Draft
RAOM Breast cancer guidelines
2021

International Statistical Classification of Diseases and Related Health Problems Coding: C50

Age group: adults

Developed by:
Russian Association of Oncological Mammology
VERSION 2.0
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>SLNB</td>
<td>sentinel lymph node biopsy</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenously</td>
</tr>
<tr>
<td>i.m.</td>
<td>intramuscularly</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>GnRH</td>
<td>gonadotropin-releasing hormone</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry (study)</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>RT</td>
<td>radiation therapy</td>
</tr>
<tr>
<td>IU</td>
<td>international units</td>
</tr>
<tr>
<td>MAB</td>
<td>monoclonal antibodies</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MCT</td>
<td>monochemotherapy</td>
</tr>
<tr>
<td>LE</td>
<td>life expectancy</td>
</tr>
<tr>
<td>s.c.</td>
<td>subcutaneously</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>BC</td>
<td>breast cancer</td>
</tr>
<tr>
<td>RM</td>
<td>radical mastectomy</td>
</tr>
<tr>
<td>SBD</td>
<td>single boost dose</td>
</tr>
<tr>
<td>PR</td>
<td>progesterone receptors</td>
</tr>
<tr>
<td>ER</td>
<td>estrogen receptors</td>
</tr>
<tr>
<td>SLN</td>
<td>sentinel lymph node(s)</td>
</tr>
<tr>
<td>TBD</td>
<td>total boost dose</td>
</tr>
<tr>
<td>FNAB</td>
<td>fine-needle aspiration biopsy</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound study</td>
</tr>
<tr>
<td>CT</td>
<td>chemotherapy</td>
</tr>
<tr>
<td>PBI</td>
<td>partial breast irradiation</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>BRCA</td>
<td>breast cancer gene</td>
</tr>
<tr>
<td>CHEK2</td>
<td>checkpoint kinase 2</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>DCIS</td>
<td>ductal carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ER</td>
<td>estrogen receptor</td>
</tr>
<tr>
<td>HER2</td>
<td>human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>ISH</td>
<td><em>in situ</em> hybridization</td>
</tr>
<tr>
<td>Ki67</td>
<td>antigen expressed by dividing cells</td>
</tr>
<tr>
<td>LCIS</td>
<td>lobular carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>pCR</td>
<td>pathomorphological complete response</td>
</tr>
<tr>
<td>PR</td>
<td>progesterone receptor</td>
</tr>
<tr>
<td>SERM</td>
<td>selective estrogen receptor modulator</td>
</tr>
<tr>
<td>TNC</td>
<td>triple-negative carcinoma</td>
</tr>
<tr>
<td>OPS-BCS</td>
<td>oncoplastic surgery – breast conserving surgery</td>
</tr>
</tbody>
</table>

**Terms and definitions**

The section does not contain any terms presented in these Clinical Guidelines only and not found in publicly available sources.
Summary of disease or condition (group of diseases or conditions)

1.1 Definition of disease or condition (group of diseases or conditions)

Breast cancer (BC) is a malignancy that develops from breast epithelial cells.

1.2 Ethiology and pathogenesis of disease or condition (group of diseases or conditions)

A family history of BC has long been recognised as a risk factor for the disease, but only 5% to 10% of women who develop breast cancer have a true hereditary predisposition. In addition, up to 50% of patients with BC have no significant risk factors. The most significant breast cancer risk factors are listed below (Table 1) [1].

Table 1. Significance of Known Breast Cancer Risk Factors

<table>
<thead>
<tr>
<th>Slightly increased relative risk: 1&lt;risk&lt;2</th>
<th>Increased relative risk: 2-4</th>
<th>Significantly increased relative risk: &gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menarche</td>
<td>First-degree relative with BC</td>
<td>Predisposition gene mutations**</td>
</tr>
<tr>
<td>Use of hormonal contraceptives*</td>
<td>Age at first delivery of &gt;35 years</td>
<td>Lobular carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>No births</td>
<td>Proliferative breast diseases without atypia</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Late menopause</td>
<td>High radiological density of the mammary glands</td>
<td>Radiation exposure to the mammary glands in persons under 30 years of age</td>
</tr>
<tr>
<td>Postmenopausal obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: * - increased risk of triple-negative BC;
** - quantitative risk assessment should be performed by a genetic physician.

1.3 Epidemiology of disease or condition (group of diseases or conditions)

Breast cancer is the most common malignancy affecting women in Russia. In 2018, 70,682 new cases were reported, representing 20.9% of all pathological tumour conditions in women. The mean age of all affected individuals was 61.5 years. The annual standardised morbidity rate has increased by 1.97% over the last 10 years. In 2018, cumulative risk of BC was 5.87% with a life expectancy of 74 years. In recent years, the
number of patients diagnosed with stages I-II has increased. Thus, in 2018 this rate was 71.2%, compared with a 62.7% rate a decade ago. Over the decade period, the mortality rate in the first year after diagnosis has been decreasing from 9.7% in 2008 to 5.8 in 2018. The percentage of women undergoing regular medical check-ups for ≥5 years or more is 60.9%. The percentage of those who underwent surgical treatment alone was 34.5%, while the percentage of those who received combined and complex treatment was 65.5%. In the structure of mortality of female population, BC is also ranked first, accounting for 16.2%. In men, BC accounts for <1% of tumours of this localisation. Principles of diagnostics and treatment of BC in men do not differ from those in women [2, 3].

1.4 Characteristics of coding disease or condition (group of diseases or conditions) according to the International Statistical Classification of Diseases and Related Health Problems

Malignant neoplasm of breast (C50):
C50.0: malignant neoplasm of nipple and areola
C50.1: malignant neoplasm of central portion of breast
C50.2: malignant neoplasm of upper-inner quadrant of breast
C50.3: malignant neoplasm of lower-inner quadrant of breast
C50.4: malignant neoplasm of upper-outer quadrant of breast
C50.5: malignant neoplasm of lower-outer quadrant of breast
C50.6: malignant neoplasm of axillary tail of breast
C50.8: breast cancer that extends beyond one or more of the above location
C50.9: malignant neoplasm of breast of unspecified site

1.5 Classification of disease or condition (group of diseases or conditions)

The 2020 World Health Organisation (WHO) International Histological Classification of Breast Cancer is presented below (Table 2).

<table>
<thead>
<tr>
<th>Table 2. WHO classification, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial-myoepithelial tumours</strong></td>
</tr>
<tr>
<td>8983/3</td>
</tr>
<tr>
<td>8562/3</td>
</tr>
<tr>
<td><strong>Papillary tumours</strong></td>
</tr>
<tr>
<td>8503/2</td>
</tr>
<tr>
<td>8504/2</td>
</tr>
<tr>
<td>8504/3</td>
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<td>Code</td>
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<tr>
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<td>8246/3</td>
</tr>
<tr>
<td>8041/3</td>
</tr>
<tr>
<td>8013/3</td>
</tr>
</tbody>
</table>

Treatment-oriented classification of subgroups of BC is presented below (Table 3).

Table 3. Treatment-oriented classification of subgroups of breast cancer
<table>
<thead>
<tr>
<th>Clinical grouping</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triple-negative</strong></td>
<td>Negative ER*, PR**, and HER2***</td>
</tr>
<tr>
<td>Hormone receptor-negative and HER2-positive</td>
<td>ASCO/CAP**** guidelines</td>
</tr>
<tr>
<td>Hormone receptor-positive and HER2-positive (ER +/- HER2+)</td>
<td>ASCO/CAP guidelines</td>
</tr>
<tr>
<td>Hormone receptor-positive and HER2-negative (ER +/- HER2-)</td>
<td>ER and/or PR positive ≥1% 1</td>
</tr>
<tr>
<td>1) High receptor, low proliferation, low tumour burden (luminal A-like). Favourable prognosis. Low risk for recurrence.</td>
<td>“Prognostically favourable” multi-parameter molecular markers. High ER/PR expression and low Ki-67(^2), few or no metastatic lymph nodes (N0-3), small tumour size T (T1, T2)</td>
</tr>
<tr>
<td>2) Intermediate prognosis</td>
<td>Intermediate value from several multi-parametric molecular markers according to the 21-gene risk score (RS) only. Uncertain risk and sensitivity to endocrine therapy and cytotoxic treatment.</td>
</tr>
<tr>
<td>3) Low receptor, high proliferation, significant tumour burden (luminal B-like). High risk of recurrence.</td>
<td>“Unfavourable” multi-parameter molecular markers. Low ER/PR expression and high Ki-67(^2), greater number of metastatic lymph nodes, Grade 3 histological malignancy, increased lymphovascular invasion, large tumour size T (T3).</td>
</tr>
</tbody>
</table>

*ER  estrogen receptors  
**PR  progesterone receptors  
***HER2  human epidermal growth factor receptor 2  
****ASCO American Society of Clinical Oncology  

1 ER values between 1% and 9% are considered equivocal.  
2 Ki-67 (antigen expressed by dividing cells) scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in hormone receptor-positive BC of 20%, values of 30% or above can be considered high; those of 10% or less low.
TNM classification (8th edition 2017)

T: primary tumour
T0: no evidence of primary tumour
Tis: carcinoma in situ
Tis (DCIS): ductal carcinoma in situ
Tis (LCIS): lobular carcinoma in situ
Tis (Paget’s disease of the nipple): Paget’s disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast tissue.
T1: tumour ≤2 cm in greatest dimension
T1mi: microinvasive tumour ≤0.1 cm in greatest dimension
T1a: tumour >0.1 cm but ≤0.5 cm in greatest dimension
T1b: tumour >0.5 cm but ≤1 cm in greatest dimension
T1c: tumour >1 cm but ≤2 cm in greatest dimension
T2: tumour >2 cm but ≤5 cm in greatest dimension
T3: tumour >5 cm in greatest dimension
T4: tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a: extension to the chest wall, not including only pectoralis muscle invasion
T4b: ulceration or tumour satellites of the skin on the affected side or skin oedema, including peau d’orange
T4c: extension to the chest wall, not including only pectoralis muscle invasion in combination with ulceration or tumour satellites of the skin on the affected side or skin oedema, including peau d’orange
T4d: inflammatory carcinoma

N: regional lymph nodes
N0: no regional lymph node metastasis
N1: metastasis to movable level I or II axillary lymph node(s) on the affected side
N2: metastasis to axillary lymph node(s) on the affected side
generated to other lymph nodes or structures
N2b: metastasis only in clinically apparent internal mammary lymph node(s) on the affected side in the absence of clinically evident axillary lymph node metastasis
N3
N3a: metastasis in the infraclavicular lymph node(s) (level III axillary) on the affected side with or without level I or II axillary lymph node involvement
N3b: metastasis in clinically apparent internal mammary lymph node(s) on the affected side with clinically evident level I or II axillary lymph node metastasis
N3c: metastasis in the supraclavicular lymph node(s) on the affected side with or without axillary or internal mammary lymph node involvement

M: distant metastases
M0: no distant metastases
M1: distant metastasis

Pathologic classification (pTNM)

pT: primary tumour
Pathological classification is used only to assess the primary tumour without macroscopic evidence of tumour growth at the margins of resection. A case can be classified as pT if there is only microscopic evidence of tumour growth at the margins of resection.
pT categories correspond to the T clinical categories.

Note
When classifying pT, the tumour size is a measurement of the invasive component only. If there is a large in situ carcinoma (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm), the tumour is classified as pT1a.

pN: regional lymph nodes
Pathological classification requires the examination of at least the lower axillary lymph nodes (level I). When resecting lower axillary lymph nodes, ≥6 lymph nodes are usually removed. If no metastases were detected in lymph nodes and fewer lymph nodes were examined, the case is classified as pN0.
pNx: regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study).
pN0: no regional lymph node metastases identified
pN1: micrometastases or metastases in 1-3 axillary lymph nodes on the affected side and/or in internal mammary lymph nodes detected by sentinel lymph node biopsy but not clinically apparent

pN1mi: micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm) on the affected side.

pN1a: metastases in 1-3 axillary lymph nodes on the affected side (at least 1 metastasis >2 mm in greatest dimension)

pN1b: internal mammary lymph nodes with metastases on the affected side detected by sentinel lymph node biopsy but not clinically apparent

pN1c: metastases in 1-3 axillary lymph nodes and internal mammary lymph nodes on the affected side

pN2: metastases in 4-9 axillary lymph nodes on the affected side or metastases in clinically apparent internal mammary lymph node(s) on the affected side in the absence of axillary lymph node metastasis

pN2a: metastases in 4-9 axillary lymph nodes on the affected side (at least 1 metastasis >2 mm in greatest dimension)

pN2b: metastasis in clinically apparent internal mammary lymph node(s) on the affected side in the absence of axillary lymph node metastasis

pN3a: metastases in ≥10 axillary lymph nodes on the affected side (at least 1 metastasis >2 mm in greatest dimension) or metastases in infraclavicular lymph nodes on the affected side (level III)

pN3b: metastasis in clinically apparent internal mammary lymph node(s) on the affected side and the presence of metastasis in axillary lymph node(s) or metastases in ≥3 axillary lymph nodes and in internal mammary lymph nodes on the affected side with microscopic metastases detected by sentinel lymph node biopsy but not clinically apparent

pN3c: metastasis in the supraclavicular lymph node(s) on the affected side.

**Post-treatment ypN classification**

Post-treatment ypN category should be evaluated as for clinical pre-treatment N category. The modifier (sn) is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the lymph node evaluation was performed after axillary node dissection.

The X (ypNX) classification is used if no post-treatment sentinel node evaluation or axillary node dissection was performed.

N categories are the same as those used for pN.
pM: distant metastases
pM1: distant metastasis histologically confirmed
pM0 and pMX are not valid categories

**Tumour grade of differentiation:**

To assess the grade of differentiation of invasive carcinoma, the Nottingham Histologic Score is recommended.

Breast cancer stages are presented below (Table 4).

**Table 4. Breast cancer staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T0, T1</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

1.6 **Clinical presentation of disease or condition (group of diseases or conditions)**

The clinical presentation of breast cancer includes symptoms associated with locoregional changes (changes in the size and shape of the breast, changes in the skin and nipple-areola complex) and symptoms caused by spreading of the disease and the presence of paraneoplastic syndromes.
1.7 Complaints and medical history

It is recommended that all complaints and symptoms resulting from both underlying disease and concomitant pathology be evaluated to adequately assess the patient’s condition.

**Recommendation grade B** (level of evidence 2) [4].

It is recommended that a detailed medical history be taken to identify factors that may influence the choice of treatment strategy.

**Recommendation grade B** (level of evidence 2) [4].

1.8 Physical examination

A complete physical examination is recommended, including assessment of the breast and regional metastatic areas, as well as assessment of the patient’s status by organs and systems.

**Recommendation grade C** (level of evidence 3) [4].

**Comments:** mammary gland symmetry evaluation is required along with the status of the nipple-areola complex and the skin of the mammary glands. Palpation of the mammary glands and regional lymph nodes should be done in the patient’s standing and lying position. The examination should include evaluation for the presence of nodal and infiltrative lesions of the breast with specification of tumour size measurements with palpation, consistency, and displaceability; the presence, size and consistency of lymph nodes should be determined.

**Recommendation grade C** (level of evidence 3) [4].

1.9 Laboratory tests

Complete blood cell count with differential and platelet count, urinalysis, and biochemistry tests with measurements of liver and kidney function, ALP, electrolytes, calcium, and glucose are recommended for diagnostic purposes.

**Recommendation grade C** (level of evidence 3) [4].

Tests for follicle stimulating hormone and oestradiol levels are recommended for diagnostic purposes to evaluate ovarian function (see section “Menopause criteria”).

**Recommendation grade B** (level of evidence 2) [5].
Cytology of discharge and breast tumour and lymph node biopsy specimens is recommended for diagnostic purposes.

**Recommendation grade B** (level of evidence 2) [6].

Fine-needle aspiration biopsy (FNAB) is recommended in the triple test for breast cancer screening programs. The diagnostic accuracy is about 70-90% for clinical examination (palpation), 85-90% for mammography, and 90-99% for FNAB [1]. However, the total diagnostic accuracy of all 3 tests comprising the so-called triple test is 100%. If all 3 parameters of this triad are malignant (MMM, malignant), the error probability is <1%. On the other hand, if all 3 parameters are benign (BBB, benign), there is a 98% chance that the tumour is benign and requires clinical observation only. Any other combinations should be evaluated carefully in the clinical context and a core biopsy is likely to be required. If the triple test is used, the number of biopsies is significantly reduced, which is highly cost-effective and yields a quite high accuracy in detecting malignancies. Therefore, the triple test is a cost-effective measure in the evaluation of palpable breast tumours.

Categories for reporting FNAB cytology are defined as follows:

- C1: inadequate smear
- C2: benign disease
- C3: atypical, probably benign
- C4: suspicious, probably malignant
- C5: malignant

Results classified as C3 or C4 cannot be used to justify surgical or therapeutic intervention. C3, C4, and C5 categories are direct indications for core-biopsy.

### 1.10 Pathologic studies

It is recommended to perform histological, immunohistochemical and molecular genetic studies of biopsy and/or surgical material to determine clinical prognostic groups and select therapy.

Repeated testing of the resection material is recommended in cases of residual tumour after neoadjuvant therapy with discordant results between histological conclusions on biopsy and operational materials (change of tumour grade, combined histological variant). If metastatic lymph nodes are detected, conduct a comparative analysis of the primary tumour and the metastatic one.
It is necessary to compare marker expression in the primary tumour/pre-treatment tumour and in the residual and/or metastatic tumour, to assess for the persistence or changes in marker expression.

Intraductal carcinoma (carcinoma *in situ*) should only be tested for ER status.

When determining HER2 expression level (0, 1+, 2+, 3+), the updated ASCO/CAP guideline recommendations (2018) should be followed. HER2-status scored as 0 and 1+ should be considered negative, 3+ - positive.

**Recommendation grade B** (level of evidence 2) [7].

**Histological test.** The histological conclusion based on examination of both biopsy and surgical materials should report histological variant and grade of the tumour.

The conclusion based on the examination of surgical materials should report the following:

- Histological variant of the tumour with ICD-O code
  1. Tumour grade (G)
  2. For biopsy material testing, the concordance between the clinical and morphological diagnosis with a possible explanation of reasons for discordant results should be indicated separately
  3. Largest tumour size in mm, including data following microscopic examination
  4. Distance to the nearest resection margin
  5. State of resection margins
  6. State of the skin (if involved), presence or absence of ulceration, lymphovascular invasion
  7. Presence of lymphovascular invasion
  8. Number of lymph nodes examined, number of lymph nodes involved, the presence or absence of extracapsular extension
  9. Pathological stage using pT, pN, pM categories
  10. In case of neoadjuvant therapy, pre-treatment tumour phenotype (in biopsy material) should be recorded (if possible) to evaluate the change in phenotype after neoadjuvant treatment, tumour regression using RCB grading system; tumour stage using ypT, ypN categories, repeated analysis of residual tumour material for comparative evaluation of phenotype changes, the number of lymph nodes examined (the presence of signs of regression both in lymph nodes with and without metastases and the number of metastatic lymph nodes should be recorded separately).
Recommendation grade B (level of evidence 2) [7].

Immunohistochemistry study.
1. Each newly diagnosed invasive breast cancer (biopsy or surgical material, primary tumour or metastasis) requires the determination of hormonal receptors (ER, PgR) and HER2 status using the recommended IHC protocol in order to select endocrine or targeted therapy for a patient. Intraductal carcinoma (carcinoma *in situ*) should only be tested for ER status.

2. Repeated testing of the resection material is recommended in cases of residual tumour after neoadjuvant therapy with discordant results between histological conclusions on biopsy and operational materials (change of tumour grade, combined histological variant). If metastatic lymph nodes are detected, conduct a comparative analysis of the primary tumour and the metastatic one.

3. It is necessary to compare marker expression in the primary tumour/pre-treatment tumour and in the residual and/or metastatic tumour, to assess for the persistence or changes in marker expression.

4. ER and PgR expression levels should be evaluated using the Allred score, ranging from 0 to 8.

<table>
<thead>
<tr>
<th>Scores</th>
<th>Percentage of stained tumour cell nuclei, %</th>
<th>Staining intensity of tumour cell nuclei</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>No staining</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>&lt;1</td>
<td>Weak staining</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1 - 10</td>
<td>Moderate staining</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>11 - 33</td>
<td>Severe staining</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>34 - 66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>≥67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[\text{total scores}= \text{percentage of stained cells} \times \text{staining intensity}\]
An integrative estimate of ER expression level allows to classify the study case into one of three main groups: no expression (complete absence of stained nuclei, 0 scores), low level of expression (1-10% of stained cells, the first digit of the sum of 1 or 2 scores, the second one is to be ignored), presence of expression (>10% of stained cells, 5-8 scores, the first digit of the sum of at least 3 scores). In addition to the sum of scores, the percentage of tumour cells expressing ER/PR should be recorded.

- **ER expression in 1-100% of tumour cells is considered to be a positive result.** Patients with such results are recommended to undergo endocrine therapy (both for invasive cancer and carcinoma in situ).
- **Despite limited clinical data on efficacy of endocrine therapy in the subgroup with low ER expression (1-10%), it is believed that patients in this subgroup can benefit from endocrine therapy, therefore they are also recommended to receive endocrine therapy. However, the biological behaviour of some carcinomas with low ER expression is more similar to that of ER-negative carcinomas, which requires additional investigation.**
- **Carcinomas with <1% of ER expression are considered negative; patients with these carcinomas are not indicated for endocrine therapy.**

5. For maximum accuracy and reproducibility of tests, laboratories performing testing should have standard operating procedures (SOPs). In cases of low ER expression or the number of stained cells <10%, the status of internal positive control should be evaluated and reported.

6. Determination of PgR status of invasive carcinomas is required for a predictive clinical classification and control for adequacy of ER expression levels. Patients with ER-negative but PgR-positive status can be considered as candidates for endocrine therapy. For evaluation of PgR, the same principles as for ER are used, but only two groups are distinguished: 1-100% for positive status and 0-1% for negative status.

7. If there are any contradictions between the identified status of hormonal receptors and the morphological pattern (carcinoma variant, grade, etc.), explanations should be given. Clinicians should inform the pathologist of any uncoordinated/contradictory histological and IHC findings.

8. Examples of discrepancies are provided in Table 5.

**Table 5. Discrepancies between ER expression and histological variant of BC**

<table>
<thead>
<tr>
<th>Low-probability ER-negative result in:</th>
<th>Low-probability ER-positive result in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma (unspecified type) with low malignancy potential</td>
<td>Any type of metaplastic carcinoma</td>
</tr>
<tr>
<td>Classic lobular carcinoma</td>
<td>Adenoid cystic carcinoma and other breast tumours, like salivary gland tumours</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Encapsulated papillary or solid papillary carcinoma</td>
<td>Carcinomas with apocrine differentiation</td>
</tr>
</tbody>
</table>

9. When determining HER2 expression level (0, 1+, 2+, 3+), the updated ASCO/CAP guideline recommendations (2018) should be followed. HER2-status scored as 0 and 1+ should be considered negative, 3+ - positive.

10. In case of HER2-positive status in low-malignancy carcinoma of any histological type (pure tubular, classic lobular, mucinous and cribriform carcinomas), repeated histological examination of tissue specimens should be performed to confirm the adequacy of identified variant considering ER, PR and Ki-67 expression levels, along with evaluation of internal control (staining intensity in normal acynaric and duct structures of all markers, especially HER2) and, if necessary, repeated testing.

11. In case of indeterminate HER2 (2+) level according to immunohistochemical results, the amplification of HER2 is determined by double-label in situ hybridisation (ISH HER2). Two probes are used to perform the measurement: the HER2 probe binds to the locus of the HER2 gene on chromosome 17 and the CEP17 probe binds to the centromere site of chromosome 17. Results are evaluated as the ratio of the number of copies of the HER2 gene to the number of copies of chromosome 17; the calculation of the average number of HER2 signals and centromere sites is more important than a simple ratio of the number of the gene copies to the number of centromere sites. It is recommended to distinguish the following five groups:

- **group 1**: HER2/CEP17≥2.0; average number of HER2 signals per cell ≥4.0: **amplified** status
- **group 2**: HER2/CEP17≥2.0; average number of HER2 signals per cell <4.0. For status determination, a comparison with ICH findings is required: for assessment of HER2 +2 and recalculation of 20 additional tumour cell nuclei, the result is negative; for +3, the result is positive
- **group 3**: HER2/CEP17<2.0; average number of HER2 signals per cell ≥6.0. For status determination, a comparison with ICH findings is required: for assessment of HER2 +2 and recalculation of 20 additional tumour cell nuclei, the result is positive; for +3, the positive status is **amplified**
- **group 4**: HER2/CEP17<2.0; average number of HER2 signals per cell ≥4.0, but <6.0. For status determination, a comparison with ICH findings is required: for
assessment of HER2 +2 and recalculation of 20 additional tumour cell nuclei, the result is negative; for +3, the result is positive

- group 5: HER2/CEP17<2.0; average number of HER2 signals per cell <4.0: non-amplified status

The Ki-67 expression has low reproducibility, therefore the Ki-67 index should not be used as a criterion to define a prognostic group. However, it can be useful in assessing the adequacy of specimen fixation, in a complex evaluation of breast cancer (validity of identified tumour grade, ER expression, and HER2 to a lesser extent) and can be used in combination with other markers as a prognostic group indicator.

The molecular subtype of a tumour can only be determined by molecular genetic testing. A pathologist may not conclude on molecular subtyping based on surrogate immunohistochemistry results.

**Recommendation grade – Recommendation grade B** (level of evidence 2) [7].

*Note: Molecular biological testing should only be performed by accredited and certified laboratories.*

### 1.11 Instrumental and diagnostic tests

2D bilateral mammography + breast and regional ultrasound examination are recommended for diagnostic purposes.

