CLINICAL PRACTICE GUIDELINES

An ESMO Product

Early Breast Cancer

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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Screening, Diagnosis, Pathology & Molecular biology

Summary of recommendations
Regular (annual or every 2 years) mammography in women aged 50–69 years and annual MRI of women with familial breast cancer are recommended
Diagnosis is based on clinical examination and imaging and confirmed by pathological assessment
Bilateral mammogram and US of breasts and axillae are recommended
Tumours should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data
Genetic counselling and testing for germline *BRCA1* and *BRCA2* mutations should be offered to high-risk groups

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Diagnostic work-up for Early Breast Cancer

Diagnostic work-up for Early Breast Cancer	
Assessment of general health status	• History • Menopausal status • Physical examination • Full blood count • Liver, renal and cardiac (in patients planned for anthracycline and/or trastuzumab treatment) function tests, alkaline phosphatase and calcium
Assessment of primary tumour	• Physical examination • Mammography • Breast US • Breast MRI in selected cases • Core biopsy with pathology determination of histology, grade, ER, PgR, HER2 and Ki67
Assessment of regional lymph nodes	• Physical examination • US • US-guided biopsy if suspicious
Assessment of metastatic disease	• Physical examination • Other tests are not routinely recommended, unless high tumour burden, aggressive biology or when symptoms suggestive of metastases are present

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Surrogate definitions of intrinsic subtypes of breast cancer

Luminal A and Luminal B

*Ki-67 scores should be interpreted in light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.

†Suggested cut-off value is 20%; quality assurance programmes are essential for laboratories reporting these results.

Adapted from the 2013 St Gallen Consensus Conference

Intrinsic subtype	Clinicopathological surrogate definition
Luminal A	Luminal A-like: • ER-positive • HER2-negative • Ki67 low* • PgR high† • Low-risk molecular signature (if available)
Luminal B	Luminal B-like (HER2-negative): • ER-positive • HER2-negative and either • Ki67 high or • PgR low or • High-risk molecular signature (if available) Luminal B-like (HER2-positive): • ER-positive • HER2-positive • Any Ki67 • Any PgR

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Surrogate definitions of intrinsic subtypes of breast cancer

HER2 and basal-like

‡There is ~80% overlap between 'triple-negative' and intrinsic 'basal' subtype, but 'triple-negative' also includes some special histological types such as carcinoma with a rich lymphocytic stroma (former medullary), secretory carcinoma, low-grade metaplastic carcinoma and adenoid cystic carcinoma.

Adapted from the 2013 St Gallen Consensus Conference

Intrinsic subtype	Clinicopathological surrogate definition
HER2	HER2-positive (non-luminal): • HER2-positive • ER and PgR absent
Basal-like	Triple negative‡: ER and PgR absent‡ HER2-negative‡

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Staging and risk assessment

Summary of recommendations
Disease stage should be assessed according to the AJCC TNM staging system
Minimum blood work-up is recommended before surgery and systemic (neo)adjuvant therapy, with chest, abdomen and bone imaging for higher-risk patients
Postoperative pathological assessment of surgical specimens should be made according to the pathological TNM system

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Treatment

Summary of recommendations
Treatment should be carried out by a specialised breast cancer multidisciplinary team in specialised breast units/centres and patients should be actively involved in all management decisions
Treatment should be based on the tumour burden/location and biology, as well as age, menopausal status, general health status and patient preference
Fertility and fertility-preservation should be discussed with younger premenopausal patients prior to the initiation of any systemic treatment

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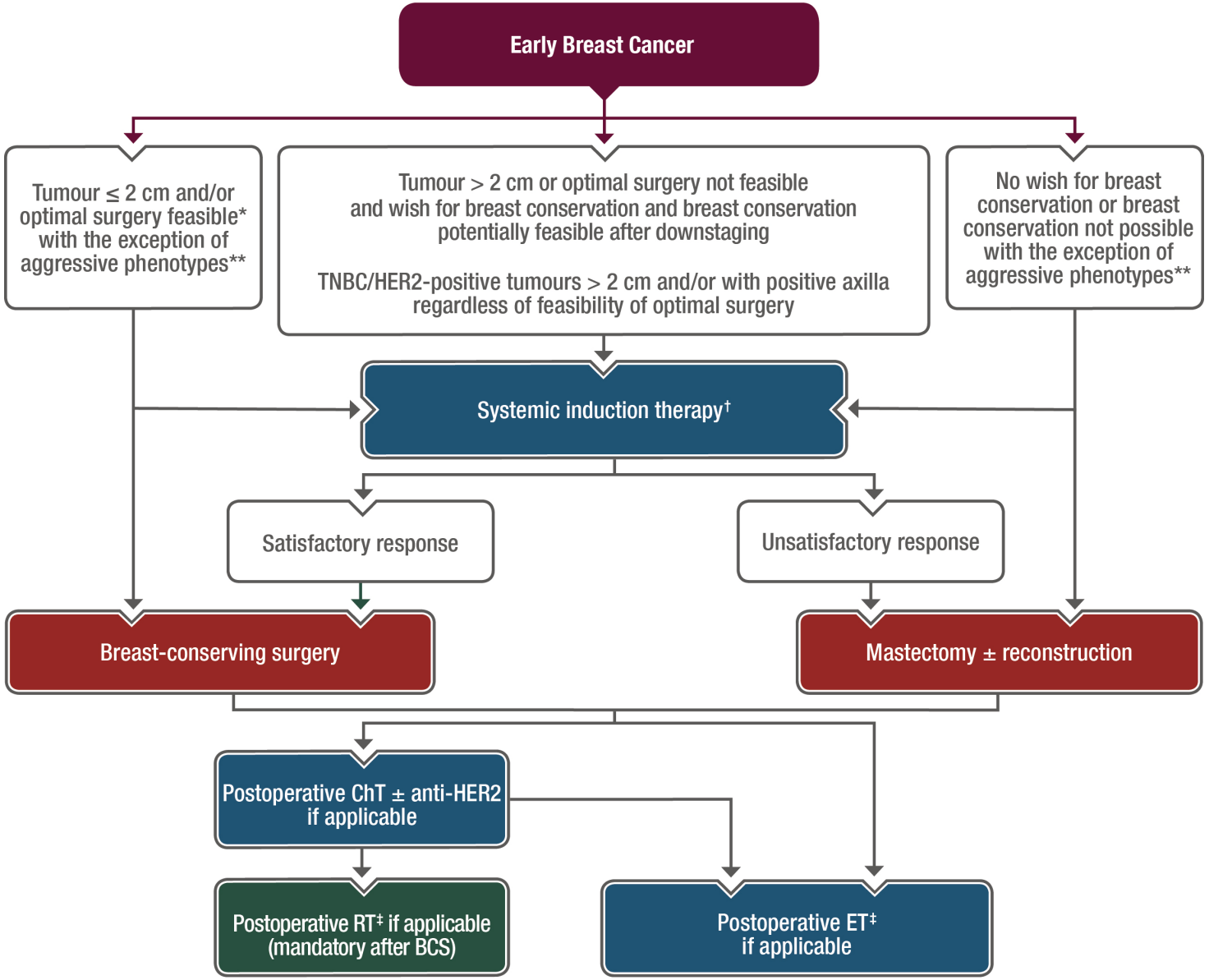
Treatment



* Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT

** Aggressive phenotypes: TNBC or HER2-positive breast cancer

† If ChT is planned, it should all be given as neoadjuvant

‡ Concomitant postoperative RT, postoperative ET and anti-HER2 therapy

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Local treatment

Surgery

In all women undergoing mastectomy, breast reconstruction should be available and immediate reconstruction is suitable for the vast majority of cases except inflammatory cancer; the optimal reconstruction technique for each patient should be discussed individually

Type of tumour	Method
Most early breast cancers	BCS is the preferred local treatment option
Early, clinically node-negative breast cancer	• SLNB is the standard of care for axillary staging • If positive SLNB, further axillary surgery is not required for low axillary disease burden, axillary RT is an alternative
DCIS	BCS (with a 2 mm margin) followed by WBRT or total mastectomy are acceptable treatment options
Occult breast cancer	ALND and WBRT are the preferred locoregional management

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Local treatment

Risk-reducing mastectomy and Surgery after PST

Summary of recommendations	
Risk-reducing mastectomy	
Very high risk patients	Risk-reducing surgery may be offered and presurgery genetic assessment and psychological counselling are mandatory
Non-high-risk patients opting for bilateral mastectomy	should be counselled that survival outcomes with BCS may be better
Surgery after PST	
If BCS is anticipated, the tumour site should be marked and pre- and post-treatment breast MRI carried out	
In clinically negative axilla, post-PST SLNB is preferred to pre-PST SLNB	
SLNB may be carried out in selected cases of baseline limited axillary involvement converting to negative	
Tumour deposits in post-PST SLNB prompt ALND	

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Local treatment

RT

Type of situation	Indications on RT
Routine postoperative RT	Moderate hypofractionation schedules (15–16 fractions of ≤ 3 Gy/fraction) are recommended
After BCS	Postoperative WBRT is strongly recommended • Boost RT where there is a high risk of local recurrence Accelerated partial-breast RT where the risk of recurrence is low
Post-mastectomy: high-risk patients / patients with 1-3 positive axillary lymph nodes	PMRT is recommended
Patients with involved lymph nodes	Regional comprehensive nodal RT is recommended
After ALND	Routine axillary irradiation should not be applied to the operated part of the axilla
After immediate breast reconstruction	Postoperative RT can be administered, if indicated
In DCIS	WBRT is recommended for most women undergoing BCS, with tumour bed boost being a consideration for patients at a high risk of local failure

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Systemic treatment

Recommendations for early breast cancer subtypes

For special histological types, the authors recommend following the St Gallen recommendations that propose ET for endocrine-responsive histologies (cribriform, tubular and mucinous), ChT for high-risk endocrine-nonresponsive histologies (medullary, metaplastic) and no systemic therapy for low-risk endocrine nonresponsive histologies (adenoid cystic and apocrine)

Subtype	Recommended therapy	Comments
Luminal A-like	ET alone in the majority of cases	Consider ChT if high tumour burden (≥ 4 LNs, T3 or higher)
Luminal B-like (HER2-negative)	ChT followed by ET for the majority of cases	-
Luminal B-like (HER2-positive)	ChT + anti-HER2 followed by ET for all patients	If contraindications for the use of ChT, one may consider ET + anti-HER2 therapy, although no randomised data exist
HER2-positive (non-luminal)	ChT + anti-HER2	-
Triple-negative (ductal)	ChT	-

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(Neo)Adjuvant systemic treatment

Summary of biomarkers used in treatment-decision making – ER, PgR, HER2

Biomarker	Method	Use
ER	IHC Positive if ≥ 1%	Essential to the characterization of the IHC luminal-like group Poor prognostic marker if negative Predictive marker for ET Mandatory for ET prescription
PgR	IHC Positive if ≥ 1%	If negative tumour classified as IHC luminal B-like Strong poor prognostic marker if negative Predictive marker for ET
HER2	IHC Positive if > 10% complete membrane straining (3+) ISH • Single probe if HER2 ≥ 6 copies • Dual probe Positive if HER2/CEP17 ≥ 2 and HER2 copies ≥ 4 or HER2/CEP17 < 2 and HER2 copies ≥ 6	Essential to the characterization of: • HER2-enriched (ER-negative) • Luminal B-like, HER2-positive Prognostic marker Predictive marker of anti-HER2 treatment Mandatory for anti-HER2 therapy regardless of treatment line

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(Neo)Adjuvant systemic treatment

Summary of biomarkers used in treatment-decision making – Ki67, intrinsic subtypes

Biomarker	Method	Use
Ki67	IHC No final consensus on cut-off but values below 10% are considered low and above 30% are considered high*	Absence of international consensus for scoring and threshold Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant residual tumour) Absence of prognostic value in HER2-positive or triple-negative tumours Predictive of response to neoadjuvant ET† Predictive of response to neoadjuvant ChT If elevated, ChT is often prescribed in ER-positive, HER2-negative tumours Part of the IHC definition of luminal-like tumours • Ki67 low, luminal A-like • Ki67 high, luminal B-like
Intrinsic subtypes	Gene expression profile, N-Counter™ technology	Prognostic Predictive: Different responses to neoadjuvant ChT and anti-HER2 therapy according to the subtype

* According to the International Ki67 Working Group Guidelines, Dowsett M et al. J Natl Cancer Inst 2011;103:1656–64.

† A decrease in Ki67 expression during neoadjuvant ET is highly predictive of response

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(Neo)Adjuvant systemic treatment

Summary of biomarkers used in treatment-decision making – First and second-generation signatures

Biomarker	Method	Use
First-generation signatures (MammaPrint, Oncotype DX)	Gene expression profile, RT-PCR	For ER-positive, HER2-negative tumours Prognostic (Neo)Adjuvant ChT is indicated if high risk or high score Can be carried out in biopsy or surgical specimen
Second-generation signatures (Prosigna®, Endopredict®)	N-Counter™ technology, RT-PCR	For ER-positive, HER2-negative tumours, include T size and N status in their final score Prognostic (Neo)Adjuvant ChT is indicated if high risk or high score Can be carried out in biopsy or surgical specimen

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(Neo)Adjuvant systemic treatment

Treatment choice by marker expression and intrinsic phenotype

(Neo)-adjuvant systemic treatment choice by marker expression and intrinsic phenotype.

