine therapy sequentially after CT	2a	B	+
■ Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)	2b	B	+
■ Not sensitiv to endocrine therapy	1a	A	--

General Principles in Adjuvant Endocrine Therapy

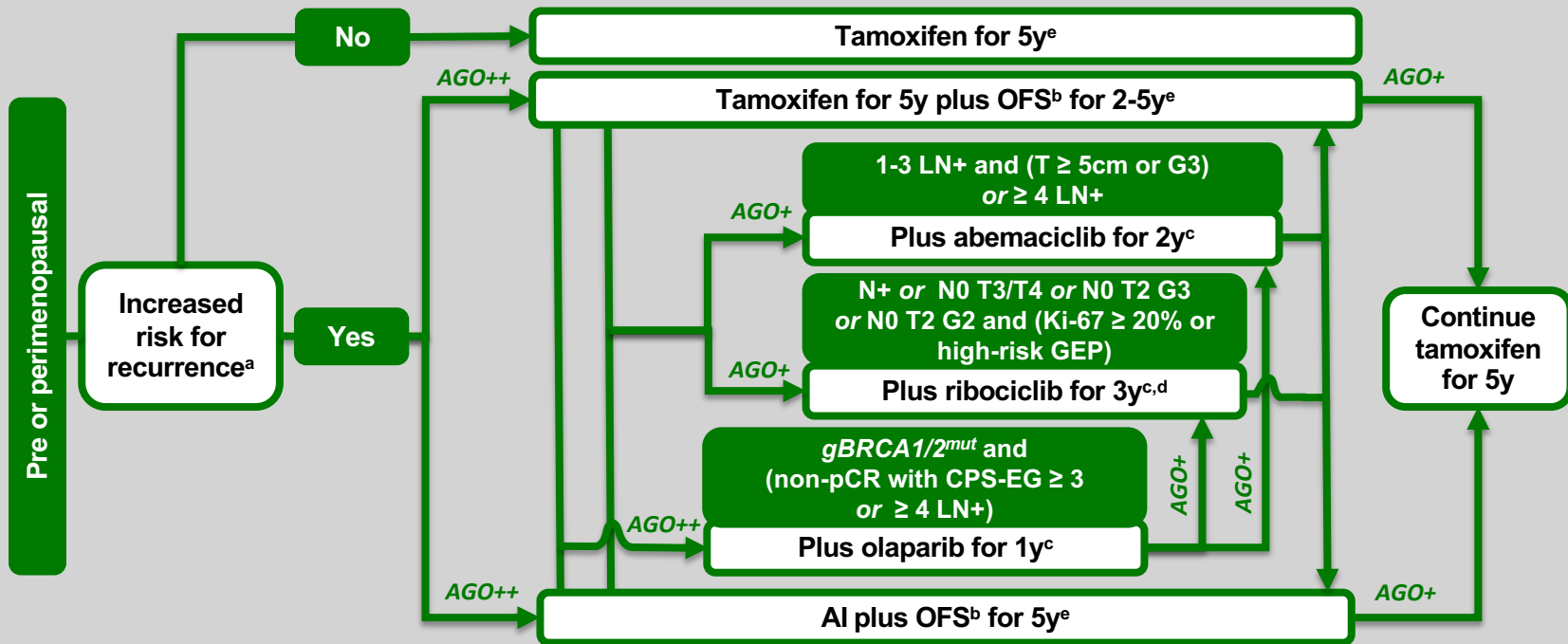
- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5), extended adjuvant therapy (EAT, years 6-10+) and adjuvant endocrine-based treatment.**
- **Standard treatment duration is 5 years.**
- **Extended therapy and initial adjuvant endocrine-based therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam or the combination with GnRHa mainly depend on menopausal status, tolerability, and risk of recurrence.**

General Principles in Adjuvant Endocrine Therapy

- **Switch to another better tolerated endocrine treatment (Tam or AI) or Tam low dose is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, in case of high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker for identification of patients at risk for early versus late recurrence.**
- **Bisphosphonates (see also chapter on bone health)**
 - **Osteoprotection**
 - **Improvement of prognosis**
- **Women who undergo medical or surgical a hormone ablation are to be equated with postmenopausal women.**

