Contents
1. **Neo-adjuvant or Primary Medical Treatment** .......................................................... 3
   1.1. Neo-adjuvant or Primary Chemotherapy ............................................................ 3
   1.2. Neo-adjuvant or Primary Endocrine Therapy ....................................................... 4
   1.3. Peri-operative Treatment ................................................................................... 5
2. **Adjuvant Treatment** .............................................................................................. 6
   2.1. Adjuvant Chemotherapy ..................................................................................... 6
   2.2. Adjuvant HER2-targeted therapy ....................................................................... 7
   2.3. Adjuvant Endocrine Therapy ............................................................................. 8
3. **Locally Advanced or Metastatic Disease** ............................................................. 13
   3.1. Diagnosis ............................................................................................................. 13
   3.2. Management principles ...................................................................................... 13
   3.3. Endocrine treatment .......................................................................................... 14
   3.4. Chemotherapy (and Targeted Therapy) ............................................................... 14
   3.5. Organ-specific treatment .................................................................................... 17
Appendix 1: **Chemotherapy Regimens for Early Breast Cancer** .......................... 19
   Chemotherapy ........................................................................................................... 19
   HER2-targeted therapy .............................................................................................. 20
Appendix 2: **Chemotherapy Regimens for Metastatic Breast Cancer** .................. 24
   Chemotherapy ........................................................................................................... 24
   HER2-targeted therapy .............................................................................................. 26
   Intrathecal therapy .................................................................................................. 27
Appendix 3: **Supportive Care** ................................................................................... 28

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1. Neo-adjuvant or Primary Medical Treatment

(See NICE Clinical Guideline 80, 2009)

- All patients are to be discussed by an MDT
- MDT recommendation must be available in clinic to discuss with patient
- Breast Care Nurse should be available for discussion (and/or for follow-up of discussion)
- Appropriate clinical trials should be discussed (and outcome recorded in trial screening log).

1.1. Neo-adjuvant or Primary Chemotherapy

Indications:
1. Inoperable locally advanced (LABC) breast cancer to permit later surgery
2. Inflammatory breast cancer
3. Large tumour relative to the size of the breast to facilitate breast conserving surgery

- Neo-adjuvant chemotherapy should not routinely be used when a cosmetically and oncologically satisfactory outcome can be achieved with initial surgery.
- Breast surgery for local control following initial chemotherapy may be appropriate for patients with limited-volume metastatic disease.

Treatment intent:
- The treatment intent and post-treatment surgical plan must be determined by the MDT and clearly documented

Pre-treatment assessments:
- All patients undergoing neo-adjuvant systemic treatment should have axillary nodal status determined prior to starting treatment.
  - Axillary U/S (+ core biopsy/ FNAC if nodes are suspicious)
  - Sentinel node biopsy where U/S ± core/ FNAC are normal
- Patients undergoing neo-adjuvant chemotherapy should ordinarily be staged if the tumour is locally advanced or inflammatory (T3-4), or if there are involved lymph nodes determined by U/S and core/ FNAC.
- A marker clip should be inserted to identify the tumour bed. This is particularly important for those patients thought likely to achieve a complete clinical response e.g. with HR –ve or smaller tumours especially where there is no microcalcification.
- The choice of imaging modality to determine treatment response should be made by the MDT on the basis of pre-treatment imaging assessment – e.g. MRI is preferred for diffuse tumours whilst ultrasound is satisfactory for well visualised and well circumscribed tumours

Monitoring treatment:
- All patients undergoing neo-adjuvant treatment must have regular review of tumour response. Ultrasound is the most practical imaging technology for on-treatment tumour response monitoring.
Post chemotherapy management:

- The timing and extent of surgery (or radiotherapy) should be discussed by the MDT following end of chemotherapy response assessment.
- Surgery should be performed if possible, normally 4-6 weeks from the final chemotherapy administration. Breast radiotherapy for local control once maximum response has been achieved, can be considered if surgery is not possible.
- Patients with positive axillary lymph nodes at pre-treatment assessment will need clearance at the time of definitive local surgery.
- Following surgery histology should be reviewed in the MDT and recommendation re further treatment and follow-up made.
- The role for post-operative chemotherapy in patients who have received neo-adjuvant chemotherapy and who remain node positive is unclear. There are currently no clinical trials to address this. Where both anthracyclines and taxanes have been used pre-operatively there is probably no role for further chemotherapy.
- Radiotherapy and endocrine therapy should be given as per guidelines.

Treatment Regimens:

- Docetaxel-FEC100
- Paclitaxel 2-weekly-EC90
- FEC100-Docetaxel ± Trastuzumab
- EC90-Docetaxel ± Trastuzumab

Trastuzumab should be given concurrently with taxane following completion of anthracycline for HER2 positive tumours.

1.2. Neo-adjuvant or Primary Endocrine Therapy

Indications:

1. For the down-staging of primary breast cancer to enable breast conserving surgery (usually for post-menopausal patients with low-grade and HER2 –ve tumours or who are not suitable for chemotherapy)
2. To render inoperable locally advanced disease operable or amenable to radiotherapy
3. Inflammatory cancer in elderly patients or those not fit for chemotherapy
4. For disease control in patients who are unfit for surgery or for who surgery needs to be delayed

Breast surgery for local control after a period of primary endocrine therapy may be appropriate for patients with limited-volume metastatic disease.

Treatment intent:

- The treatment intent and post-treatment surgical plan must be determined by the MDT and clearly documented

The following may not apply to patients where the treatment intent is disease control and assessments will not result in a change of management.

Pre-treatment assessments:

- Patients undergoing neo-adjuvant systemic treatment should have axillary nodal status determined by Axillary U/S (+ core biopsy/ FNAC if nodes are suspicious).
• Patients with positive axillary lymph nodes will need clearance at the time of definitive local surgery.
• Patients undergoing neo-adjuvant endocrine therapy treatment should undergo staging to exclude metastatic disease where the tumour is locally advanced (T3-4) or where there is overt nodal involvement.
• The choice of imaging modality to determine treatment response should be made by the MDT on the basis of pre-treatment imaging assessment.

Monitoring treatment:
• All patients undergoing neo-adjuvant endocrine treatment must have regular review of tumour response and discussion in MDT regarding timing/extent of surgery (or radiotherapy). Ultrasound is the most practical imaging technology for on-treatment tumour response monitoring.
• Patients should be reviewed 6 weeks after starting treatment to exclude early progression and thereafter at least every 3 months. (Applies irrespective of treatment intent.)
• The optimal duration of treatment is not established. Meaningful response is unusual in less than 3 months. There is a significant risk of acquired resistance when the duration of treatment exceeds 12 months.

Surgical and post-surgical treatment:
• Consideration should be given to sentinel node biopsy at the time of definitive surgery for patients with unknown axillary nodal status to limit the number of surgical procedures. There is no evidence on the optimal timing of sentinel node procedures for patients treated with neo-adjuvant endocrine therapy.
• Post-surgical treatment (continuation endocrine therapy, radiotherapy and possibly chemotherapy) should be given as per guidance.

Treatment Regimens:
• Letrozole 2.5mg PO OD (post-menopausal)

1.3. Peri-operative Treatment
• Peri-operative treatment has no proven benefit and is a research tool
2. Adjuvant Treatment

(See NICE Clinical Guideline 80, 2009)

- All patients are to be discussed by an MDT
- MDT recommendation must be available in clinic to discuss with patient
- Breast Care Nurse should be available for discussion (and/or for follow-up of discussion)
- Appropriate clinical trials should be discussed (and outcome recorded in trial screening log).
- Adjuvant Online (AoL) (www.adjuvantonline.com) is recommended to support estimates of individual prognosis and the absolute benefit of adjuvant treatment over a ten-year period. Other prognostic tools e.g. PREDICT plus (www.predict.nhs.uk/predict.shtml) provide similar information
- Nottingham Prognostic Index (NPI) may be used to estimate prognosis but does not predict treatment benefit.

2.1. Adjuvant Chemotherapy

- Discuss chemotherapy with patients with:
  - HR -ve (i.e. ER –ve and PR –ve) breast cancer
  - HER2 +ve breast cancer
  - HR +ve breast cancer where benefit of chemotherapy in addition to endocrine therapy estimated as >3% increase in 10-year overall survival by AoL/ PREDICT).
- Discussion should be based on:
  - Risk or relapse/mortality
  - Co-morbidity
  - Patient preference
- Risk of long-term complications should be considered when selecting chemotherapy regimen – e.g. limit or avoid anthracycline exposure for patients with hypertension and LV hypertrophy, use taxanes cautiously for patients with diabetes at risk of peripheral neuropathy.
- Oncotype DX tests may be used to aid chemotherapy decisions for patients with pN0 HR +ve HER2 –ve tumours with NPI score >3.4 subject to availability of funding; chemotherapy is recommended for all patients with Recurrence Score > 25
- Chemotherapy should be started within 31 days of the decision to treat and given prior to radiotherapy and endocrine therapy (where these are indicated).
- Advice re wigs, scarfs etc should be available at initial consultation.
- Pre-menopausal women should be given advice concerning menopause and if appropriate, the risk of infertility and should be given the opportunity of fertility preservation at or before the initial chemotherapy consultation.
- Where anthracycline use is planned, all patients should have a base-line cardiac history taken; ECG and formal measurement of ejection fraction should be performed if there is a cardiac history or significant cardiac risk factors including age >65
Treatment Regimens (HER2 –ve disease)

A. High risk patients
   - Triple Negative disease: stage: pT ≥1c, pN any, G any
   - HR +ve HER2 –ve disease: stage: pT any, pN ≥1, G3
     - pT3, pN0, G3
     - pT any, pN ≥1 G1-2 with AoL 10 yr mortality risk >35% (c.3% marginal benefit for taxane - chemotherapy vs anthracycline alone)

   - **FEC100-Docetaxel**

B. Medium risk patients
   - ER+ve HER2 –ve disease: stage: pT2 pN0 G3
     - pT2-3 pN1 G1-2 with AoL 10 yr mortality risk 15-35% (chemotherapy benefit of c.≥3% vs no chemo)

   - **FEC75** } choice between FEC75 & FEC100 depends on fitness/age
   - **FEC100** }

C. Special Circumstances
   a. High risk patients unsuitable for FEC-Docetaxel (e.g. less fit, prior anthracycline treatment)
      - **Docetaxel cyclophosphamide** (TC) x4 (consider 6 cycles for fit patients with prior anthracycline treatment)

   b. Reduced intensity treatment for unfit patients
      - **AC x4**
      - **CMF**

2.2. Adjuvant HER2-targeted therapy

   - Patients with HER2/erbB2 positive tumours (IHC 3+ or ISH positive in accredited laboratory) should be considered for adjuvant Trastuzumab 3 weekly combined with chemotherapy where the tumour stage is
     - pT any, pN ≥1
     - pT ≥1c, pN 0
     - pT1b, pN0 AND additional risk factors (G3 OR HR –ve)
   - The duration of trastuzumab treatment is for 1 year.
   - All patients considered for HER2 targeted therapy must undergo initial cardiac assessment (history, ECG, formal measurement of left ventricular function) with regular on-treatment monitoring as detailed in appendix 1
   - A taxane containing chemotherapy regimen should be considered for all women undergoing HER2 targeted therapy for reasons of efficacy and to limit cardiac risks from anthracycline exposure
- Endocrine treatment should be offered to all women with HR +ve disease; treatment should be concurrent with targeted therapy and started following completion of chemotherapy
- Radiotherapy should be given as per guidelines but concurrent with targeted therapy

**Treatment Regimens (HER2 +ve disease)**
- FEC100-Docetaxel + Trastuzumab (to start with docetaxel)
- Docetaxel+Carboplatin + Trastuzumab (TCH) (unsuitable for anthracycline)
- Docetaxel+Cyclophosphamide + Trastuzumab (less fit patients)
- Trastuzumab monotherapy following anthracycline chemotherapy

### 2.3. Adjuvant Endocrine Therapy
- All patients with HR +ve (ER +ve and/or PR +ve defined as Allred/Quick Score ≥3) breast cancer should be offered adjuvant endocrine therapy.
  - The benefit of adjuvant endocrine therapy is not clear for patients with borderline HR +ve disease
- The duration of endocrine therapy should be at least 5 years; consideration should be given to extending the treatment duration to up to 10 years for women with a significant risk of late relapse (e.g. node +ve disease) paying due regard to the potential harms of treatment.
- Patients should be advised at the start of treatment of the likely planned duration of endocrine treatment, accepting that this may change as new evidence becomes available. The clinician reviewing the patient should ensure appropriate cessation of treatment.
- For patients on endocrine therapy beyond 5 years a designated local clinician must be responsible for monitoring and cessation.
- Endocrine therapy is started after chemotherapy (if given) but may be given concurrently with anti-HER2 therapy.
- Endocrine therapy should not be delayed for radiotherapy

#### 2.3.1. Pre-menopausal Women
- Tamoxifen 20 mg/day should be offered to all patients for at least 5 years
- If chemotherapy is indicated (but declined) or is of low predicted benefit consider ovarian suppression/ablation. The optimal duration of ovarian suppression is uncertain (current evidence supports 2-3 years but there are theoretical grounds to believe that longer may be superior).
- Goserelin 3.6 mgs s/c q 28 days is recommended (the three monthly preparation is not licensed and oestradiol levels may rise towards the end of 3 months).
- The benefit of ovarian suppression in addition to tamoxifen is not established in women who maintain menses following chemotherapy although there is indirect evidence to support this. It may be discussed, particularly with younger women (<40) in the light of available data.
• Aromatase inhibitors should not be prescribed for women undergoing ovarian suppression as standard treatment.

2.3.2. Post-menopausal Women

• All post-menopausal women with ER +ve and/or PR +ve breast cancer should be considered for an aromatase inhibitor as part of their adjuvant endocrine treatment.
• Available options include:
  o Up-front AI
  o Tamoxifen 2-3 years then switch to AI.
  o AI for 3-5 years in women who have completed 5 years of Tamoxifen.
• The recommendation will depend on:
  o Risk (AI “upfront” preferred in high risk disease)
  o Co-morbidity (e.g. osteoporosis, history of venous thromboembolism etc) that may favour one agent.
  o Patient preference
• Patients with very good prognosis disease (e.g. NPI score ≤3.4 with predicted 10-year survival >93%) may be treated with tamoxifen alone.
• Women receiving AI therapy who require vaginal oestrogens for atrophic vaginitis should be treated with low-strength preparations (e.g. estriol 0.01%) and for limited duration or switched to tamoxifen with which topical estrogens pose no risk..

2.3.3. Women with uncertain menopausal status

• Definition of menopause
  o Age ≥ 60
  o Bilateral surgical oophorectomy
  o Age 45-59 years and > 1 year natural amenorrhoea
  o Age < 45 years and amenorrhoea > 5 years
  o For amenorrhoea not fulfilling the above criteria including hysterectomy without bilateral surgical oophorectomy age <60, then FSH, LH and oestradiol must be assayed to confirm postmenopausal status according to local guidelines.
• Women who are peri-menopausal naturally should NOT be given AI until such time as menopause is established as defined above.
• The diagnosis of menopause in women who have undergone or are undergoing systemic anticancer treatment should be made with great caution:
  o Ovarian function may recover up to 2 years after completion of chemotherapy.
  o Tamoxifen may suppress menstruation, especially following chemotherapy.
  o Biochemical tests of ovarian function can be misleading, especially for women treated with tamoxifen.
• If a switch from Tamoxifen to an AI is considered for a woman with uncertain menopausal status then the patient must be advised of the risk of resuming menses. FSH, LH and oestradiol should be checked 6 months after starting an AI to ensure that the patient is still postmenopausal as return of ovarian function is not always associated with resumption of menses.
Treatment
- Anastrozole 1mg OD (post-menopausal)
- Letrozole 2.5mg OD (post-menopausal)
- Exemestane 25mg OD (post-menopausal)
- Tamoxifen 20mg OD (pre- and post-menopausal)
- Goserelin 3.6mg SC monthly (pre-menopausal)

2.3.4. Bone Health
- After menopause a reduction in bone mineral density occurs at a rate that can be as high as 5% per year for the first 3 years reducing to about 0.5% annually. All aromatase inhibitors are associated with significant bone loss related to further oestrogen deprivation, and an increased risk of osteoporosis and fracture rate compared with either tamoxifen or placebo. Currently no therapies are approved specifically for preventing cancer treatment induced bone loss in patients receiving adjuvant therapy for breast cancer.
- Pre-menopausal women treated with ovarian suppression and those experiencing premature menopause as a result of chemotherapy are also at increased of developing osteoporosis.
- Bone health for patients treated with an AI should be managed according to the NCRI guidelines (http://ncrndev.org.uk/downloads/csg/Bone%20Health%20Guidelines%20-%20FINAL.pdf)
- Patients starting on AI should have a baseline bone mineral density assessment within 3 months of starting an AI.
  - This result should be communicated to the patient and the GP with appropriate advice regarding management of bone health in primary care.
  - If BMD is normal then further routine assessment of BMD during adjuvant therapy is not required.
  - For patients with osteoporosis or at risk of osteoporosis, appropriate treatment should be initiated with monitoring of BMD according to the Bone Health Guidelines.
There are 2 algorithms to follow as shown:

**Algorithm 1: For Women who Experience Premature Menopause due to Chemotherapy or Ovarian Suppression, Ablation or Removal** (taken from NCRN Guidelines)
Algorithm 2: Postmenopausal Women Receiving an AI (adapted from NCRN Guidelines)

Algorithm for assessment of bone health in patients with breast cancer who are started on an aromatase inhibitor

- Age
  - ≥ 75
  - < 75

Risk factor assessment
- Previous fragility #
- Parental history of fragility #
- BMI < 22
- Alcohol > 4 units/day
- Premature menopause
- Rheumatoid arthritis
- Ankylosing spondylitis
- Crohn’s disease
- Immobility
- Oral steroids

RF assessment

DEXA

T ≤ -2.0 HIGH RISK
-2.0 < T > -1.0 MEDIUM RISK
T ≥ -1.0 LOW RISK

Lifestyle advice
- Adcal D3 x2/day
- Alendronate 70mg weekly
- Repeat DEXA two years
- No further DEXAs

Blood tests to exclude secondary osteoporosis
- FBC
- UE
- LFT
- Bone profile
- TFT
- Vitamin D

Treat underlying cause as appropriate

Vitamin D replacement
- Deficiency (<30)
  - Load with colecalciferol 100,000 IU OD for 2/7
  - Or ergocalciferol 300,000 IU IM stat
  - Maintenance colecalciferol 1000 IU OD (≥25mg)
- Insufficiency (30-80)
  - Treat as per maintenance

Lifestyle advice
- Healthy diet: Adequate dietary calcium (700mg/day) and Vitamin D intake (400IU/day)
- Sun exposure (10 mins to face + arms twice/day in summer months)
- Weight-bearing exercise (30 mins three times/week)
- Smoking cessation
- Reduce caffeine intake
- Measures to reduce falls risks
3. Locally Advanced or Metastatic Disease

*(See NICE Clinical Guideline 81, 2009)*

- A specific Metastatic MDT should be established to support patient management.
- Patients should have access to a Breast Care Nurse trained in the management of patients with metastatic disease.
- Consideration should be made as to appropriate access to benefits and supportive/palliative care as early as possible to ensure seamless care.

3.1. Diagnosis

3.1.1. Imaging

- CT scan to assess lung/liver/other visceral metastases
- Isotope bone scan to assess extent/presence of metastases (in some patients CT with bone windows may be sufficient).
- Additional bone imaging (plain films or MRI) to evaluate local problems eg to assess fracture risk, or early spinal cord compression.
- MRI with contrast (preferred) or CT with contrast for suspicion of brain metastases.
- PET CT is an adjunct to conventional staging in case of diagnostic uncertainty (eg solitary lung lesion)

3.1.2. Pathology

- Ensure ER/PR/HER2 status is known from original biopsy.
- Consider biopsy of metastasis to re-evaluate receptor status, as this may change on recurrence. Biopsy may be especially valuable where original receptor status is uncertain or unavailable, or where the disease-free interval is long. N.B. Receptor determination on de-calcified bone biopsy is not considered reliable.

3.2. Management principles

- In selecting systemic treatment, consider:
  - Treatment history
  - Endocrine responsiveness
  - HER2 status
  - Performance status
  - Disease-free interval
  - Disease-burden
  - Threat from visceral disease
  - Co-morbidity
  - Patient preference
- An attempt at initial endocrine treatment should be made for hormone receptor positive disease that is not immediately life threatening because of extensive visceral disease. In situations where a faster response is desired or a response to endocrine treatment is unlikely, chemotherapy should be considered.
- Endocrine treatment should be given until there is evidence of disease progression.
Whenever possible patients should be considered for entry into clinical trials.

Patients should ordinarily undergo staging (usually CT scan, isotope bone scan) to assess disease at the start of a new course of treatment.

Patients should undergo periodic re-staging to assess disease response to treatment. Re-staging intervals will vary with disease aggressiveness and treatment type.
  - CT is preferred in most situations for visceral and soft-tissue disease. Isotope bone scan is not reliable for assessing response.
  - Patients treated with chemotherapy should have staging repeated after 3 cycles and on completion of the planned course of treatment.
  - Patients on maintenance or open-ended treatment (e.g. endocrine therapy) should have re-staging performed after 3 months and at intervals dictated by clinical assessment. CT scans should be repeated at least every 12 months. Bone scans should normally be performed every 6-12 months.

3.3. Endocrine treatment

Most patients with ER positive breast cancer will be offered endocrine treatment, either as sole initial treatment or as maintenance treatment following chemotherapy.

There is little evidence for what order endocrine treatments should be used other than non-steroidal AI’s are preferred as the initial treatment in post-menopausal women. A suggested schema is shown below.

**Treatment Options: Pre-menopausal women**
- **Tamoxifen** 20mg OD alone or in combination with Goserelin (preferred)
- **Goserelin** 3.6mg SC monthly

**Post-menopausal treatment options in combination with Goserelin**

**Treatment Options: Post-menopausal women**
- **Non-steroidal AI: Anastrozole** 1mg OD or **Letrozole** 2.5mg OD (initial treatment for post-menopausal women if not previously used or re-challenge appropriate)
- **Tamoxifen** 20mg OD (following NSAI if not previously used or re-challenge appropriate)
- **Fulvestrant** 500mg q4weeks with loading dose
- **Exemestane** 25mg OD alone or in combination with **Everolimus** 10mg daily (*funded by CDF*)
- **Megesterol acetate** 160mg OD or **Medroxyprogesterone Acetate** 100mg TDS (use following other options)

3.4. Chemotherapy (and Targeted Therapy)

The choice of regimen will depend on prior treatment and co-morbidity.

Chemotherapy is offered to patients with endocrine non-responsive disease and to potentially endocrine sensitive disease with early/aggressive relapse, or on failure of endocrine treatment.
In most situations serial single agents are preferred to multi-agent combinations. While combination chemotherapy can achieve a higher response rate this is usually with only a modest survival advantage and with more toxicity.

Treatment duration is traditionally 6 cycles. Treatment until progression/ intolerance is an option for well-tolerated drugs such as capecitabine, vinorelbine and weekly paclitaxel and should be considered especially where there is no option for post-chemotherapy maintenance such as endocrine therapy or trastuzumab.

In general:
- Anthracycline naïve: consider anthracycline unless contra-indicated.
- Anthracycline pre-treated: consider taxane-based regimen unless contra-indicated.
- Anthracycline/taxane pre-treated: consider taxane re-challenge unless contra-indicated, or non-taxane based treatment

Treatment options are considered separately according to tumour receptor status: namely HR +ve and HER2 –ve; HR –ve and HER2 –ve (Triple Negative); HER2 +ve and any HR status

A. Suggested Scheme for HR +ve HER2 -ve Disease requiring Chemotherapy:

First Line in Anthracycline Naïve Patients:
- EC75

Second Line (or first line for those patients who have already received a prior anthracycline) AND are more than 1 year after receiving a taxane in the (neo)-adjuvant setting.

If patients relapse within 1 year of a (neo)-adjuvant taxane treatment should be with a ‘third line’ agent:
- Docetaxel (NICE approved)
- Weekly paclitaxel

Other options
- Docetaxel+Capecitabine (NICE approved) – may be used for young fit women with life-threatening disease but significantly toxic – caution advised)
- Paclitaxel+Gemcitabine (NICE approved) - evidence for superiority to paclitaxel monotherapy is conflicting – not recommended

Third/Fourth/Fifth Line:
All of these regimens can be used in sequence; there is no clear evidence to support the order in which they should be used.
- Capecitabine (NICE approved)
- Vinorelbine (NICE approved)
- Eribulin (funded by CDF)

Later lines of treatment:
- 3M
- Oral (metronomic) CM
- CMF
B. Suggested Scheme for HR -ve HER2 -ve (Triple Negative) Disease
Follow the scheme for HR +ve HER2 –ve disease, but consider the early use of platinum containing regimens

- Carboplatin+Gemcitabine
- MVP

Other options
- Paclitaxel weekly + bevacizumab *(funded by CDF)* – evidence to support its use is controversial in this group of patients – not recommended

C. Suggested Scheme for HER2 +ve Disease
The use of trastuzumab in combination with chemotherapy as first-line therapy is associated with an overall survival benefit. This probably applies to patients who have received prior trastuzumab in the adjuvant setting.

Pertuzumab is licensed for use in combination with *intravenous* trastuzumab and docetaxel for first line treatment of metastatic breast cancer.

HER2 targeted therapy is normally continued after completion of chemotherapy until disease progression.

Available evidence supports the use of a second line of trastuzumab in combination with chemotherapy beyond disease progression (not supported by NICE).

**First/ Second Line:**
All of these regimens are well-established chemotherapy-trastuzumab combinations. The choice of regimen will depend on prior treatment history and patient fitness. Trastuzumab should be continued following chemotherapy until disease progression; the development of brain metastases as an isolated event does not constitute disease progression.

- Docetaxel + Trastuzumab
- Docetaxel + Trastuzumab (IV ONLY) + Pertuzumab *(first line use only)* – *(to be funded by CDF)*
- Paclitaxel weekly + Trastuzumab
- Vinorelbine + Trastuzumab
- Capecitabine + Trastuzumab *(when capecitabine + lapatinib is not planned)*

**Post Trastuzumab:**
- Capecitabine + Lapatinib *(funded by CDF)*

**Post Anti-Her2 Therapy:**
Select from regimens for HER2 –ve disease. It is recommended to leave a gap of 6 months if possible between discontinuation of trastuzumab and initiation of potentially cardiotoxic chemotherapy regimens.

**Patients with HR +ve disease:**
For patients with HR +ve HER2 +ve disease who are not suitable for chemotherapy regimens (including capecitabine + trastuzumab), there is evidence that combining anti-HER2 therapy and an AI is more effective than an AI alone.

- **AI + trastuzumab** (not supported by NICE)

### D. Special Circumstances

#### Frail/elderly patients

The following regimens are particularly suitable for this patient group

- Weekly paclitaxel
- Capecitabine
- Vinorelbine
- 3M
- Oral (metronomic) CM

#### Bone marrow failure or severe liver dysfunction

- Weekly paclitaxel
- Capecitabine
- MVP
- Weekly epirubicin

### 3.5. Organ-specific treatment

#### 3.5.1. Bone metastases

- Bone prophylaxis is recommended for all patients with bone metastases with either regular bisphosphonates or RankL inhibitors (denosumab). The necessity for early treatment for patients with few asymptomatic sites is not clear.
- Treatment should be continued indefinitely. Skeletal-related events are not an indication to stop treatment or to change agent.
- The optimum frequency of administration is not established. Treatment is normally at 3-4 weekly intervals but may be given less frequently. There is some evidence of reduced effectiveness if treatment is given every 16 weeks.
- Patients are advised to take regular calcium/vitamin D supplements (e.g. Calcichew D3 forte or AdCal D3) to prevent hypocalcaemia/secondary hyperparathyroidism.
- Bisphosphonates are nephrotoxic. Renal function should be monitored and dose adjustments made according to manufacturer’s guidelines
- All bisphosphonates and denosumab are associated with a risk of osteonecrosis of the jaw (ONJ). Patients being considered for bisphosphonate treatment are advised to have a dental check-up and complete any required surgical treatment prior to commencing therapy.

### Treatment:

Available treatments are listed in decreasing order of effectiveness.

- **Denosumab 120mg SC q3-4w** (NICE approved subject to local funding arrangement)
- **Zoledronic acid 4mg IV**
- Pamidronate 90mg IV 90mins q3-4w
- Ibandronic acid 50mg PO OD
- Clodronate 800mg PO BD

See appendix 4 for an algorithm on the use of denosumab

3.5.2. CNS metastases
- For solitary/oligo (≤3) brain metastases and stable extra-cranial disease, consider neurosurgery, radiosurgery or other specialised radiotherapy techniques. MRI with contrast is the preferred imaging modality. Patients should be referred to a specialist neuro-oncology MDT (UCLH, BLT)
- For patients with multiple brain metastases whole brain radiotherapy is recommended.
- Consider intra-thecal methotrexate for patients with lepto-meningeal disease and minimal/ stable extra-cranial disease

3.5.3. Pleural effusion
- Consider drainage under ultrasound control for symptomatic pleural effusions.
- If a pleurodesis is considered this should be done in consultation with the chest team, preferably by VATS procedure.

3.5.4. Solitary or Oligometastases
- Consider surgical removal or other local therapy (e.g. radiofrequency ablation of liver or lung metastases) as part of multidisciplinary approach.
Appendix 1: Chemotherapy Regimens for Early Breast Cancer

Note: Multiple versions of some regimens are in use; the descriptions given are the versions used in London Cancer including drug doses, details of administration and supportive care other than anti-emetics. Wherever possible a reference to a clinical trial describing the regimen is given; this may not contain all relevant published efficacy data.

Chemotherapy

**FEC100-Docetaxel** (adjuvant or neo-adjuvant)
- Fluorouracil 500mg/m² IV bolus q21days x3
- Epirubicin 100mg/m² IV bolus
- Cyclophosphamide 500mg/m² IV bolus
  - GCSF SC Prophylaxis OD d2-6

*followed by*
- Docetaxel 100mg/m² IV 1hr 250ml 0.9%NaCl q21d x 3
  - premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)
  - GCSF SC Prophylaxis OD d2-6


**EC90-Docetaxel** (neo-adjuvant)
- Epirubicin 90mg/m² IV bolus q21days x4
- Cyclophosphamide 600mg/m² IV bolus

*followed by:
- Docetaxel 100mg/m² IV 1hr 250ml 0.9%NaCl q21d x 4
  - premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)
  - GCSF SC Prophylaxis OD D2-6


**Docetaxel-FEC100** (neo-adjuvant)
- Docetaxel 100 mg/m² IV 1hr 250ml 0.9%NaCl q21d x 3
  - premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)
  - GCSF SC Prophylaxis OD d2-6

*followed by:
- Fluorouracil 500mg/m² IV bolus q21days x3
- Epirubicin 100mg/m² IV bolus
- Cyclophosphamide 500mg/m² IV bolus
  - GCSF SC Prophylaxis OD d2-6

*Reference*: ARTemis trial http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/artemis/

**Paclitaxel 2weekly-EC90**
- Paclitaxel 175mg/m² IV 3hr 500ml 0.9%NaCl q14d x 4
  - premedication: Dexamethasone 20mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV

*followed by:
- Epirubicin 90mg/m² IV bolus q21days x4
- Cyclophosphamide 600mg/m² IV bolus

**FEC100** (adjuvant)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>500mg/m²</td>
<td>IV bolus</td>
<td>q21days x3</td>
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<tr>
<td>Epirubicin</td>
<td>100mg/m²</td>
<td>IV bolus</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500mg/m²</td>
<td>IV bolus</td>
<td></td>
</tr>
</tbody>
</table>

GCSF SC Prophylaxis OD d2-6


**FEC75** (adjuvant for less-fit/ lower-risk patients)

<table>
<thead>
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<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td>q21days x3</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>75mg/m²</td>
<td>IV bolus</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td></td>
</tr>
</tbody>
</table>

**Docetaxel-Cyclophosphamide (TC)** (adjuvant or neo-adjuvant for anthracycline-pre-treated & less-fit patients)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>75mg/m²</td>
<td>IV 1hr 250ml 0.9%NaCl</td>
<td>q21days x4 (-6)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td></td>
</tr>
</tbody>
</table>

Premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)


**AC** (adjuvant for older/less-fit patients)

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorubicin</td>
<td>60mg/m²</td>
<td>IV bolus</td>
<td>q21days x4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td></td>
</tr>
</tbody>
</table>


**CMF** (adjuvant when taxanes and anthracyclines are contra-indicated)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td>q28days x6</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>40mg/m²</td>
<td>IV bolus</td>
<td>d1,8</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td>d1,8</td>
</tr>
</tbody>
</table>

Folinic acid 15mg PO 6hrly x 6 may be given 24hr after methotrexate oral cyclophosphamide is not used


**HER2-targeted therapy**

It should be noted that sub-cutaneous trastuzumab has recently become available and should be considered for all patients. Even though the current evidence is limited for switching from IV to SC trastuzumab existing intravenous trastuzumab patients can be offered a switch to the sc preparation.
**Trastuzumab** subcutaneous (HER2 +ve disease)

Trastuzumab 600mg/5ml SC over 2-5 min q21days x 18

This is a flat dose regardless of weight. A loading dose is not recommended.
The observation period following the first dose is 6 hours. For subsequent doses patients are observed for 2 hours if no reaction to the previous dose.
Given the limited experience to date with sc trastuzumab the observation period as per the SPC is recommended.

**Trastuzumab** intravenous (HER2 +ve disease)

Trastuzumab 6mg/kg IV 90/30min 250ml 0.9%NaCl q21days x18

1st dose is administered over 90min followed by 4.5 hours observation period
Subsequent doses are over 30min followed by 1.5 hours observation period if no reaction to previous dose
Local policies may vary with regard to the observation period.
There is no pharmacological justification for an initial (loading) dose of Trastuzumab 8mg/kg.

Either formulation of trastuzumab should be started with the first cycle of non-anthracycline chemotherapy (FEC100-Docetaxel or EC90-Docetaxel) and continued for a total 1 year (18 infusions).