**Recommendation grade A** (level of evidence 1) [8].

Dual-energy contrast-enhanced spectral mammography (DCESM) is recommended as an additional method for diagnostics of breast cancer in patients with dense glandular background tissues.

According to different authors, DCESM increases the sensitivity of the X-ray method with a dense background from 50% to 85-95%, which is almost not inferior in sensitivity to dynamic contrast-enhanced MR mammography, but is superior to it in terms of specificity.

Indications for DCESM are as follows:

- dense image background;
- evaluation of multicentricity and multifocality;
- differential diagnosis of mammary gland microcalcifications and structural alterations;
- contraindications to MR mammography.

**Recommendation grade C** (level of evidence 3).

Breast MRI with contrast is recommended for diagnostic purposes when indicated.

**Recommendation grade A** (level of evidence 1) [9].
Comment:

Indications for breast MRI:

1. Individuals under 30 years of age.
2. The presence of BRCA1, BRCA2, CHECK, NBS1, tP53 mutations
3. High radiological density of the mammary glands
4. The presence of breast implants if high-quality mammography is impossible
5. Signs or suspicion of multicentric breast cancer
6. Occult BC: BC metastases to axillary lymph nodes without primary focus
7. Primary inflammatory BC
8. Intraductal BC.

Abdominal, retroperitoneal, and pelvic ultrasound examination is recommended for diagnostic purposes to exclude remote metastases.

Recommendation grade C (level of evidence 3) [4].

In case of ambiguous or uninformative results of abdominal ultrasound, abdominal CT or MRI with i/v contrast is recommended for diagnostic purposes.

Recommendation grade C (level of evidence 3) [4].

2D chest X-ray or CT is recommended for diagnostic purposes to exclude remote metastases.

Recommendation grade B (level of evidence 3) [10].

In case of suspected metastatic bone disease, bone scintigraphy is recommended for diagnostic purposes.

Recommendation grade B (level of evidence 3) [11], [12].

In case of suspected metastatic disease according to CT or MRI data, which, if confirmed, may substantially change the treatment strategy, PET-CT is recommended for diagnostic purposes.

Recommendation grade B (level of evidence 3) [13].

In case of suspected metastatic brain disease, brain MRI or CT scan with i/v contrast is recommended for diagnostic purposes.

Recommendation grade B (level of evidence 2) [14].

ECG is recommended for diagnostic purposes to exclude cardiac abnormalities.

Recommendation grade B (level of evidence 4) [15].
1.12 Other diagnostic tests

Genetic testing in breast cancer patients is recommended for diagnostic purposes: in primary tumour multiplicity, in patients under 45 years of age, in patients with any malignancies in 1st and 2nd degree relatives, in triple-negative tumour phenotype; in men [16].

**Recommendation grade B** (level of evidence 3)

If the response is negative with the standard panel, but clinical signs of hereditary disease are evident, BRCA1 and 2 sequencing analysis is recommended.

**Recommendation grade C** (level of evidence 3)

**Comment:** conclusion on the hereditary nature of breast cancer should be given by a board-certified physician in clinical genetics. DNA diagnostics should be performed via molecular genetic testing by a certified laboratory.

### Treatment, including drug and non-drug therapies, dietary treatment, pain management, medical indications and contraindications to treatment methods

Management of BC patients should be determined based on principles of multidisciplinary approach. The treatment should be planned in a consultation involving a surgeon, chemotherapist, and radiotherapist.

**Recommendation grade B** (level of evidence 3) [17].

Considering individual characteristics of BC patients, a team comprising a therapist, anesthesiologist, morphologist, radiologist and doctors of other specialties is required.

1.13 Management of breast cancer patients depending on the stage of the disease

After morphological confirmation of the diagnosis (histological or histological + immunohistochemical), the appropriate management approach can be selected.

**Recommendation grade B** (level of evidence 3) [7].

1.13.1 Stage 0. TisN0M0

**1.13.1.1 TisN0M0 (DCIS) Ductal carcinoma in situ.**

Organ-conserving surgery or mastectomy is recommended for surgical treatment (see section 3.2. “Surgical treatment”). No additional radiotherapy or systemic therapy is required for mastectomy. After organ-conserving surgery, adjuvant hormone therapy (see section “Adjuvant hormone therapy”) and adjuvant radiation therapy (see section “Radiation therapy”) are recommended. Adjuvant cytotoxic therapy is not recommended.
Recommendation grade B (level of evidence 2) [11].

When performing organ-conserving surgery with clean margins $\geq$5 mm in DCIS patients with favourable prognostic signs (age over 50 years, low or intermediate grade of malignancy, absence of comedonecrosis, tumour size <2.5 cm), it is possible not to carry out radiation therapy and endocrine therapy [18].

**Level of evidence A** (recommendation grade 1)

**Comment:** if a patient who has undergone surgery for suspected DCIS is found to have an invasive BC, the follow-up treatment should be comparable to that for patients with an established pathological diagnosis and biological subtype of BC.

**Level of evidence A** (recommendation grade 1) [19].

1.13.1.2 **Paget’s disease of the nipple**

The extent of breast intervention depends on the extent of the lesion identified. Given the high incidence of peripheral lesions and multicentricity, contrast-enhanced breast MRI is recommended as an additional diagnostic method.

If there are any clinical and instrumental data on the involvement of only the nipple-areola complex in the presence of large or medium-sized breast, oncoplastic surgery with sentinel lymph node biopsy is recommended.

The mastectomy can be performed either without reconstruction or with primary reconstruction. In case of primary reconstruction, skin-preserving mastectomy (with removal of the nipple and areola) should be performed. If technically possible, sentinel lymph node biopsy is recommended; if not, axillary lymph node dissection is recommended. If invasive cancer is identified, the treatment should be planned according to the stage, histological and molecular characteristics of the invasive disease.

Recommendation grade B (level of evidence 2) [20].

1.13.2 **Stages I (T1N0M0), IIa (T2N0M0)**

Primarily operable BC. Tactical issues to be addressed: possibility of organ-conserving surgery, saving the main group of axillary and infraclavicular lymph nodes using sentinel lymph node biopsy technique (see section “Surgical treatment”). In case of a relatively large primary tumour and inability to perform organ-conserving surgery with acceptable aesthetic results, neoadjuvant systemic therapy is recommended (see section “Systemic adjuvant and neoadjuvant therapy”). Postponement of chemotherapy to the preoperative period is also recommended in cases of primary reconstruction planning, as it reduces the incidence of postoperative complications. In the vast majority of cases, systemic adjuvant therapy is recommended (see section “Systemic adjuvant and neoadjuvant therapy”);
radiation therapy is indicated for organ-conserving surgeries and/or lymph node involvement (see section “Radiation therapy”).

**Recommendation grade C** (level of evidence 4) [21].

In order to clarify the necessity of adjuvant chemotherapy at early stages of BC, molecular genetic methods can be used, e.g. prognostic indices based on profiling of gene expression in tumour tissues and approved in Russia.

**Recommendation grade C** (level of evidence 4)

If tumour elements are identified on the resection margin, the resection should be repeated to achieve negative resection margins.

Histological assessment of resection margins is a key characteristic of the oncological adequacy of organ-conserving surgeries. The system for marking four (Superior, Medial, Lateral, Inferior) to six resection margins (Superior, Medial, Lateral, Inferior, Deep-Posterior, Anterior-Skin) [22–25] of the tissue sample should be agreed with the pathologist conducting the examination, so that, when tumour elements are identified in the margin, it is clear which part of the wound needs to be resected.

The presence of the tumour on the resection margin requiring repeated intervention is defined as the margin of invasive tumour or its intraductal component, but not tumour cell complexes or classic lobular carcinoma *in situ*.

**Recommendation grade A** (level of evidence 1) [19].

Mastectomy is recommended if adequate resection margins cannot be achieved.

**Recommendation grade A** (level of evidence 1) [19].

Sentinel lymph node biopsy (SLNB) is recommended. If SLNB is impossible or in case of sentinel lymph node metastatic involvement, axillary lymph node dissection (levels I-II) is recommended.

**Recommendation grade A** (level of evidence 1) [26].

Immediate or delayed breast reconstruction is possible.

**Recommendation grade B** (level of evidence 3) [21].

Contralateral breast symmetry surgery is possible to achieve better aesthetic results.

**Recommendation grade B** (level of evidence 4) [27].

For therapeutic purposes, it is recommended to decide on adjuvant therapy in a risk-oriented manner (see section “Radiation therapy”).

**Recommendation grade B** (level of evidence 3) [21].
For therapeutic purposes, it is recommended to decide on adjuvant drug therapy and hormone therapy considering morphological characteristics of the tumour and extent of performed treatment (see sections on systemic and hormonal therapy).

**Recommendation grade B** (level of evidence 3)

**Comment:**

*Sentinel lymph node biopsy (SLNB): surgical removal of sentinel lymph node(s) followed by histopathomorphological evaluation. SLNB is one of the modern diagnostic methods with sensitivity of 92-96%.*

**Recommendation grade B** (level of evidence 3) [28].

**Recommendation grade B** (level of evidence 3) [29].

Sentinel lymph node biopsy is recommended for patients with clinical N0 disease. Minimum methods for preoperative assessment of regional lymph nodes include palpation, ultrasound and fine-needle biopsy with cytology of suspicious lymph nodes.

Radionuclide-guided method for sentinel lymph node detection is currently the most widely used method in the world.

**Recommendation grade B** (level of evidence 2) [30].

Fluorescent-guided method for sentinel lymph node detection is based on generation of excitation IR radiation and registration of fluorescence response from indocyanine green migrating through lymphatic viae. The use of indocyanine green (ICG) fluorescence lymphography allows for sentinel lymph node biopsy with a high detection rate of lymph nodes (98%) and low false-negative rate (3.6%) [31].

**Recommendation grade B** (level of evidence 2)

Sentinel lymph node biopsy with ICG is possible in pregnancy as the use of the tracer in pregnancy is authorised by the Ministry of Health of the Russian Federation.

If it is technically impossible to perform sentinel lymph node biopsy in N0 and in N1, axillary lymph node dissection (levels I-II) is recommended [32],[33], [34].

In cN1 patients who converted to cN0 after neoadjuvant therapy, sentinel lymph node biopsy can be performed to potentially minimise the extent of resection in morphologically confirmed absence of axillary lymph node metastases. However, this requires a number of conditions to be met:

- Pre-treatment marking of lymph node metastases and use of target sentinel lymph biopsy. If marked: marked LN + 1-2 SLNs should be evaluated
- If not marked: at least 3 SLNs should be evaluated.
Recommendation grade B (level of evidence III) [35], [36], [37].

The current indications for SLNB include early breast cancer with no signs of regional lymph node involvement. SLNB may also be indicated to patients with resectable disease, but with multicentric or ductal carcinoma in situ and without history of breast surgery. Advanced breast cancers (T3/T4) are considered as contraindications for this intervention.

Table 6. Indications for sentinel lymph nodes biopsy

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Biopsy option</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_1 or T_2</td>
<td>Possible</td>
</tr>
<tr>
<td>T_3 or T_4</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Multicentric disease</td>
<td>Possible</td>
</tr>
<tr>
<td>Ductal carcinoma <em>in situ</em> (mastectomy)</td>
<td>Possible</td>
</tr>
<tr>
<td>Suspicious, palpable LNs</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Parasternal LN evaluation</td>
<td>Possible</td>
</tr>
<tr>
<td>Previous breast and axillary surgeries</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Russia has an approved technique for sentinel lymph node biopsy, which involves the injection of radioactive colloidal particles into the tumour, around the tumour or subcutaneous breast tissues above the tumour. This technique, referred to as radio navigation, is based on the active colloidal particle accumulation by sentinel lymph nodes.

1.13.3 Stages IIA (T1N1M0), IIB (T2N1M0, T3N0M0) and T3N1M0

It is recommended to determine treatment strategy after consideration of biological subtype. Neoadjuvant chemotherapy is highly effective in triple-negative and HER2/neu-positive tumours, as it is associated with a high probability of achieving complete morphological remission and reducing the extent of surgery. In case of failure to achieve such response, adjuvant therapy regimens have been developed to improve long-term treatment outcomes in this group of patients. In patients with luminal types of tumours, treatment strategy should be defined individually; the primary objective of neoadjuvant treatment is to potentially minimise the extent of surgery. In some cases, skin-preserving mastectomy with possible immediate reconstruction and subsequent adjuvant systemic therapy may be performed (see section “Systemic adjuvant and neoadjuvant therapy”).

Recommendation grade B (level of evidence 3) [21].

If tumour elements are identified on the resection margin, repeated resection is recommended the resection to achieve negative resection margins.

Recommendation grade A (level of evidence 1) [38].
Mastectomy is recommended if adequate resection margins cannot be achieved. **Recommendation grade A** (level of evidence 1) [38].

Immediate or delayed breast reconstruction is possible. **Recommendation grade B** (level of evidence 3) [21].

Contralateral breast symmetry surgery is possible to achieve better aesthetic results. **Recommendation grade B** (level of evidence 3) [27].

It is recommended to decide on neoadjuvant therapy for the purpose of subsequent organ-conserving treatment. **Recommendation grade B** (level of evidence 3) [21].

Adjuvant radiotherapy is recommended considering morphological characteristics of the tumour and extent of performed treatment (see section “Radiation therapy”). **Recommendation grade B** (level of evidence 3) [21].

It is recommended to decide on adjuvant drug therapy and hormone therapy considering morphological characteristics of the tumour and extent of performed treatment (see sections on systemic and hormonal therapy). **Recommendation grade B** (level of evidence 3) [21].

1.13.4 Stages IIIA (T0-3N2M0), IIIB (T4N0-2M0), IIIC (T0-4N3M0)

Primarily inoperable BC. Preoperative systemic therapy is recommended as the first stage of treatment (see section “Systemic adjuvant and neoadjuvant therapy”). Assessment for potential resectability after systemic therapy should be based on assessment of symptomatic changes over time (primary tumour, skin swelling, regional metastases).

Adjuvant systemic treatment should be planned with due consideration of baseline and postoperative histological and immunohistochemical tumour characteristics (see section “Systemic adjuvant and neoadjuvant therapy”). Radiation therapy is recommended in all cases (see section “Radiation therapy”). **Recommendation grade B** (level of evidence 3) [21].

Neoadjuvant systemic therapy with subsequent resectability evaluation is recommended. **Recommendation grade B** (level of evidence 2) [39].

Marking of primary tumour and regional lymph nodes is recommended prior to the start of neoadjuvant therapy. **Recommendation grade B** (level of evidence III) [35], [36], [37].
Mastectomy with axillary lymph node dissection or organ-conserving surgery is recommended in patients with resectable disease responding to systemic therapy.

**Recommendation grade B** (level of evidence 2) [39].

Preoperative radiotherapy is recommended in patients with no response and non-resectable persisting disease (see section “Radiation therapy”).

**Recommendation grade B** (level of evidence 2) [40], [41].

It is recommended to decide on adjuvant therapy in a risk-oriented manner (see section “Radiation therapy”).

**Recommendation grade B** (level of evidence 2) [42].

It is recommended to decide on adjuvant drug therapy and hormone therapy considering morphological characteristics of the tumour and extent of performed treatment (see sections on systemic and hormonal therapy).

**Recommendation grade B** (level of evidence 2) [21].

Individualised treatment is recommended in patients with no response and non-resectable persisting disease after preoperative radiotherapy.

*Tumour lysis*. The process is associated with a risk of bleeding and infectious complications most commonly encountered during chemotherapy. Palliative mastectomy is recommended for all stages of the disease. The purpose of the surgery is the management of tumour-related complications rather than radicalism. Technically, this can be a simple mastectomy or mastectomy with greater pectoral muscle resection and removal of accessible metastases.

1.13.5 Stage IV. T0-4N0-3M1

Disseminated disease. Systemic therapy is of primary importance. Primary tumour excision with clean resection margins is recommended in the presence of bone metastases and systemic treatment response [43].

Radiation therapy is indicated to patients with complicated bone metastases and brain metastases (see section “Radiation therapy”).

**Recommendation grade B** (level of evidence 2) [44], [45].

Surgical removal of single (surgically accessible) brain metastases is recommended if extracranial metastases are controlled.

**Recommendation grade B** (level of evidence 2) [46].
1.14 Surgical treatment (organ-conserving and reconstructive plastic surgeries for breast cancer, sentinel lymph node biopsy)

Surgical treatment is recommended: organ-conserving surgery or mastectomy. Organ-conserving surgery is possible if the following conditions are met: removal of the entire area of intraductal growth by achieving clear resection margins with extra space of at least 2 mm and formation of aesthetically acceptable breast shape. Intraoperative tumour bed marking is recommended for subsequent radiotherapy using a boost technique to the tumour bed.

Organ-conserving treatment includes the removal of the primary tumour with negative margins, ideally with the shape and size of the breast preserved for subsequent cosmetic effect.

Indications for organ-conserving treatment:

- Primary operable disease with tumour volume allowing for acceptable aesthetic appearance following organ-conserving treatment.
- Primarily operable or locally advanced cancer after effective systemic treatment with a relatively small residual tumour volume allowing for acceptable aesthetic appearance following organ-conserving treatment.

Contraindications for organ-conserving treatment:

- Involved resection margins after repeated excision.
- Impossibility of postoperative radiation therapy.
- Swelling of breast skin.

For relatively small tumours (up to 2 cm for medium-sized breast), lumpectomy, sectoral or oncoplastic surgeries are preferred. The selection of particular surgical technique depends on the surgeon. For lumpectomy and sectoral surgery, it is necessary to use incisions in accordance with aesthetically important areas. It is recommended to remove the skin over the tumour with the entire tissue sample if the tumour grows to the skin or causes dimpled skin, or spreads from the glandular tissue to the subcutaneous tissue.

Oncoplastic surgery involves breast cancer resection using plastic surgery techniques to restore the breast shape with an immediate symmetry operation performed on the contralateral breast, if necessary. Currently, there are many options for oncoplastic surgeries. The technique and method of the operation is dictated by the oncological situation, the shape of the breast, specific features of the state of tissues, and skills of the surgeon.

**Recommendation grade B** (level of evidence 3) [47].
The advantage of oncoplastic surgeries is the ability to remove large amounts of glandular tissues in large-sized breasts and to recreate the breast shape using various reduction mammoplasty techniques, which can also be used in patients with locally advanced BC after neoadjuvant drug exposure with partial or complete regression effects; organ-conserving treatment can be performed if desired by the patient. Each oncoplastic surgery technique is based on preoperative skin markings including the vertical axis, lateral and median lines, the new location of the nipple-areola complex, and the glandular pedicle. For all methods, sentinel lymph node biopsy or lymph node dissection, if medically required, should be performed through an additional incision according to the generally accepted technique and vacuum wound drainage. The extent of lymph node dissection should be determined depending on the presence or absence of metastatic lymph nodes.

Recommended types of oncoplastic surgery in breast cancer depending on tumour localisation and size of mammary glands are listed below (Table 7).

Table 7. Types of oncoplastic surgery in breast cancer depending on tumour localisation and size of mammary glands

<table>
<thead>
<tr>
<th>Quadrant (tumour localisation)</th>
<th>Mammary gland size</th>
<th>Medium</th>
<th>Large/ptosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>Small</td>
<td>Round-block S-reduction, Modified Batwing</td>
<td>Grisotti Lower pedicle S-reduction, Batwing</td>
</tr>
<tr>
<td>Lower external</td>
<td>Thoracoepigastri c flap</td>
<td>Upper pedicle</td>
<td>Upper pedicle</td>
</tr>
</tbody>
</table>
### Thoracodorsal flap

- Modified technique acc. to Grisotti
- Subglandular technique

- Method acc. to E. H-Findlay (superomedial glandular pedicle)
- Subglandular technique

### Lower boundary

- Thoracoepigastric flap
- Upper pedicle
- Thoracoepigastric flap
- Method acc. to E. H-Findlay (superomedial/superolateral glandular pedicle)
- Subglandular technique

### Lower inner

- Thoracoepigastric flap
- Subglandular technique
- Upper pedicle
- Thoracoepigastric flap
- Method acc. to E. H-Findlay (superomedial/superolateral glandular pedicle)
- Subglandular technique
- Upper/lower pedicles

---

**Recommended options for oncoplastic surgeries**

- Modified version of oncoplastic breast surgery acc. to M. LeJour
- Oncoplastic breast surgery by an inverted T type
- Modified version of oncoplastic breast surgery acc. to E. Hall-Findlay
- Oncoplastic breast surgery by round-block
- Oncoplastic breast surgery by technique acc. to Batwing
- Oncoplastic breast surgery by technique acc. to Grisotti
- Oncoplastic breast surgery with thoracodorsal flap
- Oncoplastic breast surgery using S-reduction technique

**Indications for radical skin-preserving mastectomy with immediate reconstruction**

1. Pre-invasive carcinoma (DCIS)
2. Breast cancer: I st. cT1N0M0; IIA st. cT2N0M0, cT1N1M0; IIB st. cT2N1M0
3. Breast cancer: IIB st. cT3N0M0, IIIA st. cT1N2M0, cT2N2M0, cT3N1M0 after neoadjuvant treatment with partial or complete regression (PR, CR)
4. Tumour distance to the projected skin flap is <1 cm
5. Presence of breast ptosis
6. Tumour localisation close to the nipple-areola complex, presence of tumour cells under the nipple according to data from urgent intraoperative morphological investigation

**Recommendation grade B** (level of evidence 3) [47].

**Contraindications for radical subcutaneous/skin-preserving mastectomy with immediate reconstruction**

1. cT4bN0-3M0-1 breast cancer
2. Breast cancer: IIB st. cT3N0M0, IIIA st. cT2N2M0, cT3N1M0 after neoadjuvant treatment with no responses (NR)
3. Skin lesions (chronic dermatitis, cicatricial deformities, keloid scars)
4. Severe concomitant diseases
5. Psychiatric disorders

**Recommendation grade B** (level of evidence 3) [47].

**Options of reconstructive plastic surgeries for BC**

I. One-step reconstructions: subcutaneous/skin-preserving radical mastectomies with immediate reconstruction. According to data compiled by the IPRAS (International Plastic Reconstructive Aestetic Surgery) conference, autologous tissues are considered to be optimal materials for reconstructive surgeries, although the process is technically more difficult. However, 80% of breast reconstructive surgeries are performed using implants due to the fact that the endoprosthetic technique is technically easier, less traumatic, and requires less postoperative recovery time.

One-step reconstructions: subcutaneous/skin-preserving radical mastectomies with immediate reconstruction using a silicone textured or polyurethane-coated implant placed either prepectorally or in combination with an autologous flap, mesh implant, biological implant (acellular dermal matrix)

II. Two-step reconstructions: subcutaneous/skin-preserving radical mastectomies with immediate reconstruction using a tissue expander followed by replacement with a silicone textured or polyurethane-coated implant or an autologous flap.

Silicone implant replacement is possible in the following options:

1. in combination with autologous flap
2. mesh implant
3. biological implant (acellular dermal matrix)
4. independent implant in the presence of sufficient cutaneous and subcutaneous layer thickness of the reconstructed breast
In case of contraindications to subcutaneous/skin-preserving mastectomy, the patient’s refusal from immediate breast reconstruction, indications for postoperative radiation therapy and refusal from two-step reconstruction, preference should be given to delayed breast reconstruction.

Comment regarding the width of the distance from the resection margin and the likelihood of local recurrence. The proposals are based on the results of two extensive meta-analyses. A meta-analysis of 33 studies involving 28162 patients (N.Houssami et al., 2014) demonstrated a dangerous increase in the incidence of local recurrence in the presence of a tumour at the resection margin and the absence of a statistically significant decrease in the probability of recurrence with an increase in the width of the distance from the resection margin from 1 mm to 2 mm and up to 5 mm. This pattern persisted across all compared subgroups, including biological subtypes, age, and treatment options. This analysis was the basis for the recommendation of the SSO-ASTRO to the effect that the optimal surgical approach is the absence of a tumour at the resection margin and no additional expansion of resection margins is required as it does not reduce the probability of recurrence. A meta-analysis by Shah C. et al. (2017) based on updating the same database as the one previously described and included 2 times more patients (55302) with a follow-up period of at least 50 months (median 7.2 years) confirmed the high probability of local recurrence with in patients with “positive” resection margin (10.3%). In addition, statistically significant differences were obtained in local recurrence incidence depending on the width of the distance from the resection margin: 7.2% for patients with distance of “>0” to 2 mm, 3.6% for distance of 2-5 mm, and 3.2% for distance of >5 mm (p<0.001 for all comparisons). Thus, for practical purposes, the presence of a tumour at the resection margins should be recognised unacceptable and a distance of >2 mm from the tumour should be recognised as highly desirable.

**Recommendation grade A** (level of evidence 1) [38].

Mastectomy is recommended, if it is impossible to conduct organ-conserving surgery or additional radiation therapy, as well as at the patient’s discretion.

**Recommended options of reconstructive plastic surgeries for BC**

I. One-step reconstructions using autologous tissues and/or silicone textured or polyurethane-coated implants covering the lower slope with additional materials as indicated.

II. Two-step reconstructions, in cases requiring skin excision followed by replacement of a tissue expander with a silicone textured or polyurethane-coated implant or an autologous flap.
Recommendation grade B (level of evidence 3) [47].

Technical difficulties and special cases

*Multifocal or multicentric tumour growth.* Organ-conserving surgery is possible if the following conditions are met: removal of all tumour foci by achieving clear resection margins and formation of aesthetically acceptable breast shape.

*Abnormal microcalcifications extending beyond the tumour node* or other signs of extended intraductal growth according to mammography and/or MRI data. Organ-conserving surgery is possible if the following conditions are met: removal of the entire area of intraductal growth by achieving clear resection margins with extra space of at least 2 mm and formation of aesthetically acceptable breast shape.

*Paget’s disease of the nipple* without lesion formation: organ-conserving surgery involving the removal of the nipple-areola complex and immediate mammoplasty with glandular flaps (e. g. according to Grisotti) is possible.

*Paget’s disease* involving breast lesion formation. Organ-conserving surgery is not recommended, except as part of research programmes, mastectomy is recommended. The mastectomy can be performed either without reconstruction or with primary reconstruction. In case of primary reconstruction, skin-preserving mastectomy with removal of the nipple-areola complex should be performed.

*Breast tumours close to or behind the nipple.* Organ-conserving surgery involving the removal of the nipple-areola complex and immediate mammoplasty with glandular flaps (e. g. according to Grisotti) is possible.

**Pregnancy** (See treatment of breast cancer in pregnancy).

1.15 Radiation therapy

In order to reduce the rate of locoregional recurrences, modern 3D-conformal external-beam RT is **recommended** to be performed using linear electron accelerators with multileaf diaphragm collimators or a proton beam accelerator.

**Recommendation grade A (level of evidence I)**

In the absence of linear electron accelerators, external-beam RT is recommended to be carried out using distant gamma-therapy units.

**Recommendation grade B (level of evidence IIa)**

Special holding fixture systems are **recommended** to be used to improve the accuracy and repeatability of patient positioning during radiation therapy. Volumetric planning with contouring of the lung, heart and contralateral breast tissues is recommended to
minimise their radiation burden. Dose should be calculated for a given target according to the recommendations of the International Commission on Radiation Units and Measurements ICRU-50, 62 and 83 [6]; it is recommended to limit doses in normal tissues according to QUANTEC data, but without affecting the coverage of the planned treatment volume [48–53].

The volume and timing of radiation therapy should be selected in joint consultation with a surgeon, radiotherapist, and chemotherapist.

**Recommendation grade A (level of evidence I)**

### 4.3.1. Radiation therapy in primary operable BC (0, I, IIA, IIB, IIIA (T3N1M0) stages) after organ-conserving treatment

Adjuvant radiation therapy after organ-conserving treatment is recommended in patients with TisN0M0, T1-3N0-1M0 breast cancer

**Recommendation grade A (level of evidence 1)** [54], [55], [56], [57]. [58–60]

**Extent of radiation exposure after organ-conserving treatment:**

- Tis (ductal carcinoma *in situ*, DCIS): residual mammary gland (18)
- T1-3N0-1M0:
  - in patients with N1 (1-3 LN involved): residual mammary gland +/- additional irradiation of the removed tumour bed (level of evidence 1), to consider the possibility of RT to the supra-/infraclavicular region, ipsilateral parasternal lymph nodes, and part of the axillary region (as a recurrence risk area)
  - in patients with N0: residual mammary gland +/- additional irradiation of the removed tumour bed (level of evidence 1), consider the possibility of RT to the supra-/infraclavicular region and ipsilateral parasternal lymph nodes in patients with central/medial tumour location or tumour size of >2 cm and the presence of recurrence risk factors

**Comment:** RT should be initiated 4-12 weeks after the organ-conserving surgery without adjuvant polychemotherapy (provided that the surgical wound is completely healed) or 3-4 weeks after the completion of all planned adjuvant chemotherapy, if prescribed. Radiation therapy concomitant with endocrine or target therapy is possible [61–64].

**Comment:** RT after organ-conserving surgeries may be omitted in BC patients over 70 years old, T1N0M0, Grade I-II, in the absence of tumour cells at the resection margins, ER-positive tumour status if hormone therapy is prescribed [65].
Comment: doses and regimens of RT: for residual mammary gland, classic fractionation regimen: SBD 2 Gy, TBD 46-50 Gy or hypofractionated RT regimen (possible subject to 3D-conformal radiation therapy): SBD 2.67-2.66 Gy to TBD 40-42.56 Gy per 15-16 fractions [66–69].

For lymph drainage areas, RT should be administered in classic fractionation regimen: SBD 2 Gy, TBD 46-50 Gy

Additional irradiation of the removed tumour bed should be carried out using 3D-conformal radiation therapy, brachytherapy, and intraoperative radiation therapy. In case of external-beam RT, it is recommended to use SBD of 2-2.5 Gy and TBD of 10-16 Gy [70,71].

Radiation therapy is carried out 5 times a week.

Comment: indications for additional irradiation to the tumour bed (boost) in BC patients:

- age ≤50 years old
- in patients over 51 years of age, Grade III, positive or close (<1 mm) resection margin (in case of refusal to undergo repeated surgery)
- lymphovascular invasion is considered as an additional risk factor in doubtful cases
- clear landmarks for determining the removed tumour bed are postoperative seroma, radiopaque clips (5-6) installed by surgeons during the surgical intervention [72–76]

Additional irradiation of the removed tumour bed (boost) can be omitted in patients with early BC aged ≤50 years with G1 tumour and/or favourable molecular subtype with planned adjuvant endocrine therapy [58]

Comment: in patients with T1-2N0 as part of extensive research protocols, accelerated partial breast irradiation is possible, if the following eligibility criteria are met [77–85]:

- age ≥50 years old
- histological structure: invasive NST cancer without LCIS and EIC
- presence of one lesion of 2-3 cm
- pN0
- distance from the tumour to the resection margins of ≥2 mm
- Grade 1-2
- + ER / + PR (luminal A subtype)

4.3.2. Radiation therapy in primary operable BC (0, I, IIA, IIB, IIIA (T3N1M0) stages) after radical mastectomy
Adjuvant RT is **recommended** following mastectomy as part of combined treatment in patients with T1-3N0-1M0 BC, if indicated

**Recommendation grade A** (level of evidence 1) [42].

**Indications for RT after mastectomy:**

- pT1-3N1 (1-3 lymph nodes involved + ≥1 risk factors for recurrence)
- pT3N0 (tumour of >5 cm)
- pT1-2N0 in the presence of tumour cells at a distance of <1 mm from the resection margins or in central/medial tumour location, tumour size of >2 cm, triple-negative tumour subtype in combination with recurrence risk factors

**Comment:** *recurrence risk factors* [86]:

- *Individuals under 50 years of age.*
- *Grade III*
- *Tumour cells at the resection margins*
- *Lymphovascular invasion is considered as an additional risk factor in doubtful cases*

**Comment:** *RT should be initiated 4-6 weeks after the surgery (provided that the surgical wound is completely healed) or 3-4 weeks after the completion of all planned adjuvant chemotherapy. Radiation therapy concomitant with endocrine or target therapy is possible.*

**Recommendation grade B** (level of evidence 3)

**Extent of radiation exposure after mastectomy:**

- pT1-3N1 (1-3 lymph nodes involved) + recurrence risk factors (one or more): anterior chest wall soft tissues ± additional irradiation of the recurrence risk area around the surgical scar, supra-/infraclavicular region, ipsilateral parasternal lymph nodes, any part of the axillary region (as a recurrence risk area)
- pT3N0 (tumour of >5 cm): anterior chest wall soft tissues ± additional irradiation of the recurrence risk area around the surgical scar, consider the possibility of RT to the cervical-supra-/infraclavicular region, ipsilateral parasternal lymph nodes
- pT1-2N0 in the presence of tumour cells at a distance of <1 mm from the resection margins, in central/medial tumour location or tumour size of >2 cm, or triple-negative tumour subtype + the presence of recurrence risk factors: anterior chest wall soft tissues ± additional irradiation of the recurrence risk area around the surgical scar, +/- supra-/infraclavicular region and ipsilateral parasternal lymph nodes [87]
Recommendation grade B (level of evidence 2) [88,89]

Doses and regimens of RT: For anterior chest wall soft tissues (+ reconstructed breast) and lymph drainage areas, the following regimen of RT is used: SBD of 2 Gy, TBD of 46-50 Gy. Additional irradiation of the recurrence risk area around the surgical scar should be performed using 3D-conformal RT, brachytherapy, in case of external-beam RT: SBD of 2 Gy, TBD of 10 Gy. Radiation therapy is carried out 5 times a week.

Consideration should be given to possible use of a special bolus when irradiating the anterior chest wall soft tissues or the surgical scar to ensure an adequate dose to the skin in the irradiated site [90–92]

Comment: indications for RT after neoadjuvant chemotherapy and radical mastectomy are determined according to T and N criteria at baseline and do not depend on response to systemic therapy

Recommendation grade B (level of evidence 2)

Comments: prior to oncoplastic surgeries, it is recommended to discuss the treatment plan jointly with a surgeon and a radiotherapist; if there are indications for postoperative RT, it is recommended to perform breast reconstruction surgery after the completion of RT course [13, [54], [93],[94], [92,95]

4.3.3. Radiation therapy in patients with locally advanced (primarily inoperable) BC (IIIA (except for T3N1M0), IIIB, IIIC stages)

It is recommended to administer external-beam 3D-conformal RT to patients with locally advanced (primarily inoperable) BC IIIA (except for T3N1M0), IIIB, IIIC stages (17, 55)

Extent of radiation exposure after mastectomy/organ-conserving surgery in patients with locally advanced breast cancer after neoadjuvant drug therapy:

anterior chest wall soft tissues (or residual mammary gland) + additional irradiation of the recurrence risk area around the surgical scar or removed tumour bed, supra-/infraclavicular region, ipsilateral parasternal lymph nodes, any part of the axillary region (as a recurrence risk area)

Doses of RT in patients with locally advanced BC after mastectomy or organ-conserving surgery
• For anterior chest wall soft tissue (± reconstructed breast / residual mammary gland) and lymph drainage areas, RT is administered as follows: SBD of 2 Gy, TBD of 46-50 Gy.

if additional irradiation of the recurrence risk area around the surgical scar is indicated, it should be performed using 3D-conformal RT, brachytherapy, in case of external-beam RT: SBD of 2 Gy, TBD of 10 Gy [89,96,97].

**It is recommended** to consider the possible use of a special bolus when irradiating the anterior chest wall soft tissues or the surgical scar to ensure an adequate dose to the skin in the irradiated site (e.g. evidence of tumour ingrowth in the breast skin) [90–92]

**Recommendation grade A (level of evidence I).**

• In patients with initially involved and verified metastatic lymph nodes in the supra-/infraclavicular region in the presence of residual metastases, their local irradiation is recommended at TBD of up to 60-64 Gy for the entire course of RT (when selecting local irradiation fields, ultrasound or CT scans should be performed)

**Comments:** indications for RT after neoadjuvant chemotherapy and radical mastectomy/organ-conserving surgery in patients with locally advanced BC are determined according to T and N criteria at baseline and do not depend on response to systemic therapy

**Recommendation grade A (level of evidence I).**

**Comments:** start of RT: 4-6 weeks after the surgery (provided that the surgical wound is completely healed); in case of adjuvant chemotherapy: 3-4 weeks after the end of drug therapy.

**In patients with inoperable/non-resectable disease** after completion of drug treatment or in patients refused from surgery, a course of external-beam RT is recommended within 3 to 4 weeks after completion of drug therapy, concomitant drug treatment is allowed (after a consultation with a radiotherapist and chemotherapist). [20]

**Recommendation grade B (level of evidence IIb).**

**Volumes and doses of RT:**

Breast RT **it is recommended** at SBD of 2-2.5 Gy, TBD of 50-60 YGy and to all lymph drainage areas on the affected side at SBD of 2-2.5 Gy, TBD of 45-50 YGy followed by response assessment and repeated discussion of treatment strategy with a surgeon and radiotherapist. If surgical treatment is possible, RM is preferred. [20]

**Recommendation grade B (level of evidence IIb).**
When surgery is impossible or refused by the patient, RT is recommended to be performed using a radical programme with a total dose over the entire course of treatment of 60–65 YGy to the breast and up to 65-70 YGy given locally to the tumour, depending on the number of courses and the efficacy of the previous CT; up to 60-65 YGy given locally to individual detectable metastatic lymph nodes; when selecting local irradiation fields, ultrasound or CT scans should be performed. [20]

**Recommendation grade B (level of evidence IIb).**

**Comments:** in case of nodal BC, it is effective to use local microwave hyperthermia (after administering TBD of 16 YGy) with a temperature inside the tumour of 42-43 °C; the number of hyperthermia sessions: 6-8.

Recommendation grade B (level of evidence 3) [40].

It is recommended to consider the possible use of a special bolus when irradiating the breast to ensure an adequate dose to the skin in the irradiated site (e.g. evidence of tumour ingrowth in the breast skin, in the presence of intracutaneous satellites)

3.3.4. **Radiation therapy in patients with distant metastases**

External-beam radiation therapy is recommended to manage pain and prevent complications that may cause bone metastases (spinal cord compression, hypercalcaemia, pathologic fractures) [54-58],[100].

**Recommendation grade B (level of evidence 3)**

The following irradiation regimens are recommended for metastatic bone disease: 30-36 Gy/10-12 fractions, 24 Gy/6 fractions, 20 Gy/5 fractions, 8 Gy/1 fraction, 26 Gy/2 fractions, 21-30 Gy/3 fractions.

**Recommendation grade B (level of evidence 2)**

**Comment:** the possibility of repeated external-beam RT in case of recurrence of symptoms associated with bone metastases should be determined individually in each particular case and depends on the localisation of bone metastasis and the possibility of additional radiation exposure with due consideration of the tolerance of tissues (especially in the spinal cord) to be exposed to the radiation, as well as the severity of radiation damage to normal tissues after previous radiation therapy

**Recommendation grade B (level of evidence 2)**

Stereotactic RT is possible in patients with single bone metastases without evidence of spinal cord compression in the absence of visceral metastases and predicted high life expectancy.
**Recommendation grade C** (level of evidence 3)

Irradiation of oligometastatic sites using a stereotactic radiation regimen from 40-50 Gy in 4-5 fractions to 60 Gy in 3 fractions [101].

Irradiation of oligometastatic changes in a stereotactic radiation regimen can be given as a single exposure at doses of 8-24 Gy or using regimens of 4 Gy/5 fr, 6 Gy/5 fr, 8 Gy/3 fr.

**Recommendation grade B** (level of evidence 2)

Postoperative external-beam RT in patients who underwent surgical spinal cord decompression can be performed under the following regimen: 40 Gy×20 fr., 30 Gy×10 fr., single exposure of 8 Gy.

**Recommendation grade B** (level of evidence 2)

Systemic radiation therapy with strontium-89 or samarium-153 is recommended in the presence of multiple osteoblastic metastases accompanied by pain syndrome [44], [45], [102].

**Recommendation grade B** (level of evidence 2)

**Comment:** The use of bisphosphonates does not exclude the need for external-beam RT in patients with pain syndrome. Concomitant use of external-beam RT and bisphosphonates improves palliative care outcomes. External-beam RT and bisphosphonates have a complementary mechanism of action with only slightly overlapping toxicity profiles. Bisphosphonates may be used with various fractions of external-beam RT.

**Radiation therapy for BC patients with metastatic brain disease**

Brain MRI with i/v contrast is recommended for accurate diagnosis of metastatic lesions (the number of metastases, the presence of perifocal oedema, midline shift). Contrast-enhanced computed tomography for diagnosing metastatic brain lesions is recommended only if there are contraindications to MRI.

**Recommendation grade A** (level of evidence 1b)

Additional tests are recommended to identify extracranial metastases if the obtained data may change the treatment strategy. The presence of extracranial metastases is a factor of poor prognosis. Examination by a neurologist and an ophthalmologist is recommended (to clarify the presence or absence of congestion in the fundus).

**Recommendation grade A** (level of evidence 1a)

It is recommended to determine management strategy for patients with metastatic brain disease in a multidisciplinary consultation with a neurosurgeon, oncologist, and radiotherapist.
External-beam radiation therapy is recommended in patients with brain metastases (BM) to provide local control over intracranial metastatic lesions, maintain the quality of life, and improve overall survival in certain clinical situations. Whole-brain radiation therapy is recommended in the following cases:
• patients after surgery for metastatic lesion
• patients with multiple (≥4 lesions) BM
• patients with leptomeningeal and pachymeningeal progression
• in the presence of large BM (>3 cm in diameter) and contraindications for surgical treatment and stereotactic radiation therapy (SRT)
• in the presence of intracranial recurrences after surgical treatment or SRT
• patients with low performance status and poor prognosis of overall survival (median overall survival of <3 months) [103, 104, 105, 106, 110].

**Recommendation grade B** (level of evidence 2b)

**Comment:** whole-brain radiation therapy does not increase overall survival in patients with multiple BMs, but improves the quality of life; increases overall survival in patients after surgical removal of a single metastasis; improves local control; and reduces intracranial disease progression. The standard fractionation regimen for WBRT is as follows: 30 Gy per 10 fractions or 37.5 Gy per 15 fractions. In patients with poor prognosis of overall survival and a low performance status, a fractionation regimen of 20 Gy per 5 fractions may be used.

Stereotactic radiation treatment (stereotactic radiosurgery/radiotherapy) is recommended for patients with a limited number of BMs and good prognosis of overall survival. It is recommended to conduct stereotactic radiosurgery in patients with BMs of up to 3 cm in diameter without clinical evidence of mass effect and localised outside functional brain areas; with contraindications to surgical treatment [107, 108, 109, 110].

**Recommendation grade A** (level of evidence 1b)

**Comment:** Ionising radiation doses for radiosurgery are as follows: 15 Gy for BM with a maximum diameter of 3-4 cm; 18 Gy for BM with a maximum diameter of 2-3 cm; 24 Gy for BM with a maximum diameter of up to 2 cm. Hypofractionated stereotactic radiation therapy is recommended in the presence of a lesion with a maximum diameter of ≥3 cm, without clinical evidence of mass effect and without contraindications for surgical treatment or lesions of any size localised in functional brain areas.

**Recommendation grade B** (level of evidence III)

**Comment:** equivalent fractionation regimens are as follows: 24 Gy per 3 fractions; 30 Gy per 5 fractions; 35 Gy per 7 fractions.

Adding whole-brain radiation therapy to stereotactic radiotherapy improves local control of metastatic brain lesions, but does not improve overall survival, and increases the risk of neurocognitive disorders [105, 106, 111].
Symptomatic treatment is recommended in patients with limited metastatic brain lesions (≤3 lesions) and poor prognosis of overall survival (Karnofsky index ≤70, ECOG 2-4, RPA class 3, GPA 0-2 scores), with multiple extracranial metastases, with uncontrolled extracranial disease, with the absence of systemic treatment reserves. **Recommendation grade B** (level of evidence 2a)

1.16 Systemic adjuvant and neoadjuvant therapy

The principles of systemic adjuvant and neoadjuvant therapy for BC are described below (Table 8 - Table 25).

Table 8. Systemic neoadjuvant therapy for BC. Stages: partial IIA (if the tumour size does not allow OCS), IIB (T2N1M0-T3N0M0)

<table>
<thead>
<tr>
<th>Biological (IHC) subtype. Material: needle core biopsy of the primary tumour. G- any, Ki- any. ER+(Allred score 4-8), HER2 - (neg.)</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Endocrine therapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal age</td>
<td>AC×4→P×12{**doxorubicin 60 mg/m² on day 1 + **cyclophosphamide 600 mg/m² on day 1 } up to 4 cycles followed by **paclitaxel 80 mg/m² 1-hour weekly i.v. infusion for 12 weeks. For a full list of regimens, see non-adjuvant treatment</td>
<td>See non-adjuvant hormone therapy</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12 For a full list of regimens, see non-adjuvant treatment</td>
<td>Aromatase inhibitors 4 years</td>
</tr>
</tbody>
</table>

Table 9. Systemic neoadjuvant therapy for BC. Stages: partial IIA (if the tumour size does not allow OCS), IIB (T2N1M0-T3N0M0)
<table>
<thead>
<tr>
<th>Material: needle core biopsy of the primary tumour. G-any, KI-any. ER-(Allred score 0-3). HER2 - (neg.)</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12{ <strong>doxorubicin</strong> 60 mg/m² on day 1 + <strong>cyclophosphamide</strong> 600 mg/m² on day 1} up to 4 cycles followed by <strong>paclitaxel</strong> 80 mg/m² 1-hour weekly i.v. infusion for 12 weeks. <em>For a full list of regimens, see non-adjuvant treatment</em></td>
<td>FAC-4 cycles FEC-4 cycles</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12{ <strong>doxorubicin</strong> 60 mg/m² on day 1 + <strong>cyclophosphamide</strong> 600 mg/m² on day 1} up to 4 cycles followed by <strong>paclitaxel</strong> 80 mg/m² 1-hour weekly i.v. infusion for 12 weeks. <em>For a full list of regimens, see non-adjuvant treatment</em></td>
<td>FAC-4 cycles FEC-4 cycles</td>
</tr>
</tbody>
</table>
### Table 10. Systemic neoadjuvant therapy for BC. Stages: partial IIA (if the tumour size does not allow OCS), IIB (T2N1M0-T3N0M0)

<table>
<thead>
<tr>
<th>Material: needle core biopsy of the primary tumour. G-any, KI-any. ER+(Allred score 4-8). HER2+ (pos.)</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td><strong>Target therapy</strong></td>
<td><strong>Endocrine therapy</strong></td>
</tr>
<tr>
<td><strong>Reproductive and premenopausal age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel 4 cycles (NB! In adjuvant settings, FEC therapy includes 3 cycles) (NeoSphere)</strong></td>
<td><strong>Pertuzuma b+ trastuzumab 4 cycles</strong></td>
<td>See adjuvant treatment</td>
</tr>
<tr>
<td><strong>Docetaxel + Carboplatin 6 cycles (NB! No FEC in adjuvant setting) (TRYPHAEINA)</strong></td>
<td><strong>Pertuzuma b+ trastuzumab 6 cycles</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopause</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel 4 cycles (NB! In adjuvant settings, FEC therapy includes 3 cycles) (NeoSphere)</strong></td>
<td><strong>Pertuzuma b+</strong></td>
<td>See adjuvant treatment</td>
</tr>
<tr>
<td></td>
<td><strong>trastuzumab 4 cycles</strong></td>
<td></td>
</tr>
</tbody>
</table>

**NB!** In adjuvant settings, FEC therapy includes 3 cycles.
Table 11. Systemic neoadjuvant therapy for BC. Stages: partial IIA (if the tumour size does not allow OCS), IIB (T2N1M0-T3N0M0)

<table>
<thead>
<tr>
<th>Material: needle core biopsy of the primary tumour. G- any, Ki- any. ER- (Allred score 0-3). HER2+</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive and premenopausal</td>
<td>Docetaxel 4 cycles (NB! Adjuvant FEC therapy includes 3 cycles) (NeoSphere)</td>
<td>**Pertuzumab +**trastuzumab 4 cycles</td>
</tr>
<tr>
<td>**Docetaxel+**Carboplatin 6 cycles (TRYPHAENA) (NB! No FEC in adjuvant settings)</td>
<td>**Pertuzumab +**trastuzumab 6 cycles</td>
<td><strong>Trastuzumab</strong></td>
</tr>
</tbody>
</table>

Table 12. Systemic neoadjuvant therapy for BC. Stages: IIIA, IIB, IIC

<table>
<thead>
<tr>
<th>Material: needle core biopsy of the primary tumour. G- any, Ki- any. ER+(Allred score 4-8). HER2-(neg.)</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive and premenopausal</td>
<td>Chemotherapy</td>
<td>Endocrine therapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12{ **doxorubicin 60 mg/m² on day 1 + **cyclophosphamide 600 mg/m² on day 1} up to 4 cycles followed by **paclitaxel 80 mg/m² 1-hour weekly i.v. infusion for 12 weeks. For a full list of regimens, see</td>
<td>See non-adjuvant hormone therapy</td>
</tr>
<tr>
<td>**Docetaxel+**Carboplatin 6 cycles (TRYPHAENA) (NB! No FEC in adjuvant settings)</td>
<td>**Pertuzumab +**trastuzumab 6 cycles</td>
<td>See non-adjuvant hormone therapy</td>
</tr>
</tbody>
</table>
Table 13. Systemic neoadjuvant therapy for BC. Stages: IIIA, IIIB, IIIC

<table>
<thead>
<tr>
<th>Material: needle core biopsy of the primary tumour. G-any, KI-any. ER-(Allred score 0-3). HER2-(neg.)</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12</td>
<td>See non-adjuvant hormone therapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12</td>
<td>For a full list of regimens, see non-adjuvant treatment</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>FAC-4 cycles</td>
<td>For a full list of regimens, see non-adjuvant treatment</td>
</tr>
</tbody>
</table>

Table 14. Systemic neoadjuvant therapy for BC. Stages: IIIA, IIIB, IIIC

<table>
<thead>
<tr>
<th>Material: needle core biopsy of the primary tumour. G-any, KI-any. ER+(Allred score 4-8). HER2+ (pos.)</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive and premenopausal</td>
<td><strong>Docetaxel 4 cycles (NB! Adjuvant FEC therapy includes 3 cycles) (NeoSphere)</strong></td>
<td>See adjuvant treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Pertuzumab+ trastuzumab 4 cycles</strong></td>
<td>AT×3 cycles →T cycles →CMF × 6 cycles (NOAH)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td><strong>Docetaxel+ Carboplatin 6 cycles (NB! No FEC in adjuvant settings) (TRYPHAENA)</strong></td>
<td>See adjuvant treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Pertuzumab+ trastuzumab 6 cycles</strong></td>
<td><strong>Trastuzumab</strong></td>
</tr>
<tr>
<td>Postmenopause</td>
<td><strong>Docetaxel+ Carboplatin 6 cycles (NB! Adjuvant FEC therapy)</strong></td>
<td>See adjuvant treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Pertuzumab+ trastuzumab 4 cycles</strong></td>
<td>AT×3 cycles →T cycles →CMF × 6 cycles (NOAH)</td>
</tr>
<tr>
<td></td>
<td><strong>Trastuzumab</strong></td>
<td><strong>Trastuzumab</strong></td>
</tr>
<tr>
<td>Material: needle core biopsy of the primary tumour. G- any, KI- any, ER-(Allred score 0-3). HER2+ (posit.)</td>
<td>Preferred standard</td>
<td>Recommended standard</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td><strong>Target therapy</strong></td>
<td><strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td><strong>Docetaxel 4 cycles (NB! In adjuvant FEC therapy, 3 cycles) (NeoSphere)</strong></td>
<td>**Pertuzumab +**trastuzumab 4 cycles</td>
</tr>
<tr>
<td></td>
<td>**Docetaxel +**Carboplatin 6 cycles (TRYPHAENA) (NB! No FEC in adjuvant settings)</td>
<td>**Pertuzumab +**trastuzumab 6 cycles</td>
</tr>
<tr>
<td>Postmenopause</td>
<td><strong>Docetaxel 4 cycles (NB! In adjuvant FEC therapy, 3 cycles) (NeoSphere)</strong></td>
<td>**Pertuzumab +**trastuzumab 4 cycles</td>
</tr>
<tr>
<td></td>
<td>**Docetaxel +**Carboplatin 6 cycles (TRYPHAENA) (NB! No FEC in adjuvant settings)</td>
<td>**Pertuzumab +**trastuzumab 6 cycles</td>
</tr>
</tbody>
</table>
Table 16. Systemic adjuvant therapy for BC. Stages: I-IIA (pT1-2N0M0)

| ER+/PR±, ± (Allred score 4-8) HER2(-) G1, or G2 Ki 67-low according to your laboratory | TREATMENT |
|---|---|---|---|
| Preferred standard | Acceptable standard | Preferred standard | Acceptable standard |
| Chemotherapy | Endocrine therapy | Chemotherapy | Endocrine therapy |
| Reproductive and premenopausal | Not recommended | TAM 5 years | Not recommended | TAM 5 years; For a full list, see adjuvant hormone therapy |
| Postmenopause | Not recommended | TAM 5 years | Not recommended | TAM 5 years; For a full list, see adjuvant hormone therapy |

Table 17. Systemic adjuvant therapy for BC. Stages: IIA (pT1-2N0M0)

| Biological (IHC) subtype of ER+/PR± (Allred score 4-8) G2, Ki67-high according to your laboratory, HER2 (-) BC | TREATMENT |
|---|---|---|---|
| Preferred standard | Acceptable standard | Preferred standard | Acceptable standard |
| Chemotherapy | Endocrine therapy | Chemotherapy | Endocrine therapy |
| Reproductive and premenopausal | AC×4→P×12; For a full list of regimens, see adjuvant treatment | TAM 5 years + ovarian function suppression | For a full list of regimens, see adjuvant treatment | TAM 5 years; For a full list, see adjuvant hormone therapy |
| Postmenopause | AC×4→P×12; For a full list of regimens, see adjuvant treatment | TAM 2 → AI 2-3 yrs+osteomodifying agents; AI 5+ osteomodifying agents | For a full list of regimens, see adjuvant treatment | TAM 5 years; For a full list, see adjuvant hormone therapy |
### Table 18. Systemic adjuvant therapy for BC. Stages: I (pT1N0M0)

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/PR± (Allred score 4-8) G3, HER2 (-) BC</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred standard</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
</tr>
</tbody>
</table>

### Table 19. Systemic adjuvant therapy for BC. Stages: IIa (pT2N0M0)

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/PR± (Allred score 4-8) G3, HER2 (-) BC</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred standard</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
</tr>
</tbody>
</table>

### Table 20. Systemic adjuvant therapy for BC IIb, partially IIIa (pT1-2N1, pT3N0M0, pT2N2M0)

<p>| TREATMENT |</p>
<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/PR± (Allred score 4-8) BC</th>
<th>Preferred standard</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1-G3, HER2 (-)</td>
<td>Chemotherapy</td>
<td>Endocrine therapy</td>
</tr>
</tbody>
</table>

Reproductive and premenopausal

- AC×4→P×12; For a full list of regimens, see adjuvant treatment
- TAM 5 years + ovarian suppression aromatase inhibitors 5 years + ovarian suppression
- FAC
- FEC; For a full list of regimens, see adjuvant treatment
- TAM 5 years; For a full list, see adjuvant hormone therapy

Postmenopause

- AC×4→P×12; For a full list of regimens, see adjuvant treatment
- TAM 2 → AI 2-3 yrs+osteomodifying agents
- AI 5 years + osteomodifying agents
- FAC x 6 cycles, FEC x 6 cycles; For a full list of regimens, see adjuvant treatment
- TAM 5 years; For a full list, see adjuvant hormone therapy

Table 21. Systemic adjuvant therapy for BC. Stages: I-IIA (pT1-2N0M0)

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/PR± (Allred score 4-8) G2-3, Ki67-high according to your laboratory, HER2 (-) BC</th>
<th>Preferred standard</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Endocrine therapy</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

Reproductive and perimenopausal

- AC×4→P×12; For a full list of regimens, see adjuvant treatment
- TAM 5 years + ovarian function suppression
- FAC x 6 cycles, FEC x 6 cycles; For a full list of regimens, see adjuvant treatment
- TAM 5 years; For a full list, see adjuvant hormone therapy

Postmenopause

- AC×4→P×12; For a full list of regimens, see adjuvant treatment
- TAM 2 → AI; 2-3 yrs+osteomodifying agents
- AI 5 yrs + osteomodifying agents
- Not recommended
- TAM 5 years; For a full list, see adjuvant hormone therapy

Table 22. Systemic adjuvant therapy for BC. Stages: I-IIA (pT1-2N0M0)
<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/ PR± (Allred score 4-8) G1-3, Ki67 any HER2 (+++), BC</th>
<th>TREATMENT</th>
<th>Preferred standard</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>For a full list of regimens, see adjuvant treatment</td>
<td>FAC x 6 cycles, FEC x 6 cycles, For a full list of regimens, see adjuvant treatment</td>
</tr>
</tbody>
</table>

**Table 23. Systemic adjuvant therapy for BC. Stages: IIB, partially IIIA (pT1-2N1-2, pT3N0M0)**

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/ PR± (Allred score 4-8) G1-3, Ki67 any HER2 (+++), BC</th>
<th>TREATMENT</th>
<th>Preferred standard</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>TAM 5 years + ovarian function suppression; For a full list, see adjuvant hormone therapy</td>
<td>FAC x 6 cycles, FEC x 6 cycles; For a full list of regimens, see adjuvant treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Trastuzumab 52 weeks</strong></td>
<td><strong>Trastuzumab 52 weeks</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of ER+/ PR± (Allred score 4-8) G1-3, Ki67 any HER2 (+++), BC</th>
<th>TREATMENT</th>
<th>Preferred standard</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>TAM 2 → AI 2-3 yrs+osteomodifying agents; For a full list, see adjuvant hormone therapy</td>
<td>FAC x 6 cycles, FEC x 6 cycles; For a full list of regimens, see adjuvant treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Trastuzumab 52 weeks</strong></td>
<td><strong>Trastuzumab 52 weeks</strong></td>
<td><strong>Trastuzumab 52 weeks</strong></td>
</tr>
</tbody>
</table>
Table 24. Systemic adjuvant therapy for BC. Stages: IIB, partially IIIA (pT1-2N1-2, pT3N0M0)

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of BC ER-/PR- (Allred score 0-3) G1-3, Ki67 any HER2 (+++)</th>
<th>TREATMENT</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred standard</td>
<td>Acceptable standard</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Target therapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>**Trastuzumab 52 weeks</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>**Trastuzumab 52 weeks</td>
</tr>
</tbody>
</table>

Table 25. Systemic adjuvant therapy for BC. Stages: IIB, partially IIIA (pT1-2N1-2, pT3N0M0)

<table>
<thead>
<tr>
<th>Biological (IHC) subtype of BC ER-/PR- (Allred score 0-8) G1-3, Ki67 any HER2 (-)</th>
<th>TREATMENT</th>
<th>Acceptable standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred standard</td>
<td>Acceptable standard</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Reproductive and premenopausal</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>FAC × 6 cycles, FEC × 6 cycles; For a full list of regimens, see adjuvant treatment</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>AC×4→P×12; For a full list of regimens, see adjuvant treatment</td>
<td>FAC × 6 cycles, FEC × 6 cycles; For a full list of regimens, see adjuvant treatment</td>
</tr>
</tbody>
</table>

1.16.1 Neoadjuvant drug therapy for BC

Morphological examination of resected breast tissues after neoadjuvant treatment is the gold standard for evaluation of the efficacy of the therapy, and diagnostics of complete morphological regression is the most important indicator of recurrence-free and overall survival. Complete morphological response is defined either as the absence of invasive carcinoma in the primary tumour (T0) and lymph nodes (N0), or as the presence of components of carcinoma in situ only (Tis) in the primary tumour and the absence of lymph node metastases (N0). Current recommendations of the Working Group provide a detailed description of morphological assessment of breast tissues after neoadjuvant treatment. The recommendations give particular attention to re-examination of biological markers as part of assessment of the residual tumour and its metastases in the settings of neoadjuvant HT.
**Recommendation grade A** (level of evidence 1) [112].

Neoadjuvant clinical trials analysing the efficacy of preoperative treatment of locally advanced BC (with T1 and N2-3 or T2-4 with any N and M0) is an attractive model for evaluation of efficacy of medicines allowing to determine product efficacy in a short time period based on the degree of complete pathomorphological response (pCR).

**Recommendation grade A** (level of evidence 1) [113].

A meta-analysis initiated by FDA and performed by the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) working group fully confirmed the improvement in long-term treatment outcomes in patients who achieved pCR compared to those who had residual tumour at the time of surgery (Cortazar P. et al., 2012). The most significant correlation between pCR and overall and recurrence-free survival rates was observed in aggressive BC subtypes: triple-negative, luminal B (HER2-negative), and HER2-positive subtype, especially when adding anti-HER2 agent **trastuzumab**. Therefore, based on the results of a meta-analysis of 12 clinical trials (involving 11,955 patients), the CTNeoBC working group proposed to interpret the definition of a complete pathomorphological response as ypT0ypN0 or ypT0/isypN0 (as the presence or absence of ductal carcinoma does not affect long-term outcomes)

**Recommendation grade A** (level of evidence 1).

1.16.2 Neoadjuvant drug therapy for triple-negative BC

Most of the Panel members (Consensus St. Gallen Breast Cancer Conference 2017 Voting Results) consider it necessary to prescribe anthracycline taxane-containing chemotherapy to such patients and to use platinum agents in patients with BRCA mutations [114].

**Recommendation grade B** (level of evidence 3) [115].

Increased pCR rate was observed in patients with triple-negative BC who received **carboplatin** [116]; no such correlation was observed in patients with HER2-positive BC.

**Recommendation grade A** (level of evidence 1)

1.16.3 Neoadjuvant drug therapy for HER2-positive BC

Most of the members of the 2015/2017 St. Gallen Consensus Conference on Breast Cancer (Consensus St. Gallen Breast Cancer Conference 2015, 2017 Voting Results) support dual anti-HER2 therapy with **trastuzumab** and **pertuzumab** based on taxane-containing CT in patients with HER2-positive BC, which treatment should preferably be prescribed after anthracycline antibiotics.

**Recommendation grade A** (level of evidence 1)
Adding adjuvant **pertuzumab** to standard therapy with **trastuzumab** and chemotherapy significantly reduces the risk of disease recurrence and death in patients with early HER2-positive BC and does not increase the toxicity profile.

**Recommendation grade B** (level of evidence 2)

**Subcutaneous trastuzumab can replace intravenous trastuzumab:** its dosage regimen is different from that of the i.v. agent: **Herceptin s.c.:** fixed dose of 600 mg (5 mL for 5 min) **Herceptin i.v.:** loading dose of 8 mg/kg, maintenance dose of 6 mg/kg. Should be used in patients with the following indications, including in patients with difficult venous access. Early stages of breast cancer with HER2 overexpression: in combination with neoadjuvant chemotherapy and subsequent adjuvant monotherapy with Herceptin in locally advanced (including inflammatory) disease or patients with tumour size >2 cm in diameter. The study showed no differences in clinical efficacy and safety of subcutaneous and standard administration of trastuzumab [136-139].

1.16.4 Neoadjuvant CT regimens with **trastuzumab** for HER2-positive BC

AC 4 cycles followed by **docetaxel** (75-100 mg/m² i.v. on day 1 once every 3 weeks, 4 cycles) + **trastuzumab** (6 mg/kg; loading dose of 8 mg/kg, i.v. on day 1 once every 3 weeks), continue in the adjuvant setting for up to 1 year. If 100 mg/m² of **docetaxel** is used, administration of colony-stimulating factors for prophylactic purposes is mandatory. Cardiac function monitoring.

AC 4 cycles followed by **paclitaxel** (80 mg/m² 12 weekly i.v. injections) + **trastuzumab** (2 mg/kg with loading dose of 4 mg/kg) i.v. every week, continue in the adjuvant setting for up to 1 year. **Trastuzumab** should be initiated concomitantly with **paclitaxel.** Cardiac function monitoring.

**Recommendation grade B** (level of evidence 2) [117].

PTD { **pertuzumab** (420 mg (loading dose of 840 mg) i.v. on day 1 once every 3 weeks) + **docetaxel** (75-100 mg/m² i.v. on day 1 once every 3 weeks) + **trastuzumab** (6 mg/kg (loading dose of 8 mg/kg) i.v. on day 1 once every 3 weeks then continue in the adjuvant setting for up to 1 year)} 4 cycles followed by FEC { **cyclophosphamide** (600 mg/m² on days 1 and 8) + **epirubicin** (90 mg/m² on day 1) + **fluorouracil** (600 mg/m² on day 1)} 4 cycles. Cardiac function monitoring [Gianni L., 2012].

**Recommendation grade B** (level of evidence 2) [118].

6 cycles of therapy with **pertuzumab** and **trastuzumab** in combination with **docetaxel** and **carboplatine** (with **trastuzumab** in adjuvant settings with a total duration of up to 1 year) • **pertuzumab** (at a loading dose of 840 mg, then at a dose of 420 mg once every 3 weeks). • **trastuzumab** (at a loading dose of 8 mg/kg of body
weight, then at a dose of 6 mg/kg every 3 weeks) • **docetaxel 75 mg/m² (**docetaxel dose increase above 75 mg/m² is not recommended) • **carboplatine AUC6.

**Recommendation grade B** (level of evidence 2) [119].

1.16.5 Neoadjuvant hormone therapy for ER+ BC

An alternative option to neoadjuvant CT in elderly patients with ER+ PR+ BC is pre-surgery HT preferably with *aromatase inhibitors* for up to 4-8 months or until maximum response.

**Recommendation grade B** (level of evidence 2) [120].

The feasibility of HT in elderly patients with ER+ PR+ BC is also due to the fact that complete morphological regression in response to CT is less common than in patients with ER-/PR- tumours. In postmenopausal patients with ER+ tumours receiving HT with aromatase inhibitors have the similar rate of pCR, organ-conserving surgeries, and 5-year recurrence free survival as in CT.

**Recommendation grade B** (level of evidence 2) [120].

**Recommendation grade B** (level of evidence 2)

Absence of Ki-67 expression decrease after 2 weeks of HT helps to identify groups of patients who are candidates for an earlier shift to alternative treatment options [121].

Exemestan (25 mg/day × 3 months) or **anastrozole** (1 mg/day × 3 months), or AT regimen { **doxorubicin** (60 mg/m²) + **paclitaxel** (200 mg/m²); 4 three-week cycles} = Rm: 78.9%, 75.0% and 75.6% in the groups of 38, 40 and 74 postmenopausal patients with ER+/PR+ BC, respectively. Organ-conserving surgeries were performed in 34.2%, 30%, and 24.3% of patients, respectively.

**Recommendation grade B** (level of evidence 2) [120].

**anastrozole** (1 mg/day × 3 months) [120].
1.16.6 Neoadjuvant chemotherapy regimens for BC

**AC×4→P 12**

\{ **doxorubicin** 60 mg/m² on day 1 + **cyclophosphamide** 600 mg/m² on day 1 \} up to 4 cycles followed by **paclitaxel** 80 mg/m² 1-hour weekly i.v. infusion for 12 weeks.

**Recommendation grade B** (level of evidence 2) [122].

**AC×4→D ×4**

\{ **doxorubicin** 60 mg/m² on day 1 + **cyclophosphamide** 600 mg/m² on day 1 \} up to 4 cycles followed by **docetaxel** (100 mg/m² i.v. 1-hour infusion on day 1) 4 three-week cycles. Administration of CSF for prophylactic purposes is mandatory.

vs. AC (4 cycles) = 91% and 85% Rm, respectively (incl. 65% and 40% complete clinical Rm, 25% and 13% complete pathomorphological Rm)

**Recommendation grade B** (level of evidence 2) [123], [124].

**AT×4→ FAC ×4**

\{ **doxorubicin** + **paclitaxel** \} 4 cycles + FAC 4 cycles

**Recommendation grade B** (level of evidence 2) [125].

**FAC**

\{ **fluorouracil** (600 mg/m² on day 1) + **doxorubicin** (60 mg/m² on day 1) + **cyclophosphamide** (600 mg/m² i.v. on day 1) \} 4 three-week cycles

**Recommendation grade B** (level of evidence 2) [126], [127].

**FEC×4→ D×4**

FEC **cyclophosphamide** (500 mg/m² on day 1) + **epirubicin** (100 mg/m² on day 1) + **fluorouracil** (500 mg/m² on day 1) every 3 weeks up to 4 cycles → **docetaxel** (100 mg/m² i.v. 1-hour infusion on day 1) 4 three-week cycles

**Recommendation grade B** (level of evidence 2) [128], [129].

**FEC**

FEC **cyclophosphamide** (500 mg/m² on day 1) + **epirubicin** (100 mg/m² on day 1) + **fluorouracil** (500 mg/m² on day 1) every 3 weeks up to 6 cycles
**Recommendation grade B** (level of evidence 2) [129].

\[ P \times 12 \rightarrow FAC \times 4 \]

**Paclitaxel** 80 mg/m\(^2\) 1-hour weekly i.v. infusion for 12 weeks. **Fluorouracil** (600 mg/m\(^2\) on day 1) + **Doxorubicin** (60 mg/m\(^2\) on day 1) + **Cyclophosphamide** (600 mg/m\(^2\) i.v. on day 1) 4 three-week cycles

**Paclitaxel** followed by CT as per FAC regimen, comparison of once-weekly and once-every-3 weeks regimens = 29% vs. 13.6% of complete morphological Rm, respectively (p<0.01)

**Recommendation grade B** (level of evidence 2) [130].

1.16.7 Adjuvant CT

**Recommendation grade B** (level of evidence 2)

Adjuvant CT should be initiated within the next 3-4 weeks after the surgery.

PCT regimens: 1) AC; 2) AC×4→D×4; 3) AC×4→P×12; 4) CAF (GALGB; SWOG); 5) DC; 6) CMF; 7) FEC, 8) FEC-100; 9) TAC.

**AC** up to 4-6 cycles {**Doxorubicin** (60 mg/m\(^2\) i.v. on day 1) + **Cyclophosphamide** (600 mg/m\(^2\) i.v. on day 1) in 3-week cycles}. In a study of patients with 0-3 lymph node involvement, regardless of hormone receptor levels, HER2, or menopausal status, there was no benefit of 6 cycles vs. 4 cycles of AC [131].

**Recommendation grade A** (level of evidence 1)

\[ AC \times 4 \rightarrow D \times 4 \]

**AC** 4 three-week cycles followed by **Docetaxel** (75 mg/m\(^2\) i.v. 4 cycles once in 3 weeks). rhG-CSF for prophylactic purposes is acceptable.

**Recommendation grade A** (level of evidence 1) [132], [133].

\[ AC \times 4 \rightarrow P \times 12 \]

{**Cyclophosphamide** (600 m/m\(^2\)) + **Doxorubicin** (60 mg/m\(^2\), 75 mg/m\(^2\) or 90 mg/m\(^2\)) 4 three-week cycles} + **Paclitaxel** (175 mg/m\(^2\) 4 cycles once in 3 weeks after completion of AC) in the group of BC patients with metastatic disease in regional lymph nodes vs. 4 cycles of AC w/o further use of **Paclitaxel** = reduction in recurrence risk by 17% (p=0.0023) and death risk by 18% (p=0.0064). 5-year recurrence free survival did not depend on the dose of **Doxorubicin** in the AC regimen (69%, 66% and 67%, respectively).

**Recommendation grade B** (level of evidence 2) [134].

\[ AC \times 4 \rightarrow P \times 12 \]
AC 4 cycles once in 3 weeks followed by **paclitaxel** 80 mg/m² 12 weekly i.v. injections.

**Recommendation grade A** (level of evidence 1) [135].

CEF { **cyclophosphamide** (75 mg/m² orally on days 1-14) + **epirubicin** (60 mg/m² i.v. on days 1 and 8) + **fluorouracil** (500 mg/m² i.v. on days 1 and 8) vs. CMF regimen { **cyclophosphamide** (100 mg/m² orally on days 1-14) + **methotrexate** (40 mg/m² i.v. on days 1 and 8) + **fluorouracil** (600 mg/m² i.v. on days 1 and 8) } as adjuvant CT in a group of 710 pre- and perimenopausal BC patients with LN involvement = 77% vs. 70% 5-year survival, respectively (p=0.03); 63% vs. 53% 5-year recurrence free survival, respectively (p=0.09)

**Recommendation grade B** (level of evidence 2) [136]

EC { **epirubicin** (120 mg/m²) + **cyclophosphamide** (600 mg/m²) once every 3 weeks, 4 cycles} vs. CMF (6 cycles) in the group of premenopausal patients with ≥4 positive axillary lymph nodes = recurrence free survival: 5.5 vs. 4.2 years, respectively; overall survival: 8.3 vs. 6.8 years, respectively [137].

FEC { **fluorouracil** (600 mg/m² on day 1) + **epirubicin** (90 mg/m² on day 1) + **cyclophosphamide** (600 mg/m² on day 1) every 3 weeks} vs. CMF { 600/40/600 mg/m² once every 3 weeks}= 6-year survival: 93% vs. 83%, respectively; comparable haemotoxicity, alopecia: 87% vs. 7%, respectively; menopause onset rate: 80% vs. 60%, respectively [138].

**Recommendation grade B** (level of evidence 2)

FEC-100 (500/100/500 once every 3 weeks, 6 cycles) [139].

**Recommendation grade B** (level of evidence 2)

N+ patients or N0 patients at high risk of recurrence

Dose-dense AC regimen followed by mono-chemotherapy with paclitaxel

- Doxorubicin 60 mg/m² on day 1 + cyclophosphamide 600 mg/m² on day 1 (+ filgrastim 300 μg once daily on days 5-7 starting from the 3rd day of the cycle). A 14-day interval between cycles, up to 4 cycles in total followed by • Paclitaxel 175 mg/m², a 3-hour infusion on day 1, a 14-day interval between cycles, up to 4 cycles in total (all cycles with filgrastim prophylaxis) or paclitaxel 80 mg/m² once a week (no. 12).

A large number of randomised phase III trials have demonstrated the benefits of dose-dense adjuvant chemotherapy regimens (e.g. AC regimens with a 2-week interval) compared with standard 3-week intervals in patients with early BC at high risk of recurrence. In an earlier meta-analysis, a statistically significant increase in recurrence-free and overall survival in patients treated with dose-dense CT was limited to ER-
negative tumours. The recent more extensive meta-analysis included individual data from 37,298 patients from 26 studies. It has been shown that intensification of dosing regimens of adjuvant chemotherapy by reducing intervals between courses, as well as sequential use of anthracyclines and taxanes (instead of their concomitant administration) reduces the 10-year risk of recurrence and death from BC without increasing the rate of death from other causes. The decrease in the recurrence rate for dose-intensive chemotherapy was similar and highly significant (p<0.0001) in both ER-positive and ER-negative tumours and did not differ significantly depending on other characteristics of patients or tumours.

A large EBCTCG meta-analysis that evaluated benefits and risks of intensive adjuvant chemotherapy (ACT) regimens compared to standard chemotherapy in early BC, included individual data from 37,298 patients from 26 studies. It compared 2-week and standard 3-week chemotherapy regimens, as well as the sequential versus concomitant administration of anthracyclines and taxanes. It was demonstrated that the recurrence rate of BC was significantly lower in the group of dose-intensive regimens (10-year risk of recurrence of 28.0% vs. 31.4%; RR: 0.86, 95% CI 0.82-0.89; p<0.0001), as well as 10-year BC mortality (18.9% vs. 21.3%; RR: 0.87, 95% CI 0.83-0.92; p <0.0001), and mortality from all causes (22.1% vs. 24.8%; RR: 0.87, 95% CI 0.83-0.91, p <0.0001). Recurrence-free mortality rate was also lower in the dose-intensive regimen group (10-year risk of 4.1% vs. 4.6%; RR: 0.88, 95% CI 0.78-0.99, p=0.034), which indicates the absence of long-term toxicity and associated mortality from intercurrent diseases after dose-intensive regimens. A pooled subanalysis of 7 studies (n=10,004) comparing 2- and 3-week chemotherapy regimens showed a significant decrease in the disease recurrence rate along with reduction of intervals between courses (10-year risk of 24.0% vs. 28.3%; RR: 0.83, 95% CI 0.76-0.91, p<0.0001). In addition, a pooled sub-analysis of 6 studies (n=11,028) comparing sequential chemotherapy with anthracyclines and taxanes showed a significant decrease in BC recurrence rate for the sequential treatment strategy (28.1% vs. 31.3%; RR: 0.87, 95% CI 0.80-0.94; p=0.0006). A pooled subanalysis of studies (n=6532) comparing both shorter intervals and sequential administration of anthracyclines and taxanes showed a significant reduction in the 10-year risk of BC recurrence in the group of short intervals and sequential CT (30.4% vs. 35.0%; RR: 0.82, 95% CI 0.74-0.90; p<0.0001). The decrease in the recurrence rate for dose-intensive chemotherapy was similar and highly significant (p<0.0001) in both ER-positive and ER-negative tumours and did not differ significantly depending on other characteristics of patients or tumours. Thus, the meta-analysis has shown with high reliability that intensification of dosing regimens of adjuvant chemotherapy by reducing intervals between courses, as well as sequential use of anthracyclines and taxanes (instead of their
concomitant administration) reduces the 10-year risk of recurrence and death from BC without increasing the rate of death from other causes.

1.16.8 Adjuvant drug therapy for HER2-positive BC

In patients with HER2+ with pT1b-cN0M0 and more advanced BC stages, it is recommended to initiate treatment with anthracycline antibiotics followed by taxanes in combination with **trastuzumab** (the latter treatment should last for up to one year).

Results for 10-year recurrence-free survival in HER2+ BC patients in the HERA study (n=5099):

in the groups of 1-year and 2-year adjuvant **trastuzumab** vs. observation, 10-year recurrence-free survival was 69% vs. 69% vs. 63% [140].

**Recommendation grade B** (level of evidence 2)

Patients with HER2+ER+PR+ BC (n=2571): in groups of 1-year vs. 2-year adjuvant **trastuzumab** vs. observation: 72% vs. 70% vs. 66% [140].

**Recommendation grade B** (level of evidence 2)

Patients with HER2+ER2-PR- BC (n=2528): in groups of 1-year vs. 2-year adjuvant **trastuzumab** vs. observation: 67% vs. 67% vs. 59% [140].

**Recommendation grade B** (level of evidence 2)

*Subcutaneous trastuzumab can replace intravenous trastuzumab: its dosage regimen is different from that of the i.v. agent: **Herceptin s.c.: fixed dose of 600 mg (5 mL for 5 min) **Herceptin i.v.: loading dose of 8 mg/kg, maintenance dose of 6 mg/kg. Should be used in patients with the following indications, including in patients with difficult venous access. Early stages of breast cancer with HER2 overexpression: - as adjuvant therapy after surgery, completion of chemotherapy (neoadjuvant or adjuvant) and radiation therapy; - in combination with paclitaxel or docetaxel after adjuvant chemotherapy with doxorubicin and cyclophosphamide; - in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin; the study showed no differences in clinical efficacy and safety of subcutaneous and standard administration of trastuzumab [127-130].

**Trastuzumab emtansine (T-DM1) is given at 3.6 mg/kg i.v. on day 1 once every 3 weeks for 14 cycles or until disease recurrence or intolerable toxicity.

HER2-positive breast cancer and invasive residual tumour following neoadjuvant therapy with taxane and **trastuzumab [141].

**Recommendation grade B** (level of evidence 2)
1.16.9 Recommended adjuvant CT regimens with **trastuzumab:

**AC×4→D×4 + **trastuzumab:** AC 4 cycles i.v. once every 3 weeks followed by **docetaxel** (75-100 mg/m² i.v. on day 1 once every 3 weeks, 4 cycles) + **trastuzumab** (6 mg/kg (loading dose of 8 mg/kg) i.v. on day 1 once every 3 weeks for up to 1 year). If 100 mg/m² of **docetaxel** is used, administration of CSF for prophylactic purposes is mandatory [142].

**Recommendation grade B** (level of evidence 2)

**AC×4→P×12 + **trastuzumab:** AC 4 cycles i.v. once every 3 weeks followed by **paclitaxel** (80 mg/m² 12 weekly i.v. injections) + **trastuzumab** (2 mg/kg; loading dose of 4 mg/kg, i.v. every week for up to 1 year). **Trastuzumab** should be initiated concomitantly with **paclitaxel** [143].

**Recommendation grade B** (level of evidence 2)

**DCH + **trastuzumab:** 6 cycles of **docetaxel** (75-100 mg/m² i.v. on day 1 once every 3 weeks) in combination with **carboplatin** (AUC6 i.v. on day 1 once every 3 weeks) + **trastuzumab** (at a loading dose of 8 mg/kg and maintenance dose of 6 mg/kg i.v. on day 1 once every 3 weeks for up to 1 year). **Trastuzumab** should be initiated concomitantly with cytostatics [142].

1.16.10 Recommended adjuvant CT regimens with **trastuzumab+pertuzumab:**

BC patients at high risk of recurrence tumour ≥pT1c or N+ with
pT1b and N0 - if one of the following criteria is met: – G3; – ER- and PR-negative; – age under 35 years.

**AC×4→D×4 + **trastuzumab:** AC 4 cycles i.v. once every 3 weeks followed by **docetaxel** (75-100 mg/m² i.v. on day 1 once every 3 weeks, 4 cycles) + **trastuzumab** (6 mg/kg (loading dose of 8 mg/kg) i.v. on day 1 once every 3 weeks + **pertuzumab** (at a loading dose of 840 mg, then at a dose of 420 mg once every 3 weeks for up to 1 year) [144].

**Recommendation grade B** (level of evidence 2)

**AC×4→P×12 + **trastuzumab:** AC 4 cycles i.v. once every 3 weeks followed by **paclitaxel** (80 mg/m² 12 i.v. weekly injections) + **trastuzumab** (2 mg/kg; loading dose of 4 mg/kg **pertuzumab** (at a loading dose of 840 mg, then at a dose of 420 mg once every 3 weeks for up to 1 year). **Trastuzumab** should be initiated concomitantly with **paclitaxel** [142], [144].
**Recommendation grade B** (level of evidence 2)

**DCH+ trastuzumab**: 6 cycles of **docetaxel** (75 mg/m² i.v. on day 1 once every 3 weeks) in combination with **carboplatin** (AUC6 i.v. on day 1 once every 3 weeks) + **trastuzumab** (at a loading dose of 8 mg/kg and maintenance dose of 6 mg/kg i.v. on day 1 once every 3 weeks) + **pertuzumab** (at a loading dose of 840 mg, then at a dose of 420 mg once every 3 weeks) for up to 1 year. **Trastuzumab** should be initiated concomitantly with cytostatics [142], [144].

### 1.16.11 Adjuvant hormone therapy for BC

Adjuvant hormone therapy is recommended for all patients with hormone-dependent tumours.

Tumours with detectable ER expression in ≥10% of invasive BC cells are recommended to be considered as hormone-dependent.

**Recommendation grade B** (level of evidence 3) [7].

**Recommendation grade A** (level of evidence 1)

Ovarian function is recommended to be evaluated prior to the start of hormone therapy. The choice of hormone therapy is dependent on ovarian function (see menopause criteria) [136].

**Recommendation grade C** (level of evidence 4)

**Comment:**

**Menopause criteria:**

- *bilateral ovariectomy;*
- *age ≥60 years old;*
- *age <60 years old and amenorrhoea for ≥12 months in the absence of chemotherapy, therapy with tamoxifen or toremifene and ovarian suppression with postmenopausal follicle stimulating hormone (FSH) and oestradiol levels."

*In premenopausal women receiving chemotherapy, amenorrhoea is not an indicator of ovarian function. These women require an ovariectomy or regular FSH and oestradiol measurements to confirm menopause.*

Patients with positive hormone receptors and positive HER2 (ER+/HER2+) require HT coinciding with their menopausal age in addition to initial cytotoxic CT and anti-HER2 therapy. HER2-positive tumour status may be the basis for inclusion of *aromatase inhibitors* [146].

**Recommendation grade A** (level of evidence 1)
For patients with positive hormonal receptors, but are HER2-negative, there is a range of different types of HT depending on the risk and sensitivity to cytotoxic HT [147].

**Recommendation grade B** (level of evidence 2)

Low-risk patients, regardless of menopausal status, with high hormonal receptor expression (luminal A) can be adequately treated with HT alone using **tamoxifen** [147].

**Recommendation grade B** (level of evidence 2)

In postmenopausal patients at high risk of recurrence (≥4 axillary LNs involved; Grade III), the initial prescription should include **aromatase inhibitors** (aromatase inhibitors for 2 years followed by **tamoxifen** for 3 years or aromatase inhibitors for 5 years) [146].

**Recommendation grade B** (level of evidence 2)

HT in low-risk premenopausal patients includes **tamoxifen** for 5 years [148].

**Recommendation grade B** (level of evidence 2).

In high-risk premenopausal patients with LN involvement (pN+) who have completed 5 years of adjuvant treatment with **tamoxifen**, it is reasonable to continue the same treatment for up to 10 years.

**Recommendation grade B** (level of evidence 2)

In patients with Grade II-III disease and artificial or natural postmenopause, adjuvant hormone therapy for 10 years is recommended. Possible combinations:

- Aromatase inhibitors 10 years;
- Aromatase inhibitors 5 years + tamoxifen (or toremifene) 5 years;
- tamoxifen (or toremifene) 5 years + aromatase inhibitors 5 years.

**Recommendation grade B** (level of evidence 2)

1.16.12  **Adjuvant hormone therapy in patients of reproductive and premenopausal age who received chemotherapy and retained menstrual function**

Termination of ovarian function is recommended using **triptorelin** 3.75 mg once every 28 days, **goserelin** (3.6 mg i.m. once every 28 days); + hormone therapy: **tamoxifen** or aromatase inhibitors for 5 years [146].

**Recommendation grade B** (level of evidence 2)

Allowed use: **tamoxifen** 20 mg per day for 5 years [146].
1.16.13  Adjuvant hormone therapy in postmenopausal patients

The following is recommended for use:

**Tamoxifen 20 mg per day for 5 years [149], [150].**

**Recommendation grade A** (level of evidence 1)

**Tamoxifen 20 mg per day for 10 years [150].**

Letrozole 2.5 mg once daily, switch regimen after 2-3 years of **tamoxifen, up to 5 years in total [151].**

**Recommendation grade B** (level of evidence 2)

**Anastrozole 1 mg once daily, switch regimen after 2-3 years of tamoxifen, up to 5 years in total [152].**

**Recommendation grade B** (level of evidence 2)

Exemestane 25 mg once daily, switch regimen after 2-3 years of tamoxifen, up to 5 years in total [153].

**Recommendation grade B** (level of evidence 2)

**Preferred treatment regimen:** aromatase inhibitors + osteomodifying agents.

**Denosumab 60 mg s.c. every 6 months. + calcium and vitamin D agents**

Bisphosphonates (zoledronic acid 4 mg once every 6 months + calcium and vitamin D)

In a prospective double-blind phase III study ABCSG-18 involving 3420 postmenopausal patients with early hormone positive BC receiving aromatase inhibitors, **denosumab increased the time to the first clinical fracture by 50% compared to placebo (p<0.0001).** Treatment with **denosumab for 36 months increased bone mineral density (BMD) in the lumbar spine, femur and femoral neck by 10.0%, 7.9%, and 6.5%, respectively, compared to placebo (p<0.0001).** Intermediate analysis of recurrence-free survival showed the benefit of denosumab vs. placebo in terms of reduction of recurrence risk by 18%, (RR: 0.816, 95% CI 0.66-1.00, p=0.051). In absolute terms, the benefit in PFS is 1.2% after 3 years of follow-up, 2.1% and 3.1% after 5 and 7 years of follow-up, respectively [154].

Treatment of bone loss in women on aromatase inhibitors is recommended.

**Recommendation grade B** (level of evidence 2)

**Comments:** tamoxifen can be used in patients with preserved ovarian function and in menopausal patients. Aromatase inhibitors can be used only in patients with stable menopause.
The analysis of the BIG1-98 study suggests that patients with intermediate risk are characterised by favourable outcomes in any treatment regimen that includes *aromatase inhibitors*, while patients with the lowest risk demonstrate favourable long-term outcomes with **tamoxifen** alone [151].

**Recommendation grade B** (level of evidence 2)

In high-risk premenopausal patients with LN involvement (pN+) who have completed 5 years of adjuvant treatment with **tamoxifen**, it is reasonable to continue the same treatment for up to 10 years [141].

**Recommendations for treatment of loco-regional recurrences in BC**

Local and regional recurrences should be treated in the same way as the primary tumour with necessary diagnostic methods including determination of PR, ER, Her2neu, Ki67 in the recurrent tumour. The purpose of the treatment is to recover from the disease. Treatment can be combined (surgical + drug), complex (drug + surgical + radiation + drug), combined (drug + radiation), and combined (radiation + drug).

The treatment method should be selected with due consideration of type of recurrence (local, regional, locoregional), spread of the recurrent tumour to the breast wall, breast, histological and immunohistochemical subtype of the recurrent tumour, and previous treatment. Treatment method should be determined in a consultation with a surgeon, chemotherapist, and radiotherapist [155, 156, 157, 158, 159].

**Recommendation grade B** (level of evidence 2)

**Surgical treatment**

The surgical stage should be performed in the presence of surgical treatment reserves (local recurrences in the area of surgical scar, recurrence in the residual mammary gland, regional recurrence, a combination of local and regional recurrences).

Possible surgical treatment options:

1. Completing mastectomy (in case of recurrence in the breast). Completing regional lymph node dissection is possible.
2. Excision of the recurrent node within healthy tissues. (in postmastectomy recurrences). Completing regional lymph node dissection is possible.
3. Subcutaneous or skin-preserving mastectomy (with or without primary breast reconstruction). In subcutaneous mastectomy, histology of the glandular ducts crossing behind the nipple is mandatory. Tumour elements identified in this area are an indication for removal of the nipple-areola complex. Completing regional lymph node dissection is possible.
4. Regional lymphadenectomy. In regional recurrence [160].

**Recommendation grade B** (level of evidence 2)

**Drug treatment**

The medication stage of the combined treatment should be carried out in accordance with medication therapy standards for localised and locally advanced invasive breast cancer depending on molecular and biological subtypes of the tumour node and prior systemic treatment: systemic drug therapy for primary inoperable breast cancer, adjuvant chemotherapy, adjuvant targeted therapy, adjuvant endocrine therapy. (see section “Systemic drug treatment”) [155, 156, 157, 158, 159].

**Recommendation grade B** (level of evidence 2)

**Radiation treatment**

Radiation therapy should be planned with due consideration of prior radiation treatment (if any), previously administered doses, and irradiation fields.

Radiation therapy options in the absence of prior radiation treatment:

- Radiation therapy of the anterior thoracic wall and regional drainage sites

Radiation of the chest wall and surgical scar:

**Regimen:**

- Conventional: SBD =2.0 Gy to TBD=46-50 Gy

Methodology: tangential fields. For left-side localisation: irradiation using photons with tangential fields with TBD of up to 30 Gy and additional direct field irradiation with electrons at 20 Gy × 10 fractions with TBD of up to 50 Gy.

Additional boost on the tumour bed for close or positive resection margins: 10 Gy per 5 fractions.

Irradiation of supra-/infraclavicular lymph nodes (axillary LN if indicated):

**Regimen:**

- SBD =2.0 Gy to TBD=44-46 Gy

Methodology: direct field irradiation at a depth of 3.0 cm.

- Radiation therapy after plastic surgery with implants, subcutaneous or skin-preserving mastectomies
- Without an expander: RT should be initiated after healing of postoperative wounds and upon completion of CT.

Radiation volume: chest wall including muscles and ribs, and the entire implant.
• With an expander: Start of RT:
  - delayed: upon temporary expander replacement with a permanent implant.
  - early: irradiation with a temporary expander followed by placement of a permanent implant 4-12 months after the end of radiation therapy.

Note: when planning RT in the presence of the implant, it is important to consider CT artifacts from the inner metal port used to fill the expander; the port should be outlined with HUs being assigned based on the type of material used.

• Preoperative radiation therapy
  Indications: Locally advanced non-resectable disease (preoperative course).
  Radiation volume: entire breast and regional LNs (SNL, INL, PLN). External-beam RT regimen: radiation therapy in hypofraction regimen with SBD=2.5 Gy up to TBD=45 Gy (50 YGy) to the breast and up to TBD=40 Gy (45 YGy).

The intervention should be performed 3-4 weeks after the completion of RT.

In case of refusal of surgery (with or without a 2-3 week gap after the 1st stage), the 2nd stage is carried out with delivery of 10-16 Gy × 5-8 fractions up to TBD=60-66 YGy to the residual breast tumour.

• Concomitant chemotherapy with paclitaxel
  Indications:
  • Preoperative or postoperative radiation therapy in locally advanced BC (Grade III)
  • Independent RT for locally advanced disease in case of refusal of surgery.

Eligibility criteria: satisfactory overall status, no pronounced cardiac abnormalities (IHD, PICS) and Grade III-IV COPD, age ≤65 years, and the presence of indications for CT with paclitaxel, CT-based topometry.

RT regimen: radiation therapy in standard fractionation regimen up to TBD=46-50 Gy to the breast and up to TBD=44-46 Gy to the regional LNs.

CT: during RT, paclitaxel is administered at a dose of 30 mg/m 1-2 times weekly [161-162].

**Recommendation grade B** (level of evidence 2)
1.17 Treatment of metastatic BC

1.17.1 Surgical treatment of metastatic BC

Surgical removal of the primary tumour in patients with stage IV may be recommended in those with bone metastases who responded to systemic treatment [43].

**Recommendation grade B** (level of evidence 2)

Biopsy from available metastatic lesion with assessment of biological subtype of the tumour is recommended. Further treatment should be planned based on the obtained results [163], [164], [165].

**Recommendation grade – A** (level of evidence IA)

Radiation therapy for metastatic BC, see section - Radiation therapy in patients with distant metastases.

1.17.2 Drug treatment of metastatic BC

The modern antitumour drug treatment strategy for of metastatic breast cancer (mBC) is aimed at increasing progression-free survival and overall survival, reducing treatment toxicity and improving the quality of life of patients (N.I. Perevodchikova, 2011).

Tables 25-39 provide summary data on systemic therapy for metastatic breast cancer.

<p>| Table 26. Systemic therapy for metastatic ER(+)PR(±) BC; HER-2(-) Premenopause*(For a full list of treatment regimens, see Systemic treatment for metastatic BC) |
|---|---|---|---|
| A) Recurrence-free period of &gt;5 years. B) No visceral metastases C) No clinical evidence of organ metastases | Prior treatment | Treatment | Endocrine therapy |
| | | Chemotherapy | Preferred standard A | Recommended standard B | A | B |
| | | Chemotherapy regimen | Endocrine therapy option |
| | Anthracyclines <strong>Tamoxifen</strong> Taxanes Taxanes | Termination of ovarian function <strong>Fulvestrant + Palbociclib</strong> | ± termination of ovarian function |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Endocrine therapy</th>
<th>Chemotherapy</th>
<th>Preferred standard</th>
<th>Recommended standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
<td>Terminatio of ovarian function **Fulvestrant + Palbociclib ± terminatio of ovarian function</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
<td>Terminatio of ovarian function **Fulvestrant + Palbociclib ± terminatio of ovarian function</td>
</tr>
<tr>
<td>Taxanes + anthracyclines</td>
<td><strong>Tamoxifen</strong></td>
<td><strong>Eribulin</strong> (the patient should receive at least 2 chemotherapy lines)</td>
<td>Fluorafur, <strong>capecitabine</strong></td>
<td>Terminatio of ovarian function **Fulvestrant + Palbociclib ± terminatio of ovarian function</td>
</tr>
</tbody>
</table>

Table 27. Systemic therapy for metastatic ER(+)/PR(±) BC; HER-2(-) Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

The presence of one or more signs: 
- a) recurrence-free period of over 5 years, 
- b) presence of visceral metastases, 
- c) clinical evidence of organ metastases

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment Chemotherapy</th>
<th>Endocrine therapy</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>Endocrine therapy option</td>
<td>Preferred standard</td>
<td>Recommended standard</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td><strong>Tamoxifen</strong></td>
<td>Taxanes</td>
<td>Termination of ovarian function **Fulvestrant + Palbociclib ± terminatio of ovarian function</td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
<td>Terminatio of ovarian function **Fulvestrant + Palbociclib ± terminatio of ovarian function</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
<td>Terminatio of ovarian function **Fulvestrant + Palbociclib ± terminatio of ovarian function</td>
</tr>
<tr>
<td>Taxanes + anthracyclines</td>
<td><strong>Tamoxifen</strong></td>
<td><strong>Eribulin</strong> (the patient should receive at least 1 chemotherapy line)</td>
<td>Fluorafur, <strong>capecitabine</strong></td>
<td>ant + Palbociclib ± terminatio n of ovarian function <strong>Fulvestrant + Palbociclib</strong></td>
</tr>
</tbody>
</table>
Table 28. Systemic therapy for metastatic ER(-)PR(-)HER-2(-) BC. Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>Preferred standard A</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Taxanes</td>
</tr>
<tr>
<td>**Docetaxel</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>**Paclitaxel</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Taxanes + anthracyclines</td>
<td>**Ixabepilone + **capecitabine; **eribulin (the patient should receive at least 1 chemotherapy line)</td>
</tr>
</tbody>
</table>

Table 29. Systemic therapy for metastatic ER(-)PR(-)HER-2(-) BC. Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>Preferred standard A</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Taxanes</td>
</tr>
<tr>
<td>**Docetaxel</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>**Paclitaxel</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Taxanes + anthracyclines</td>
<td>**Ixabepilone + **capecitabine; **eribulin (the patient should receive at least 2 chemotherapy lines)</td>
</tr>
</tbody>
</table>
Table 30. Systemic therapy for metastatic ER(+) /PR(±) BC; HER-2(+) Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>A) Recurrence-free period of &gt;5 years.</td>
<td></td>
</tr>
<tr>
<td>B) No visceral metastases</td>
<td></td>
</tr>
<tr>
<td>C) No clinical evidence of organ metastases</td>
<td></td>
</tr>
<tr>
<td>Chemo therapy regimen</td>
<td>Endocrine therapy option</td>
</tr>
<tr>
<td>Anthracylines <strong>Tamoxifen</strong></td>
<td>**Trastuzumab</td>
</tr>
<tr>
<td>Anthracylines <strong>Tamoxifen</strong></td>
<td>W/o **trastuzumab</td>
</tr>
<tr>
<td><strong>Docetaxel</strong> <strong>Tamoxifen</strong></td>
<td>**Trastuzumab</td>
</tr>
<tr>
<td><strong>Docetaxel</strong> <strong>Tamoxifen</strong></td>
<td>NB (w/o chemotherapy)</td>
</tr>
</tbody>
</table>
Table 31. Systemic therapy for metastatic ER(+) / PR(±) BC; HER-2(+) Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>The presence of one or more signs:</th>
<th>Prior treatment</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Endocrine therapy</th>
<th>Target therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) recurrence-free period of &lt; 5 years, b) presence of visceral metastases, c) clinical evidence of organ metastases</td>
<td>Chemo therapy regimen</td>
<td>Endocrine therapy option</td>
<td>Target therapy</td>
<td>Preferred standard A</td>
<td>Recommended standard B</td>
</tr>
<tr>
<td>Anthra cyclines</td>
<td><strong>Tamoxifen</strong></td>
<td><strong>Trastuzumab</strong></td>
<td>Taxanes</td>
<td>± termination of ovarian function</td>
<td>*<em>Lapatinib+<em>trastuzumab</em></em></td>
</tr>
<tr>
<td>Anthra cyclines</td>
<td><strong>Tamoxifen</strong></td>
<td>W/o <strong>trastuzumab</strong></td>
<td>Taxanes</td>
<td>± termination of ovarian function</td>
<td>**Pertuzumab+**trastuzumab</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td><strong>Trastuzumab</strong></td>
<td><strong>Paclitaxel</strong></td>
<td>± termination of ovarian function</td>
<td>**Lapatinib+**trastuzumab</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td><strong>Trastuzumab</strong></td>
<td>± termination of ovarian function</td>
<td><strong>Trastuzumab emtansine, NB (w/o chemotherapy)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Tamoxifen</strong></td>
<td>W/o <strong>trastuzumab</strong></td>
<td><strong>Paclitaxel</strong></td>
<td>± termination of ovarian function</td>
<td><strong>Trastuzumab</strong></td>
</tr>
</tbody>
</table>

Table 32. Systemic therapy for metastatic ER/PR(-) BC; HER-2(+) Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)
A) Recurrence-free period of >5 years.
B) No visceral metastases
C) No clinical evidence of organ metastases

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
<th>Target therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Preferred standard A</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Taxanes</td>
<td>**Lapatinib + trastuzumab; pertuzumab + trastuzumab</td>
</tr>
<tr>
<td>W/o trastuzumab</td>
<td>Taxanes</td>
<td>**Pertuzumab + trastuzumab</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Paclitaxel</strong></td>
<td><strong>Lapatinib + trastuzumab</strong></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td>NB (w/o chemotherapy)</td>
<td><strong>Trastuzumab emtansine</strong></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Paclitaxel</strong></td>
<td><strong>Trastuzumab</strong></td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td><strong>Docetaxel</strong></td>
<td><strong>Lapatinib + trastuzumab; pertuzumab + trastuzumab</strong></td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td>NB (w/o chemotherapy)</td>
<td><strong>Trastuzumab emtansine</strong></td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td><strong>Docetaxel</strong></td>
<td><strong>Pertuzumab + trastuzumab</strong></td>
</tr>
</tbody>
</table>

Table 33. Systemic therapy for metastatic ER/PR(-) BC; HER-2(+)
Premenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)
The presence of one or more signs: a) recurrence-free period of <5 years, b) presence of visceral metastases, c) clinical evidence of organ metastases