Adjuvant Endocrine-based Therapy in Premenopausal Patients

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AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; *gBRCA1/2^{mut}*, germline *BRCA1/2* mutation; GEP, gene expression signature; LN, lymph node; non-pCR, no pathological complete response; OFS, ovarian function suppression; y, years; ^aadministration of chemotherapy was a surrogate marker for higher risk of recurrence in clinical trials; ^bOFS in case of remaining or recurring ovarian function within 24 months after chemotherapy induced amenorrhea; ^conly HER2-negative; ^donly combined with AI + OFS; ^ein case patients wish to become pregnant interruption of adjuvant endocrine therapy after 18 months for a maximum of 2 years is possible without short-term survival disadvantage with a median F/U of only 3.5 years (AGO+).

Premenopausal Patients

Initial Adjuvant Endocrine Therapy (Year 1-5)

Oxford

LoE GR AGO

<ul style="list-style-type: none"> Low recurrence risk: <ul style="list-style-type: none"> Tamoxifen for 5 years Increased recurrence risk: <ul style="list-style-type: none"> OFS 2-5 years* + tamoxifen for 5 years OFS[#] + AI for 5 years GnRHa monotherapie (If severe contraindications for Tam exist, compared to no therapy) 	1a	A	++
	1a	A	++
	1a	A	++
	1a	B	+

OFS: ovarian function suppression;

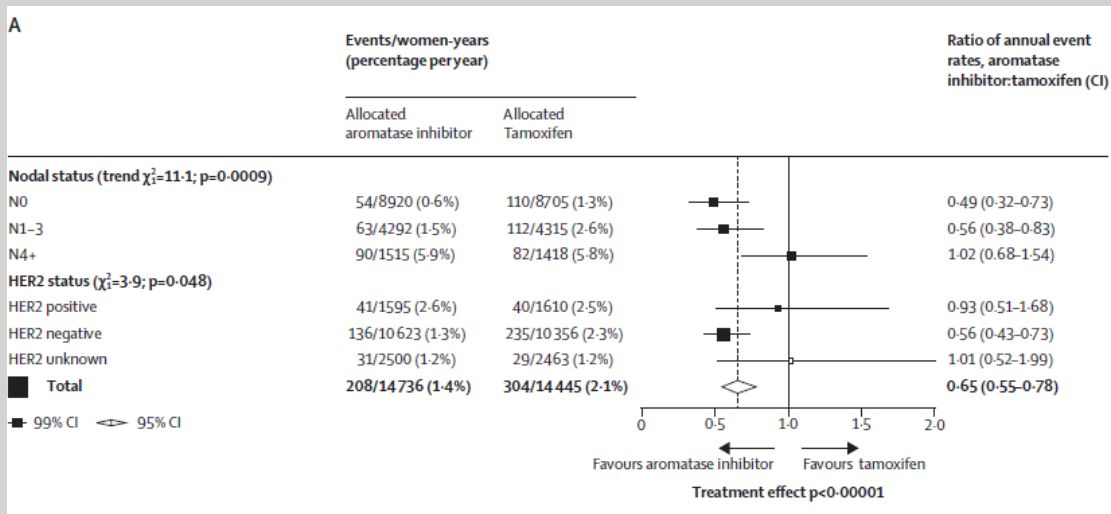
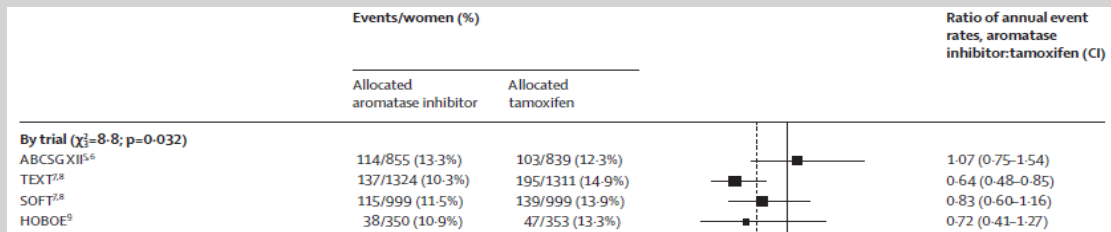
* as long as tolerated and the patient is clearly premenopausal after chemotherapy if ovarian function resumes within 24 months. The application of chemotherapy in the trials served as surrogate for high recurrence risk

in premenopausal women AI only in combination with OFS

Adjuvant Endocrine Therapy in Premenopausal Patients (OFS + TAM / AI)

