BREAST UNIT GUIDELINES

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Initial Workup

Every newcomer to the breast oncology department should be seen at the new patient's clinic with the following assessments:

- Complete medical history:
  - Risk factors of breast cancer (BC)
  - Presentation
  - Family history
  - Comorbidities
  - Menstrual status
  - Patient/family compliance
  - Availability of insurance coverage
- Physical examination:
  - Including body surface area (BSA)
  - Performance status (PS)
- Laboratory investigations:
  - Complete blood count
  - Hepatic and renal profile
  - Electrolytes profile
  - Tumor markers
    - The clinical value of tumor markers is not well established for diagnosis or follow-up after adjuvant therapy.
    - Tumor markers (if elevated) may evaluate response to treatment, particularly in patients with non-measurable metastatic disease.
    - A change in tumor markers alone should not be used to initiate a change in treatment.
- Cardiac assessment:
  - MUGA scan / 2D echocardiography for all patients who are planned to receive chemotherapy or anti-HER2 therapy.
- Pathology specimen review, including biomarkers:
  - Estrogen receptor (ER)
  - Progesterone (PR)
  - Human epidermal growth factor receptor 2 (HER2)
  - Tumor Grade
  - Ki67
- When appropriate predictive biomarker tests:
  - Breast cancer gene (BRCA)
  - PI3Km,
  - Programmed cell death 1 receptor/ programmed cell death ligand 1 (PD1/ PDL1)
- Viral Hepatitis and human immunodeficiency virus (HIV) screening.

- Pregnancy test for premenopausal women.
- Counseling for fertility.
- Imaging

○ Early BC (Stage I and II)	- Ultrasound abdomen and pelvis - Chest X-Ray - Bilateral Mammogram - Ultrasound of axilla - Unless there are symptoms or suspicion.
○ Advanced BC (Stage ≥2)	- CT scan chest/abdomen/pelvis or - Fluorodeoxyglucose positron emission tomography scan (18F-FDG PET/CT) - Bone scan - Sodium Fluoride (NaF-PET/CT) should be considered - Brain imaging should be requested in: ▪ Symptomatic patients ▪ HER-2 positive BC ▪ Triple-negative metastatic breast cancer (MBC)

Adjuvant Therapy

Adjuvant chemotherapy

General Considerations:

- Adjuvant chemotherapy reduces the risk of metastatic disease or cancer recurrence:
  - The actual benefit of adjuvant chemotherapy depends on the baseline risk of developing metastatic disease (predicted by standard prognostic factors at diagnosis).
  - All patients with early breast cancer should have their risk of recurrence assessed and benefits of systemic therapies discussed in the multidisciplinary team (MDT) meeting and the breast cancer unit weekly meeting.
  - The final plan of systemic therapy should be made in the oncology clinic using the risk of recurrence, benefits of systemic therapies, and other patient information and taking into account their views.
- Anthracyclines should be avoided if:
  - There is a significant history of cardiac disease
- Anthracyclines should be used with caution in:
  - Patients above 60 years of age or
  - Patients with significant hypertension or
  - Patients with a pre-treatment left ventricular ejection fraction carried out.
  - Patients with previous thoracic irradiation.
- The choice of systemic adjuvant therapies must consider:

  - Surrogate intrinsic phenotypes
  - Predicted benefit,
  - Possible side effects and
  - Patient preference.

- Adjuvant treatment should start within 2-6 weeks of surgery.
- Triple-negative breast cancer should have a priority in commencing adjuvant chemotherapy as soon as possible.
- Chemotherapy should not be used concomitantly with endocrine therapy.
- Trastuzumab should routinely be combined with non-anthracyclines-based chemotherapy and endocrine therapy.
- Radiotherapy may be delivered safely during trastuzumab and possibly endocrine therapy.
- Treatment for breast cancer may impair fertility. Therefore, all premenopausal patients should be informed about the potential impact of chemotherapy on fertility. If appropriate, consider fertility preservation referral.
- Ovarian function preservation should be considered during adjuvant chemotherapy. gonadotropin-releasing hormone agonist (GnRHa) should be given prior to chemotherapy, preferably by 2 weeks, independently of hormone receptor status.
- Breast cancer does occur in men and should be treated similarly to post-menopausal women, except aromatase inhibitor (AI) is ineffective without concurrent suppression of testicular steroid genesis.

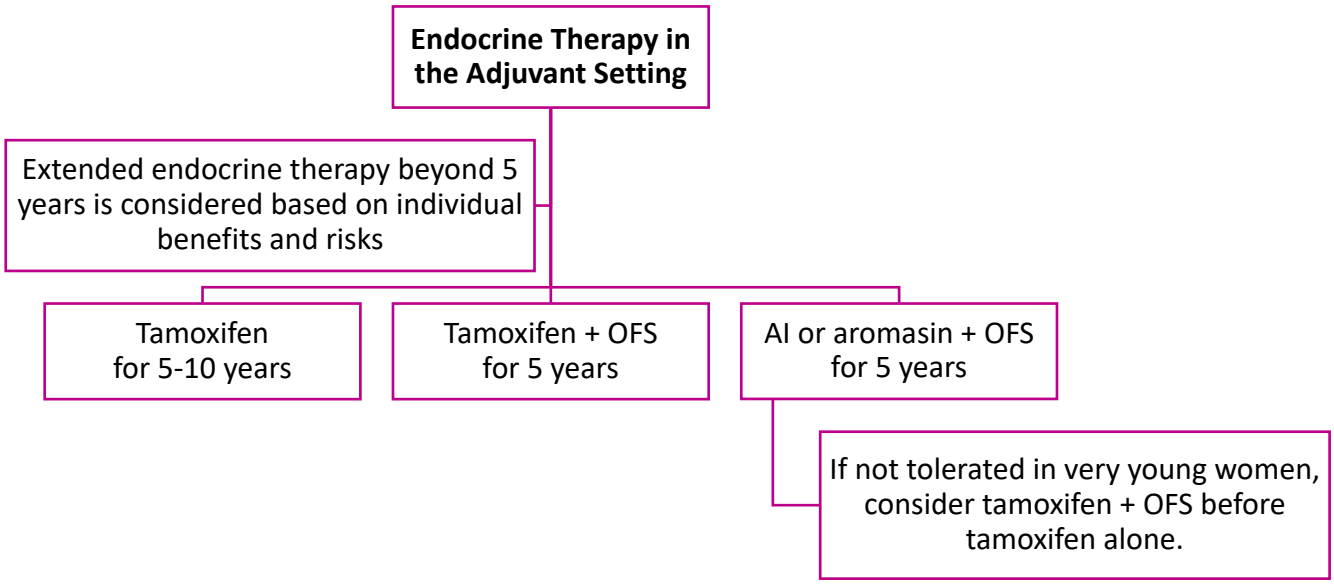
- **A number of online tools are available to assist, such as the National Health Service (NHS) PREDICT.**

○ **Oncotype DX**	- For patients with ER-positive disease, a number of molecular tests can give further refinement of the likely benefit from chemotherapy. - Oncotype DX is recommended to be used in ER-positive, HER2-ve where the benefit of adjuvant chemotherapy is uncertain. - A proportion of patients who might otherwise have had adjuvant chemotherapy can avoid this on the basis of this test.
○ **Indication of Oncotype DX**	- Node negative pre/post-menopause patients (TAILORx trial) - 1-3 N+ in selected patients. (Plan B) - Women older than 50 years with hormone receptor-positive, HER2-negative, node-negative breast cancer, and OncotypeDx Recurrence Score of ≤ 25 did not benefit from receiving adjuvant chemotherapy (TAILORx trial). - Chemotherapy can be considered in pre/post-menopausal with score ≥ 25. Whereas with a score between 20 – 25 in pre-menopausal women, chemotherapy may be considered in some cases but and this should be discussed with the patient at all time.