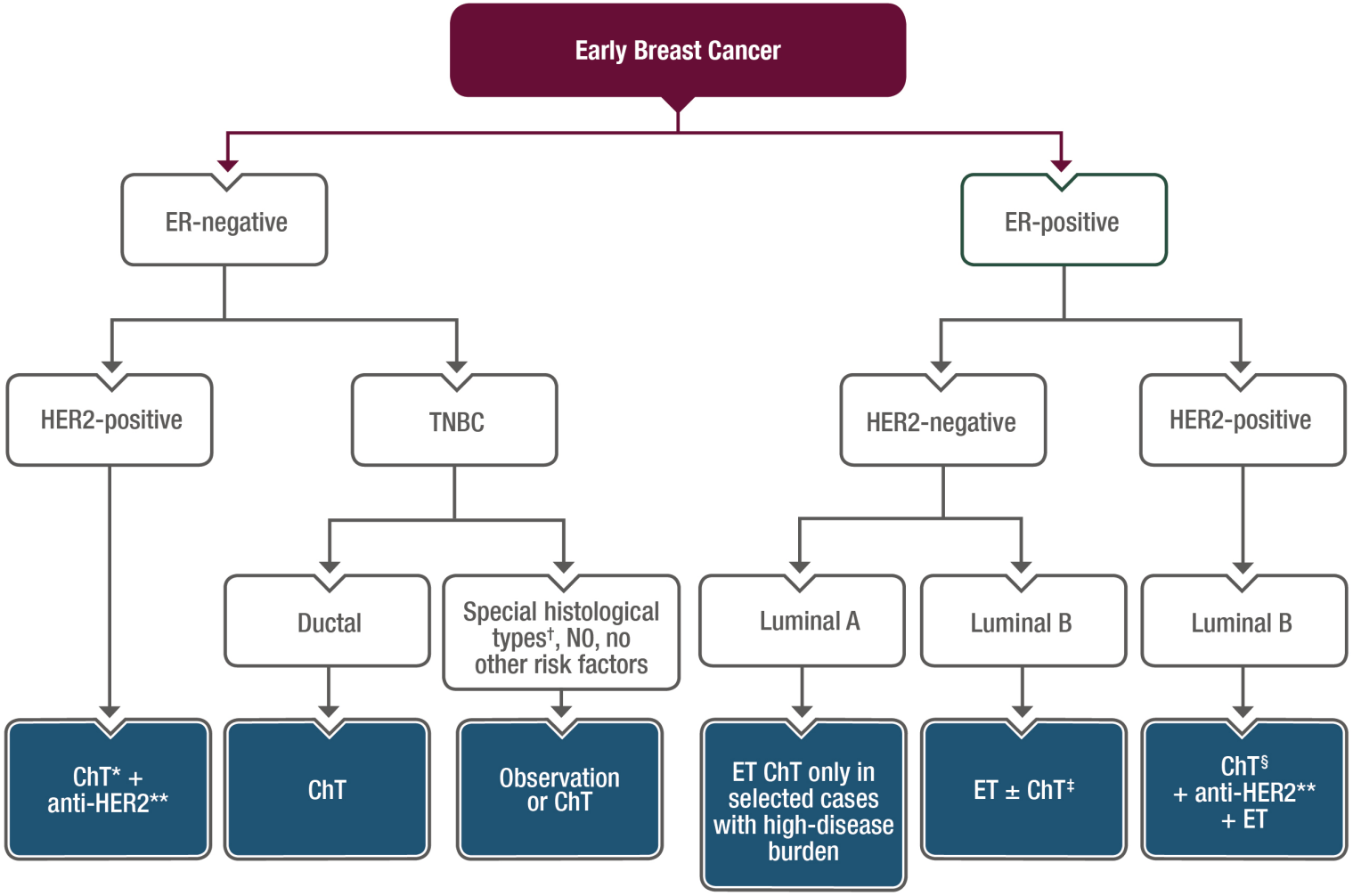
* With possible exception of selected cases with very low risk T1abN0.

** Anti-HER2: trastuzumab ± pertuzumab.

† Adenoid cystic or apocrine, secretory carcinoma, low-grade metaplastic carcinoma.