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Adjuvant Endocrine Therapy in Premenopausal Patients (OFS + TAM / AI)



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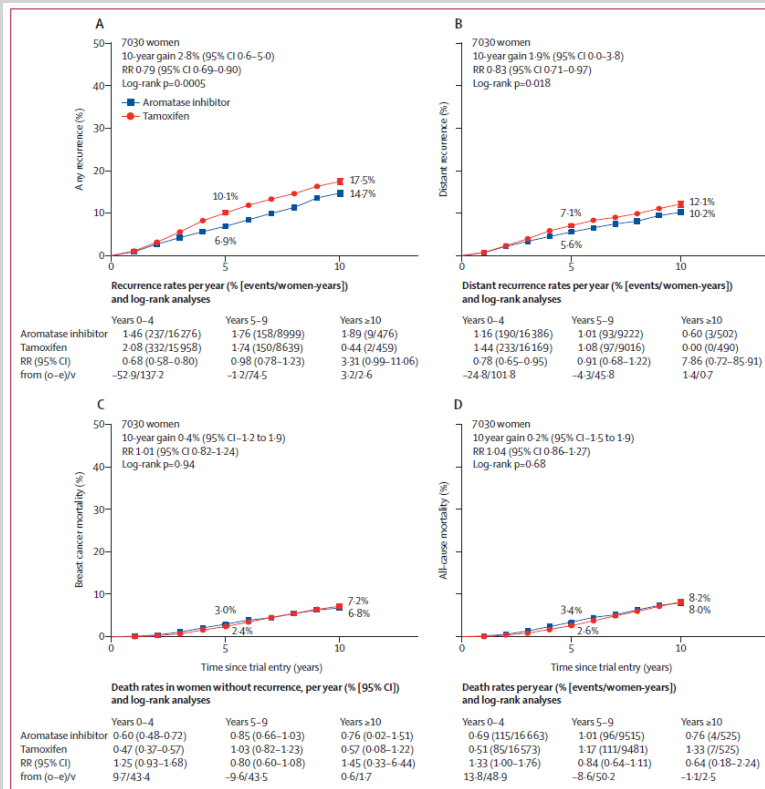
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Any recurrence