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Targeted therapy option</th>
<th>Preferred standard A</th>
<th>Recommended standard B</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxanes, Anthracyclines, <strong>Trastuzumab</strong></td>
<td><strong>Eribulin</strong>, <strong>Ixabepilone</strong></td>
<td>Platinum compounds, <strong>gemcitabine</strong>, <strong>vinorelbine</strong></td>
<td><strong>Lapatinib + trastuzumab</strong></td>
<td><strong>Lapatinib</strong></td>
<td><strong>Lapatinib</strong></td>
</tr>
<tr>
<td>Taxanes + anthracyclines, <strong>Trastuzumab</strong></td>
<td>W/o chemotherapy</td>
<td>W/o chemotherapy</td>
<td><strong>Trastuzumab emtansine</strong></td>
<td><strong>Trastuzumab emtansine</strong></td>
<td><strong>Trastuzumab emtansine</strong></td>
</tr>
</tbody>
</table>
### Table 34. Systemic therapy for metastatic ER(+)PR(±) BC; HER-2(-) Postmenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Endocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Recurrence-free period of &gt;5 years. B) No visceral metastases C) No clinical evidence of organ metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>Endocrine therapy option</td>
<td>Preferred standard A</td>
<td>Recommended standard B</td>
</tr>
<tr>
<td>Anthracycline-containing ± taxane-containing</td>
<td><strong>Tamoxifen</strong></td>
<td><strong>Fulvestrant, Palbociclib + Aromatase inhibitors</strong></td>
<td>Non-steroid aromatase inhibitors</td>
</tr>
<tr>
<td>Anthracycline-containing ± taxane-containing</td>
<td>Non-steroid aromatase inhibitors</td>
<td>**Fulvestrant, Palbociclib + **Fulvestrant, if non-steroid aromatase inhibitors were used in the first-line settings, therapy with **Everolimus is possible + steroid aromatase inhibitors</td>
<td>Steroid aromatase inhibitors</td>
</tr>
<tr>
<td>Anthracycline-containing ± taxane-containing</td>
<td>Steroid aromatase inhibitors</td>
<td>–</td>
<td>**Everolimus + non-steroid aromatase inhibitors, **Fulvestrant, Palbociclib +**Fulvestrant</td>
</tr>
</tbody>
</table>
**Table 35. Systemic therapy for metastatic ER(+) /PR(±) BC; HER-2(-) Postmenopause** *(For a full list of treatment regimens, see Systemic treatment for metastatic BC)*

<table>
<thead>
<tr>
<th>The presence of one or more signs: a) recurrence-free period of &lt;5 years, b) presence of visceral metastases, c) clinical evidence of organ metastases</th>
<th>Prior treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy regimen</td>
<td>Endocrine therapy option</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy regimens, table 25</td>
<td><strong>Tamoxifen</strong></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy regimens, table 25</td>
<td>Non-steroid aromatase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy regimens, table 25</td>
<td>Steroid aromatase inhibitors</td>
</tr>
</tbody>
</table>
Table 36. Systemic therapy for metastatic ER/PR(-) BC; HER-2(-) Postmenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>Preferred standard A</td>
<td>Recommended standard B</td>
</tr>
</tbody>
</table>

Table 37. Systemic therapy for metastatic ER /PR(-) BC; HER-2(-) Postmenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>Preferred standard A</td>
<td>Recommended standard B</td>
</tr>
</tbody>
</table>

Table 38. Systemic therapy for metastatic ER(+)/PR(±) BC; HER-2(+) Postmenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>Endocrine therapy</td>
<td>Target therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy option</th>
<th>Endocrine therapy option</th>
<th>Target therapy option</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>
Table 39. Systemic therapy for metastatic ER/PR(-) BC; HER-2(+)
Postmenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Treatment</th>
<th>Target therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>Targeted therapy option</td>
<td>Preferred standard A</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>**Trastuzumab</td>
<td>Taxanes</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>W/o **trastuzumab</td>
<td>Taxanes</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>Chemotherapy</td>
<td>Targeted therapy option</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td><strong>Trastuzumab</strong></td>
<td>Taxanes</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Trastuzumab</strong></td>
<td><strong>Paclitaxel</strong></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td>W/o <strong>trastuzumab</strong></td>
<td>Taxanes</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Trastuzumab</strong></td>
<td><strong>Paclitaxel</strong></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>Trastuzumab</strong></td>
<td>W/o chemotherapy</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td><strong>Trastuzumab</strong></td>
<td><strong>Docetaxel</strong></td>
</tr>
</tbody>
</table>

Table 40. Systemic therapy for metastatic ER/PR(-) BC; HER-2(+) Postmenopause* (For a full list of treatment regimens, see Systemic treatment for metastatic BC)
1.17.3 Hormone therapy for metastatic BC

Luminal metastatic BC (ER+, HER2-) is a disease with a wave-like progression and a high incidence of bone metastases.

All patients with luminal BC who do not need to start chemotherapy (symptomatic metastases, visceral crisis) should receive endocrine therapy as the principal method of drug therapy. In case of disease progression during the first-line therapy in the absence of signs of visceral crisis, endocrine therapy may be continued.

**It should be borne in mind that benefits from ET in patients with low ER expression (1-10%) are insufficiently substantiated; the treatment strategy (CT vs. ET) in patients of this group should be decided on an individual basis only with due consideration of all existing clinical and morphological factors.**

Criteria for visceral crisis*: Visceral crisis is defined as severe organ dysfunction characterised by pronounced clinical symptoms, laboratory changes and rapid disease progression. Visceral crisis is a clinical indication for faster and more effective treatment (chemotherapy), as other treatment options for disease progression are likely to be impossible [166].

Endocrine therapy options in premenopausal patients are limited to the use of **tamoxifen** that was generally used previously in adjuvant settings. In addition, the efficacy of therapy with **tamoxifen** in metastatic BC is low, which makes termination of ovarian function (either medically or surgically) reasonable. Subsequent endocrine therapy corresponds to that administered to menopausal patients [167], [168], [169].

The most important factor for selecting the endocrine regimen is the recurrence-free interval implying the classification of tumours into hormone sensitive or hormone-resistant.

**Hormone sensitivity/hormone resistance criteria***:

**Hormone sensitivity** of luminal BC is determined by the absence of disease progression during adjuvant endocrine therapy and 1 year after its completion; in such clinical situation, previously used endocrine agents can be prescribed again.

**Primary hormone resistance (hormone refractoriness)** is progression of luminal BC in patients with stage I-III BC in the first 2 years of adjuvant endocrine therapy; in addition, primary hormone resistance is defined as disease progression during the first 6 months of endocrine therapy in patients with metastatic BC.

**Secondary hormone resistance** is the progression of luminous BC in patients with stage I-III BC in the course of adjuvant endocrine therapy after 2 years from the start of treatment,
as well as during the first year after its completion. In addition, primary hormone resistance is interpreted as disease progression in patients with metastatic luminal BC after 6 months from the start of endocrine therapy. In patients with hormone resistance, change of endocrine therapy regimen should be considered.

Disease progression after three consecutive therapy lines suggests the tumour insensitivity to endocrine therapy and is the basis for the transition to subsequent chemotherapy [166].

The most important factor for selecting the endocrine regimen is the recurrence-free interval implying the classification of tumours into hormone sensitive or hormone-resistant.

Sequential use of several lines of hormone therapy: antiestrogens (**tamoxifen, **fulvestrant), non-steroid aromatase inhibitors (letrozole or **anastrozole), steroid aromatase inhibitors (exemestane), progestins (megestrol) allows maintaining high quality of life in this category of patients for a relatively long time. The priority and sequence of HT lines should be considered individually in each case and depend on the patient’s age, duration of recurrence-free period, efficacy of prior HT, comorbidities, etc.

History of highly effective HT may suggest a good response to subsequent therapy with hormonal agents. **Tamoxifen is prescribed to women of both menopausal and reproductive age group; aromatase inhibitors are used only in menopausal women. In postmenopausal patients with HER-2 hyperexpression, aromatase inhibitors are preferable.

Similarly to **tamoxifen, toremifene may also be used. This compound is close to tamoxifen in terms its activity and efficacy in treating advanced BC [170].

**Recommendation grade B (level of evidence 2)

**Tamoxifen and toremifene are compounds that bind to estrogen receptors (SERM) and affect their activity in different tissues and in different ways. By exhibiting antiestrogenic effect in the breast epithelium, they can act as estrogens in some other tissues. These compounds exert different estrogenic activity and therefore have different side effects. **Tamoxifen exerts a more potent estrogenic effect to the endometrium and in terms of venous thromboembolism than toremifene and other agents [171].

**Recommendation grade B (level of evidence 2)
1.17.4 HT and combined therapy for metastatic BC

1.17.4.1 Premenopausal period

Endocrine therapy in premenopausal patients should be carried out along with ovarian suppression (either surgical or drug induced with the use of GnRH analogues).

1st line: antiestrogens **tamoxifen, after ovarian suppression, aromatase inhibitors ± cycline-dependent kinase inhibitors (palbociclib; **ribociclib, abemaciclib), **fulvestrant ± **ribociclib, **fulvestrant ± palbociclib (in patients who have received prior hormonal therapy).

2nd line: antiestrogens **tamoxifen, after ovarian suppression, aromatase inhibitors ± **Ribociclib, **fulvestrant ± **ribociclib, **fulvestrant ± palbociclib, fulvestrant ± abemaciclib. Aromatase inhibitors+**Everolimus

3rd line: Aromatase inhibitors+**Everolimus, if the regimen is used for the first time. Monotherapy with abemaciclib: in patients that progressed during ET and one or more CT lines. Progestins.

Surgical castration seems appropriate in cases of disease progression, persistent ovarian cysts, and failure to achieve menopausal status according to laboratory findings (oestradiol level) in patients receiving GnRH analogues.

Recommendation grade A (level of evidence 1)

1.17.4.2 Postmenopausal period

1st line: antiestrogens **tamoxifen or toremifene, aromatase inhibitors ± cycline-dependent kinase inhibitors (palbociclib; **ribociclib, abemaciclib), **fulvestrant ± **ribociclib, **fulvestrant ± palbociclib (in patients who have received prior hormonal therapy). **Fulvestrant ± **alpelisib for patients with PIK3CA (PIK3CA+) mutation with disease progression during/after endocrine therapy regimens.

2nd line: antiestrogens **tamoxifen, aromatase inhibitors ± **ribociclib, **fulvestrant ± **ribociclib, **fulvestrant ± palbociclib, fulvestrant + abemaciclib. Aromatase inhibitors+**Everolimus. **Fulvestrant ± **alpelisib for patients with PIK3CA (PIK3CA+) mutation

3rd line: Aromatase inhibitors+**Everolimus, if this regimen is used for the first time. Monotherapy with abemaciclib: in patients that progressed during HT and one or more CT lines. Progestins.

Recommendation grade A (level of evidence 1)
Non-steroidal antiestrogens **tamoxifen and toremifene** have different target effects in different tissues. Their effect is antiestrogenic on the breast epithelium and estrogenic on the endometrium (although the adverse effect of **tamoxifen is much more severe). The treatment with **tamoxifen is associated with a number of side effects which generally include endometrial cystic glandular hyperplasia; in rare cases, endometrial cancer, pulmonary artery thromboembolia, and angina pectoris. In women of reproductive age, the use of **tamoxifen is frequently associated with the development of ovarian cysts accompanied by excessive production of estrogens. The rate of cyst formation is 34-49% in premenopausal patients compared to 1.1% in menopausal patients [172].

**Recommendation grade B** (level of evidence 2)

Serum oestradiol levels may reach 1305-3765 pm/L for at least certain period of time [172].

Ovarian cysts may resolve on their own during treatment with **tamoxifen, otherwise concomitant use of GnRH agonists with tamoxifen is discussed as stated above.

In most women who become menopausal during CT had their menstrual cycle restored during the subsequent therapy with **tamoxifen or aromatase inhibitors, which requires constant monitoring of estrogen and gonadotropin levels [173].

**Recommendation grade B** (level of evidence 2)

If CT does not disrupt menstrual cycle in reproductive-age patients, they still have decreased ovarian reserve. This is determined based on changes in the following parameters: gonadotropins, oestradiol, anti-Müllerian hormone, inhibin B, and certain other parameters [174].

**Recommendation grade B** (level of evidence 2)

In contrast to non-steroidal estrogen agonists, selective steroid antiestrogen **fulvestrant** is an estrogen antagonist without any estrogen-like activity. Contrary to non-steroidal antiestrogens, this agent is also characterised by its higher ability to bind with estrogen receptors and better tolerability.

The following compounds belong to the group of GnRH agonists: 1) **buserelin (3.75 mg i.m. once every 28 days); 2) goserelin (3.6 mg i.m. once every 28 days); 3) leuprorelin (3.75 mg i.m. once every 28 days), 4) triptorelin. Depot agents are widely used. Toremifene 60 mg/day [170].

**Recommendation grade B** (level of evidence 2)

**Anastrozole (1 mg once daily) = complete Rm of 4.2% + partial Rm of 8.4% + stable disease 31.1% in postmenopausal patients with advanced BC in [175].**

**Recommendation grade B** (level of evidence 2)
Letrozole (2.5 mg/day) vs. **tamoxifen (20 mg/day) in groups of 453 and 454 patients with advanced BC, respectively = median time to progression: 9.4 vs. 6.0 months, respectively; median lifespan: 34 vs. 30 months, respectively. [176].

**Recommendation grade B** (level of evidence 2)

Letrozole + palbociclib

Letrozole (2.5 mg/day orally every day) + palbociclib (CDK 4/6 inhibitor; orally at a dose of 125 mg daily for 3 weeks followed by one week of no treatment) showed superiority over letrozole alone in terms of a significant increase in median time to progression (PALOMA-1: 20.2 vs. 10.2 months, HR 0.49; PALOMA-2: 24.8 vs. 14.5 months, HR 0.58) and objective response rate.

**Recommendation grade A** (level of evidence 1)

Letrozole + ribociclib

Letrozole (2.5 mg/day orally every day) + ribociclib (CDK 4/6 inhibitor; orally at a dose of 600 mg daily for 3 weeks followed by one week of no treatment) showed superiority over letrozole alone in postmenopausal patients in MONALEESA-2 phase III study in terms of a significant increase in median time to progression (25.3 vs. 16 months, HR 0.57) and objective response rate [177, 178].

In premenopausal patients, MONALEESA-7 phase III study showed superiority of ribociclib + AI + ovarian suppression over AI + ovarian suppression in terms of a significant increase in median PFS (27.5 vs. 13.8, HR 0.569), OS (not achieved vs. 40.9 months, HR 0.712, p=0.009) and objective response rate.

**Recommendation grade A** (level of evidence 1)

Aromatase inhibitors + abemaciclib

Abemaciclib at daily doses of 300 mg (in two intakes) in combination with AI demonstrated the efficacy in the first-line settings (MONARCH-3 study) in terms of a significant increase in objective response rate (59 vs. 44%) and a significant increase in the median time to progression (not achieved vs. 14.7 months, HR 0.54, p<0.05).

**Recommendation grade A** (level of evidence 1)

Exemestane (25 mg/day) vs. **tamoxifen as the first line therapy for advanced breast cancer in postmenopausal patients = Rm of 44% vs. 30%, respectively; median lifespan: 11 and 7 months, respectively [179].

**Recommendation grade B** (level of evidence 2)

**Fulvestrant (500 mg i.m. once per month (in the first month: 500 mg) on days 1 and 15). Median OS was 26.4 months in the 500 mg group and 22.3 months in the 250 mg group (p=0.02). No significant differences in terms of toxicity between the groups have**
been reported in the CONFIRM study: 7.5% of patients were treated with tamoxifen, 42.5% of patients were treated with aromatase inhibitors after adjuvant therapy, 48.3% of patients had disease progression during adjuvant therapy at the time of enrolment (described in the instruction as progression after the treatment of locally advanced disease), 35.9% of patients had disease progression in the first line treatment of primary metastatic BC (described in the instruction as progression of primary disseminated disease) with ER (+) HER (+)-status.

Clinical effect of **fulvestrant in patients with visceral metastases across different studies (CONFIRM, 020-021, etc.) amounts to 50% [180].

**Recommendation grade B** (level of evidence 2)

**Fulvestrant** (500 mg i.m. once per month; in the first month: 500 mg, on days 1 and 15) vs. **anastrozole** 1 mg orally every day as the first line therapy for metastatic BC [181].
**Recommendation grade B** (level of evidence 2)

**Fulvestrant + palbociclib**

Fulvestrant (500 mg i.m. once per month; in the first month: 500 mg, on days 1 and 15) + palbociclib (CDK 4/6 inhibitor; orally at a dose of 125 mg daily for 3 weeks followed by one week of no treatment) demonstrated a significant clinical efficacy in the second-line settings over **fulvestrant** alone in a randomised PALOMA-3 study (increase in median time to progression from 4.6 to 9.5 months; p<0.0001) [182].

**Recommendation grade A** (level of evidence 1)

**Fulvestrant + ribociclib**

Fulvestrant (500 mg i.m. once per month; in the first month: 500 mg, on days 1 and 15) + ribociclib (CDK 4/6 inhibitor; orally at a dose of 600 mg daily for 3 weeks followed by one week of no treatment) showed superiority over fulvestrant alone in the first- or second-line settings in menopausal patients in the MONALEESA-3 phase III study in terms of a significant increase in median PFS (20.6 vs. 12.8 months, HR 0.587), OS (not achieved vs. 40.0 months, HR 0.724, p=0.004) and objective response rate. When used as first-line treatment: median PFS: 33.6 vs. 19.2 months, HR 0.546; median OS: not achieved vs. 45.1 months, HR 0.7. When used as second-line treatment + early recurrence: median PFS: 14.6 vs. 9.1 months, HR 0.571; median OS: 40.2 vs. 32.5 months, HR 0.730.

**Recommendation grade A** (level of evidence 1)

**Fulvestrant + abemaciclib**

Fulvestrant 500 mg i.m. once per month (in the first month: 500 mg, on days 1 and 15) + abemaciclib 300 mg/day orally (divided into two oral intakes until disease progression or unacceptable toxicity) has been shown to be highly effective in the second-line settings (MONARCH-2 study) in terms of objective response rate (48 vs. 21%), median PFS (16.4 vs 9.3 months, HR 0.55), and median OS (46.7 vs. 37.3 months, HR 0.757, p=0.01).

**Recommendation grade A** (level of evidence 1)

**Fulvestrant + alpelisib**

Fulvestrant (500 mg i.m. once per month; in the first month: 500 mg, on days 1 and 15) + alpelisib 300 mg orally once daily with meals: the regimen is indicated for patients with PIK3CA (PIK3CA +) mutation with disease progression during/after endocrine therapy regimens.

The results of a randomised SOLAR-1 phase III study have shown the superiority of combined treatment with alpelisib and fulvestrant compared with fulvestrant alone in patients with HR+/HER2-advanced breast cancer with PIK3CA tumour mutation in terms
of increased median PFS (median PFS: 11.0 months vs. 5.7 months; HR = 0.65, 95% CI: 0.50-0.85; p<0.001), increased objective response rate (26.6% vs. 12.8%), including in patients with measurable lesions (35.7% vs. 16.2%). The combination of Alpelisib + Fulvestrant has demonstrated significant efficacy compared to fulvestrant alone in the first- or second-line settings, including in patients treated with CDK4/6 inhibitors [261].

Use of abemaciclib alone at a dose of 400 mg/day orally (divided into two oral intakes until disease progression or unacceptable toxicity) in the MONARCH-1 phase II study demonstrated efficacy in patients pre-treated with CT or HT: the median PFS was 6.0 months; objective response rate was 20% [260].

**Recommendation grade B** (level of evidence 2)

*Exemestane* (25 mg/day) + **everolimus** (10 mg/day) orally every day in patients resistant to non-steroidal aromatase inhibitors (*letrozole* or **anastrozole**).

In patients with disease progression during treatment with AI (BOLERO-2), “everolimus + exemestane” resulted in a significant increase in median PFS (7.8 vs. 3.2 months, HR 0.45, p<0.0001) [183].

**Recommendation grade B** (level of evidence 2)

The progestins most commonly used in BC hormone therapy: **medroxyprogesterone** and *megestrol*.

*Megestrol acetate* (40 mg orally 4 times a day) = 4.3% for complete Rm + 7.9% for partial Rm + 28.5% for stable disease in postmenopausal patients with advanced BC [175].

Maintenance hormone therapy is recommended for patients with rapidly progressive, aggressive GH+ breast cancer who have achieved clinical effect from the first-line chemotherapy (disease control after 4-8 cycles of the first-line CT) and have not received first-line hormone therapy.

**Fulvestrant 500 mg i.m. once per month** (in the first month: 500 mg, on days 1, 15 and 28). Progression-free survival: in the FANCY study, median progression-free survival with fulvestrant was 16.1 months. Or maintenance hormone therapy with AI: **Anastrozole** (1 mg/day once daily); **Letrozole** (2.5 mg/day) **Exemestane** (25 mg/day). Results of retrospective studies of maintenance hormone therapy for breast cancer: median progression-free survival in the group of patients receiving maintenance therapy with fulvestrant was 16.3 months and was 2 or more times higher than median PFS in the group of patients who did not receive maintenance HT. The differences in PFS were translated into differences in OS. Median OS in the group of patients receiving maintenance therapy was 48.1 months and was 18.1 months higher than that in the group of patients who did not receive maintenance HT.
**Chemotherapy for metastatic breast cancer**

Chemotherapy as a first-line therapy is recommended in the following clinical scenarios: treatment of ER- tumours; treatment of patients with visceral crisis; treatment of rapidly progressing aggressive tumours [184-186].

MCT for breast cancer:

**Vinorelbine;**

**Gemcitabine;**

**Doxorubicin;**

**Pegylated liposomal doxorubicin;**

**Docetaxel;**

**Ixabepilone;**

**Carboplatin;**

**Capecitabine;**

**Paclitaxel;**

**Paclitaxel+albumin;**

**Cisplatin;**

**Epirubicin;**

**Eribulin.**

**Doxorubicin** vs. **paclitaxel** as first-line MCT for advanced BC = **doxorubicin** more effectively eliminates pain, especially bone pain, but is worse tolerated than **paclitaxel** [187].

**Recommendation grade B** (level of evidence 2)

**Epirubicin** 100 mg/m² on day 1 of the 3-week cycle [189], [190].

**Recommendation grade B** (level of evidence 2)
**Docetaxel** (100 mg/m² on day 1 of the 3-week cycle) = Rm of 30% in the group of 203 BC patients refractory to anthracyclines [191].

**Recommendation grade B** (level of evidence 2)

**Paclitaxel** (175 mg/m² 3-hour i.v. infusion once every 3 weeks) with premedication with **dexamethasone** (20 mg orally or i.m. 12 and 6 hours before **paclitaxel**), **diphenhydramine** (50 mg i.v. 30-60 minutes before paclitaxel) and **cimetidine** (300 mg) or **ranitidine** (50 mg i.v. 30-60 minutes before **paclitaxel**) [192], [193].

**Recommendation grade B** (level of evidence 2)

**Paclitaxel 80 mg/m² weekly as a 1-hour infusion until disease progression or toxicity yields an objective response rate of 25% in the second-line settings and 33% in the first line settings [194].**

**Recommendation grade B** (level of evidence 2)

**Paclitaxel+albumin** (260 mg/m² 30-minute infusion) = shows superiority over standard **paclitaxel** in terms of efficacy (p<0.001) and in terms of time to progression (p<0.03), does not require premedication, associated less frequently with grade 4 neutropenia, has pronounced neurotoxicity; partial Rm in 4 (24%) of 17 BC patients with disease progression during treatment with **paclitaxel** or **docetaxel** [195].

**Recommendation grade A** (level of evidence 2)

**Vinorelbine** (60 mg/m² orally every week (after 3 doses: 80 mg/m²) = median progression-free survival in patients with metastatic BC in oral treatment with **vinorelbine** varies from 4.0 to 8.2 months [196].

**Recommendation grade B** (level of evidence 2).

**Gemcitabine** (800-1250 mg/m² 30-minute infusions on days 1, 8, 15 in 28-day cycles) = of Rm 25% [197].
**Recommendation grade B** (level of evidence 2)

**Ixabepilone** (40 mg/m² i.v. on day 1 every 3 weeks) as monotherapy (in case of resistance to anthracyclines, taxanes, **capecitabine**) = total efficacy: 11.5%, median progression-free survival (PFS): 3.1 months, median overall survival (OS): 8.6 months [198].

**Recommendation grade B** (level of evidence 2)

**Capecitabine** (2510 mg/m² divided into two oral intakes, daily, from 1 to 14 days in 3-week cycles)

**Capecitabine** (2510 mg/m² divided into two oral intakes, daily, from 1 to 14 days in 3-week cycles) = complete and partial Rm in 20% of patients with metastatic BC resistant to **paclitaxel** and in 29% of patients with BC resistant to **paclitaxel** and anthracyclines [199].

**Recommendation grade B** (level of evidence 2).

**Capecitabine** (2510 mg/m² divided into two oral intakes, daily, from 1 to 14 days in 3-week cycles) vs. **paclitaxel** (175 mg/m² i.v. once every 3 weeks) = Rm of 36% and 26%, respectively; stable disease 23% and 45%, respectively. Grade 3-4 neutropenia: 14 and 58%, respectively [200].

**Recommendation grade B** (level of evidence 2)

**Eribulin** (1.4 mg/m² i.v. on days 1 and 8 of the 21-day cycle)

**Eribulin** (1.4 mg/m² i.v. on days 1 and 8 of the 21-day cycle) in metastatic BC patients who previously received anthracyclines and taxanes = median survival: 13.1 and 10.6 months, respectively, for patients who received **eribulin** and treatment at their physician’s choice [201].

**Recommendation grade B** (level of evidence 2)

**Eribulin** (1.4 mg/m² i.v. on days 1 and 8 of the 21-day cycle) vs. **capecitabine** = median OS: 15.9 and 14.5 months, respectively, p=0.056; objective response rate: 11.0% and 11.5%, respectively [202].

**Recommendation grade B** (level of evidence 2)

**PCT regimens for metastatic breast cancer**

**Vinorelbine** 60 mg/m² orally on days 1, 8, 15; starting from day 22: 80 mg/m² once a week + **capecitabine** 1000 mg/m² orally on days 1-14 every 3 weeks.

NorCap-CA223 study. Final Results of the Randomized Phase II NorCap-CA223 Trial Comparing First-Line All-Oral Versus Taxane-Based Chemotherapy for HER2-Negative Metastatic Breast Cancer. Clinical Breast Cancer, 2016 [203].


### Recommendation grade B (level of evidence 2)

**Docetaxel (75 mg/m² on day 1) + capecitabine (1650 mg/m²/day on days 1-14)** 4 three-week cycles vs. MCT with **docetaxel (100 mg/m² on day 1)**, 4 three-week cycles in groups of 31 and 30 patients with breast cancer resistant to anthracyclines = Rm of 45% and 30%, respectively; median lifespan: 14 and 11 months. In group I of **docetaxel + capecitabine**, toxicity (hand-foot syndrome, myelosuppression, alopecia, abdominal discomfort) was reported in 68% (grade 2-3) and 29% (4 grade) of patients. In group II, toxicity (fever, myalgia, arthralgia, neutropenia) was reported in 50% (grade 2-3) and 33% (grade 4) of patients [204].

### Recommendation grade B (level of evidence 2)

**Ixabepilone + capecitabine:** Ixabepilone 40 mg/m² single administration on day 1 of the 21-day cycle + capecitabine 2 g/m² per os from day 1 to day 14 of the 21-day cycle. CA163-046, CA163-048 study. Advantage in terms of increased duration of PFS in combined use of **ixabepilone + capecitabine** vs. **capecitabine** alone has been shown in both studies. Median PFS is 5.8 months for **ixabepilone** and **capecitabine**, and 4.2 months for **capecitabine** [205].

### Recommendation grade B (level of evidence 2)

**Paclitaxel (80 mg/m² on days 1, 8 and 15 every 28 days)+10 mg/kg every 2 weeks.** Bevacizumab in combination with **paclitaxel** significantly increased progression-free survival compared to **paclitaxel** alone (median of 11.8 and 5.9 months, respectively); relative risk (RR) of progression: 0.6 [206].

### 1.17.6 Targeted therapy for disseminated HER2-positive BC

#### Table 41. Regimens of **trastuzumab**-based anti-HER2 therapy

<table>
<thead>
<tr>
<th>Drug therapy line</th>
<th>Patients who did not receive prior treatment with <strong>trastuzumab</strong> or received it in adjuvant settings more than a year ago</th>
<th>Patients pre-treated with <strong>trastuzumab</strong> and received <strong>trastuzumab</strong> less than 6 months ago in adjuvant settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Trastuzumab + docetaxel</strong></td>
<td><strong>Trastuzumab emtansine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Trastuzumab + paclitaxel</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Trastuzumab + HT</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pertuzumab + trastuzumab + docetaxel</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><strong>Trastuzumab emtansine</strong></td>
<td>Lapatinib + capecitabine</td>
</tr>
<tr>
<td>3</td>
<td>Lapatinib + trastuzumab</td>
<td>Lapatinib + trastuzumab</td>
</tr>
<tr>
<td>4</td>
<td><strong>Trastuzumab + CT or Trastuzumab + HT</strong></td>
<td></td>
</tr>
</tbody>
</table>
TD **trastuzumab**+**docetaxel**

{**trastuzumab** (4 mg/kg, then 2 mg/kg once every week) + **docetaxel** (100 mg/m$^2$ once every 3 weeks)} vs. MCT with **docetaxel** (100 mg/m$^2$ once every 3 weeks) in groups of 92 and 94 patients with HER2-positive metastatic BC, respectively = Rm: 61% and 34%, median Rm duration: 11.7 and 5.7 months, median lifespan: 31.2 and 22.7 months [207].

**Recommendation grade B** (level of evidence 2)

TP **trastuzumab** + **paclitaxel**

{**trastuzumab** (4 mg/kg on day 1 followed by weekly administration of 2 mg/kg) + **paclitaxel** (175 mg/m$^2$ once every 3 weeks)} vs. **paclitaxel** (175 mg/m$^2$ once every 3 weeks) in groups of 92 and 96 patients with HER2-positive metastatic BC, respectively = Rm: 41% and 17%, median Rm duration: 10.5 and 4.5 months, median lifespan: 22.1 and 18.4 months [208].

**Recommendation grade B** (level of evidence 2)

Anastrozole + **trastuzumab**

**anastrozole** 1 mg/day + **trastuzumab** (4 mg/kg on day 1 followed by weekly administration of 2 mg/kg)

**Trastuzumab in combination with anastrozole as first-line therapy in patients with metastatic breast cancer with HER2-overexpression and positive estrogen and/or progesterone receptors increases progression-free survival from 2.4 months. (anastrozole alone) to 4.8 months (anastrozole in combination with Trastuzumab) [209].

**Recommendation grade B** (level of evidence 2)

PTD {**pertuzumab** (420 mg (loading dose of 840 mg) i.v. on day 1 once every 3 weeks) + **trastuzumab** (6 mg/kg (loading dose of 8 mg/kg) i.v. on day 1 once every 3 weeks) + **docetaxel** 75-100 mg/m$^2$ i.v. on day 1 once every 3 weeks}.

The loading dose of **pertuzumab** is 840 mg with subsequent maintenance dose of 420 mg every 3 weeks. For **trastuzumab when used in combination with **pertuzumab, the following dosing regimen is recommended: loading dose of 8 mg/kg, maintenance dose of 6 mg/kg of body weight every 3 weeks. When used in combination with **pertuzumab, the recommended starting dose of **docetaxel is 75 mg/m$^2$. If well tolerated in the first cycle, the dose of **docetaxel can be increased to 100 mg/m$^2$ in subsequent cycles. **CLEOPATRA** study: median PFS evaluated by researchers was 12.4 months (95% CI 10.4-13.5) in the placebo group and 18.7 months (16.6-21.6) in the **pertuzumab group (hazard ratio: 0.69; 95% CI 0.58–0.81). With a median follow-up of
30 months, median OS in the placebo group was 37.6 months, but was not achieved in the **pertuzumab group (95% CI 42.4 - ND). An objective response was achieved in 69.3% in the placebo group and in 80.2% in the **pertuzumab group. Serious adverse events were reported in 115 (29%) of 396 patients who received placebo, **trastuzumab, and **docetaxel, and 148 (36%) of 408 patients who received **pertuzumab, **trastuzumab, and **docetaxel [210].

**Recommendation grade B** (level of evidence 2)

TV **Trastuzumab+**vinorelbine

{ **trastuzumab (4 mg/kg on day 1 followed by a weekly injection of 2 mg/kg.) + **vinorelbine (25 mg/m^2 on days 1, 8 and 15 in 3-week cycles) } vs. MCT with **vinorelbine in the group of patients with HER2-positive metastatic BC = Rm: 52% and 26%, respectively [211].

**Recommendation grade B** (level of evidence 2)

**Trastuzumab 2 mg/kg (loading dose of 4 mg/kg) i.v. weekly administration or 6 mg/kg (loading dose of 8 mg/kg on day 1 every 3 weeks) in combination with **vinorelbine (60 mg/m orally on days 1, 8, 15; starting from day 22, 80 mg/m once weekly) [212], [213].

**Recommendation grade B** (level of evidence 2)

Continued treatment with **trastuzumab after disease progression with replacement of only the “combinatorial cytostatic” as compared to discontinuation of treatment with **trastuzumab contributes to the obvious improvement of treatment results (Table 41).

**Table 42. Efficacy of continuing **trastuzumab beyond progression of HER2-positive breast cancer: overall survival (OS) [Semiglazova T.Yu., Semiglazov V.V., Filatova L.V et al., 2011]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Survival counting</th>
<th>OS, months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>with T</td>
<td>w/o T</td>
</tr>
<tr>
<td><strong>Prospective studies:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montemurro F. et al., 2005, (n=111)</td>
<td>From the start of T</td>
<td>30.1</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>From progression</td>
<td>21.0</td>
<td>18.7</td>
</tr>
<tr>
<td>Antoine E. C. et al., 2007, (n=87)</td>
<td>From the start of T</td>
<td>27.1</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>From progression</td>
<td>15.5</td>
<td>11</td>
</tr>
<tr>
<td>Bartsch, 2007, (n=40)</td>
<td>From the start of T</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>Von Minckwitz G., 2008, (n=156)</td>
<td>From the start of regimen 2</td>
<td>25.5</td>
<td>20.4</td>
</tr>
<tr>
<td>Blackwell R. L., 2010, (n=148)</td>
<td>From the start of regimen 2</td>
<td>12.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Extra J. M., 2010, (n=107)</td>
<td>From the start of T</td>
<td>-</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>From progression</td>
<td>21.3</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Retrospective studies:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stemmler H. J., 2005, (n=23)</td>
<td>From the recurrence</td>
<td>62.4</td>
<td>38.5</td>
</tr>
<tr>
<td>Montemurro F., 2006, (n=40)</td>
<td>From the start of T</td>
<td>30.1</td>
<td>30.2</td>
</tr>
<tr>
<td>Jackisch C., 2007, (n=112)</td>
<td>From progression</td>
<td>20.1</td>
<td>13.4</td>
</tr>
</tbody>
</table>
Note. T = **Trastuzumab

Continuation of **trastuzumab vs. discontinuation of **trastuzumab in patients after detection of brain metastases = median time to progression of intracranial lesions: 7.8 vs. 2.9 months, respectively (p=0.006).

**Recommendation grade B** (level of evidence 2)

TC regimen {**trastuzumab + **capecitabine} vs. MCT **capecitabine in 156 patients with HER2-positive BC who progressed after first-line drug therapy or adjuvant treatment based on **trastuzumab, = Rm: 48% vs. 27%, respectively (p=0.011), median survival to progression: 8.2 vs. 5.6 months, respectively [214].

**Recommendation grade B** (level of evidence 2)

TL regimen (trastuzumab + lapatinib)

EGF104 900 study. Lapatinib + **trastuzumab: lapatinib 1000 mg/day + **trastuzumab at a loading dose of 4 mg/m\(^2\) + 2 mg/m\(^2\), weekly injections. vs. lapatinib alone in HER2-positive patients with disease progression during treatment with **trastuzumab.

Progression-free survival: 12, 0 and 8.1 weeks, respectively (p<0.008); clinically relevant response (Rm + stable disease): 24.7 and 12.4%, respectively (p=0.01); median overall survival: 51.8 and 39 weeks, respectively; OS for patients with double HER-2-blockade is 4.5 months in the general population and 8.3 months in the population of HR patients [215].

**Recommendation grade B** (level of evidence 2)

**Trastuzumab emtansine** (T-DM1; conjugate of **trastuzumab, stable binding agent and cytostatic; prescribed at a dose of 3.6 mg/kg i.v. on day 1 once every 3 weeks in patients who received **trastuzumab)

= median PFS: 9.6 months vs. 6.4 months for the combination of **capecitabine + lapatinib (p<0.001); median OS: 30.9 months vs. 25.1 months (p<0.001); 3-4 grade toxicity: 40.8% and 57%, respectively; the most common 3-4 grade side effects in T-DM1 therapy: thrombocytopenia (12.9% vs. 0.2%), increased transaminases AST (4.3% vs. 0.8%) and ALT (2.9% vs. 1.4%); typical and expected 3-4 grade complications for the combination of **capecitabine + lapatinib included: diarrhoea (20.7% vs. 1.6%), hand-foot syndrome (16.4% vs. 0), and vomiting (4.5% vs. 0.8). The study was conducted in the Russian investigational site [216].

**Recommendation grade B** (level of evidence 2)
Subcutaneous trastuzumab can replace intravenous trastuzumab: its dosage regimen is different from that of the i.v. agent: **Herceptin s.c.: fixed dose of 600 mg (5 mL for 5 min)** **Herceptin i.v.: loading dose of 8 mg/kg, maintenance dose of 6 mg/kg. Should be used in patients with the following indications, including in patients with difficult venous access. Metastatic breast cancer with HER2 overexpression: - as monotherapy after the receipt of one or more chemotherapy regimens; - in combination with paclitaxel or docetaxel, in the absence of previous chemotherapy (first-line therapy); - in combination with aromatase inhibitors in postmenopausal women with positive hormone receptors (estrogen and/or progesterone). The study showed no differences in clinical efficacy and safety of subcutaneous and standard administration of trastuzumab [127-130].

Regimens of lapatinib-based anti-HER2 therapy

Lapatinib (1250 mg/day orally every day) in combination with **capecitabine (2000 mg/m²/day orally on days 1-14 every 3 weeks).

Lapatinib + **capecitabine vs. **capecitabine in 399 patients with HER2+BC = time to progression: 27.1 and 18.6 months, respectively (p=0.00013) [217].

**Recommendation grade B (level of evidence 2)

Lapatinib 1500 mg/day orally every day in combination with aromatase inhibitors (letrozole 2.5 mg/day orally every day) [218].

**Recommendation grade B (level of evidence 2)

Metronomic therapy

- **Capecitabine 650 mg/m² orally twice daily continuously on a long-term basis [219]
- **Capecitabine 1500 mg/day orally continuously on a long-term basis [220]
- **Capecitabine 800 mg/m² orally twice daily continuously on a long-term basis [221] or 825 mg/m² twice daily for 21 days every 4 weeks (Taguchi et al., 2010)
- **Vinorelbine 50 mg/m orally on a weekly basis on the 1st, 3rd, 5th days of the week regardless of the body surface area. The dosing regimen is indicated in accordance with the conducted study [222].
- **Vinorelbine 70 mg/m² once a week, with fractionation on days 1, 3 and 5 for 3 weeks followed by a 1-week interval without treatment [223]
- **Vinorelbine 40 mg/day orally on days 1, 3 and 5 continuously + **capecitabine 500 mg 3 times daily continuously + cyclophosphamide 50 mg/day [224].
- **Vinorelbine 40 mg/day orally on days 1, 3 and 5 continuously + **capecitabine 500 mg 3 times daily continuously) [225].
**Recommendation grade B** (level of evidence 2)

- **Capecitabine 828 mg/m² twice daily + cyclophospham 33 mg/m² twice daily on days 1-14 of the 21-day cycle or without interruption.** 1st and 2nd lines. objective effect rate: 44.4%; clinical effect rate: 57.8%; PFS: 10.7 months [226].
- **Cyclophospham 65 mg/m² on days 1-14 + capecitabine 1000 mg/m² twice daily on days 1-14 of the 21-day cycle [227].
- **Temozolomide 75 mg/m² + RT for the brain or vinorelbine 70 mg/m² orally on days 1, 3, 5 + temodal 75 mg/m² on days 1-21.** objective effect rate: 52%; clinical effect rate: 77%; TTP: 8 months. (brain metastases) [228].

**Cyclophosphamide (50 mg/day every day on a long-term basis) + **methotrexate (2.5 mg twice daily on days 1 and 2 every week) = in a group of 63 patients with advanced BC: Rm of 19%, clinically relevant effect (Rm+ stable disease) is 39%; 1-year progression-free survival is 26%. The observed toxicity is minimal [229], [230].

**Recommendation grade B** (level of evidence 2)

1.17.7 Tumour infiltrating lymphocytes (TILs)

Tumour infiltrating lymphocytes (TILs) are most commonly observed in triple-negative, HER2-positive, and other highly proliferating BCs.

**Triple-negative breast cancer**

*Triple-negative breast cancer and first-line therapy in combination with nab-**paclitaxel (PD-L1 expression ≥1%)*

**Atezolizumab 840 mg/day on day 1 and day 15 every 2 weeks with sequential administration of nab**paclitaxel in a dose of 100 mg/m²; nab**paclitaxel should be administered on days 1, 8 and 15 of each 28-day cycle. The group of atezolizumab in combination with nab**paclitaxel demonstrated a 38% decrease in the risk of progression or death, as well as a clinically significant increase in overall survival by almost 10 months (25.0 vs. 15.5 months) compared to nab**paclitaxel alone in patients with PD-L1 expression >1% [231].

**Recommendation grade B** (level of evidence 2)

**Hereditary breast cancer (BC)** is a malignancy diagnosed in a carrier of a mutation in gene(s) responsible for BC. Hereditary BC accounts for 5-10% of BC cases. Depending on the risk of BC development, there are high- and moderate-penetrance genes. High-penetrance genes are identified in 5-10% of BC patients with lifetime risk of tumour development exceeding 70-80%. This group of genes includes: BRCA1,2, PTEN
(Cowden syndrome), TP53 (Li-Fraumeni syndrome), STK11 (Peutz-Jeghers syndrome) and CDH1. Moderate-penetrance genes are found in 4-6% of BC patients with lifetime risk generally not exceeding 25-30%. This group of genes comprises: PALB2, CHEK2, ATM.

Treatment strategy for patients with hereditary BC depends on the degree of gene penetrance [232].

**Treatment of patients with high-penetrance mutation:**

**1. Local treatment:**

1.1 Newly diagnosed BC patients with BRCA1,2 mutation who comply with all criteria for organ-conserving surgery (OCS) should not be deprived of this possibility [233-234].

1.2 Surgical management of the parental tumour (OCS or ipsilateral therapeutic and contralateral risk-reducing mastectomy (CRRM) in carriers of BRCA1,2 mutation should be discussed with due consideration of the high risk of contralateral breast and ipsilateral cancer [235].

1.3 For newly diagnosed BC patients with BRCA1,2 mutation, mastectomy with conservation of the nipple-areola complex may be offered in cases where this type of surgery is possible considering oncological treatment approaches [236].

1.4 In BC patients with BRCA1,2 mutation who are indicated for radiation therapy after surgical treatment (OCS or mastectomy), this treatment should not be discontinued due to mutation status, except for TP53 mutation [237-246].

1.5 For BC patients with BRCA1,2 gene mutation who have undergone (or are planning to undergo) a unilateral therapeutic mastectomy, CRRM should be offered. CRRM is associated with a reduced risk of contralateral BC; however, there is no convincing evidence that this surgery improves survival. The following factors should be taken into account to assess the risk of contralateral BC and the importance of risk-reducing mastectomy in BRCA1,2 mutation: the patient’s age at the time of diagnosis, family history of BC, general prognosis, possibility of close monitoring (MRI), concomitant diseases, and life expectancy [247-248].

1.6 BC patients with BRCA1,2 mutation who are interested in CRRM should be provided with information on the possibility of mastectomy with preservation of the nipple-areola complex as an acceptable treatment option [249].

1.7 Carriers of BRCA1/2 mutation who have not had bilateral mastectomy should undergo thorough screening, including annual mammography and MRI [250-261].

**2. Systemic treatment:**

2.1 For patients with metastatic BC with BRCA1,2 mutation, platinum-based chemotherapy regimens are preferable to taxane-based chemotherapy regimens, if they have not previously been treated with platinum agents [261-262].

2.2 According to available literature data, routine addition of platinum agents to anthracycline- and taxane-containing regimens is not advisable in BC patients with BRCA1,2 mutation receiving (neo)adjuvant therapy [246, 257-258].
3. **Carboplatin** appeared to be more active than **docetaxel** in patients with metastatic BC and BRCA mutation [217].

For patients with metastatic HER2-negative BC with BRCA1,2 mutation, olaparib or talazoparib can be considered as alternative options to the first-third line chemotherapy regimens.

**PARP inhibitors:**

Olaparib is indicated as monotherapy for metastatic HER2-negative BC in adult patients with germline BRCA mutations who previously received neoadjuvant or adjuvant chemotherapy or chemotherapy for metastatic disease. The recommended dose of **OLAPARIB** is 300 mg (two tablets, 150 mg each) twice daily, which is equivalent to a daily dose of 600 mg.

The Olympiad clinical trial has shown a statistically significant increase in PFS (OR=0.58 (95% CI 0.43-0.80), p=0.0009). At the same time, the median PFS in the olaparib group was 7.0 months compared to 4.2 months in the physician’s choice group [246, 259-261].

**Talozaparib** appeared to be more active than **treatment at the physician’s choice** in patients with metastatic BC and BRCA mutation [260].

Progression-free survival (PFS) was 8.6 and 5.6 months in the talazoparib and chemotherapy groups, respectively (HR 0.54; 95% CI 0.41, 0.71; P<0.0001). The objective response rate in the talazoparib group was higher than that in the chemotherapy group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; P<0.001).

Grade 3-4 haematological toxicity (mainly anaemia) is the most common adverse event in patients treated with talozaparib: 68.2%; anaemia 34.8%; neutropenia 15.6%; thrombocytopenia 12.8% [263].

**Recommendation grade B** (level of evidence 2)

**Talozaparib: 1 mg/day.**

As monotherapy for patients with locally advanced or metastatic Her2-negative breast cancer with germline BRCA mutations who previously received treatment with anthracyclines and/or taxanes as neoadjuvant or adjuvant therapy or for locally advanced or metastatic disease, except in cases where patients are not eligible for such treatment. Patients with HR + positive breast cancer should undergo endocrine therapy as prior treatment or be considered ineligible for endocrine therapy.

### Treatment of patients with moderate-penetrance mutation:

1. **Local treatment:**
1.1 Newly diagnosed BC patients with moderate-penetrance mutation, the mutation status should not affect the decision on whether to choose a surgical treatment for the parental tumour or a contralateral risk-reducing mastectomy [246].

1.2 Newly diagnosed BC patients with moderate-penetrance mutation should be offered OCS (if indicated). No conclusive data are available on cases of ipsilateral BC after OCS in this category of patients [246].

1.3 For patients newly diagnosed BC with moderate-penetrance mutation, mastectomy with conservation of the nipple-areola complex is a reasonable treatment approach in properly selected patients [246].

1.4 BC patients with ATM mutation should undergo radiation therapy when indicated. No conclusive data are available on differences in the toxicity of radiation therapy in patients with and without ATM mutation. Further clinical trials in this regard are required, therefore the feasibility of the OCS should be discussed with ATM mutation carriers [246].

1.5 For BC patients with moderate-penetrance mutation who underwent (or are planning to undergo) unilateral therapeutic mastectomy, the decision on CRRM should not be based primarily on their mutation status. Additional factors predicting the risk of contralateral BC (such as the patient’s age at the time of diagnosis and family history of BC) should be taken into account in all cases. The effect of CRRM on the reduction of the risk of contralateral BC depends on the risk of contralateral BC for each individual gene. Available data on the risk of contralateral BC in patients with moderate-penetrance mutation are limited [246].

1.6 Data on the risk of contralateral BC in patients with moderate-penetrance mutation are limited, except for CHEK2 1100delC. Information on the particular gene and risk of contralateral BC should be discussed with the patient as part of joint decision [246-266].

1.7 BC patients with moderate-penetrance mutation who are interested in CRRM should be provided with information on the possibility of mastectomy with preservation of the nipple-areola complex as an acceptable treatment option [246].

1.8 BC patients with moderate-penetrance mutation who have not had bilateral mastectomy should undergo screening, including annual mammography and MRI [246].

2. **Systemic treatment:**

No conclusive data are available to recommend PARP-inhibitors and platinum-containing chemotherapy regimens for BC patients with moderate-penetrance mutation in routine practice [268].
Medical rehabilitation, medical indications and contraindications for rehabilitation methods

A set of measures aimed at recovery and maintenance of the quality of life, family and social adaptation is recommended in BC patients.

Prophylaxis and follow-up care, medical indications and contraindications for prevention methods

The following is recommended for the prevention of BC recurrence:

The 2017 St. Gallen Consensus supports the use of physical exercise and diet to reduce body weight (or at least to prevent weight gain). There are no specific dietary recommendations to improve prognosis, but most experts support vitamin D supplementation in patients with vitamin D deficiency. The extent of motor activity should be at least 150 minutes per week. There are yet insufficient data to determine the effect of excessive body weight at baseline (i.e. before treatment) as well as diabetes mellitus on the final outcome of chemo-, hormone-, targeted and immunotherapy of pre- and postmenopausal breast cancer; the accumulation and generalisation of such data can be helpful from a practical point of view.

Follow-up care is recommended:

It is recommended to conduct post-treatment examinations 1 to 4 times a year (depending on the specific clinical situation) during the first 5 years, then on an annual basis.

**Recommendation grade A** (level of evidence 1)

Annual bilateral (in case of organ-conserving surgery) or contralateral mammography in combination with ultrasound of regional areas and postoperative scar area is recommended.

**Recommendation grade A** (level of evidence 1)

In the absence of complaints and symptoms suggesting disease progression, routine laboratory and instrumental tests (R-graphic, ultrasound, radioisotope, etc.) are not recommended.

**Recommendation grade A** (level of evidence 1)

Annual gynaecological examination of women with preserved uterus who receive tamoxifen in adjuvant settings is recommended.

**Recommendation grade A** (level of evidence 1)

Densitometry is recommended in women who receive a long-term treatment with aromatase inhibitors.
**Recommendation grade B** (level of evidence 3)

**Medical care organisation**

Indications for planned hospital admission:
Need for treatment and diagnostic procedures in hospital inpatient settings.

Indications for emergency hospital admission:
Emergency admission to a specialised oncological care institution is possible in the presence of life-threatening conditions associated with special treatment methods (e.g. febrile neutropenia in patients receiving systemic therapy).

Indications for the patient’s discharge:
Completion of planned treatment stage and the patient’s compensated condition allowing to stay at home or to complete treatment in outpatient settings.

**Additional information (including factors affecting the outcome of disease or condition)**

1.18 Management of BC patients during pregnancy

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy and/or within one year after pregnancy.

- If the patient decides to maintain the pregnancy, all diagnostic interventions must be evaluated in terms of foetal safety.
- At the time of diagnosis, breast ultrasound examination should be performed.

**Recommendation grade A** (level of evidence Ia)

- 2D mammography (with abdominal shielding to protect the foetus) is not contraindicated during the pregnancy.

**Recommendation grade B** (level of evidence III).

**Comments**: if breast cancer is suspected, mammography can be helpful to determine the extent of the disease, visualise microcalcifications and evaluate the contralateral breast. Radiation exposure of <5 rad is not associated with increased foetal abnormalities or spontaneous abortions (American College of Obstetrics and Gynaecology), therefore single view digital mammography (0.05-0.08 rad) with abdominal protection is considered safe. However, the sensitivity of this method in diagnostics of PABC is low, as the breast tissue in young and pregnant women has a high (>75%) density.
MRI without contrast is recommended for diagnosis of distant metastases. It can be used from the 1st trimester. According to FDA, gadolinium is classified as a category C contrast agent (allowed to be used in pregnant women if the expected benefit outweighs the potential harm to the foetus); the method is therefore recommended to be used as indicated.