Adjuvant Endocrine Therapy

- Aim of endocrine therapy:
  - It reduces recurrence rates
  - It reduces BC specific mortality rates in women with estrogen receptor/progesterone receptor (ER/PR) positive early breast cancer.
- Supporting evidence:
  - The most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview showed a 30% reduction in breast cancer mortality throughout the first 15 years following 5 years of adjuvant treatment with tamoxifen (RR= 0.71 for years 0 – 4 and 0.66 for years 5 – 9).
  - The proportional reduction in risk of relapse for all time periods was 39% (RR= 0.53 for years 0 – 4 and 0.68 for years 5 – 9). This benefit was independent of patient and tumor characteristics.
- General rules for adjuvant endocrine therapy:
  - Adjuvant endocrine therapy is divided into:
    - Initial therapy (years 0 – 5) and
    - Extended adjuvant therapy (years 6 – 15).
  - Duration of ovarian function suppression (OFS) is 5 years.
  - OFS can be achieved either by:
  - Bilateral oophorectomy or
  - Gonadotropin-releasing hormone (GnRH) agonist: clinicians should be alert to the possibility of incomplete ovarian suppression with GnRH agonist therapy.
  - Currently, tamoxifen and AI are the mainstays of adjuvant treatment in women with ER+ early breast cancer (ER >1% on immunohistochemistry).
- Definition of menopause:
  - Prior bilateral oophorectomy
  - Age ≥ 60
  - Age < 60 with amenorrhea for ≥ 12 months
  - In the absence of chemotherapy, tamoxifen, ovarian suppression,
  - With follicle-stimulating hormone (FSH) and estradiol in postmenopausal level.
  - In the case of therapy-induced amenorrhea, serial FSH/estradiol measurement is necessary.

Adjuvant Endocrine Therapy of Premenopausal



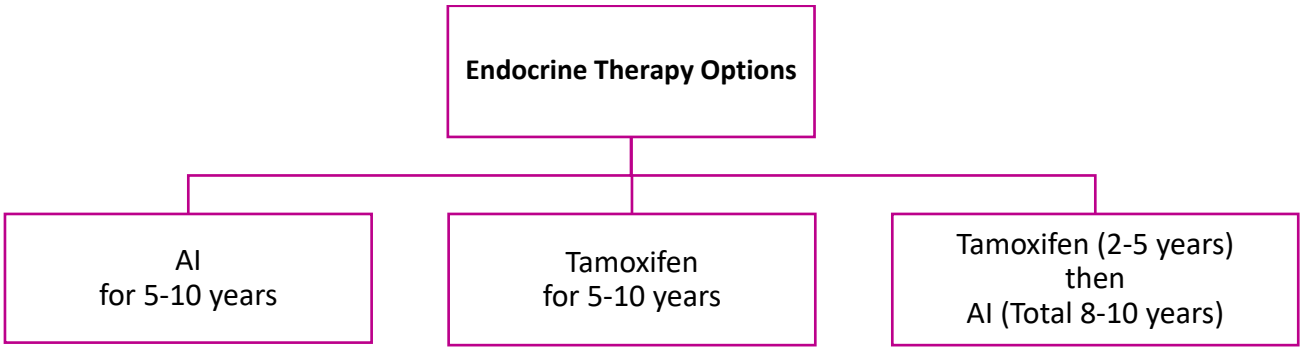
Low-risk Disease	High-risk Disease (stage II and beyond)
Tamoxifen alone should be sufficient	OFS should be added.

- General considerations
  - Duration, choice, and sequence of AI mainly depend on:
    - Menopausal status,
    - Tolerability and
    - Risk of recurrence.
  - Switching to another tolerable endocrine treatment (Tamoxifen or AI) is better stopping therapy.

Condition	Management
Women with Significant risk for recurrence (based on combined clinical-pathological features)	Exemestane (AI) + OFS is more effective (preferred) endocrine therapy over tamoxifen + OFS or tamoxifen alone. *
Women with stage 1 breast cancers at higher risk recurrence (who might consider chemotherapy)	Offered OFS in addition to endocrine therapy.
Women with stage 1 breast cancers that do not warrant chemotherapy	Should not receive OFS
Women with stage 2 or 3 breast cancers who would ordinarily be advised to receive adjuvant chemotherapy	Should receive OFS in addition to endocrine therapy.
Women <35 years of age, with hormone receptor-positive early breast cancer.	Consider OFS

* Use of Exemestane + OFS may provide a large absolute increase (10-15%) in 8-year freedom from distant recurrence in women at highest risk of recurrence.

Adjuvant Endocrine Therapy of Postmenopausal



- Duration of endocrine therapy:

LN + ve	○ Consider extended therapy (including AI) for up to a total of 10 years
LN – ve	○ Consider extended therapy for up to a total of 10 years based on recurrence risk considerations using established prognostic factors. ○ Low-risk node negative should not routinely be offered extended therapy

- General considerations:
  - AI should be used as a first treatment instead of Tamoxifen in postmenopausal patients, especially in cases of:
    - Invasive lobular carcinoma (ILC) histological subtype and
    - High risk of recurrence.
  - Women on AI should receive calcium with vitamin D supplement.
  - Bone mineral density (BMD) should be measured at baseline and repeated every two years.
  - If T score < -2.5, bisphosphonates should be administrated:
    - Zoledronic acid: 4 mg once every six months for three years or
    - Denosumab 60 mg SC every 6 months **(Read more about adjuvant bisphosphonates)**.

Neoadjuvant Therapy

Introduction

Neoadjuvant systemic therapy (NST), systemic treatment before surgery, has become a frequently used option for systemic therapy in primary operable breast cancer.

Meta-analyses results showed no difference between neoadjuvant therapy and adjuvant therapy in terms of survival and overall disease progression. However, if chemotherapy is indicated due to tumor biology, neoadjuvant therapy is preferred as:

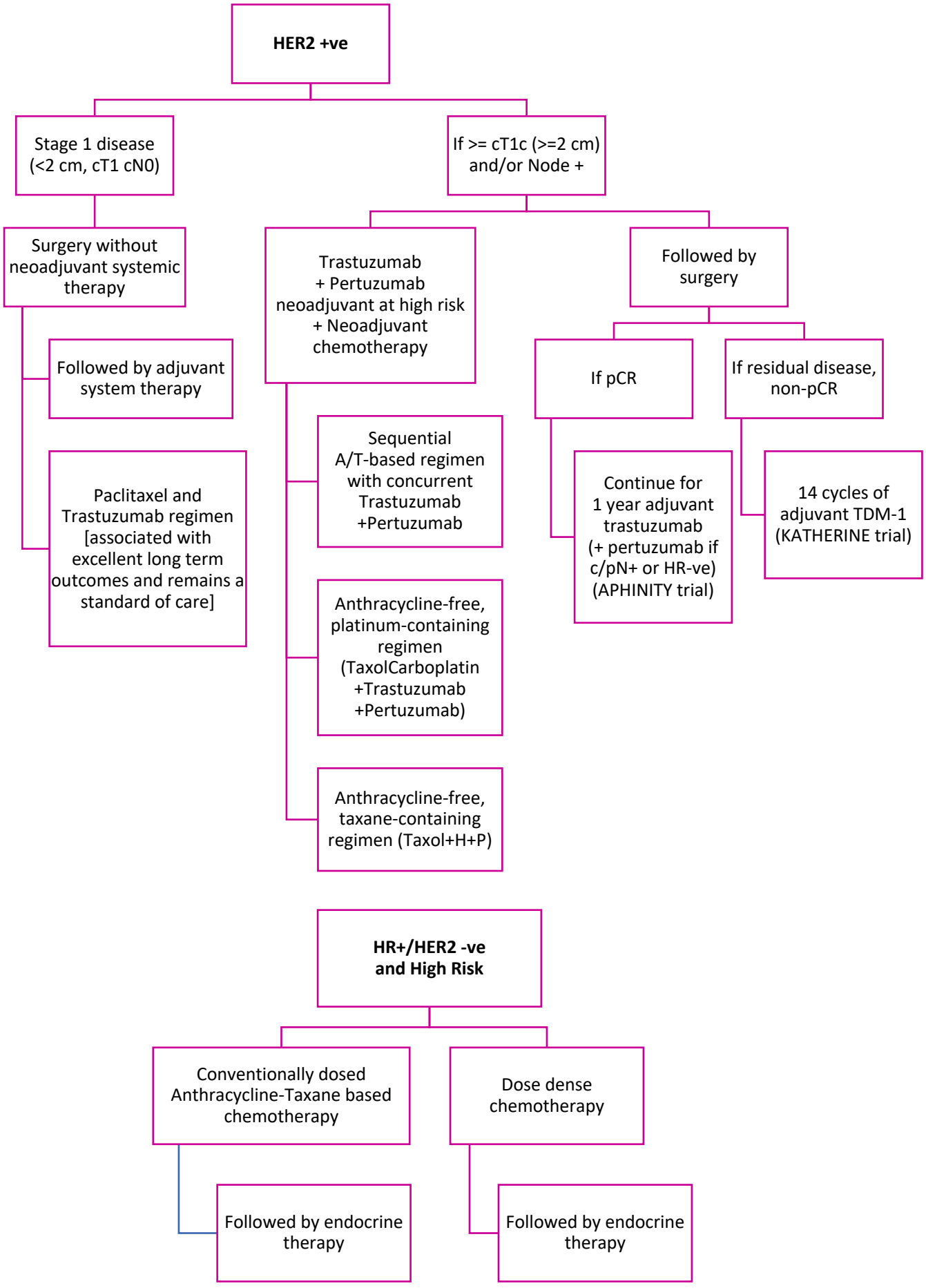
- it improves rate of breast conservation therapy,
- potentially targeting micro-metastatic disease earlier and
- it allows assessment of tumor response to therapy.

