London Cancer
Systemic Treatment for Breast Cancer

August 2017: Version 2.0
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 .......................................................... 5
   1.3. Peri-operative Systemic Treatment ........................................................................... 6

2. Adjuvant Treatment ........................................................................................................ 7
   2.1. Adjuvant Chemotherapy ......................................................................................... 7
   2.2. Adjuvant HER2-targeted therapy .......................................................................... 9
   2.3. Adjuvant Endocrine Therapy ................................................................................ 9
   2.4. Adjuvant Bisphosphonates and Bone Health ....................................................... 11

3. Locally Advanced and Metastatic Disease .................................................................. 16
   3.1. Diagnosis .................................................................................................................. 16
   3.2. Management principles ........................................................................................... 16
   3.3. Endocrine treatment ............................................................................................... 17
   3.4. Chemotherapy and HER2-Targeted Therapy ........................................................ 17
   3.5. Organ-specific treatment ....................................................................................... 20

Appendix 1: Treatment Regimens for Early Breast Cancer .............................................. 24
   Chemotherapy ................................................................................................................. 24
   HER2-targeted therapy ...................................................................................................... 27

Appendix 2: Treatment Regimens for Metastatic Breast Cancer ...................................... 32
   Chemotherapy .................................................................................................................. 32
   HER2-targeted therapy ...................................................................................................... 34
   Intrathecal therapy ............................................................................................................ 35

Appendix 3: Supportive Care ............................................................................................ 36

Appendix 4: AI therapy and women who are not known to be definitively post-menopausal 37

Version History
   1.0 8 July 2013
   1.1 31 January 2014
   2.0 24 August 2017
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
4. To avoid delays to initiation of chemotherapy
   - where mastectomy with immediate reconstruction is the intended surgical treatment
   - for high-risk tumour types (i.e. HER2-positive and Triple Negative)

- 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:**

- 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
  Sentinel node biopsy following chemotherapy is an option but if adopted needs careful attention to detail and audit.
- 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 positive sentinel node biopsy is not an indication for staging per se.
- 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

**Monitoring treatment:**
• All patients undergoing neo-adjuvant treatment must have regular clinical review of tumour response. Ultrasound is the most practical imaging technology for on-treatment tumour response monitoring by imaging. A mid-point ultrasound is recommended.

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 normally be performed 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.
• If sentinel node biopsy is performed post chemotherapy (see pre-treatment assessments, above) then thorough histological examination of revised nodes is mandatory; identification of any tumour cells including deposits <0.2mm diameter is considered evidence of nodal involvement.
• Following surgery histology should be reviewed in the MDT and recommendation for 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.

1.1.1 Neo-adjuvant Treatment Regimens (HER2 –ve disease)
• Docetaxel-(F)EC100 (FEC100-Docetaxel possibly slightly less effective)
• Paclitaxel~2weekly-EC90
• Docetaxel+Cyclophosphamide (TC) (less fit, anthracycline unsuitable)
• EC90-Paclitaxel~weekly + carboplatin (consider for patients with BRCA-mutation)

Consider capecitabine mono-therapy for patients with residual disease post-surgery, especially for triple negative disease

1.1.2 Neo-adjuvant Treatment Regimens (HER2 +ve disease)
Pertuzumab in combination with trastuzumab is approved by NICE for locally advanced, inflammatory or early breast cancer at high risk of recurrence (i.e. T2-T4b and M0) – either maximum 6 cycles if prescribed concurrently with docetaxel, carboplatin and trastuzumab; or maximum 4 cycles if prescribed with single agent docetaxel and trastuzumab following anthracycline-containing regimen.
• (F)EC100-Docetaxel + Trastuzumab + Pertuzumab (6-8 cycles)
• EC90-Docetaxel + Trastuzumab + Pertuzumab (6-8 cycles)
• Docetaxel+Carboplatin + Trastuzumab + Pertuzumab (TCHP)
• Docetaxel+Cyclophosphamide (TC) + Trastuzumab (less fit, anthracycline unsuitable)

Trastuzumab is continued as mono-therapy following completion of chemotherapy to a total of 1 year/ 18 doses.
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. 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 should undergo clearance at the time of definitive local surgery. Axillary radiotherapy is an alternative option.
• Pre-treatment sentinel lymph node biopsy should not be considered usual care.
• Patients undergoing neo-adjuvant endocrine therapy 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.

1.2.1 Neo-adjuvant Endocrine Therapy Regimens:
• Letrozole 2.5mg PO OD (post-menopausal)
• Tamoxifen 20mg daily OD (pre-menopausal)
• Anastrozole in combination with goserelin (pre-menopausal)

Note: Data supporting neoadjuvant endocrine therapy in pre-menopausal women is limited. The STAGE trial compared ovarian suppression + Tamoxifen with OS+ Anastrozole. Anastrozole was superior in terms of response as measured by ultrasound, MRI and CT. More patients in the anastrozole group had breast conservation, compared to tamoxifen. (Masuda N. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol. 2012;13(4):345–52).

1.3. Peri-operative Systemic 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).
- PREDICT (www.predict.nhs.uk/predict.shtml) is recommended to support estimates of individual prognosis and the absolute benefit of adjuvant treatment over a ten-year period.
- Nottingham Prognostic Index (NPI) may be used to estimate prognosis but does not predict treatment benefit.
- Oncotype DX should be requested for eligible patients for whom adjuvant chemotherapy is an option (see NICE Diagnostics Guidance DG10) to help guide decision making.