Breast cancer mortality

Distant recurrence

All-case mortality



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Premenopausal Patients

Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

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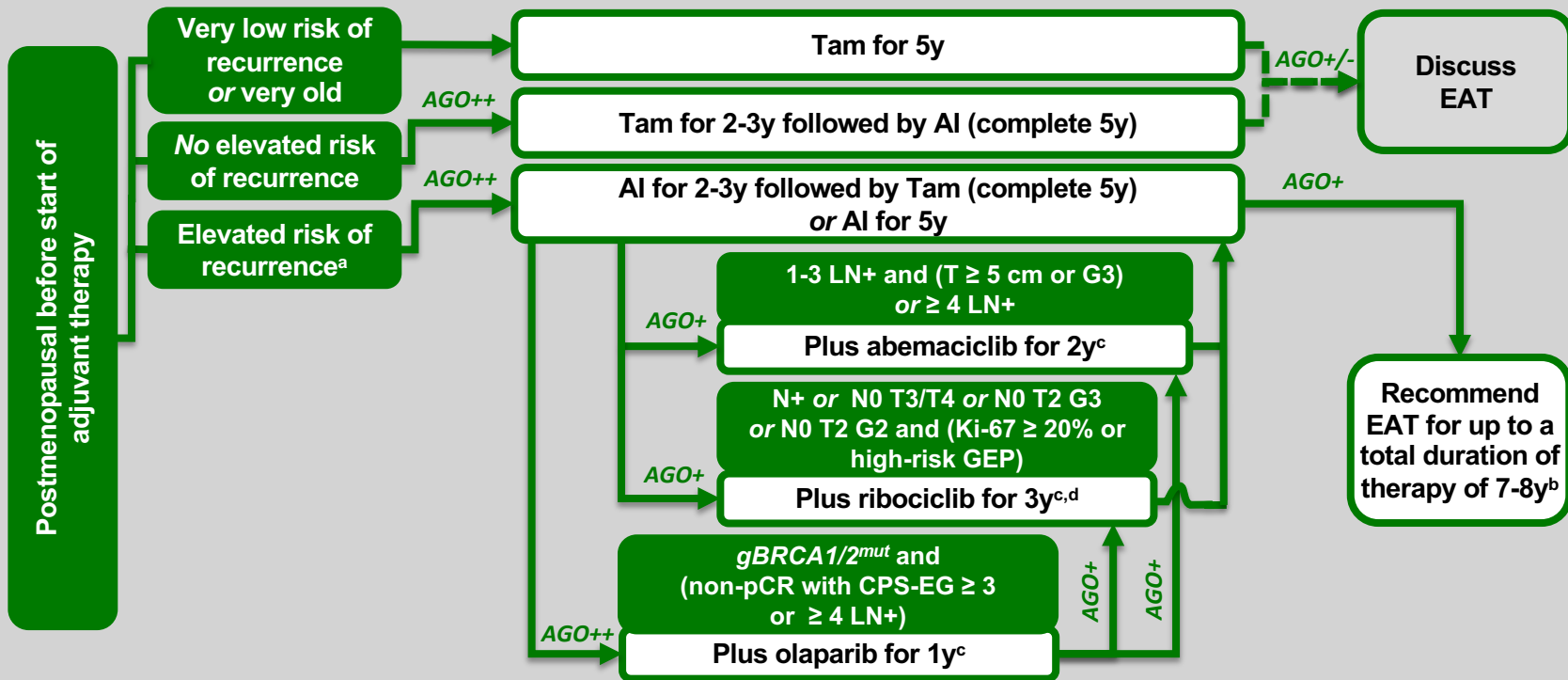
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	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	++
▪ 2,5-5 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

Adjuvant Endocrine-based Therapy in Postmenopausal Patients

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AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; EAT, extended adjuvant therapy; *gBRCA1/2^{mut}*, germline *BRCA1/2* mutation; GEP, gene expression signature; LN, lymph node; non-pCR, no pathological complete response; Tam, tamoxifen; y, years; ^adecision criteria may include: condition after neo(adjuvant) chemotherapy (indicating high risk), positive lymph node status, T2/T3 tumors, elevated risk of recurrence based on immuno-histochemical criteria or based on multi-gene expression assays, regarding EAT high CTS5-Score; ^bup to date no impact on overall survival; ^conly HER2 negative; ^donly combined with AI.

Postmenopausal Patients

Initial Adjuvant Endocrine Therapy (Years 1-5)

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- **Aromatase inhibitor (AI) for first 5 years**
 - High risk of recurrence
- **Sequential therapy for first 5 years ***
 - Tam (2-3 yrs.) followed by AI to complete 5 years
 - AI (2-3 yrs.) followed by tamoxifen to complete 5 years
- **Tamoxifen 20 mg/d for 5 years****

Oxford		
LoE	GR	AGO
1a	A	++
2b	B	+
1a	A	++
1a	A	++
1b	C	++
1a	A	+

* in postmenopausal patients, AI should be integrated in the first five years

** Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present

Postmenopausal Patients

Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

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Oxford

LoE	GR	AGO
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In case of high risk of recurrence

- | | | | |
|--|----|---|--------|
| <ul style="list-style-type: none"> 5 years tamoxifen after 5 years tamoxifen | 1a | A | + |
| <ul style="list-style-type: none"> 2–5 years AI after 5 years tamoxifen | 1a | A | ++ |
| <ul style="list-style-type: none"> After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI in total for 7-8 years* <ul style="list-style-type: none"> High-risk of recurrence and good tolerability of AI, good bone health Low-risk, poor tolerability of AI | 1a | A | +
- |
| <ul style="list-style-type: none"> Interruption of endocrine treatment up to 3 months during EAT with AI | 1b | B | +/- |

* No impact on OS

Decision Criteria for Extended Adjuvant Therapy

Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and / or T2 / T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score
- BCI (H/I) (Breast Cancer Index)

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence