Stage 4 disease.
Originally collated by Miss Amy Robinson.
Last reviewed October 2024 by Dr Ahmed Shaheen

STAGE 4 DISEASE

INTRODUCTION

EBC, 5yr survival up to 96% BUT Metastatic BC ~38% and BC metastases account for ~15% of cancer deaths in women in the UK (21% lung in the UK - in Europe Breast ca is 1st). Metastases as recurrence have a worse prognosis than *de novo* diagnoses. Patterns of disease have evolved with treatments so increases in liver and CNS metastases and a decrease in bony metastases seen (likely to continue with use of bisphosphonates).

The NICE guidance is a little outdated and would point you to the paper uploaded in the guidance section which has great flow diagrams summarising the guidance: ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Annals oncology 2021;32(12) at https://doi.org/10.1016/j.annonc.2021.09.019

A summary of the "novel" therapies and some key trials is found in sheets for "Targeted Therapies".

GUIDELINES

ESMO:

Work-up

"Staging: history and physical examination, haematology, biochemistry, tumour markers, CT of the chest and abdomen and bone scintigraphy (or PET-CT), brain imaging (symptomatic patients or according to subtype if the presence of CNS metastases will alter the choice of therapy)"

- Biological markers in addition to routine include gBRCA and then:
    - MSI*, TMB*, NTRK*
    - ESR1** (in ER+/HER2– tumours if further AI-based therapy is considered), somatic BRCA mutations**
    - PDL1 for TNBC
    - PIK3CA if ER+, HER2-
    - BRCA mutations in both - olaparib eligibility

* Where corresponding therapies are available

** Optional assessments with potential to guide treatment

Monitoring

- Interval between imaging and treatment start <4 weeks.
- Evaluation of response every 2-4 months but variable of course on disease/treatment
- Bone scans mainstay (further evidence needed for PET-CT) but be aware of flare in first few months.

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Treatment

- ER+ HER-
  - CDK4/6- and ET = standard-of-care for ER-positive, HER2-negative MBC (Post menopausal) e.g. of CDK4/6 = palbociclib (abemaciclib, ribociclib) *OS data from palbociclib shows no benefit in 1st line settings (PALOMA- 2)
  - OFS in pre-menopausal
  - If imminent organ failure - ChT (as combination e.g. Taxane or capecitabine with bevacizumab). Then it is clinically acceptable to use ET plus a CDK4/6 inhibitor as a subsequent therapy in cases of progressive disease. But maintenance ET alone at this point an option if disease has stabilised.
  - Outside of the context of organ failure, at least 2 rounds of ET based options preferred prior to chemo. If given, single agent sequential preferred over combination and can go for: anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums
  - 2nd line therapies include:
    - BRCA mutation -PARP (Olaparib, OlympiAD) or (Talazoparib, EMBRACA)
    - PIK3CA mutation- Fulverstrant + Alpelisib (alpha-specific class 1 protein kinase inhibitor) (Alpelisib is now appoved by NICE to be used for some indications
    - Fulvestrant (SERD, IV) +/- exmetasane
    - Fulvestrant +/- everolimus (mToR inhibitor)
    - Fulvestrant alone

- HER2+ ER- MBC
  - 2nd line is:
    trastuzumab-deraxtecan (DESTINY-Breast03) or TDM-1 (EMILIA)
  - Brain mets in HER2+ recommend 1-10 and favourable resect/RadioTx, unfavourable -whole brain radioTx, or if cannot treat locally then ChT: Tucatinib + capecitabine + trastuzumab. Of note, trastuzumab does not cross the blood brain barrier.
  - 3rd line options - see paper -depends on prior treatment! Tucatinib =Tyrosine Kinase inhibitor which is recommended by NICE based on HER2CLIMB trial after 2 or more anti-her2 drugs have been tried. So give dual (CLEOPATRA) then trastuzumab emtansine (kadcyla = KATHERINE) then this. Alternatives are non HER specific eg capecitabine, vinorelbine, eribulin. Main regime is Trastuzumab +Capecitabine + Tucatinib

HER2-targeted therapy is recommended for patients with HER2-positive advanced breast cancer, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis

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- TN MBC
    - Go in search of what you can target!
    - PDL1+ tumours- Atezolizumab+nab+paclitaxel OR Pembrolizumab + ChT (nab-paclitaxel, paclitaxel or gemcitabine+carboplatin)
    - If you have a gBRCA mutation then you benefit from carboplatin over doxetaxel (same as EBC) and PARP inhibitors
    - Patients with triple-negative, PD-L1-negative MBC should be offered single-agent chemotherapy rather than combination chemotherapy as first-line treatment
    - Sacituzumab govitecan is recommended, as an option for treating unresectable triple-negative locally advanced or metastatic breast cancer in adults after 2 or more systemic therapies, at least 1 of which was for advanced disease. (TROPiCS-02)

NICE

Staging

- Staging is CT for the mainstay; use a combination of USS, plain X-ray and CT, then MRI if required e.g. spinal metastases encroaching on the canal.
- PET-CT only for NEW diagnosis where imaging is suspicious but not diagnostic of metastases.
- For Bony Mets:
    - “Assess the presence and extent of metastases in the bones of the axial skeleton using bone windows on a CT scan or MRI or bone scintigraphy”.
    - “Assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone scintigraphy and/or plain radiography”.

Treatment

- Endocrine
    - Endocrine essentially the same but more of an emphasis on OFS in pre-menopausal
- Chemotherapy
    - Advanced breast cancer NOT suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting):
        - 1st line: Docetaxel
        - 2nd line: Vinorelbine or Capecitabine, then whichever not used is the 3rd line therapy.
        - Gemcitabine + paclitaxel ONLY when docetaxel monotherapy (or docetaxel plus capecitabine) are also considered appropriate.
        - Trastuzumab should be stopped if disease progresses while on treatment (non CNS progression)

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- Brain metastases
    - Excision for single lesions with good control elsewhere (and good PS)
    - Radiotherapy if surgery not considered and ok prognosis
- Bone metastases
    - Give bisphosphonate
    - 8Gy 1Fr for painful bony metastases
    - Orthopaedics if at risk of a long bone fracture, to consider prophylactic surgery.
    - Assess the instability to determine if needs fixation - Both the Mirel score and SINS score assess the **LREP - location, radiographic appearance, extent, pain.**
    - Extremity = **Mirel scoring** (1-3 for all, >-9 fix as 33%rx Fx, <7 leave):
        - Location: UL, LL, peritrochanteric
        - Radiographic appearance: blastic, mixed, lytic
        - Extent: 1/3, 2/3, >2/3
        - Pain: mild, mod, severe
    - **Spine instability neoplastic score (SINS)** by Fisher et al for vertebral metastases:
        - Location: Rigid (S2-S5), Semirigid (T3-T10), Mobile (C3-C6, L2-L4) , Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)
        - Radiographic appearance: blastic, mixed, lytic
        - Extent is according to vertebral body collapse* and %, alignment** and posterolateral involvement***
        - Pain: Pain free, Occasional pain but not mechanical, Pain 1

*Vertebral body collapse: no collapse and <50%, no collapse but >50% involved, collapse <50%, collapse >50%

**Radiographic spinal alignment: Normal, De novo deformity (kyphosis/scoliosis), Subluxation/translation

***Posterolateral involvement of spinal elements: None, Unilateral, Bilateral

If interested you can read more at **Fisher et al.** Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. **Radiation Oncology 2014**, 9:69 http://www.ro-journal.com/content/9/1/69

For more information: visit Systemic Treatment of Patients With Metastatic Breast Cancer: ASCO Resource–Stratified Guideline | JCO Global Oncology (ascopubs.org)

General Notes:

1. Palliative care needs should be addressed for all patients at presentation of MBC, including situations in which no antineoplastic interventions are accessible.

2. Patients who are premenopausal can only receive aromatase inhibitors if accompanied by ovarian ablation or ovarian suppression.

3. Clinicians should recommend treatment according to pathological and biomarker features when quality (following established guidelines) testing results are available.

4. Cases should be discussed using a multidisciplinary approach with the core team including the surgeon, pathologist, oncologist, and radiation oncologist.