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 testing for patients with pN0 HR +ve HER2 –ve tumours with NPI score >3.4 or according to NHS England guidance provides a more individualised estimate of individual patient risk than AoL and PREDICT. Oncotype DX Recurrence Score (RS) can be combined with stage information using tools provided by Genomic Health (https://tools.genomichealth.com/Tools) to provide additional prognostic information. The likelihood of benefit from chemotherapy for most patients with RS ≤ 25 is significantly < a 10-year OS gain of 5%; chemotherapy should be considered for all patients with RS > 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 to all patients before starting treatment.
The use of lines to facilitate chemotherapy administration and reduce the risk of venous damage should be considered for all women receiving anthracycline chemotherapy, particularly epirubicin.

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

1.3.1 Adjuvant Chemotherapy Regimens (HER2 –ve disease)
Division by risk group is to provide general guidance on selection of chemotherapy

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 if Oncotype DX not available
   pT any, pN ≥1 G1-2 with AoL/ PREDICT 10 yr mortality risk >25%
   
   - (F)EC100-Docetaxel note benefit of F is questionable
   - EC90-Paclitaxel weekly/ 2weekly
   - EC90-Paclitaxel weekly + carboplatin (consider for patients with BRCA-mutation)

B. Medium risk patients
   Triple Negative disease: stage: pT1b, pN0, G any
   HR+ve HER2 –ve disease: stage: pT2 pN0 G3 if Oncotype DX not available
   pT2-3 pN1 G1-2 with AoL/ PREDICT 10 yr mortality risk 15-25% (chemotherapy benefit of c.≥3% vs no chemo)
   OncotypeDx RS >25
   
   - (F)EC75 } choice between FEC75 & FEC100 depends on fitness/age
   - (F)EC100 } note benefit of F is questionable
   - Docetaxel cyclophosphamide (TC) x 4 cycles
   - AC x 4 cycles

C. Special Circumstances
   a. High risk patients unsuitable for anthracyclines (e.g. less fit, prior anthracycline treatment)
      - Docetaxel cyclophosphamide x 4 cycles (consider 6 cycles for fit patients with prior anthracycline treatment)

   b. Residual disease post-neoadjuvant chemotherapy, especially for triple negative disease
      - Capecitabine as mono-therapy for 6 months

   c. 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
  o pT any, pN≥1
  o pT ≥1c, pN0
  o pT1b, pN0 WITH additional risk factors (G3 OR HR –ve)

• The duration of trastuzumab treatment is for 1 year (18 doses in total).

• All patients considered for HER2 targeted therapy must undergo initial cardiac assessment (history, ECG). Formal measurement of left ventricular function must be performed prior to initiation of anti-HER2 therapy and monitored during treatment 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

2.2.1 Adjuvant Treatment Regimens (HER2 +ve disease)

• (F)EC100-Docetaxel + Trastuzumab (to start with taxane)
• EC90-Paclitaxel~weekly + Trastuzumab (to start with taxane)
• Docetaxel+Carboplatin + Trastuzumab (TCH)
• Docetaxel+Cyclophosphamide (TC) + Trastuzumab (less fit or lower-risk or anthracycline unsuitable)
• Paclitaxel~weekly + Trastuzumab (less fit or lower risk or anthracycline unsuitable)
• Trastuzumab monotherapy following anthracycline only chemotherapy

Trastuzumab is continued as mono-therapy following completion of chemotherapy to a total of 1 year/ 18 doses.

2.3. Adjuvant Endocrine Therapy

• All patients with HR positive (ER-positive and/or PR-positive defined as Allred/Quick Score ≥3) breast cancer should be offered adjuvant endocrine therapy.
  o 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 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 receiving 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 should be given concurrently with anti-HER2 therapy.
• Initiation of 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. Aromatase inhibitors may only be used when combined with ovarian suppression.
• Ovarian suppression (OS) in addition to anti-oestrogens should be considered following chemotherapy for women with high-risk disease who either maintain or recover menses or have biochemical evidence of premenopausal state within eight months of completing chemotherapy.
• Due consideration should be paid to the toxicities of ovarian suppression before initiating treatment.
• OS should be combined with either tamoxifen or an AI. Aromatase inhibitors have been shown to be the more effective in this setting. Extra care in monitoring bone health is required; adjuvant bisphosphonates are recommended.
• If chemotherapy is indicated (but declined) consider ovarian suppression/ablation; OS is unlikely to be benefit those with low-risk disease.
• The optimal duration of ovarian suppression is not established – durations between 2 and 5 years are effective; longer is likely to be better.
• For achieving consistent OS, only the preparations of goserelin and triptorelin for monthly administration are recommended (the three-monthly preparations are not licensed and oestradiol suppression may be less complete).

2.3.2 Post-menopausal Women
• All post-menopausal women with ER-positive and/or PR-positive 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.
There is no convincing evidence that up-front AI treatment is superior to a switch strategy.
• The recommendation will depend on:
  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
  - Age >45 and natural amenorrhoea of at least 1 year’s duration
  - Bilateral surgical oophorectomy
  - For amenorrhoea not fulfilling the above criteria the diagnosis of postmenopausal status should be supported by hormone measurement: FSH levels must be > 25IU/L with low oestradiol (i.e. within the locally defined postmenopausal range), in the event of doubt measured on 2 occasions preferably 4-6 weeks apart. Women who have undergone hysterectomy without bilateral surgical oophorectomy and are age >60 may be considered postmenopausal.

- 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. The likelihood of developing a chemotherapy-induced menopause increases with age and is greatest for women receiving cyclophosphamide and docetaxel-containing regimens and those >45. However:
  - Ovarian function may recover up to 2 years after completion of chemotherapy.
  - Tamoxifen may suppress menstruation, especially following chemotherapy.

- Refer to Appendix 4 for a practical scheme on determination of menopausal status for women with amenorrhoea where there is uncertainty

Treatment
- Anastrozole 1mg OD (post-menopausal)
- Letrozole 2.5mg OD (post-menopausal)
- Exemestane 25mg OD (post-menopausal and pre-menopausal in combination with OS)
- Tamoxifen 20mg OD (pre- and post-menopausal)

- Goserelin 3.6mg SC monthly (pre-menopausal in combination with tamoxifen or AI)
- Triptorelin 3.0mg SC monthly (pre-menopausal in combination with tamoxifen or AI)

2.4. Adjuvant Bisphosphonates and Bone Health

2.4.1 Adjuvant bisphosphonates
Algorithm: Selection of Patients Suitable for Adjuvant Bisphosphonate Therapy to Prevent Skeletal Metastases (modified from ukbcg.org).

- Bisphosphonates are recommended for post-menopausal women (either naturally or as a result of ovarian suppression therapy) as part of routine clinical practice to prevent skeletal metastases, regardless of breast cancer sub-type. Treatment is ineffective for pre- and peri-menopausal women.

- Offer to patients with intermediate- or high-risk breast cancer (>12% 10-year risk of breast cancer death).

* Patients already on weekly oral bisphosphonates for osteoporosis should be considered for a treatment change and follow algorithm

$^{a}$ Include vitamin D 800-2000IU (+calcium 1000mg daily if low calcium diet)

CTIBL; cancer therapy induced bone loss
The optimal agent and schedule/duration of administration has not been established.

- Prior to commencing adjuvant bisphosphonate therapy:
  - Patients should be advised to have a dental health assessment.
  - Baseline DEXA scan is advised for post-menopausal patients within 3 months of commencement.
  - Baseline vitamin D analysis (vitamin D loading if <50nmol/L followed by maintenance dose). Additional calcium supplementation if patient has a low calcium diet.

A patient information sheet is available from ukbcg.org.


### 2.4.2 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.

Post-menopausal patients treated with an AI who are not treated with adjuvant bisphosphonates because they are at low-risk or decline treatment, or who are not treated for other reasons are at risk of accelerated bone loss and osteoporosis. Pre-menopausal patients who are treated with ovarian suppression are also at risk of accelerated bone loss; it is anticipated that the majority of these patients will receive adjuvant bisphosphonates.

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%20FINAL.pdf](http://ncrndev.org.uk/downloads/csg/Bone%20Health%20Guidelines%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 and who are not treated with adjuvant bisphosphonates** (taken from NCRN Guidelines)
Algorithm 2: Postmenopausal Women Receiving an AI and who are not treated with adjuvant bisphosphonates (adapted from NCRN Guidelines)
3. Locally Advanced and 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

*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 e.g. 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). In some situations, it may be used in place of diagnostic CT and isotope bone scan, e.g. for bone-dominant ER-positive disease.

*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 by immunohistochemistry 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 HR-positive disease that is not immediately life threatening. 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.
  o CT is preferred in most situations for visceral and soft-tissue disease. Isotope bone scan is not reliable for assessing response.
  o Patients treated with chemotherapy should have staging repeated after 3 cycles and on completion of the planned course of treatment.
  o 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 AIs 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 if re-challenge appropriate)
• Tamoxifen 20mg OD (following NSAI if not previously used or if re-challenge appropriate)
• Fulvestrant 500mg q4 weeks with loading dose
• Exemestane 25mg OD alone or in combination with Everolimus 10mg daily (NICE approved following non-steroidal AI given in either adjuvant or metastatic setting)
• Megestrol Acetate 160mg OD or Medroxyprogesterone Acetate 400 mg daily (use following other options)

3.4. Chemotherapy and HER2-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:
  o Anthracycline naïve: consider anthracycline unless contra-indicated.
  o Anthracycline pre-treated: consider taxane-based regimen unless contra-indicated.
  o 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

3.4.1 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.

• 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 (and for patients relapsing within 1 year of a (neo)-adjuvant taxane treatment
All of these regimens can be used in sequence; there is no clear evidence to support the order in which they should be given.
• Capecitabine (NICE approved)
• Vinorelbine (NICE approved)
• Eribulin (NICE approved following failure of ≥2 chemotherapy regimens including anthracycline/ taxane & capecitabine))
• Carboplatin+Gemcitabine

Later lines of treatment:
• 3M
• Oral (metronomic) CM
3.4.2 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 which have comparable efficacy to docetaxel with less toxicity for BRCA1/2 normal breast cancer and are superior to taxanes for BRCA1/2 mutant breast cancer (see section D)

- Carboplatin+Gemcitabine
- MVP

3.4.3 Suggested Scheme for HER2 +ve Disease
HER2 targeted treatment is associated with an overall survival benefit when used in the first-line setting and should be given to all suitable patients. Pertuzumab is licensed for use in combination with trastuzumab and docetaxel for first line treatment of locally advanced or metastatic breast cancer and its use is associated with improved time to progression and overall survival compared with trastuzumab and docetaxel. Trastuzumab emtansine (T-DM1) is available for use as second-line therapy or for early relapse following primary treatment that includes trastuzumab.