Note: Baseline LVEF should be ≥ 50%; this must be assessed prior to treatment with Trastuzumab AND after anthracycline therapy (if given). Cardiac monitoring 3 monthly by ECHO or MUGA scan should be performed. An algorithm for dealing with falls in LVEF is shown in figures 1 & 2.

Even though the current evidence is limited for switching from IV to SC trastuzumab, existing intravenous trastuzumab patients can be offered a switch to the SC preparation.
**Figure 1.** Algorithm for treating falls in LVEF while on adjuvant herceptin (Taken from AFFINITY protocol). N.B. while the same general principles apply for metastatic disease it is not necessary to be so stringent.

**Figure 2.** Traffic Light system for managing changes in LVEF while on anti-HER2 targeted therapy (Taken from Jones et al 2007). N.B. while the same general principles apply for metastatic disease it is not necessary to be so stringent.
FEC100-Docetaxel + Trastuzumab SC or IV (adjuvant or neo-adjuvant)  
<see FEC100-Docetaxel (adjuvant or neo-adjuvant)>

Docetaxel + Carboplatin + Trastuzumab (TCH) (adjuvant or neo-adjuvant when anthracyclines to be avoided)  
Carboplatin AUC5 (EDTA GFR)  IV 1hr 500ml 5%Glucose  q21days x6  
Docetaxel 75mg/m²  IV 1hr 250ml 0.9%NaCl  
Trastuzumab 6mg/kg  IV 90/30min 250ml 0.9%NaCl  q21days x18  
OR 600mg/5ml  SC over 3-5min  
premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)  
NB If CG-GFR is used, Carboplatin is dosed at AUC6  

Docetaxel + Cyclophosphamide (TC) x4 cycles + Trastuzumab SC or IV (adjuvant or neo-adjuvant for less-fit high-risk patients)  
<see Docetaxel-Cyclophosphamide (TC) (adjuvant or neo-adjuvant)>
Appendix 2: Chemotherapy Regimens for Metastatic Breast Cancer

Note: Multiple versions of some regimens are in use; the descriptions given are the versions used in London Cancer including drug doses, details of administration and supportive care other than anti-emetics. Wherever possible a reference to a clinical trial describing the regimen is given; this may not contain all relevant published efficacy data.

Chemotherapy

**EC75**

Epirubicin 75mg/m\(^2\) IV bolus q21days x 6
Cyclophosphamide 600 mg/m\(^2\) IV bolus


**Docetaxel (metastatic)**

Docetaxel 75-100mg/m\(^2\) IV 1hr 250ml 0.9%NaCl q21d x 6
premedication: Dexamethasone 8mg BD PO d -1 to +1 (i.e. 3 days)


**Paclitaxel weekly (metastatic)**

Paclitaxel 80-90mg/m\(^2\) IV 1hr 250ml 0.9%NaCl d1,8,15 q28d x 6 or U/P
premedication: Dexamethasone 8mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV


**Paclitaxel weekly + bevacizumab (funded by CDF for triple negative breast cancer)**

Paclitaxel 90mg/m\(^2\) IV 1hr 250ml 0.9%NaCl d1,8,15 q28d x 6 or U/P
Premedication: Dexamethasone 20mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV
Bevacizumab 10mg/kg IV 90/30 min 250ml 0.9%NaCl d1,15
1\(^{st}\) dose is administered over 90min. Subsequent doses are over 30min if no reaction to previous dose. Volume of administration is according to manufacturer’s guidelines.


**Docetaxel+Capecitabine**

Docetaxel 75mg/m\(^2\) IV 1hr 250ml 0.9%NaCl d1-14 q21d x 6
premedication: Dexamethasone 8mg BD PO d -1 to +1 (i.e. 3 days)
Capecitabine 1000mg/m\(^2\) PO BD d1-14


**Paclitaxel+Gemcitabine**

Paclitaxel 175mg/m\(^2\) IV 3hr 500ml 0.9%NaCl q21d x 6
Premedication: Dexamethasone 20mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV
Gemcitabine 1250mg/m\(^2\) IV 30min 250ml 0.9%NaCl d1,8

Capecitabine

Capecitabine 1000-1250mg/m² PO BD d1-14 q21d U/P

Vinorelbine

Vinorelbine 25mg/m² IV bolus 40ml 0.9%NaCl d1,8 q21d x 6 or U/P
OR for patients with poor venous access;
Vinorelbine 60mg/m² PO d1,8
dose can be increased to 80mg/m² if well tolerated

Eribulin (funded by CDF)

Eribulin 1.23mg/m² (equivalent to 1.4mg/m² Eribulin Mesylate) IV bolus d1,8 q21d U/P


Carboplatin+Gemcitabine

Carboplatin AUC2 (EDTA /CG GFR) IV 1hr 500ml 0.9%NaCl d1,8 d21d x6
Gemcitabine 1000mg/m² IV 30min 500ml 0.9%NaCl d1,8


MVP

Mitomycin C 6mg/m² IV bolus d1 q42d x 3
Vinblastine 6mg/m² IV bolus d1,22
Cisplatin 50mg/m² IV 1hr 500ml 0.9%NaCl d1,22
1L 0.9%NaCl +20 mmol KCl & furosemide 40mg over2-3 hr before & after cisplatin
Useful for patients with deranged liver function


3M

Mitoxantrone 7mg/m² IV bolus d1,22 q42d x3-4
Methotrexate 35mg/m² IV bolus d1,22
Mitomycin C 7mg/m² IV bolus d1,22
folinic acid 15mg PO 6hrly x 6 may be given 24hr after methotrexate


Weekly epirubicin

Epirubicin 25mg/m² IV bolus q7d U/P

Oral (metronomic) CM

Cyclophosphamide 50mg flat dose PO OD continuous q7d U/P
Methotrexate 2.5mg flat dose PO BD 2weekly


HER2-targeted therapy

Trastuzumab (HER2 +ve disease)

Trastuzumab is given in combination with chemotherapy as described for individual regimens and may be continued after chemotherapy to disease progression. Trastuzumab has been shown to be effective in combination with a number of chemotherapy regimens. Dosing is 2mg/kg/week chosen at a frequency to suit the chemotherapy regimen.