Workup

- Thorough physical examination.
- Mammography and sonography of both breasts for:
  - Tumor localization
  - Disease multi-centricity and
  - Diffuse microcalcifications
- Consider magnetic resonance imaging (MRI) of breast if:
  - Conservative surgery is planned for better localization and assessment of response.
- Complete staging work-up:
  - Stage 2:
    - Ultrasound abdomen and pelvis, if the patient is symptomatic or has elevated alkaline phosphatase
    - Bone scan/NaF PET/CT should be thought.
  - Stage 3 and above:
    - CT Scan chest abdomen and pelvis or FDG PET/CT.
- Multiple-gated acquisition (MUGA) scan/2D echocardiography:
  - If the patient is to receive neoadjuvant Anthracycline and or Trastuzumab.
- Adequate core biopsy to assess:
  - Pathologic subtype,
  - Degree of differentiation.
  - ER/PR and HER2 status.
- Ultrasound (US)-guided application of marker at the tumor site at the time of biopsy or at the clinical evidence of the earliest response, in cases planned for conservative surgery.
- Tattooing of the tumor margins at the beginning is also an option.

Advantages of Neoadjuvant Systemic Therapy

- Neoadjuvant Systemic Therapy in HER2+ cancers:
  - Provides clinically relevant risk stratification
  - Facilitates tailoring of therapy.
  - The neoadjuvant approach should become the standard of care for stage 2 and 3 HER2+ cancers.
- Triple-negative breast cancer (TNBC):
  - Delay in delivery of chemotherapy in the adjuvant setting for TNBC has a negative impact.
  - Therefore, the earlier the systemic therapy for triple negative, the better the outcome.


HER2 +ve
Stage 1 disease (<2 cm, cT1 cN0)
If >= cT1c (>=2 cm) and/or Node +
Surgery without neoadjuvant systemic therapy
Followed by adjuvant system therapy
Paclitaxel and Trastuzumab regimen [associated with excellent long term outcomes and remains a standard of care]
Trastuzumab + Pertuzumab neoadjuvant at high risk + Neoadjuvant chemotherapy
Sequential A/T-based regimen with concurrent Trastuzumab +Pertuzumab
Anthracycline-free, platinum-containing regimen (TaxolCarboplatin +Trastuzumab +Pertuzumab)
Anthracycline-free, taxane-containing regimen (Taxol+H+P)
Followed by surgery
If pCR
If residual disease, non-pCR
Continue for 1 year adjuvant trastuzumab (+ pertuzumab if c/pN+ or HR-ve) (APHINITY trial)
14 cycles of adjuvant TDM-1 (KATHERINE trial)
HR+/HER2 -ve and High Risk
Conventionally dosed Anthracycline-Taxane based chemotherapy
Dose dense chemotherapy
Followed by endocrine therapy
Followed by endocrine therapy

Indications of Neoadjuvant Systemic Therapy

- In locally advanced tumors and inflammatory breast cancer:
  - Neoadjuvant Systemic Therapy (NST) may allow for reducing the tumor size and achieving operability or decreasing the surgery extend.
- In early breast cancer:
  - NST can be given to reduce the tumor bulk so that breast-conserving surgery (BCS) can be done later.
- In early breast cancer with Triple negative/HER2neo +ve:
  - NST can be the primary therapy with the aim to achieve a complete or near complete pathological response and to decide regarding de-escalation or escalation of adjuvant therapy.

Neoadjuvant Systemic Therapy (NST)

- The backbone of NST with chemotherapy is Anthracycline and Taxane.
- Sequential use of both is preferred as it is less toxic and yielded a better response.
- All chemotherapy should be given upfront before surgery unless indicated otherwise, and to be discussed in the MDT meeting.
- Patients with Her2neu positive disease should receive:
  - Neoadjuvant Trastuzumab and Pertuzumab (high-risk disease)
- Anti-HER2 therapy should not be given concurrently with anthracyclines.

Neoadjuvant Chemotherapy

I. HER2neo receptor negative

(1) **Dose-dense AC x 4 (biweekly)**

followed by

Paclitaxel X 4 (biweekly) or Paclitaxel x 12 weeks

- Granulocyte-colony-stimulating factors (G-CSF) support should be given with AC and Paclitaxel biweekly
- Dose-dense is the preferred schedule for:
  - High-risk patient,
  - Young patients and
  - Triple negative disease

(2) **FEC (100) x 3 cycles every 3 weeks**

followed by

Taxotere (80-100mg/m2) x 3 cycles every 3 weeks.

(3) **AC (60 mg/m2) x 4 cycles every 3 weeks**
followed by
Taxol (80mg/m2) weekly x 12

(4) **In Triple negative disease irrespective of BRCA status**
Carboplatin AUC (5-6) can be added in combination with Taxol.

II. HER2neo receptor positive

(1) **FEC (100) every 3 weeks x 3 cycles**
followed by
Taxotere every 3 weeks x 3 cycles with Trastuzumab and Pertuzumab every 3 weeks x 3 cycles.

(2) **(2) AC x 4 every 2 or 3 weeks,**
followed by
Taxol weekly x 12 weeks with Trastuzumab and Pertuzumab 3 weekly x 4 cycles.

(3) **Taxotere, Carboplatin, Herceptin, and Pertuzumab for 6 cycles.**

- Special Considerations in HER2neo Receptor Positive:
  - The addition of 4-6 courses of neoadjuvant Pertuzumab to trastuzumab and chemotherapy is recommended for patients with higher risk cancers. It has been shown to improve significantly both:
    - Pathological complete response rates and
    - 5-year survival outcome.
  - After neoadjuvant Trastuzumab and Pertuzumab; if there is a residual disease in pathology either in primary cancer or Lymph nodes; TDM-1 is recommended for 14 cycles of (CATHRINE trial).
  - In the high-risk patient with pCR to trastuzumab and Pertuzumab, an adjuvant combination of trastuzumab and Pertuzumab may be considered. (APHINITY trial).

Neoadjuvant Endocrine Therapy

Endocrine NST alone may be an option for post-menopausal women with **luminal A phenotype** in:

- Patients who are not candidates for cytotoxic chemotherapy due to the high risk of toxicity (low-performance status and comorbidities) or
- Patients who are less likely to respond to chemotherapy (low grade, invasive lobular histology).

General Rules

- Aromatase inhibitors (AI) are well established in the neoadjuvant endocrine treatment of postmenopausal women with hormone-responsive tumors.
- Endocrine therapy takes at least 3-4 months in order to show a meaningful response.

- Disease response evaluation:
  - A physical examination prior to each cycle.
  - Interval radiologic disease evaluation:
    - Likely by ultrasonography (U/S), after the 4th cycle or earlier if there is a concern of response.
    - MRI is the most accurate in assessing response to NST and may be considered at the end of therapy.
  - Cardiac assessment:
    - Required prior Herceptin intake and every 12 weeks thereafter, in cases administering sequential Anthracyclines then Taxanes and Herceptin,
  - By the end of NST radiologic disease, re-evaluation is recommended:
    - MRI/mammogram is indicated if conservative surgery is an option.

N.B. In case of clinical progression while on NST, consider surgery if the tumor is operable. It is very unlikely for the tumor to respond to alternate chemotherapy.

Adjuvant Therapy

Adjuvant Chemotherapy

General Rules

- If chemotherapy is indicated due to tumor biology, consider systemic treatment before surgery (neoadjuvant).
- The most frequently used regimens are:
  - *Anthracyclines and Taxanes based chemotherapy.*
- In the adjuvant setting, they reduce breast cancer mortality by about one third. Sequential use of these agents is preferred.

Adjuvant Chemotherapy Protocols:

(1) **Dose-dense: AC x 4 every 2 weeks**

followed by

Paclitaxel (175mg/m2) x 4 every 2 weeks

with GCSF support (preferred for triple negative breast cancer and young patients).

(2) **FEC (100) x 3**
followed by
Taxotere (100mg/mm) x 3 cycles.

(3) **Taxotere, Carboplatin, Herceptin, and Pertuzumab for 6 cycles.**

(4) **AC x 4 every 3 weeks**
followed by
Paclitaxel (80mg/mm) x 12 weeks.

(5) **Node-negative: 12 weeks of Taxol**
concurrently with Trastuzumab followed by one-year Trastuzumab.

(6) **For the patient with cardiac risk:**

HER2 –ve	**HER2 +ve**
TC (Taxotere/Cyclophosphamide) x 4-6	**TCH (Taxotere/Carboplatin/Herceptin) x 6**

Adjuvant Anti-HER2 Therapy

General Rules

- All patients with invasive HER2 positive disease (1cm or greater) should be offered adjuvant trastuzumab for 1 year along with adjuvant chemotherapy.
- The benefit of such treatment for HER2 positive cancers <1cm is less certain, and the decision should be left to the oncologist in charge.

Low-Risk HER2+ Breast Cancer

cT < 2cm (T1c)

- NST can safely be omitted
- The patient can have surgery, followed by adjuvant therapy.
- Single-agent Paclitaxel with Trastuzumab appears as effective as standard chemotherapy for small node-negative cancers (2cm or less) and is a lot less toxic.

If ER +ve

- Adjuvant Paclitaxel 12wks and Trastuzumab is recommended for 1 year (APT trial)

ER –ve

- AC-Paclitaxel and 1 year of Trastuzumab.

Intermediate/High-Risk HER2+ Breast Cancer

cT2-3 cN0, or N+ disease
○ NST in the form of AC followed by Paclitaxel and Trastuzumab + Pertuzumab.
○ Avoid Anthracycline by giving 6 cycles Taxol/Carboplatin + Trastuzumab and Pertuzumab.
○ Followed by surgery.

Pathological Response:

- Choices of the adjuvant therapy for HER2 disease will depend on the pathological response to NST:
  - If no pathologic complete response (pCR), i.e., residual disease at the primary or lymph nodes (LN), treatment recommendation with TDM-1 14 cycles.
  - If pCR is achieved, then Trastuzumab + Pertuzumab (depends on availability) to complete 1 year.
- Cardiac monitoring should be carried out based on standard guidelines.
  - Cardiac monitoring (electrocardiogram (ECG) and echocardiography) should be done at baseline and 3 monthly thereafter during anti-HER2 therapy.
  - Baseline left ventricular ejection fraction (LVEF) has to be greater than 50%. If LVEF drops by 10% (ejection) points or more from baseline and to below 50%, then Trastuzumab treatment should be suspended.
- ExteNET: High-risk patient with residual disease/N+ and ER+, after completing 1-year trastuzumab benefited from 1-year oral Neratinib adjuvant therapy (HR:0.6, invasive disease-free survival (iDFS) difference of 4%).
- Trastuzumab:
  - Trastuzumab should be started concurrently with Taxanes either weekly or 3 weekly. Thereafter, Trastuzumab should be given once every 3 weeks for 12 months.
  - Sub-cutaneous Trastuzumab is as effective as intravenous, cost-effective, and should be encouraged. The choice should be discussed with the patient.
  - Trastuzumab is safe during radiotherapy treatment.

LV Dysfunction

Symptomatic LV dysfunction:
(1) Aim: - Withdraw anti-HER2 therapy and treat cardiac dysfunction. - Refer the patient to a cardiologist with a special interest in such condition.
(2) Patients with heart failure (HF) and an LVEF < 40% should be treated with: - ACE inhibitors in combination with a beta-blocker (unless contraindicated).
(3) Patient's LVEF is between 40% and 50%: - Prevent further degradation of LVEF or the development of clinical heart failure. - ACE inhibitor should be considered.

Asymptomatic LV dysfunction:

(1) Follow the recommendations of the cardiologist according to International Cardiology Guidelines.

(2) Patients with LV dysfunction and an EF < 40%:

- ACE inhibitors should be used in all asymptomatic patients.

(3) Patients with asymptomatic LV dysfunction and an LVEF < 40% if prior to MI:

- Beta-blockers should be considered in all patients

(4) Accelerate therapy for Trastuzumab-related cardiotoxicity.

- The normal titration schedules can take several months to reach the optimal therapeutic dosage.
- Data are insufficient to make a definitive recommendation regarding the duration of treatment for cardiac dysfunction in Trastuzumab patients.

(5) Following the withdrawal of Trastuzumab therapy, it may be reinitiated on the basis of the same LVEF guidelines as the original initiation of therapy.

(6) Permanently discontinue Trastuzumab, if more than 2 consecutive holds or a total of 3 hold.

(7) Re-initiation of Trastuzumab should be given with a loading dose if the interruption is greater than 6 weeks.

(8) To repeat Echo/MUGA after 6 months and 1 year from completion of Herceptin.

Trastuzumab-related cardiotoxicity prevention:

Anthracycline therapy:

- Lisinopril or Carvedilol reduce cardiotoxicity in patients with HER2-positive BC patients receiving anthracycline followed by Trastuzumab, compared to non-anthracyline containing regimens.
- Therefore, may allow the use of an Anthracycline without compromising Trastuzumab treatment in those who might benefit from an Anthracycline.

Adjuvant Bisphosphonates

- In postmenopausal women at significant risk of disease recurrence:
  - Adjuvant bisphosphonates should be part of routine adjuvant treatment.
- In lower-risk patients:

  The absolute benefit is likely to be very small and may be outweighed by the potential side effects (in particular a 1% risk of osteonecrosis of the jaw).

Postmenopausal women (including premenopausal on OFS) with early breast cancer
Zoledronate 4mg, IV infusion 6 monthly for a minimum of 3 years.
Based on strong evidence, adjuvant bisphosphonate reduces the risk of bone recurrence and fractures, and improve breast cancer survival (17% reduction in risk of breast cancer death).

Denosumab clearly reduces fractures in postmenopausal breast cancer receiving aromatase inhibitors, but it does not reduce the risk of bone recurrence. (D-Care)

Systemic Treatment in Pregnancy Associated Breast Cancer

General Principles:

(1) Maternal /fetal medical consult to be involved early prior to treatment and throughout the treatment.

(2) Establish fetal age, estimate delivery date

(3) Adjuvant and/or neoadjuvant chemotherapy is safely given in the 2nd and 3rd trimester.

(4) Avoid chemotherapy beyond 34-35 weeks.

(5) FAC x 6 or AC x 4 is options.

(6) Trastuzumab should not be given in Pregnancy.

(7) Although there is no strong evidence of contraindication to using adjuvant Taxol during pregnancy, the consensus is to avoid it if possible.

Follow up:

(1) History taking, eliciting of symptoms, and physical examination:

- Every 3-4 months for 3 years
- Every 6 months for the next 2 years
- Then annually.

N.B.: Attention paid to long term side effects, e.g., osteoporosis.

(2) Ipsilateral (after breast-conserving surgery) and contralateral mammography annually (MRI in young patients may be indicated).

(3) Ultrasound pelvis and gynecological examination: annually for patients on Tamoxifen.

(4) BMD in patients on AIs and patients who are experiencing premature menopause to be repeated every 2 years.

Management of Metastatic Breast Cancer (MBC)

General Principles

- The management of MBC is complex and, therefore, the involvement of all appropriate specialties in a multidisciplinary team is crucial, including:
  - Medical Oncologist
  - Radiation Oncologist
  - Surgical Oncologist
  - Imaging Expert
  - Pathologist
  - Gynecologist
  - Psycho-oncologist
  - Social worker
  - Oncology Nurse
  - Palliative Care Specialist
- From the time of diagnosis of MBC, patients should be offered appropriate:
  - Psychosocial care,
  - Supportive care, and
  - Symptom-related interventions as a routine part of their care.
  - The approach must be personalized to meet the needs of the individual patient.
- Following a thorough assessment and confirmation of MBC, patients should be communicated:
  - The potential treatment goals of care.
  - MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances).

Special Consideration

- The social circumstances for people In the Gulf area and Kuwait widely differ from the West and other cultures. Physicians should be aware of such differences and should be trained in dealing with such circumstances. For example:
  - The older generation is usually looked after by the family.
  - Usually, there is a carer who is very close to the patient, and there is the next of kin (NOK), who may be the head of the family and the decision maker.
- It is always advisable from the start to build a rapport with not only the patient and the index carer but also the legal NOK in order to understand their social circumstances and to avoid future difficulties.
- It is also advisable for the physician to encourage NOK to get involved early and to be aware of the diagnosis, management, and prognosis of the patient.
- From our experience, it is always advisable to ask the patient directly before you inform them about their diagnosis and prognosis. Ask if they would like to be informed about everything related to their disease and which member of the family is allowed to be involved.
- You may be surprised how many old patients may decline to want to know. Patients may usually refer to their carer to take care of it and their management decisions.
- Patient's wishes are paramount and should be respected at all the time. Obviously, it is recommended to advise the patient against not wanting to know and to encourage patients to get involved in knowing their disease in order to enable the physicians and carers to help them.

- Kuwait's law gives the right to Do Not Resuscitate (DNR) to patients and their families only. Physicians have no rights to overcome that.

Diagnosis

- Clinical suspicion must be confirmed by:
  - Radiological and/or
  - Scintigraphy examination and
  - Blood investigations.
- Histopathology confirmation:
  - If prior hormonal receptor and/or HER2neu status is not available.
  - Easily accessible site available at time of relapse and to be considered at every progression.
  - Isolated metastatic lesion.

Risk Assessment and Investigations

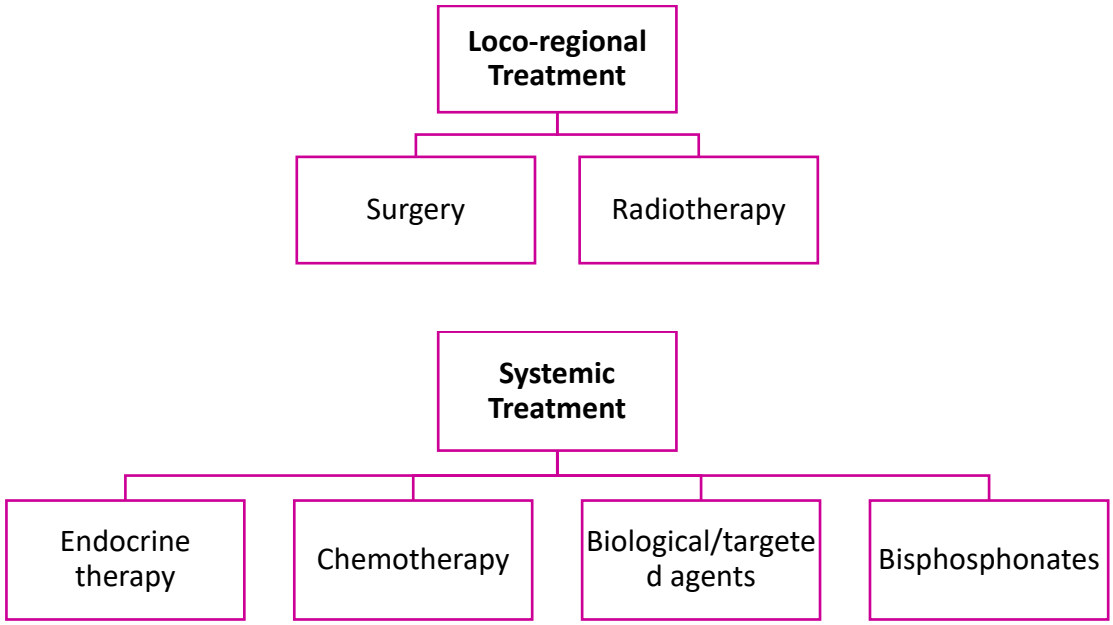
- A complete history, including:
  - Menopausal status and co-morbidities
  - A detailed history of the primary tumor, its biology, and management.
  - History of recurrent/metastatic disease, including duration, previous sites, and treatment.
  - Current symptoms and performance status.
- A detailed physical examination.
- Blood tests, including:
  - Complete blood count (CBC)
  - Oncology profile and
  - Tumor markers:
  - The clinical value of tumor markers is not well established for diagnosis or follow-up after adjuvant therapy.
  - Their use (if elevated) is to help evaluate response to treatment, particularly in patients with non-measurable metastatic disease.
  - A change in tumor markers alone should not be used to initiate a change in treatment.
- Imaging:
  - CT scan chest/abdomen/pelvis and PET FDG.
  - Bone scan with confirmation of lesions by x-ray/CT/MRI/PET NaF
  - CT and/or MRI of CNS if symptoms present. Brain imaging should not be routinely performed in asymptomatic patients.
  - MUGA scan or echocardiography.

Factors to be considered in treatment decision making of MBC

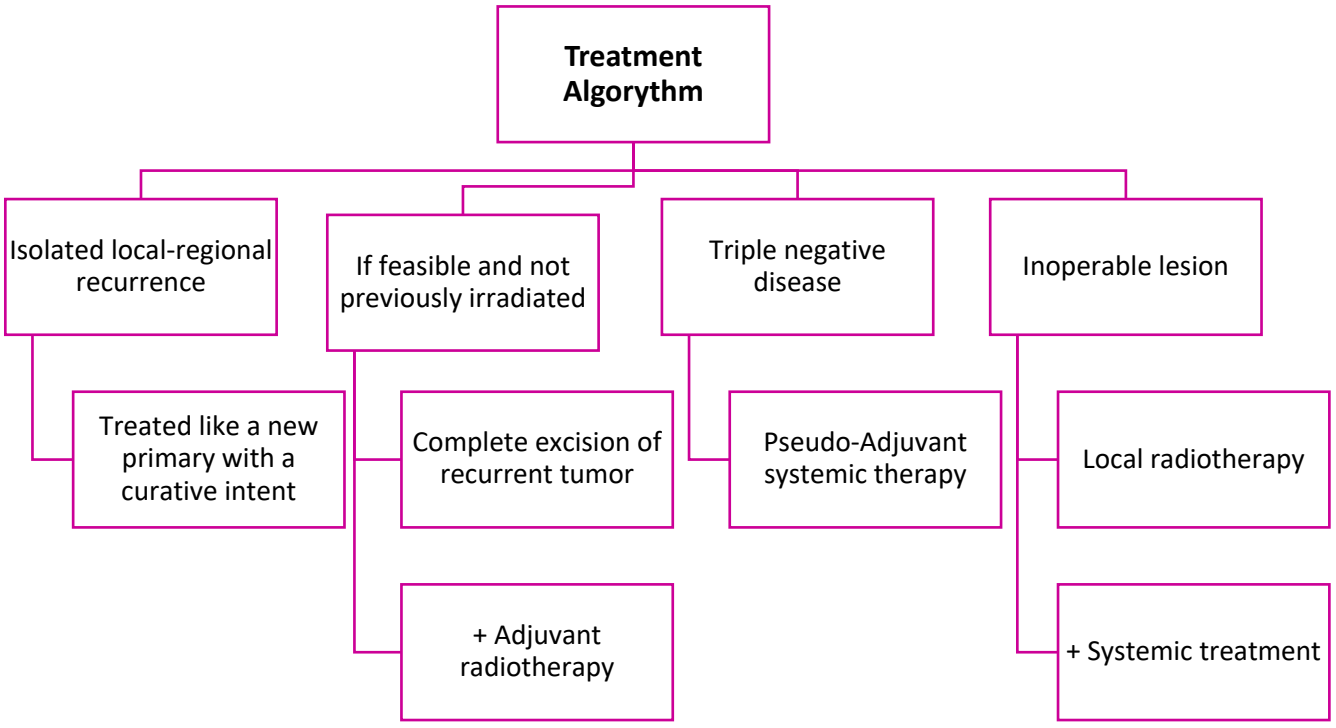
- Hormonal receptor and HER2 status.
- Disease-free survival.
- Metastatic sites and disease burden.