‡ Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

§ Except for very low-risk patients T1abN0 for whom ET/anti-HER2 therapy alone can be considered.



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(Neo)Adjuvant systemic treatment

Summary of recommendations
• Adjuvant treatment should start within 3–6 weeks after surgery • Neoadjuvant treatment should start within 2–4 weeks of diagnosis and staging
All luminal-like cancers should be treated with ET
ChT: • not required for most luminal A-like tumours • not concomitantly with ET, except for gonadotropin-releasing hormone analogues used for ovarian protection • use based on risk of recurrence and presumed responsiveness to ET (for luminal B-like HER2-negative) • with anti-HER2 therapy and followed by ET (for luminal B-like HER2-positive)
Patients with TNBC should generally receive ChT
HER2-positive cancers should generally be treated with ChT plus anti-HER2 therapy
Anti-HER2 therapy may routinely be combined with non-anthracycline-based ChT, ET and RT, and should be administered sequentially to anthracycline-based ChT
RT may be delivered safely during anti-HER2 therapy, ET and non-anthracycline, non-taxane-based ChT
When used together, ChT should usually precede RT

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(Neo)Adjuvant systemic treatment

Endocrine Therapy

Summary of recommendations	
Premenopausal patients	• Tamoxifen for 5–10 years is standard, AI alternative for high-risk patients (if AI is given, OFS/OA is mandatory) • Patients becoming postmenopausal during the first 5 years of tamoxifen, can be switched to letrozole • Patients < 35 years not requiring ChT should receive OFS combined with ET
Postmenopausal patients	• AIs (upfront, after tamoxifen or as extended adjuvant therapy) and tamoxifen are standard treatments • There is only a minimal benefit for the use of AIs for more than 5 years

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(Neo)Adjuvant systemic treatment

Chemotherapy

Summary of recommendations
ChT should be administered for 12–24 weeks (4–8 cycles)
• Sequential anthracycline (EC or AC)/taxane-based regimen is the standard • 4 cycles of anthracycline- or taxane-based ChT or CMF may be used in lower-risk patients
Non-anthracycline regimens may be used in patients at risk of cardiac complications
G-CSF-supported dose-dense schedules should be considered, particularly in highly proliferative tumours

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(Neo)Adjuvant systemic treatment

Anti-HER2 therapy

Summary of recommendations
Standard is: one year of (neo)adjuvant trastuzumab for HER2-positive patients with no contraindications
Trastuzumab can be given concomitantly with non-anthracycline-based (sequentially with anthracycline-based) ChT
Regular cardiac monitoring before starting and during trastuzumab treatment is mandatory
High-risk patients: • One year of combined trastuzumab/pertuzumab can be considered • Extended anti-HER2 therapy with neratinib may be considered in some cases
If residual invasive disease after combined neoadjuvant ChT and anti-HER2 therapy, adjuvant trastuzumab should be replaced by adjuvant T-DM1