HER2 targeted therapy (trastuzumab ± pertuzumab) following completion of chemotherapy or T-DM1 are continued until disease progression. The development of brain metastases as an isolated event does not constitute 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:
- **Docetaxel + Trastuzumab + Pertuzumab** (for first line use only; funded by CDF)
- **Trastuzumab emtansine (T-DM1)** (for second line use or relapse within 12 months of completing adjuvant trastuzumab; NICE approved)

Chemotherapy-trastuzumab combinations
All of these regimens are well-established chemotherapy-trastuzumab combinations. The choice of regimen will depend on prior treatment history and patient fitness.
- Docetaxel + Trastuzumab
- Paclitaxel~weekly + Trastuzumab
- Vinorelbine + Trastuzumab
- Capecitabine + Trastuzumab

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)

### 3.4.4 Special Circumstances

#### BRCA1/2 mutant breast cancer

Treat according to receptor status but consider the early use of platinum-containing regimens

- Carboplatin
- Carboplatin+Gemcitabine

#### Frail/ elderly patients

The following regimens are particularly suitable for this patient group

- Paclitaxel~weekly
- Capecitabine
- Vinorelbine
- 3M
- Oral (metronomic) CM

#### Bone marrow failure or severe liver dysfunction

- Paclitaxel~weekly
- Capecitabine
- MVP
- Epirubicin~weekly

### 3.5. Organ-specific treatment

#### 3.5.1 Bone metastases

- Bone prophylaxis is recommended for all patients with bone metastases with RankL inhibitors (denosumab). Bisphosphonates are acceptable but not preferred. 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 Vitamin D (colecalciferol) 1000 IU daily to prevent hypocalcaemia/ secondary hyperparathyroidism.
- Perform baseline vitamin D analysis and consider correction if <50nmol/L prior to initiating bone prophylaxis to reduce risk of hypocalcaemia. Additional calcium supplementation if patient has a low calcium diet.
- 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 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 algorithm below on the use of denosumab
Algorithm for anti-osteolysis therapy with bisphosphonate or denosumab for treatment of bone metastases

Hypercalcaemia

Give standard hydration & bisphosphonate as per local practise

Normalcaecaeemia

Solid tumour bone metastases

Systemic therapy

Hypercalcaemia

Add denosumab 120mg subcutaneously every 4 weeks in Out-patient Clinic or self-administer at home

Oral Therapy

No

IV Therapy

Yes

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.
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).
- Consider the use of CNS-penetrating drugs (e.g. capecitabine, vinorelbine, carboplatin, letrozole and tamoxifen) with careful response monitoring. N.B. These drugs may be less effective against CNS than systemic disease.
- 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. There are also anecdotal reports of response to CNS-penetrating drugs.

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 a specialised chest team.

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.

3.5.5 Chest-wall disease not suitable for conventional treatments

- Consider ElectroChemotherapy (ECT) for multiple small lesions
- Chest-wall resection and reconstruction may be an option for patients with intractable disease and adequate systemic disease control. Potentially eligible patients should be referred to a specialised Chest Wall MDT (details to be added)
Appendix 1: Treatment Regimens for Early Breast Cancer

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

Anthracycline-taxane regimens

**FEC100-Docetaxel and Docetaxel-FEC100:** these regimens have been developed in different settings but are identical with the order of anthracycline and taxane components reversed.

**(F)EC100-Docetaxel** (adjuvant or neo-adjuvant)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil 500mg/m²</td>
<td>IV bolus</td>
<td>q21days x3</td>
<td></td>
</tr>
<tr>
<td>Epirubicin 100mg/m²</td>
<td>IV bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 500mg/m²</td>
<td>IV bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF SC Prophylaxis OD d2-6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**followed by**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 100mg/m²</td>
<td>IV 1hr 250ml 0.9%NaCl</td>
<td>q21days x3</td>
<td></td>
</tr>
<tr>
<td>premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF Prophylaxis OD d2-6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Docetaxel-FEC100** (neo-adjuvant)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 100 mg/m²</td>
<td>IV 1hr 250ml 0.9%NaCl</td>
<td>q21days x3</td>
<td></td>
</tr>
<tr>
<td>premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF Prophylaxis OD d2-6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**followed by**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil 500mg/m²</td>
<td>IV bolus</td>
<td>q21days x3</td>
<td></td>
</tr>
<tr>
<td>Epirubicin 100mg/m²</td>
<td>IV bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 500mg/m²</td>
<td>IV bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF Prophylaxis OD d2-6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**EC90-Docetaxel** (neo-adjuvant)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin 90mg/m²</td>
<td>IV bolus</td>
<td>q21days x4</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 600mg/m²</td>
<td>IV bolus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**followed by**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 100mg/m²</td>
<td>IV 1hr 250ml 0.9%NaCl</td>
<td>q21days x4</td>
<td></td>
</tr>
<tr>
<td>premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF Prophylaxis OD D2-6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Paclitaxel~2weekly-EC90 and EC90-Paclitaxel~2weekly**: these regimens have been developed in different settings but are identical with the order of anthracycline and taxane components reversed.