**Recommendation grade B** (level of evidence III).

**Comments:** Contrast MRI can be safely performed in breastfeeding women. However, it can be difficult to interpret the results due to hypervascularisation and breast tissue changes associated with lactation. It is known that gadolinium-based contrast agents are excreted in milk, but the risk of potential complications, including toxic and allergic reactions, remains low. However, if MRI is planned, it is recommended that lactation be suspended for 12-24 hours after gadolinium administration.


- Biopsy (fine-needle, excisional, core biopsy).

**Recommendation grade B** (level of evidence III).

**Comments:** core biopsy is a method of choice. The sensitivity of this method is about 90%. The pathologist performing the morphological analysis should be informed about the patient’s pregnancy.


- PABC staging includes abdominal and pelvic ultrasound, if required, MRI without contrast, chest X-ray with abdominal protection, and bone scintigraphy.

**Recommendation grade B** (level of evidence III).

**Comments:** diagnostic methods using ionizing radiation are justified only in cases where diagnostic findings may have an actual effect on the treatment strategy. Otherwise, it is advisable to postpone the use of these methods until delivery to exclude negative effects on the foetus.

- Treatment for PABC should be carried out in an oncological care setting in accordance with existing standards for non-pregnant women.
- The treatment method is selected based on the disease stage, biological subtype of the tumour, gestational age of the foetus, and the mother’s decision to continue the pregnancy.
- A multidisciplinary approach is used to determine treatment and management strategies for pregnant patients with a team of experts including an oncology surgeon, obstetrician-gynaecologist, chemotherapist, radiation therapist, and specialist in oncogenetics (if indicated and if genetic counselling unit is available at a medical facility).

**Recommendation grade B** (level of evidence III).


- Surgical treatment remains the main method of treatment of PABC patients and is carried out in accordance with existing standards developed for non-pregnant women.

**Recommendation grade B** (level of evidence III)

**Comments:** The extent of surgical intervention is decided individually. Preference should be given to radical mastectomy, which does not require additional radiation therapy contraindicated at any stage of pregnancy. Both radical mastectomy and organ-conserving surgery with complete lymph node dissection or sentinel lymph node biopsy are possible. For several years, it was not allowed to perform SLNB in pregnant women due to the suspected risk of ionising radiation exposure to the foetus. However, recent studies have shown that SLNB can be performed safely during pregnancy as radionuclide is administered locally and its dose is so low that it would not cause any damaging effects on the foetus. However, it is considered more reasonable to administer a radiotracer on the morning of the day of surgery (one-day protocol) in order to reduce the time and dose of ionising radiation. Reconstructive surgeries in breastfeeding BC patients are not recommended.


- Chemotherapy should be initiated from the second trimester of pregnancy and is completed 2-3 weeks before the expected delivery date.

**Recommendation grade B (level of evidence III)**

**Comments:** before the initiation of chemotherapy in a pregnant patient, any obstetric abnormalities such as risk of premature birth and intrauterine growth retardation should be excluded. Standard regimens with an optimal dose intensity should be used; the intervals between courses should not be increased or decreased. When selecting a chemotherapy regimen, preference should be given to regimens containing anthracycline antibiotics. There are limited data on the use of other cytostatics such as taxanes and platinum agents during pregnancy. Despite the fact that results of these studies indicate the absence of a negative effect on the foetus, given the small number of publications, taxanes and platinum agents should be prescribed with caution and only in cases where chemotherapy with anthracyclines is impossible or where these regimens have been discredited during treatment. Among taxanes, paclitaxel is more preferred during pregnancy compared to docetaxel as being more safe for the foetus.


- Radiation therapy is contraindicated during pregnancy.

**Recommendation grade B (level of evidence III).**

**Comments:** Radiation therapy usually is not recommended during pregnancy due to its potential teratogenic effect. Foetal radiation exposure may result in death, malformations and developmental abnormalities. The dose of ionising radiation to the foetus depends on the proximity of the foetus to the radiation field. This dose can be reduced by 50-75% due to the use of the adequate protection [23]. Therefore, in cases where benefits of radiation therapy for the mother outweigh the potential harm to the foetus, this anticancer treatment can be initiated during the first and early second trimester of pregnancy after a thorough discussion of all issues with the patient.

- Endocrine and anti-HER2 therapy are contraindicated during pregnancy.

**Recommendation grade B (level of evidence III).**

**Comments:** **Tamoxifen is contraindicated during pregnancy as it may cause spontaneous abortion, foetal malformations (Goldenhar syndrome, genital hypoplasia), and uterine bleeding.** **Tamoxifen should be prescribed after delivery. However, it should be remembered that tamoxifen may significantly reduce milk production and be excreted in milk. Anti-HER2 therapy is contraindicated during pregnancy due to its serious side effects including the risk of oligohydramnios, pulmonary hypoplasia, skeletal abnormalities, renal failure, and neonatal death.**


- Chemotherapy, endocrine and anti-HER2 therapy are contraindicated during breastfeeding.

**Recommendation grade B (level of evidence III).**


- Low-molecular heparins are recommended for thrombophrophylaxis.

**Recommendation grade B (level of evidence III).**

**Comments:** In PABC patients, considering the high risk of thrombotic complications associated with pregnancy and oncological disease, anticoagulant therapy along with coagulation panel is required starting from the 1st course of polychemotherapy throughout the entire period of pregnancy, in the postoperative period and within 6 weeks after delivery.
The patient should be followed up by an obstetrician-gynaecologist throughout the treatment period.

**Recommendation grade A** (level of evidence Ia)

### 1.19 Algorithm for the management of PABC patients depending on stage and gestational age

The following is recommended for patients diagnosed with BC during pregnancy and having no distant metastases:

1st trimester of pregnancy. The patient is recommended to terminate the pregnancy in accordance with Order no. 736 of the Ministry of Health of the Russian Federation of 03 December 2007 (as amended on 27 December 2011). In case of primary resectable cancer (stages I-II) and the patient’s decision to maintain pregnancy (the decision should be taken based on the consultation with an obstetrician-gynaecologist), surgical treatment is recommended (see section “Surgical treatment”). Adjuvant chemotherapy is possible from gestation week 14 only. Adjuvant hormone therapy, anti-HER2 therapy, and radiation therapy are recommended only after delivery. If BC is diagnosed at stages III-IV, adequate treatment with preservation of the pregnancy is impossible (antitumour treatment during this trimester is associated with a high risk of teratogenic effects). In this regard, termination of pregnancy and further treatment according to the general plan is recommended.

2nd trimester of pregnancy. In case of primary resectable cancer (stages I-II), surgical treatment is recommended (see section “Surgical treatment”). Adjuvant chemotherapy is possible. In case of stage III disease, neoadjuvant chemotherapy with subsequent surgical intervention is recommended. Adjuvant hormone therapy, anti-HER2 therapy, and radiation therapy are recommended only after delivery.

3rd trimester of pregnancy. In case of primary resectable cancer (stages I-II), surgical treatment is recommended (see section “Surgical treatment”). Adjuvant chemotherapy is possible. In case of stage III disease, neoadjuvant chemotherapy with postpartum surgery. If BC is diagnosed at ≥35 weeks, it is advisable to perform the delivery with subsequent staging and treatment according to applicable standards. Adjuvant chemotherapy, hormone therapy, anti-HER2 therapy, and radiation therapy are recommended after delivery.
Table 43. Systemic drug treatment of BC patients depending on gestational age (trimester) and biological subtype of the tumour and subject to the patient’s desire to maintain pregnancy and complete childbearing (adapted from ESMO recommendations, 2013)

**Recommendation grade B** (level of evidence IIIB)

<table>
<thead>
<tr>
<th>BC subtype</th>
<th>Recommendations on drug treatment of breast cancer depending on gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trimester</td>
</tr>
<tr>
<td>Hormone-sensitive luminal A (ER+/PR&gt;20%/HER-2-/Ki-67&lt;20%)</td>
<td>I</td>
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<tr>
<td></td>
<td>II</td>
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<tr>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Luminal B (ER+/PR(\geq)20%/HER-2-/Ki-67&gt;20%)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Luminal B (ER+/PR&gt;20%/HER-2+/Ki-67&gt;20%); HER-2+/ER-+/PR-</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>III</td>
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<tr>
<td>Triple-negative (ER−/PR−/HER-2−)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>II</td>
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<td></td>
<td>III</td>
</tr>
</tbody>
</table>
### Medical care quality criteria

<table>
<thead>
<tr>
<th>Item no.</th>
<th>Quality criteria</th>
<th>Level of evidence</th>
<th>Recommendation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bilateral mammography and/or breast magnetic resonance imaging (as part of confirmation of diagnosis) was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>2.</td>
<td>Axillary and supraclavicular and infraclavicular lymph node ultrasound examination (as part of confirmation of diagnosis) was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>3.</td>
<td>Chest X-rays and/or CT scans (as part of confirmation of diagnosis) were performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>4.</td>
<td>Tumour and/or abnormal regional lymph node biopsy with subsequent morphological investigation (as part of confirmation of diagnosis) was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>5.</td>
<td>Immunohistochemistry study of biopsy specimens with evaluation of estrogen and progesterone receptors, HER2neu, and Ki-67 (as part of confirmation of diagnosis) was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>6.</td>
<td>Ultrasound (complex) abdominal and retroperitoneal examination and/or abdominal CT scan and/or abdominal MRI (as part of confirmation of diagnosis) was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>7.</td>
<td>Ultrasound (complex) pelvic and/or pelvic CT scan and/or pelvic MRI (as part of confirmation of diagnosis) was performed</td>
<td>Ia</td>
<td>A</td>
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<tr>
<td>8.</td>
<td>Disease stage was determined using the current TNM and WHO classifications</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>9.</td>
<td>A consultation with a surgeon, chemotherapist, and radiologist was held; a treatment plan was drawn up</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>10.</td>
<td>Antibacterial prophylaxis of infectious complications was carried out as part of surgery (in the absence of contraindications)</td>
<td>Ia</td>
<td>A</td>
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<tr>
<td>11.</td>
<td>Surgery was carried out within the next 7 days of the patient’s hospitalisation (in the absence of contraindications)</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>12.</td>
<td>Histological examination of the removed tumour was performed as recommended, including assessment of resection margins during organ-conserving treatment and extent of drug pathomorphosis if neoadjuvant drug therapy was administered.</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>13.</td>
<td>Morphological and/or immunohistochemistry study of removed tissue specimens with evaluation of estrogen and progesterone receptors, HER2neu, and Ki-67 (in case of surgery) was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>14.</td>
<td>Chemotherapy and/or hormone therapy, and/or targeted therapy, and/or radiation therapy in the presence of morphologically verified diagnosis (in case of surgery) was carried out</td>
<td>Ia</td>
<td>A</td>
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<tr>
<td>15.</td>
<td>Adjuvant chemotherapy and/or targeted therapy, and/or hormone therapy was performed no later than 30 days from the date of surgery (if in the presence of indications and absence of contraindications)</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>16.</td>
<td>Adjuvant radiation therapy was performed no later than 40 days from the date of surgery and/or the end of chemotherapy course (if in the presence of indications and absence of contraindications)</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>17.</td>
<td>Dosimetric verification was performed according to the schedule (in case of radiation therapy)</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>18.</td>
<td>Complete blood cell count (haematology) was performed no later than 5 days prior to the start of chemotherapy and/or targeted therapy, and/or radiation therapy</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>19.</td>
<td>Hormone therapy was performed (in the presence of estrogen and progesterone receptors in the tumour and in the absence of contraindications)</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>20.</td>
<td>Haematological and non-haematological toxicity assessment in the course of drug therapy was performed</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>21.</td>
<td>Drug therapy was administered within 14 days of diagnosis of metastatic disease</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>22.</td>
<td>Evaluation was performed every 2-3 chemotherapy courses or every 2-3 months of hormone therapy in patients with metastatic BC</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>23.</td>
<td>Symptomatic and supportive therapeutic agents were prescribed as indicated</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>24.</td>
<td>At least 3 lines of chemotherapy and/or hormone therapy in combination with anti-HER-2 therapy (as indicated) for metastatic disease were administered (if the patient’s general state allows antitumor therapy)</td>
<td>Ia</td>
<td>A</td>
</tr>
</tbody>
</table>
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Members of the Clinical Guideline Development and Revision Working Group

Chief expert

Vladimir Fedorovich Semiglazov, Academician of RANS, Corresponding Member of RAS, Doctor of Medicine, Professor, Head of the Surgical Department of Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Saint Petersburg;

Head

Ruslan Malikovich Paltuev, General Director of All-Russian Public Organisation “Russian Association of Oncological Mammology”, Senior Research Fellow at the Department of Breast Tumours of Federal State Budgetary Institution “Petrov Research Institute of Oncology”, Saint Petersburg;

Working Group Members

Vladimir Iosifovich Apanasevich, Doctor of Medicine, Professor at the Department of Oncology and Radiation Therapy, State Budgetary Educational Institution of Higher Education “Pacific National University”, Head of the Laboratory of Nuclear Medicine at the Far Eastern Federal University, Khabarovsk;

Elena Vladimirovna Artamonova, Doctor of Medicine, Leading Research Fellow at the Anticancer Drug Research Department of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;

Natalia Sergeevna Besova, Candidate of Medical Science, Senior Research Fellow at the Chemotherapy Department of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;

Alla Aleksandrovna Bozhok, Doctor of Medicine, State Budgetary Healthcare Institution “Saint Petersburg Clinical Research and Practical Centre of Specialised Medical Care in Oncology”, Saint Petersburg;

Yekaterina Aleksandrovna Busko, Candidate of Medical Science, Doctor of the Department of Radiation Diagnostics at the Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Scientific Clinical and Educational Centre “Radiation Diagnostics and Nuclear Medicine”, Saint Petersburg State University, Saint Petersburg;

Irina Viktorovna Vysotskaya, Doctor of Medical Sciences, Professor of the Oncology Department of the Federal State Autonomous Educational Institution of Higher Education
I. M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Moscow;

Nina Andreyevna Gorban, Candidate of Medical Science, Head of the Centre for Pathomorphology and Molecular Genetic Diagnostics at Federal State Budgetary Institution “Central Clinical Hospital with Polyclinic” of the Administrative Directorate of the President of the Russian Federation (Moscow)

Vera Andreyevna Gorbunova, Doctor of Medicine, Professor, Head of the Chemotherapy Department of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;

Vyacheslav Nikolayevich Grinevich, Candidate of Medical Science, Head of the Oncopathology Department of the P. A. Herzen Moscow Oncology Research Institute, Branch of Federal State Budgetary Institution “National Medical Radiological Research Centre” of the Ministry of Health of the Russian Federation, Head of the Department of Morbid Anatomy at State Budgetary Healthcare Institution “A. S. Loginov Moscow Clinical Research and Practical Centre” of Moscow Healthcare Department, Moscow;

Garik Albertovich Dashyan, Doctor of Medicine, Leading Research Fellow at the Department of Breast Tumours of Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Saint Petersburg;

Maria Vladimirovna Yermoshchenkova, Candidate of Medical Science, Head of Oncology Department No. 1 (Department of Oncology and Reconstructive Breast Surgery) of State Budgetary Institution “City Clinical Oncological Hospital No. 1” of Moscow Healthcare Department, Moscow;

Natalya Aleksandrovna Zakharova, Doctor of Medicine, Associate Professor at the Department of Oncology and Surgery, Radiation Diagnostics and Radiation Therapy of Budgetary Institution of Higher Education of the Khanty-Mansiysk Autonomous Okrug-Yugra “Khanty-Mansiysk State Medical Academy”, Khanty-Mansiysk;

Konstantin Yuryevich Zernov, Candidate of Medical Science, State Budgetary Healthcare Institution “Saint Petersburg Clinical Research and Practical Centre of Specialised Medical Care in Oncology”, Saint Petersburg;

Aziz Dilshodovich Zikiryakhodzhayev, Doctor of Medicine, Head of the Department of Oncology and Reconstructive Breast and Skin Surgery of the P. A. Herzen Moscow Oncology Research Institute, Branch of Federal State Budgetary Institution “National Medical Radiological Research Centre” of the Ministry of Health of the Russian Federation, Moscow;
Maria Mikhailovna Konstantinova, Doctor of Medicine, Professor, Deputy Director for Clinical Care, Chief Medical Officer at Federal State Budgetary Institution “A. V. Vishnevsky Institute of Surgery”, Moscow;

Luisa Ibragimovna Korytova, Doctor of Medicine, Professor, Head of the Department of Radiation Therapy Quality Assurance of Federal State Budgetary Institution “A. M. Granov Russian Research Centre for Radiology and Surgical Technologies” of the Russian Ministry of Health, Saint Petersburg;

Irina Vladimirovna Kolyadina, Doctor of Medicine, prof. Department of Oncology of Federal State Budgetary Educational Institution of Further Professional Education “Russian Medical Academy of Continuous Professional Education” at “N.N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation;

Aleksandr Valerievich Komyakhov, Research Fellow at the Department of Breast Tumours of Federal State Budgetary Institution “Petrov Research Institute of Oncology”, Saint Petersburg;

Pyotr Vladimirovich Krivorotko, Doctor of Medicine, Head of the Department of Breast Tumours, Leading Research Fellow at the Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Professor at the Department of Oncology of the I.I. Mechnikov North-Western State Medical University, Saint Petersburg;

Asel Galimovna Kudaibergenova, Candidate of Medical Science, Senior Research Fellow at the Research Laboratory for Tumour Morphology at the Petrov Research Institute of Oncology of the Ministry of Health of the Russian Federation, Saint Petersburg;

Dilorom Khamidovna Latipova, Doctor of Medicine, Doctor at the Department of Chemotherapy and Innovative Technologies of Federal State Budgetary Institution “Petrov Research Institute of Oncology”, Saint Petersburg;

Viktor Pavlovich Letyagin, Doctor of Medicine, Professor, Leading Research Fellow at the Department of Breast Tumours of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;

Lyudmila Nikolayevna Lyubchenko, Doctor of Medicine, Head of the Clinical Oncogenetics Laboratory at the Scientific Research Institute of Clinical Oncology of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;
Aleksey Georgievich Manikhas, Doctor of Medicine, Head of the Oncosurgery (Mammology) Department of the Saint Petersburg State Budgetary Healthcare Institution “City Clinical Oncological Dispensary”, Saint Petersburg;

Georgiy Moiseyevich Manikhas, Doctor of Medicine, Academician of RANS, Chief Medical Officer at Saint Petersburg State Budgetary Healthcare Institution “City Clinical Oncological Dispensary”, Head of the Department of Oncology of the Faculty of Postgraduate Education at Federal State Educational Institution of Higher Education “Pavlov First Saint Petersburg State Medical University” of the Ministry of Health of the Russian Federation, Saint Petersburg;

Elizaveta Aleksandrovna Maslyukova, Candidate of Medical Science, Research Fellow at the Department of Radiation Therapy of Oncological Diseases at Federal State Budgetary Institution “A. M. Granov Russian Research Centre for Radiology and Surgical Technologies” of the Russian Ministry of Health, Saint Petersburg;

Sergey Nikolayevich Novikov, Doctor of Medicine, Leading Research Fellow at the Scientific Department for Radiation Oncology and Radiation Diagnostics of the Petrov Research Institute of Oncology, Saint Petersburg;

Rashida Vakhidovna Orlova, Doctor of Medicine, Professor at the Faculty of Medicine of the Saint Petersburg State University, Saint Petersburg;

Anastasiya Anatolyevna Parokonnaya, Doctor of Medicine, Senior Research Fellow at the Radiosurgery Department of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;

Sergey Mikhailovich Portnoi, Doctor of Medicine, Leading Research Fellow at Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology” of the Ministry of Health of the Russian Federation, Moscow;

Svetlana Anatolyevna Protsenko, Leading Research Fellow, Department Head; Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Saint Petersburg;

Valery Vitalievich Rodionov, Doctor of Medicine, Federal State Budgetary Institution “Academician V.I. Kulakov National Medical Research Centre for Obstetrics, Gynaecology and Perinatology” of the Ministry of Health of the Russian Federation;

Marina Vladimirovna Savostikova, Candidate of Medical Science, Head of the Laboratory of Oncocytology of the Centre for Pathomorphology and Molecular Genetic Diagnostics at Federal State Budgetary Institution “Central Clinical Hospital with Polyclinic” of the Administrative Directorate of the President of the Russian Federation (Moscow);
Sergey Vladimirovich Sazonov, Doctor of Medicine, Professor, Deputy Chief Medical Officer for Research, Head of the Department of Morbid Anatomy at State Autonomous Healthcare Institution of the Sverdlovsk Region “Institute of Medical Cell Technologies”, Yekaterinburg;

Anna Igorevna Semenova, Candidate of Medical Science, Senior Research Fellow;

Vladimir Fedorovich Semiglazov, Academician of RANS, Corresponding Member of RAS, Doctor of Medicine, Professor, Head of the Surgical Department of Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Saint Petersburg;

Vladislav Vladimirovich Semiglazov, Doctor of Medicine, Head of the Oncology Department of Federal State Educational Institution of Higher Education “Pavlov First Saint Petersburg State Medical University” of the Ministry of Health of the Russian Federation, Leading Research Fellow of the General Oncology Department of Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Saint Petersburg;

Tatiana Yurievna Semiglazova, Doctor of Medicine, Head of the Scientific Department of Innovative Medical Oncology and Rehabilitation of Federal State Budgetary Institution “Petrov Research Institute of Oncology” of the Ministry of Health of the Russian Federation, Professor at the Department of Oncology of Federal State Budgetary Educational Institution of Higher Education “I.I. Mechnikov North-Western State Medical University”, Saint Petersburg;

Eldar Eskenderovich Topuzov, Doctor of Medicine, Professor, Chief Medical Officer at Saint Petersburg State Budgetary Healthcare Institution “City Clinical Oncological Dispensary”

Oksana Petrovna Trofimova, Doctor of Medicine, Professor, Leading Research Fellow at the Radiology Department of Federal State Budgetary Institution “N. N. Blokhin National Medical Research Centre of Oncology”, Associate Professor at the Department of Oncology of Federal State Budgetary Educational Institution of Further Professional Education “Russian Medical Academy of Continuous Professional Education” of the Ministry of Healthcare of the Russian Federation, Moscow;

Olga Sergeyevna Khodorovich, Doctor of Medicine, Head of the Clinic for Complex Methods of Diagnostics and Treatment of Breast Diseases at Federal State Budgetary Institution “Russian Scientific Centre of Roentgenoradiology” of the Ministry of Health of the Russian Federation;
Vyacheslav Grigorievich Cherenkov, Doctor of Medicine, Professor, Head of the Department for Innovation, Consultancy and Research at State Regional Budgetary Healthcare Institution “Regional Clinical Oncological Dispensary”, Veliky Novgorod.

No conflict of interest.
Appendix A2. Clinical Guidelines Development Methodology

Target audience of these clinical guidelines:

- Oncologists
- Obstetrician-gynaecologists
- Radiation therapists
- Medical students, residents and graduate students

Requirements to the structure of clinical guidelines, contents and scientific validity of the information included in the clinical guidelines approved by Order No. 103n of the Ministry of Health of the Russian Federation of 28 February 2019

Table A2.1. Levels of evidence (LE) grading scale diagnostic methods (diagnostic interventions)

<table>
<thead>
<tr>
<th>LE</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Systematic reviews of reference-controlled trials or systematic reviews of randomised clinical trials with meta-analysis</td>
</tr>
<tr>
<td>2.</td>
<td>Selected reference-controlled trials or selected randomised clinical trials and systematic reviews of studies of any design other than randomized clinical trials with meta-analysis</td>
</tr>
<tr>
<td>3.</td>
<td>Trials conducted without sequential reference control method or trials conducted with reference that is not independent of the investigational method or non-randomised comparative trials, including cohort trials</td>
</tr>
<tr>
<td>4.</td>
<td>Non-comparative studies, case report</td>
</tr>
<tr>
<td>5.</td>
<td>Only a rationale for the mechanism or expert opinion is available</td>
</tr>
</tbody>
</table>
Table A2.2. Levels of evidence (LE) grading scale for prevention, treatment and rehabilitation methods (preventive, therapeutic, and rehabilitation interventions)

<table>
<thead>
<tr>
<th>LE</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Systematic review of randomised clinical trials with meta-analysis</td>
</tr>
<tr>
<td>2.</td>
<td>Selected randomised clinical trials and systematic reviews of studies of any design other than randomized clinical trials with meta-analysis</td>
</tr>
<tr>
<td>3.</td>
<td>Non-randomised comparative studies, including cohort studies</td>
</tr>
<tr>
<td>4.</td>
<td>Non-comparative studies, case report or series of cases, case-control study</td>
</tr>
<tr>
<td>5.</td>
<td>Only a rationale for the intervention mechanism (preclinical studies) or expert opinion is available</td>
</tr>
</tbody>
</table>

Table A2.3. Recommendation grading (RG) scale for prevention, diagnostics, treatment and rehabilitation methods (preventive, diagnostic, therapeutic, and rehabilitation interventions)

<table>
<thead>
<tr>
<th>RG</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong recommendation (all efficacy criteria (outcomes) under consideration are important, all studies are of high or satisfactory methodological quality, and the conclusions regarding the outcomes are consistent)</td>
</tr>
<tr>
<td>B</td>
<td>Conditional recommendation (not all efficacy criteria (outcomes) under consideration are important, not all studies are of high or satisfactory methodological quality and/or the conclusions regarding the outcomes are inconsistent)</td>
</tr>
<tr>
<td>C</td>
<td>Weak recommendation (absence of convincing evidence (all efficacy criteria (outcomes) under consideration are insignificant, all studies are of low methodological quality, and the conclusions regarding the outcomes are inconsistent)</td>
</tr>
</tbody>
</table>