- Previous treatment and response.
- Patient symptoms.
- Patient preference.
- Anticipated side effects.
- Co-morbidities and performance status

Treatment Modalities



Local-regional modalities



Radiotherapy indications:

(1) Painful bony metastatic lesions.
(2) Cord compression if surgical intervention is not indicated.
(3) CNS metastasis.
(4) SVC syndrome.
(5) Palliative breast irradiation, e.g., pain and/or bleeding.

Surgery indications:

(1) Surgery of the primary breast disease in a patient presenting with metastatic disease on diagnosis is controversial and may be considered later if they respond to first-line treatment and/or if the systemic disease is minimal and fairly controlled (discussed in the MDT meeting)
(2) Isolated local/regional recurrence.
(3) Orthopedic fixation for pathological fractures.
(4) Surgical decompression for spinal cord compression.
(5) Limited brain metastasis.

Systemic Treatment

Definitions of Endocrine Resistance in MBC:

- Primary endocrine resistance
  - Defined as a relapse while on
  - First 2 years of adjuvant ET, or
  - Progression of disease (PD) within the first 6 months of 1st line ET for MBC, while on ET.
- Secondary (acquired) endocrine resistance
  - Defined as relapse while on
  - Adjuvant ET but after the first 2 years, or
  - relapse within 12 months of completing adjuvant ET, or
  - PD $\geq$ 6 months after initiating ET for MBC, while on ET

Hormonal Positive/HER2-Negative MBC

General Considerations:

- Endocrine therapy (ET) is the first line treatment option for hormone receptor-positive MBC.
- ET is contraindicated in case of:
  - Visceral crisis or
  - Acute life-threatening disease.
- HR status may change during the course of the disease. Thus, histology of recurrent site should be obtained whenever possible.
- All premenopausal patients should receive ovarian function suppression (OFS) and be treated according to postmenopausal patients with endocrine agents and CDK4/6 inhibitor:

- Palbociclib,
- Ribociclib, or
- Abemaciclib.

- When Tamoxifen is combined with OFS, the choice of CDK4/6 should not be Ribociclib, because of the risk of QT prolongation.
- CDK4/6 inhibitor without OFS has not been tested.
- CDK4/6 inhibitor should not be used if the patient declines OFS.
- Tamoxifen is the only available endocrine option for premenopausal women who decline ovarian suppression or ablation (OFS/OFA).

Ovarian Function Suppression (OFS)

- As all endocrine interventions for premenopausal patients with endocrine-responsive MBC require indefinite OFS, choosing one method over the other requires a balance of the patient's wish for potentially preserving fertility and compliance with frequent injections over a long period of time.
  - Adequate OFS can be obtained through:
  - Bilateral oophorectomies,
  - Continuous use of LHRH agonists or
- Ovarian function ablation through pelvic radiotherapy (this is not always effective and therefore is the least preferred option).

(1) Bilateral oophorectomies:

Ovarian ablation by laparoscopic bilateral oophorectomy ensures definitive estrogen suppression and contraception, avoids potential initial tumor flare with LHRH agonist.

(2) LHRH agonists:

If an LHRH agonist is used in this age group (premenopausal women), it should usually be given monthly to optimize OFS.

Physicians should be alert to the possibility of incomplete ovarian suppression with GrHa.

Thus, the efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered.

Patients should be informed on the options of OFS/OFA, and the decision should be made on a case by case.

Endocrine treatment in postmenopausal patients with MBC

CDK4/6 inhibitors in combination with AI or Fulvestrant [preferred]

- CDK4/6 inhibitors are recommended as first-line and/or second-line therapy in combination with AI or Fulvestrant.

- Clinical studies in both first-line and second-line therapy have shown that this combination in a patient with HR+, HER2 negative breast cancer can double PFS and produce response rate comparable if not better to single-agent chemotherapy, in the 40% to 50% range.
- The 3 currently approved and available CDK4/6 inhibitors are:
  - Palbociclib,
  - Ribociclib, and
  - Abemacilib.
- They all show similar benefit in term of PFS and HR magnitude. Therefore, there is no indication to which one to use and physician choice between them may depend on their local availabilities and side effects profile.

Endocrine Therapy Alone

- ET alone remains an option because there has not been a clear impact on survival yet demonstrated, even though recent updates on trial suggest a trend.
- Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, though it has not been assessed in randomized trials.

Everolimus

- Everolimus can be used as the second line or beyond after progression on a CDK4/6 inhibitor. Tamoxifen or Fulvestrant can also be combined with Everolimus.
- However, the prolonged PFS without OS, for Everolimus was not tested after progression on CDK4/6 inhibitor patients.
- There are no data yet on the use of Everolimus post progression on CDK4/6 inhibitors.
- The decision to use Everolimus must take into account the toxicities associated with this therapy, such as:
  - Lack of statistical significant OS benefit,
  - Cost and
  - Availability.
- Everolimus and CDK4/6 inhibitors **should not** be used after disease progression on that specific agent (i.e., beyond progression).

Other Options

- Other available options include:
  - AI,
  - Tamoxifen,
  - Fulvestrant,
  - AI/Fulvestrant,
  - Abemaciclib single agent in CDK4/6 naïve patient,
  - AI/tamoxifen.

- In later lines, also megestrol acetate and estradiol, as well as repetition of previously used agents, may be used.

- It is currently unknown how to compare the different combinations of endocrine plus targeted agents with each other and with single-agent CT, the trials are ongoing.

N.B. Due to the rapid adoption of CDK inhibitor therapy in first- and second-line ET over the past 4 years, the natural history of the disease after progression on therapy has not been well defined. Many clinical trials are ongoing that are testing several strategies in patients with progression after CDK4/6 based therapy, and we expect management options of ER+ MBC will change and evolve rapidly.

PI3CA mutant ER+ve

Alpelisib added to Fulvestrant

- According to SOLAR1 trial:
  - Alpelisib 300 mg QD added to Fulvestrant
  - In endocrine resistant, PI3CA mutated ER+ MBC
  - Benefited by 5 months in the term of PFS.

Chemotherapy for HR+ve/HER2-ve MBC

Upfront chemotherapy in HR +ve MBC is indicated in case of visceral Crisis:

- It is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of the disease.
- A visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

Treatment Options:

(1) Sequential monotherapy is the preferred choice for MBC.

(2) Combination CT should be generally avoided and only used for patients with good PS and have:

- Rapid clinical progression,
- Life-threatening visceral metastases or
- Need for rapid symptom and/or disease control

N.B. There is no improvement in OS for combination CT, added to the increased toxicity.

HER2 Negative MBC

In the absence of medical contraindications or patient concerns

- Anthracycline or Taxane-based regimens when they are not used earlier.
- Other options are, however, available and effective, such as Capecitabine and Vinorelbine, particularly if avoiding alopecia is a priority for the patient.