**Paclitaxel~2weekly-EC90 (neoadjuvant)**
- Paclitaxel 175mg/m² IV 3hr 500ml 0.9%NaCl q14days x4
  - premedication: Dexamethasone 20mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV

**Note: Routine G-CSF use is not usually required to maintain dose intensity**

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


**EC90-Paclitaxel~2weekly (adjuvant)**
- Epirubicin 90mg/m² IV bolus q21days x4
- Cyclophosphamide 600mg/m² IV bolus

**followed by**
- Paclitaxel 175mg/m² IV 3hr 500ml 0.9%NaCl q14days x4
  - premedication: Dexamethasone 20mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV

**Note: Routine G-CSF use is not usually required to maintain dose intensity**


**EC90-Paclitaxel~weekly (neo-adjuvant, adjuvant)**
- Epirubicin 90mg/m² IV bolus q21days x4
- Cyclophosphamide 600mg/m² IV bolus

**followed by**
- Paclitaxel 80mg/m² IV 1hr 250ml 0.9%NaCl weekly for 12 weeks
  - premedication: Dexamethasone 8mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV


**Anthracycline regimens**

**FEC100 (adjuvant)**
- Fluorouracil 500mg/m² IV bolus q21days x6
- Epirubicin 100mg/m² IV bolus
- Cyclophosphamide 500mg/m² IV bolus
- GCSF SC Prophylaxis OD d2-6

FEC75 (adjuvant for less-fit/ lower-risk patients)
- Fluorouracil 600mg/m² IV bolus q21days x3
- Epirubicin 75mg/m² IV bolus
- Cyclophosphamide 600mg/m² IV bolus

EC90 (adjuvant lower risk)
- Epirubicin 90mg/m² IV bolus q21days x4
- Cyclophosphamide 600mg/m² IV bolus

AC (adjuvant lower risk patients)
- Doxorubicin 60mg/m² IV bolus q21days x4
- Cyclophosphamide 600mg/m² IV bolus


Platinum containing regimens

EC90-Paclitaxel=weekly+carboplatin (neo-adjuvant & adjuvant for BRCA mutant breast cancer)
- Epirubicin 90mg/m² IV bolus q21days x3-4
- Cyclophosphamide 600mg/m² IV bolus
followed by:
- Paclitaxel 80mg/m² IV 1hr 250ml 0.9%NaCl weekly for 12 weeks
- premedication: Dexamethasone 8mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV
- Carboplatin AUC 5 (EDTA GFR) IV 1hr 500ml 5%Glucose q21days x4
OR
- Carboplatin AUC 1.5 (EDTA GFR) IV 1hr 500ml 5%Glucose weekly for 12 weeks

Note: GFR should be capped at 125 ml/min
GCSF SC Prophylaxis OD d3-d5, 10-12, 17-19


Other regimens

Docetaxel-Cyclophosphamide (TC) (adjuvant or neo-adjuvant for anthracycline-pre-treated & less-fit patients)
- Docetaxel 75mg/m² IV 1hr 250ml 0.9%NaCl q21days x4 (-6)
- Cyclophosphamide 600mg/m² IV bolus
  - premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)

Capecitabine adjuvant (for patients with residual disease after neo-adjuvant chemotherapy, especially TNBC)
Capecitabine 1250-1000mg/m² PO BD d1-14 q21days x9


CMF (adjuvant when taxanes and anthracyclines are contra-indicated)
Cyclophosphamide 600mg/m² IV bolus d1,8 q28days x6
Methotrexate 40mg/m² IV bolus d1,8
Fluorouracil 600mg/m² IV bolus d1,8
folinic acid 15mg PO 6hrly x 6 may be given 24hr after methotrexate
oral cyclophosphamide is not used


General Notes on Chemotherapy regimens
1. The role of fluorouracil in combination with anthracyclines and cyclophosphamide is uncertain, especially for patients with lower-risk disease.

2. There is evidence for equivalent efficacy between 3 weekly docetaxel and weekly paclitaxel, and paclitaxel given at licensed dose every 2 weeks
Reference:

3. Routine GCSF prophylaxis is recommended for chemotherapy regimens with a greater than 20% risk of febrile neutropenia. There optimum duration and timing are undefined.

HER2-targeted therapy
Trastuzumab is licensed for use in combination with chemotherapy for early breast cancer. Following completion of chemotherapy trastuzumab is continued as monotherapy until a total of 18 doses (equivalent to 1 year of 3-weekly treatment) have been administered

Trastuzumab subcutaneous (HER2 +ve disease)
Trastuzumab 600mg flat SC over 2-5 min q21days x18
This is a flat dose. No adjustment for weight is recommended. There is no loading dose.
The SPC recommends an observation period following the first dose of 6 hours and of 2 hours for subsequent doses provided there was no reaction to the previous dose.
Shorter observation periods have been reportedly used without increased adverse events (e.g. 30 mins following first dose and zero observation for subsequent doses – www.nescn.nhs.uk)
**Trastuzumab** intravenous (HER2 +ve disease)

Trastuzumab 6mg/kg IV 90/30min 250ml 0.9%NaCl q21days x18  
There is no pharmacological justification for an initial (loading) dose of Trastuzumab 8mg/kg as recommended in the SPC.  
The SPC recommends the initial dose is administered over 90 mins followed by an observation period of 4.5 hours and subsequent doses are administered over 30 mins followed by an observation of 2 hours provided there was no reaction to the previous dose.  
Shorter observation periods have been reportedly used without increased adverse events (e.g. 60 mins following first dose and 30 mins for subsequent doses – British Colombia Cancer Agency)  
Local policies may vary with regard to the observation period.