For details of cardiac monitoring see section on Early Breast Cancer.

For details of chemotherapy refer to regimens, above

Trastuzumab 600mg/5ml SC over 2-5min q21days
This is a flat dose regardless of weight and no loading dose is required.
The observation period following the first dose is 6 hours. For subsequent doses patients are observed for 2 hours if no reaction to the previous dose.
Trastuzumab 6mg/kg IV 90/30min 250ml 0.9%NaCl q21d U/P
OR (for 28-day regimens e.g. weekly paclitaxel)
Trastuzumab 4mg/kg IV 250ml 0.9%NaCl d1,15 q28d U/P
1st dose is administered over 90min followed by 60min observation period
Subsequent doses are over 30min followed by 30min observation period if no reaction to previous dose

Subcutaneous trastuzumab can be offered to metastatic patients with HER2+ve disease with the exception of pertuzumab combination patients.

Even though the current evidence is limited for switching from IV to SC trastuzumab existing intravenous trastuzumab patients can be offered a switch to subcutaneous trastuzumab.

Pertuzumab

Pertuzumab is only available for use in combination with intravenous trastuzumab and docetaxel as first-line treatment.

Pertuzumab is flat-dosed (420mg) with a loading dose (840mg) on cycle 1 or after ≥6 weeks from previous treatment. 1st dose is administered over 60min followed by 60min observation period before further drug administration. Subsequent doses are over 30min followed by 60min observation period before further drug administration if no reaction to previous dose.
Cardiac monitoring is the same as for trastuzumab but LVEF measurement is recommended every 9 weeks – see section on Early Breast Cancer.

Pertuzumab may be continued in combination with intravenous trastuzumab after completion of chemotherapy but should not be used as monotherapy.

**Lapatinib**

Lapatinib is only available for use in combination with capecitabine for patients who have previously been treated with a trastuzumab regimen.

Cardiac monitoring is the same as for trastuzumab – see section on Early Breast Cancer

**Docetaxel + Trastuzumab**

<see Docetaxel (metastatic)>

**Docetaxel + Trastuzumab + Pertuzumab funded by CDF**

- **Docetaxel 75mg/m²**
  - IV 1hr 250ml 0.9%NaCl
  - q21d x 6
  - Premedication: Dexamethasone 8mg BD PO d-1 to +1 (i.e. 3 days)
- **Trastuzumab 6mg/kg**
  - IV 90/30min 250ml 0.9%NaCl
  - q21d U/P
- **Pertuzumab 420mg (flat)**
  - IV 60/30min 250ml 0.9%NaCl
  - q21d U/P


**Paclitaxel weekly + Trastuzumab**

<see Paclitaxel weekly (metastatic)>

**Vinorelbine + Trastuzumab**

<see Vinorelbine>

**Capecitabine + Trastuzumab**

<see Capecitabine (metastatic)>

**Capecitabine + Lapatinib**

- **Capecitabine 1000mg/m²**
  - PO BD d1-14
  - q21d U/P
- **Lapatinib 1250mg**
  - PO OD d1-21

  Patients should be informed of the risk of diarrhoea and prescribed anti-diarrhoeal medication if required as per SPC


**Intrathecal therapy**

**IT Methotrexate**

- **Methotrexate 12.5-15mg**
  - IT
  - q7d U/P

  Twice weekly treatment until cytological/ clinical response, then reduced to once weekly
Appendix 3: Supportive Care

Anti-emetics
Follow the London Cancer anti-emetic guidelines

Colony Stimulating Factors
Primary Prophylaxis
GCSF is used for all (neo)adjuvant chemotherapy containing regimens, where the rate of neutropenic fever is greater than the 20% threshold for primary GCSF prophylaxis as recommended in the ASCO and EORTC guidelines.

This should start on D2 and continue for 5 days.

Regimens for which primary GCSF prophylaxis is recommended
- FEC100
- Docetaxel (100mg/m2 as component of other regimens)

Secondary prophylaxis
GCSF may be used in at risk patients receiving curative chemotherapy who have had a previous episode of febrile neutropenia or to maintain dose intensity for those who have had a delay due to neutropenia.

In general, GCSF will be started on D2 and continue for 5 days where no GCSF has previously been given. When 5 days of GCSF has previously been administered the duration of treatment should be extended.

Growth factors should not be routinely used in the palliative setting.

Taxane hypersensitivity/ allergy
In the event of hypersensitivity to docetaxel it is reasonable to try weekly paclitaxel. Paclitaxel albumin (Abraxane, paclitaxel-albumin) is licensed but not for this indication. However the incidence of hypersensitivity/ allergic reactions is <1% and successful use has been reported in small case series for patients unable to tolerate solvent-based taxanes. The recommended dose is 260mg/m2 q21d. Funding is currently by IFR or other local arrangements.
Appendix 4: Algorithm for anti-osteolysis therapy with bisphosphonate or denosumab for treatment of bone metastases

Precautions:
1. All normocalcaemic patients require Calcium and VitD supplements according to local practice.
2. All patients should have their serum calcium checked in first month of treatment and two monthly thereafter to detect severe hypocalcaemia.
3. Patients on bisphosphonates require serum urea and creatinine to be checked before each administration.
4. Patients with chronic dental sepsis should be monitored by dental unit expert in the treatment of BONJ and treatment may need to cease if severe ulceration develops despite antibiotic and dental care.
5. Patients on long term treatment ( >2.5 years) should be warned of the risk of atypical femoral fracture manifested as hip, groin of thigh pain.