In patients with Taxane-naive and Anthracycline-resistant MBC or
Patients with Anthracycline maximum cumulative dose or toxicity (i.e., cardiac)

- Taxane-based therapy, preferably as a single agent, is considered the treatment of choice

In patients pre-treated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane

- Single-agent Capecitabine, Vinorelbine, or Eribulin are the preferred choices.
- Additional choices include Gemcitabine and platinum agents.
- The decision should be individualized and take into account the different toxicity profiles, previous exposure, patient preferences, and availability.

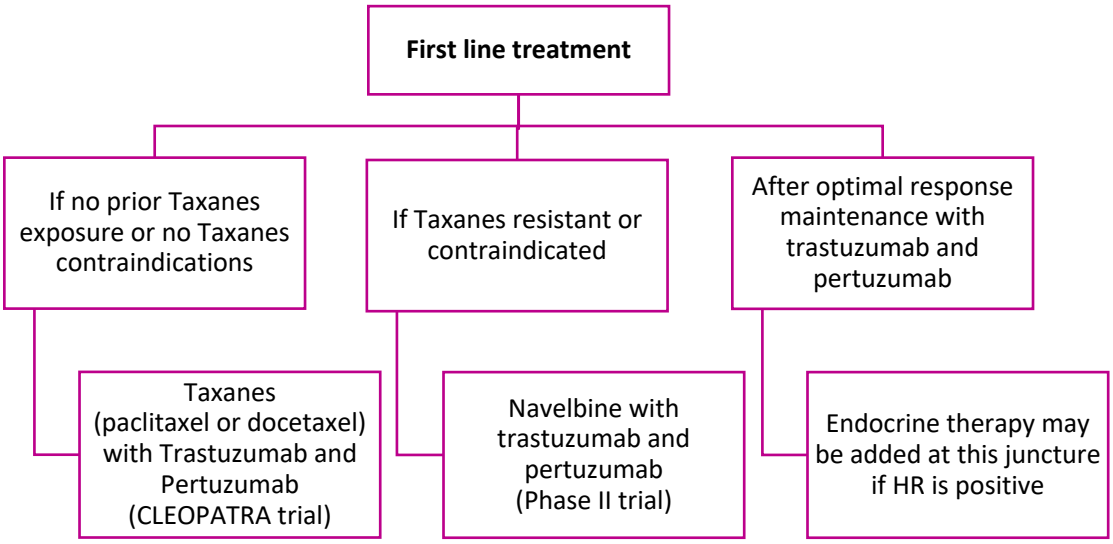
Duration of each regimen and number of regimens should be tailored to each individual patient.

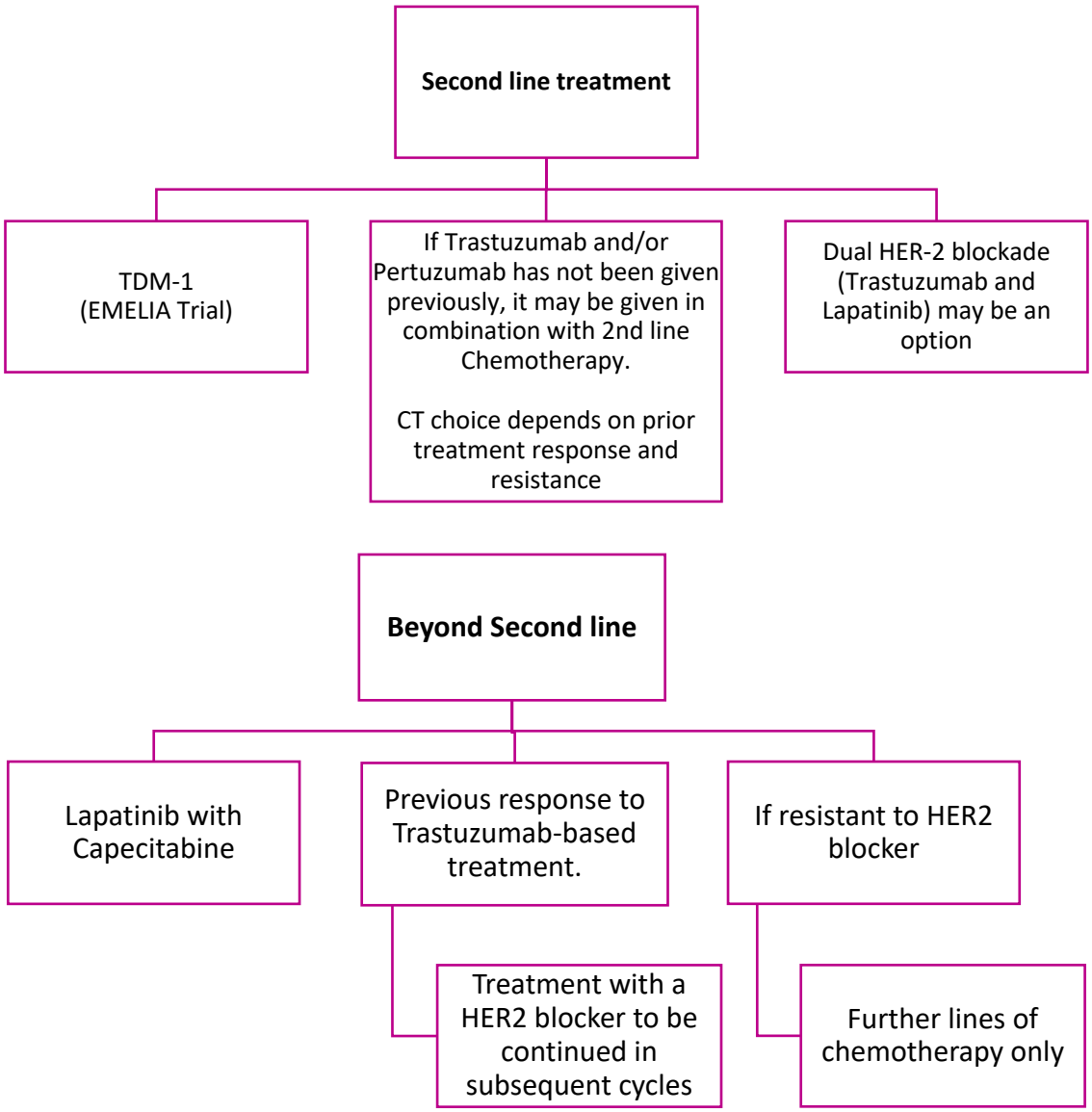
Usually, each regimen (except Anthracyclines) should be given until progression of the disease or unacceptable toxicity. What is considered unacceptable should be defined together with the patient.

Special Considerations:

- If **Taxane** was given in the adjuvant setting and there has been at least one year of disease-free survival, a taxane can be reused as 1st line therapy.
- In case of allergy/hypersensitivity to Paclitaxel then Nab Paclitaxel can be an option.
- Alternatives are Capecitabine or Eribulin depending upon patient preference and side effect profile.
- If **Anthracyclines** were given in the adjuvant setting, provided that the maximum cumulative dose has not been achieved and that there are no cardiac contraindications, anthracyclines can be re-used in MBC, particularly if there has been at least one year of disease-free survival.
- **Metronomic chemotherapy** is a reasonable treatment option in the triple negative for patients not requiring rapid tumor response.
- The better-studied regimen is CM (low dose oral cyclophosphamide and methotrexate); other regimens are being evaluated (including capecitabine and vinorelbine).