Subcutaneous trastuzumab is preferred over the IV formulation; the two are considered equally efficacious. 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%. Cardiac monitoring 3 monthly by ECHO or MUGA scan should be performed. An algorithm for managing falls in LVEF is shown in figures 1 & 2.

**Pertuzumab** intravenous (neo-adjuvant in combination with trastuzumab intravenous and chemotherapy)

Pertuzumab 840mg/ 420mg flat IV 60/30min q21days  
<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.  
Note: Baseline LVEF should be ≥55% (NICE guidance) and monitored every 9 weeks. An algorithm for managing falls in LVEF is shown in figures 1 & 2.>
Figure 1. Algorithm for treating falls in LVEF while on adjuvant trastuzumab (Taken from Aphinity 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 IV and Pertuzumab IV (neo-adjuvant)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>500mg/m²</td>
<td>IV bolus</td>
<td>q21days x3-4</td>
</tr>
<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>
<tr>
<td>GCSF SC Prophylaxis</td>
<td>OD d2-6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Followed by:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</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</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>IV 90/30min 250ml 0.9%NaCl</td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>420mg (flat)</td>
<td>IV 60/30min 250ml 0.9%NaCl</td>
<td></td>
</tr>
</tbody>
</table>

Premedication: Dexamethasone 8mg BD PO d -1 to +1 (i.e. 3 days)
GCSF SC Prophylaxis OD d2-6

Note: Docetaxel dose can be escalated to 100mg/m² from cycle 2 if 75mg/m² tolerated. Followed by:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab SC or IV</td>
<td></td>
<td></td>
<td>q21days x14</td>
</tr>
</tbody>
</table>


Docetaxel + Carboplatin + Trastuzumab + Pertuzumab (TCHP) (neo-adjuvant)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin AUC5 (EDTA GFR)</td>
<td></td>
<td>IV 1hr 500ml 5%Glucose</td>
<td>q21days x6</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75mg/m²</td>
<td>IV 1hr 250ml 0.9%NaCl</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>80mg/kg</td>
<td>IV 90/30min 250ml 0.9%NaCl</td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>840 mg flat (cycle 1) 420 mg flat (cycle 2+)</td>
<td>IV 60min 250ml 0.9%NaCl IV 30min 250ml 0.9%NaCl</td>
<td></td>
</tr>
</tbody>
</table>

Premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)
GCSF SC Prophylaxis OD D2-6

Note: If CG-GFR is used, Carboplatin may be dosed at AUC6 GFR should be capped at 125ml/min however measured

Followed by:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab SC or IV</td>
<td></td>
<td></td>
<td>q21days x12</td>
</tr>
</tbody>
</table>


EC90-Docetaxel + Trastuzumab + Pertuzumab (neo-adjuvant)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin</td>
<td>90mg/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>

Followed by:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</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</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>IV 90/30min 250ml 0.9%NaCl</td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>840 mg flat (cycle 1) 420 mg flat (cycle 2+)</td>
<td>IV 60min 250ml 0.9%NaCl IV 30min 250ml 0.9%NaCl</td>
<td></td>
</tr>
</tbody>
</table>

Premedication: Dexamethasone 8mg BD PO day -1 to +1 (i.e. 3 days)
GCSF SC Prophylaxis OD D2-6

Followed by:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab SC or IV</td>
<td></td>
<td></td>
<td>q21days x14</td>
</tr>
</tbody>
</table>
**FEC100-Docetaxel + Trastuzumab SC or IV** (adjuvant)  
*<see FEC100-Docetaxel (adjuvant or neo-adjuvant)>*  
Trastuzumab SC or IV (commenced with docetaxel) \( q_{21} \text{days x14} \)

**EC90-Paclitaxel“weekly + Trasatumab SC** (adjuvant)  
*<see EC90-Paclitaxel“weekly (adjuvant or neo-adjuvant)>*  
Trastuzumab SC or IV (commenced with paclitaxel) \( q_{21} \text{days x14} \)

**Docetaxel + Carboplatin + Trastuzumab (TCH)** (adjuvant when anthracyclines to be avoided)  
Carboplatin AUCs (EDTA GFR) \( q_{21} \text{days x6} \)  
Docetaxel 75mg/m\(^2\) \( q_{21} \text{days x14} \)  
Trastuzumab 600mg/5ml \( q_{21} \text{days x12} \)  

*Note: If CG-GFR is used, Carboplatin may be dosed at AUC6. GFR should be capped at 125ml/min however measured*

followed by  
Trastuzumab SC or IV \( q_{21} \text{days x12} \)


**Docetaxel + Cyclophosphamide (TC) x4 cycles + Trastuzumab SC or IV** (adjuvant or neo-adjuvant for less-fit high-risk and lower-risk patients))  
*<see Docetaxel-Cyclophosphamide (TC) (adjuvant or neo-adjuvant)>*  
Trastuzumab SC or IV \( q_{21} \text{days x18} \)