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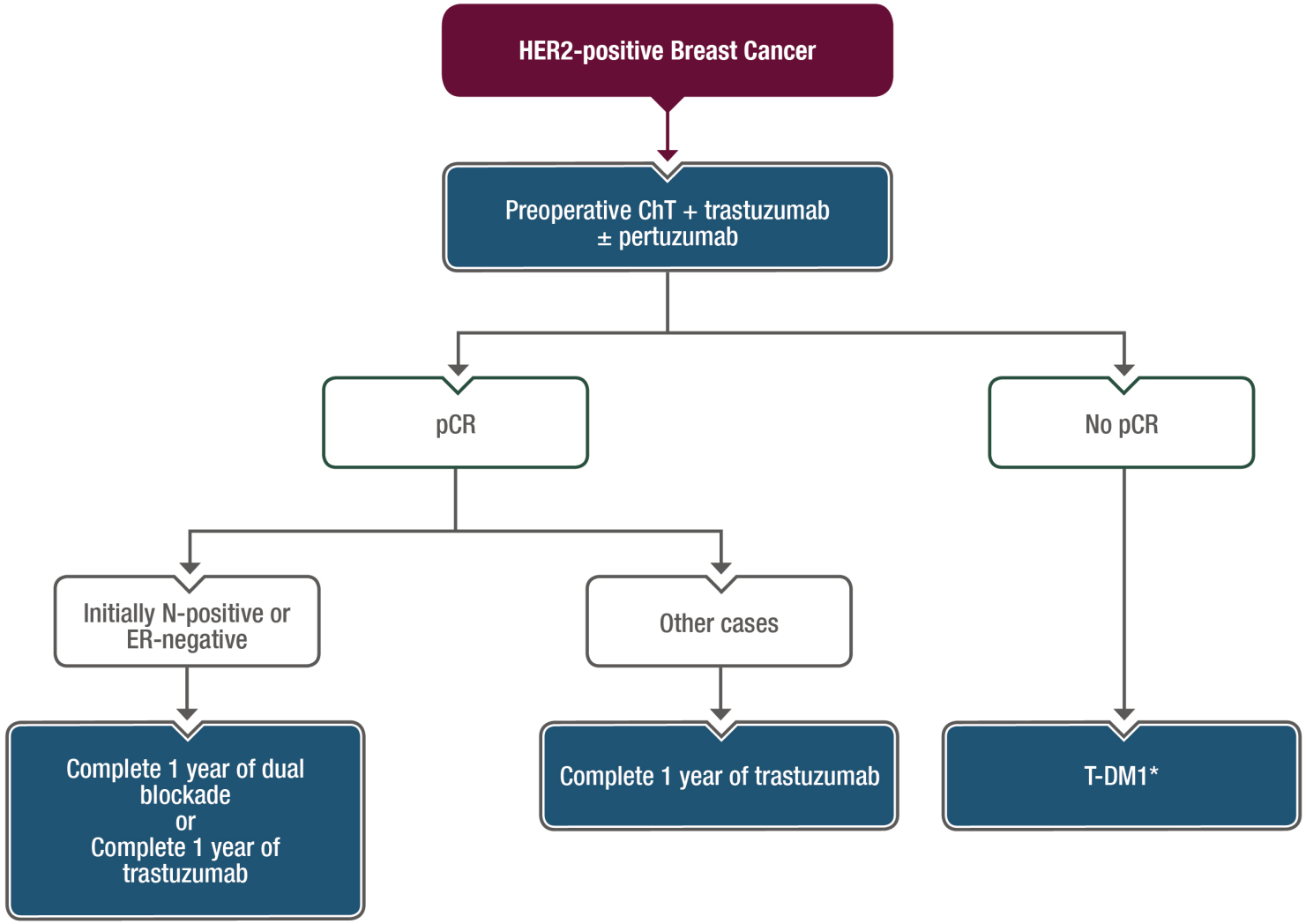
(Neo)Adjuvant systemic treatment

HER2-positive breast cancer treatment

* Not EMA-approved



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Primary (neoadjuvant) systemic therapy

Type of situation	Treatment
• Locally advanced and large operable cancers • Tumours > 2 cm requiring ChT	PST recommended
Most patients	Sequential anthracyclines and taxanes recommended
TNBC or *BRCA1/2*-mutated disease	Sequential anthracyclines + taxanes +/- platinum
Postmenopausal patients with ER-positive/HER2-negative cancers requiring PST	Preoperative ET should be considered and continued postoperatively
• Women with low-oestrogen status • Women with treatment-related bone loss	Bisphosphonates are recommended, especially if at high risk of relapse

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Other clinical scenarios

Type of situation	Treatment
Elderly patients	Treatment should be adapted to biological age: • Standard multidrug regimen recommended for suitable patients • Less aggressive regimen recommended for frail patients
Male breast cancer patients	• Standard adjuvant ET is tamoxifen • An AI alone should not be used; if needed, combine with LHRH analog
Both males and females	Same ChT/anti-HER2 therapy indications and regimen recommendations
DCIS	Both tamoxifen and AIs may be used after conservative local treatment and after mastectomy

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Personalised medicine

Summary of recommendations
ER, PgR and HER2 status should guide all systemic treatment decisions
Surrogate intrinsic tumour phenotypes, based on expression of ER, PgR, HER2 and Ki67, should be used to define subpopulations of breast cancers
Expression of uPA-PAI1 or validated multigene panels may be used in conjunction with clinicopathological factors to guide challenging systemic treatment decisions

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Follow-up, long-term implications and survivorship

* After breast-conserving treatment

** After mastectomy

Summary of recommendations
Regular follow-up visits are recommended: • every 3–4 months in the first 2 years (every 6 months for low-risk and DCIS patients) • every 6–8 months from years 3–5 • annually thereafter
Annual bilateral* and/or a contralateral mammography** and US are recommended
Regular bone density evaluation is recommended for patients receiving AIs or undergoing OFS

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This slide set provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPGs) on the management of early breast cancer. Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up.

The ESMO CPGs are intended to provide you with a set of recommendations for the best standards of care, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

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