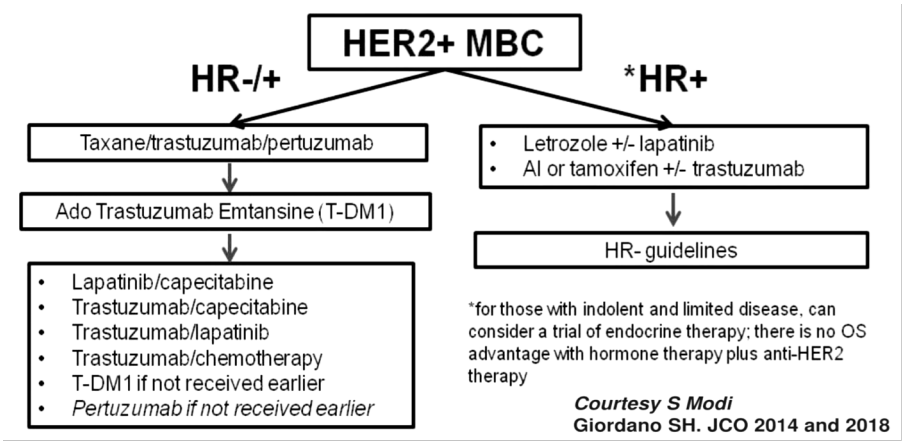
HER2 Positive Breast Cancer





ER/PR Positive and HER2 Positive

If limited metastatic disease, addition of anti-HER2 agents (Trastuzumab and Lapatinib) to endocrine therapy is an option.



Triple Negative / Basal Phenotype BC

(1) Non-BRCA-associated advanced TNBC

- There are no data supporting different or specific CT recommendations.
- Therefore, all CT recommendations for HER2-negative disease also apply for advanced TNBC.

(2) Advanced TNBC patients (regardless of BRCA status)
previously treated with anthracyclines +/- taxanes in the (neo)adjuvant setting

- Carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.

(3) BRCA-associated advanced TNBC or endocrine-resistant MBC
previously treated with anthracycline +/- taxane (in the adjuvant and/or metastatic setting)

- A platinum regimen is the preferred option, if not previously administered.

(4) BRCA-associated advanced TNBC or luminal (after progression on ET) MBC

- A PARPi (Olaparib or Talazaparib) is a reasonable treatment option
- PARPi is associated with:
  - PFS benefit,
  - Improvement in QoL and
  - Favorable toxicity profile.
  - OS results are awaited. (OlympiAD and EMBRACE trial).
- These patients were previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting).
- It is unknown how PARPis compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumors.

The Androgen Receptor (AR) is a potential target in advanced TNBC. There are, however, no standardized methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide. At this time, these agents should not be used in routine clinical practice.

PDL-1 Positive TNMB

Atezolizumab (Tecentriq) plus the chemotherapy nab-paclitaxel (Abraxane)

- On March 2019, FDA granted this regimen accelerated approval for:
  - First line treatment of unresectable locally advanced or metastatic, PDL-1 positive triple negative breast cancer (TNBC).
- The approval was based on IMPASSION 130 trial.
  - Median PFS compared to standard chemotherapy plus placebo in the PDL-1 positive was 7.5 vs 5.0m (HR= 0.62, 95% CI, 0.49 - 0.78, p< 0.0001).
  - Median OS improved 25 vs 15.5 months (HR= 0.62, 95% CI, 0.45 - 0.86).

PDL-1 Negative TNMB

General Considerations:

- The treatment options are more or less the same as the chemotherapy in HR-positive MBC.
- The addition of Bevacizumab may be considered as it has shown a better RR and PFS, but there was no difference in OS (ECOG2100, AVADO, RIBBON-1, and RIBBON-2 trials) provided that response is the endpoint, i.e., A higher response rate is needed.
- Combination chemotherapy, e.g., Carboplatin and Gemcitabine, is also an option when a higher response rate is needed.
- There is insufficient evidence that the subtype of chemotherapy matters. Thus, chemotherapy choice depends on the side effect profile and the patient's preference.
- Eribulin can be used earlier than Capecitabine.

The number of Cycles:

Optimal Cycles	A higher number of cycles	Treatment breaks
6 – 9 cycles in responding patients	Increases response rates, but no survival advantage with an increase in toxicity	In patients after optimal response/stable disease

N.B. Response to chemotherapy, side effects, quality of life, and patient preference should be taken into account.

The number of Lines of Chemotherapy:

- Tailored to individual patients.
- Best supportive care is indicated in case of:
  - Failure to achieve response to three consecutive lines of chemotherapy or
  - Deterioration of performance status to 3 World Health Organization (WHO) at any time.
- To continue beyond the third line, chemotherapy is justified in patients with good performance status (PS: 0 – 1) and who responded to previous lines of chemotherapy.

Response Evaluation of Treatment

- Evaluation of response to therapy should generally occur:
  - Every 2 to 4 months for ET or
  - After 2 to 4 cycles for CT,

  The evaluation depends on:
    - The dynamics of the disease,
    - The location and extent of metastatic involvement
    - The type of treatment.
- Imaging of a target lesion may be sufficient in many patients.
- In certain patients, such as those with indolent disease, less frequent monitoring is acceptable.

- Additional testing should be performed in a timely manner, irrespective of the planned intervals if PD is suspected or new symptoms appear.
- A thorough history and physical examination must always be performed.

Follow Up

- Patients with MBC must be seen frequently enough to provide the best possible palliation of symptoms:
  - Every 2 months if on endocrine therapy
  - Every 1-2 cycles of chemotherapy.

Bisphosphonates

Bisphosphonates are indicated for the treatment of hypercalcemia due to malignancy, in patients with clinically evident bone metastases as it delays and reduces skeletal-related events.

- Zoledronic acid (preferred):
  - Given every 3-4 weeks with monitoring of renal functions.
  - The optimal duration of Zoledronic acid is unknown.
    - After 1-2 years, it may be given 2-3 monthly if the disease is stable
- Dental considerations:
  - Examination and preventive dentistry prior to initiation of Zoledronic acid.
  - Avoid invasive dental procedures while the patient is on Zoledronic acid.
- In patients with altered RFT, Denosumab is the preferred option,
- If Denosumab is not available, a dose of Zoledronic acid should be adjusted according to creatinine clearance.
- Denosumab shows a lower rate of skeletal-related events (i.e., pain, fracture, and hypocalcemia) when compared to Zoledronic acid (18.5 vs. 15 months).

BRCA 1 and 2 Mutation

- With the FDA approval of Olaparib, results from genetic testing in the setting of MBC may have immediate therapeutic implications and should, therefore, be carried out as early as possible.
- Genetic testing should be guided by international/national guidelines and may also be considered for all patients with triple-negative disease.
- Genes to be tested depend on personal and family history, however, at present, only germline mutations in BRCA1/2 have any clinical utility and therapeutic impact.
- The OlympiAD trial [52] evaluated the role of PARP inhibitor olaparib monotherapy in 302 patients with:
  - Germline BRCA mutation and
  - Advanced ER-positive/HER2 negative or
  - TNBC, who had received no more than two previous chemotherapy regimens for metastatic disease.

- **The OlympiAD trial:**
  - Treatment was required, if prior platinum was used, no evidence of progression during treatment in the advanced setting or ≥12 months since (neo)adjuvant platinum.
  - The comparator was standard monoCT per physician's choice (capecitabine, eribulin, or vinorelbine). Median PFS was longer in the olaparib group (7.0 versus 4.2 months; HR: 0.58; 95% confidence interval (CI): 0.43–0.80; P < 0.001).
  - At this follow-up time, there were no differences in OS.
  - Toxicity and rate of treatment discontinuation due to side effects were higher in the CT arm, while QoL was significantly better in the olaparib arm.

- **The EMBRACA trial**
  - In the San Antonio Breast Cancer Symposium 2017, the first results of the EMBRACA trial were presented.
  - With a similar design to OlympiAD, this trial evaluated the role of talazaparib in 431 ABC patients with a BRCA mutation, when compared with monoCT per physician's choice (capecitabine, eribulin, vinorelbine or gemcitabine).
  - Most patients had not received prior platinum-based therapy.
  - At a median follow-up time of 11.2 months, PFS was longer in the Talazaparib arm (8.6 versus 5.6 months; HR: 0.54; 95% CI: 0.41–0.71; P < 0.0001)
  - No difference was seen at this time in OS.
  - Quality of life (QoL) was significantly better in the Talazaparib arm.
- While these trials are positive and met their primary endpoint, the benefit seen was less than anticipated.
- Nevertheless, the tolerability of these agents when given as monotherapy, the CT-free approach with improved QoL makes it an attractive option for BRCA-related ABC.
- Further studies are needed to clarify the value of PARP inhibitors in platinum-resistant disease, as well as their value when compared with platinum compounds.

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