**Paclitaxel“weekly + Trastuzumab** (adjuvant)  
Paclitaxel 80mg/m\(^2\) \( q_{21} \text{days x18} \)  
Trastuzumab 600mg \( q_{21} \text{days x18} \)  

Appendix 2: Treatment 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/m² IV bolus q21days x6
Cyclophosphamide 600 mg/m² IV bolus


**Docetaxel** (metastatic)

Docetaxel 75-100mg/m² IV 1hr 250ml 0.9%NaCl q21days x6
Premedication: Dexamethasone 8mg BD PO d -1 to +1 (i.e. 3 days)

**Paclitaxel** (weekly)

Paclitaxel 80-90mg/m² IV 1hr 250ml 0.9%NaCl d1,8,15 q28days x 6 or U/P
Premedication: Dexamethasone 8mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV


**Docetaxel+Capecitabine**

Docetaxel 75mg/m² IV 1hr 250ml 0.9%NaCl q21days x6
Premedication: Dexamethasone 8mg BD PO d -1 to +1 (i.e. 3 days)
Capecitabine 1000mg/m² PO BD d1-14


**Paclitaxel+Gemcitabine**

Paclitaxel 175mg/m² IV 3hr 500ml 0.9%NaCl q21days x6
Premedication: Dexamethasone 20mg IV, ranitidine 50mg IV, chlorphenamine 10mg IV
Gemcitabine 1250mg/m² IV 30min 250ml 0.9%NaCl d1,8


**Capecitabine**

Capecitabine 1000-1250mg/m² PO BD d1-14 q21days U/P

**Vinorelbine**
Vinorelbine $25\text{mg/m}^2$  
IV bolus $40\text{ml} 0.9\%\text{NaCl}\ d1,8$  
q21days x 6 or U/P  
OR  
Vinorelbine $60\text{mg/m}^2$  
PO d1,8  
dose can be increased to $80\text{mg/m}^2$ if well tolerated  
*Note: oral vinorelbine unlike IV vinorelbine is emetogenic*

**Eribulin**

Eribulin $1.23\text{mg/m}^2$ (equivalent to $1.4\text{mg/m}^2$ Eribulin Mesylate)  
IV bolus d1,8  
q21days U/P  

**Carboplatin+Gemcitabine**

Carboplatin AUC2 (EDTA /CG GFR)  
IV 1hr $500\text{ml} 0.9\%\text{NaCl}\ d1,8$  
d21days x6  
Gemcitabine $1000\text{mg/m}^2$  
IV 30min $500\text{ml} 0.9\%\text{NaCl}\ d1,8$  
*Note: GFR should be capped at 125ml/min however measured*  

**Carboplatin single agent** (for BRCA mutant breast cancer)

Carboplatin AUC6 (EDTA /CG GFR)  
IV 1hr $500\text{ml} 0.9\%\text{NaCl}\ d1$  
d21days x6  
*Note: GFR should be capped at 125ml/min however measured*  
*Reference: Tutt A et al. (2015) TNT: a randomized phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced triple-negative or BRCA1/2 breast cancer. Cancer Res 75 (9 Suppl): S3–01.*

**MVP**  
(Useful for patients with deranged liver function)  
Mitomycin C $6\text{mg/m}^2$  
IV bolus d1  
q42d x3  
Vinblastine $6\text{mg/m}^2$  
IV bolus d1,22  
Cisplatin $50\text{mg/m}^2$  
IV 1hr $500\text{ml} 0.9\%\text{NaCl}\ d1,22$  
1L $0.9\%\text{NaCl} +20\text{mmol KCl} \& \text{furosemide 40mg over2-3 hr before \\ & after cisplatin}$  

**3M**

Mitoxantrone $7\text{mg/m}^2$  
IV bolus d1,22  
q42d x3-4  
Methotrexate $35\text{mg/m}^2$  
IV bolus d1,22  
Mitomycin C $7\text{mg/m}^2$  
IV bolus d1  
folic acid $15\text{mg PO 6hrly x 6 may be given 24hr after methotrexate}$  

**Epirubicin~weekly**

Epirubicin $25\text{mg/m}^2$  
IV bolus  
q7d U/P  
Oral (metronomic) CM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>50mg flat dose</td>
<td>PO OD continuous</td>
<td>q7days U/P</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2.5mg flat dose</td>
<td>PO BD 2xweekly</td>
<td></td>
</tr>
</tbody>
</table>


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.

For details of cardiac monitoring see section on Early Breast Cancer. Monitoring frequency may arguably be reduced to every 6 months if 1 year of treatment is completed without significant fall in LVEF.

For details of chemotherapy refer to regimens, above.

Trastuzumab 600mg flat SC over 2-5 min q21days U/P

This is a flat dosed. No adjustment for weight is recommended. There is no loading dose.

The SPC recommends an observation period following the first dose of 6 hours and of 2 hours for subsequent doses provided there was no reaction to the previous dose.

Shorter observation periods have been reportedly used without increased adverse events (e.g. 30 mins following first dose and zero observation for subsequent doses – www.nescn.nhs.uk)

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

There is no pharmacological justification for an initial (loading) dose of Trastuzumab 8mg/kg as recommended in the SPC.

The SPC recommends the initial dose is administered over 90 mins followed by an observation period of 4.5 hours and subsequent doses are administered over 30 mins followed by an observation of 2 hours provided there was no reaction to the previous dose.

Shorter observation periods have been reportedly used without increased adverse events (e.g. 60 mins following first dose and 30 mins for subsequent doses – British Colombia Cancer Agency)

Local policies may vary with regard to the observation period.

Subcutaneous trastuzumab is preferred over the IV formulation; the two are considered equally efficacious.

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

Pertuzumab 840mg/ 420mg flat IV 60/30min q21days

<see detailed regimen below>
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.

Note: Baseline LVEF should be ≥55% (NICE guidance) and monitored every 9 weeks; see Appendix 1

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

- Docetaxel 75mg/m² IV 1hr 250ml 0.9%NaCl q21days 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
- Pertuzumab 840 mg flat (cycle 1) IV 60min 250ml 0.9%NaCl
  - 420 mg flat (cycle 2+)

followed by

- Trastuzumab 6mg/kg IV 90/30min 250ml 0.9%NaCl q21days U/P
- Pertuzumab 840 mg flat (cycle 1) IV 60min 250ml 0.9%NaCl
  - 420 mg flat (cycle 2+)


**Trastuzumab Emtansine (T-DM1) (NICE approved)**

- T-DM1 3.6mg/kg IV 90/30min 250ml 0.9%NaCl 21days U/P


**Docetaxel + Trastuzumab**

<see Docetaxel (metastatic)>

**Paclitaxel weekly + Trastuzumab**

<see Paclitaxel weekly (metastatic)>

**Vinorelbine + Trastuzumab**

<see Vinorelbine>

**Capecitabine + Trastuzumab**

<see Capecitabine (metastatic)>

**Intrathecal therapy**

**IT Methotrexate**

- Methotrexate 12.5-15mg IT q 3-7days 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.

GCSF should start on D2-3 and continue for 5 days.

Regimens for which primary GCSF prophylaxis is recommended
- FEC100
- Docetaxel (100mg/m2 as component of other regimens)
Note Paclitaxel 175mg/m2 q14 days can usually be administered without GCSG support

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/ allergic reactions to docetaxel or solvent based paclitaxel, paclitaxel-albumin (nab paclitaxel, Abraxane) should be prescribed as an alternative. Although not a licenced indication, this use is funded by NHS England specialised commissioning. The recommended dose is 260mg/m2 q21 days or 125mg/m2 weekly. Funding is currently by IFR or other local arrangements
Appendix 4: AI therapy and women who are not known to be definitively post-menopausal.

For a woman considered for AI therapy who is either thought to be post-menopausal following chemotherapy and/or to be switched from alternative endocrine therapy, then the patient must be advised of the risk of resuming menses. FSH and oestradiol should be checked at baseline and monitored 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. The following guidance is a pragmatic approach taken from the OPTIMA protocol

- Age ≥ 55 on tamoxifen monotherapy with intact ovaries and with amenorrhoea for 2 years may be considered postmenopausal.
- Age < 55 on tamoxifen monotherapy with intact ovaries and with amenorrhoea for 2 years. Assay FSH and oestradiol; consider the patient to be postmenopausal if FSH is > 25IU/L and oestradiol is within the locally defined postmenopausal range.
- Any age and on GnRH agonist combined with either tamoxifen or an aromatase inhibitor: discontinue GnRH agonist, allowing at least 4 months from final treatment prior to measurement of FSH and oestradiol. Discontinuation of tamoxifen for 8-12 weeks or aromatase inhibitor for 2 weeks is advised before hormone measurement. Consider the patient to be postmenopausal if FSH is > 25IU/L and oestradiol is within the locally defined postmenopausal range.

Notes on interpretation of FSH and oestradiol levels in women with amenorrhoea receiving anti-oestrogen treatment.

1. Tamoxifen
   Tamoxifen may suppress FSH levels in postmenopausal women and cause elevation in premenopausal women. Women with FSH ≤25IU/L measured whilst taking tamoxifen should be considered premenopausal regardless of oestradiol level. If the FSH lies close to 25 then consider repeating measurements in 6 months or following interruption of tamoxifen for 8-12 weeks. Women with FSH >25IU/L and oestradiol above the menopausal range are likely to be peri-menopausal; consider repeating measurements in 6 months.

2. Aromatase inhibitors
   Aromatase inhibitors should suppress the oestradiol level to below the lower limit of detection for all women thought to be postmenopausal on clinical grounds and additionally cause modest elevation of FSH levels in both pre- and postmenopausal women (secondary to the suppressed oestradiol production). If measurements of FSH and oestradiol are made to confirm postmenopausal status for women whilst taking an aromatase inhibitor and the FSH level lies close to 25IU/L then measurements should be repeated after a two-week interruption of aromatase inhibitor treatment to avoid an incorrect diagnosis of a postmenopausal state.

3. Ovarian suppression
   GnRH agonists suppress both FSH and serum oestradiol. If following discontinuation of a GnRH agonist, FSH is ≤25IU/L and oestradiol is within the locally defined postmenopausal range then it is likely that there is ongoing GnRH agonist activity; repeat analysis should be performed at 4-6 week intervals until menopausal status is clear. Measurements of FSH and oestradiol are much more reliably interpretable when made early (i.e. within 6 months) of discontinuation of a GnRH agonist when analysis is performed following washout of tamoxifen or an aromatase inhibitor.