

# Management of advanced breast cancer

The overall survival of patients with advanced breast cancer is improving, due in part to the increasing range of cytotoxic agents now in use. Communication between patients, specialists and GPs is vital, as is mutual understanding of the disease progress and the treatment goals.

## YOON-SIM YAP

MB BS

## BOGDA KOCZWARA

MB BS, FRACP, MBioEth

Dr Yap is Oncology Registrar, and Dr Koczwarra is Senior Medical Oncologist and Head of Department, Medical Oncology Department, Flinders Medical Centre, Bedford Park, SA.

Advanced breast cancer represents a heterogeneous group of conditions ranging from locally advanced to metastatic, relatively indolent to rapidly progressive. Appropriate management requires understanding of the natural history of the disease, the risks and benefits of treatment and the patient-related factors that may affect treatment choices.

Although the intention of treatment in advanced breast cancer is generally palliative rather than curative, the overall survival for patients continues to improve as more potent new treatments become available.<sup>1</sup> The goals of treatment are:

- improvement of quality of life
- relief of symptoms

- minimisation of treatment-related side effects
- prolongation of life
- psychosocial wellbeing of patients and their families.

The GP plays an important role in the management of advanced breast cancer because he or she is often the first point of contact and the co-ordinator of continuing care. Communication between patients, specialists and GPs is vital, with mutual understanding of the disease progress and treatment goals.

This article outlines the principles of management of advanced breast cancer. We considered the management of early breast cancer in an article published in the June 2004 issue of *Medicine Today*.

## IN SUMMARY

- **Advanced breast cancer includes locally advanced disease, metastatic disease and cancer recurring locoregionally after previous surgery. Treatment intent is usually palliative rather than curative, with the emphasis on physical and psychosocial wellbeing.**
- **Locally advanced breast cancer is usually treated with a combination of chemotherapy, radiotherapy, surgery and endocrine therapy. Systemic therapy may substantially reduce the tumour size before local therapy.**
- **Locoregional recurrence after previous surgery may be treated with further surgical excision and/or radiotherapy for local control. Systemic therapy may prevent or delay systemic relapse.**
- **Metastatic breast cancer typically requires a combination of anticancer and supportive therapies. Quality of life is important and a key determinant of success of palliative treatment.**
- **GPs are integral members of the multidisciplinary team because they are often the doctor of first contact and the co-ordinator of care. Communication between patients, specialists and GPs is vital, with mutual understanding of the disease progress and treatment goals.**

## Planning management

Various factors need consideration when establishing a management plan for the patient with advanced breast cancer. These include the presentation of the cancer, previous treatment, the bulk of the disease and the patient's comorbidities and preferences.

## Presentation

The different presentations of advanced breast cancer are associated with different prognoses and management strategies.

### Locally advanced breast cancer

Locally advanced breast cancer represents only 10 to 20% of all cases of breast cancer.<sup>2</sup> The breast may display a 'peau d'orange' appearance, skin ulceration or fixation to the underlying chest wall. The axillary lymph nodes may be fixed to other structures, and the internal mammary nodes may be involved. Locally advanced breast cancer requires multimodal treatment.

### Locoregional recurrence

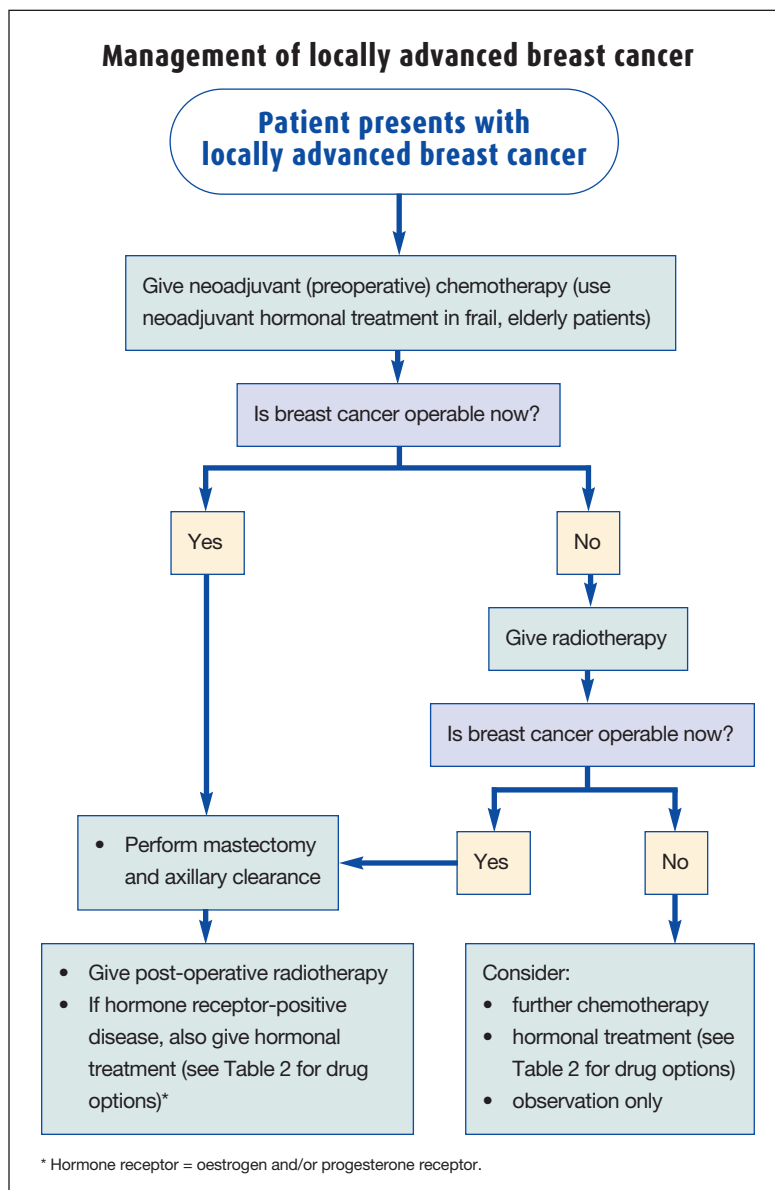
Up to about 5% of patients treated with mastectomy or breast conserving surgery and radiotherapy will present with locoregional recurrence, usually within the first five years of therapy. Local recurrence after mastectomy carries a worse prognosis than local recurrence after breast conserving surgery. It often heralds progression of systemic disease, especially if it occurs within the first year.<sup>2</sup>

### Metastatic breast cancer

Treatment of metastatic breast cancer is based mainly on systemic therapy. Although the median survival has been reported at 18 to 24 months, some patients live much longer, especially if the tumour is confined to slow-growing bony or soft tissue metastases. The likelihood of response is reduced by the presence of the following adverse prognostic factors:

- rapid growth
- large tumour volume
- extensive visceral involvement
- short disease-free or response interval
- failure of prior therapy
- poor performance status
- hormone (oestrogen and/or progesterone) receptor-negative status

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- human epidermal growth factor receptor 2 (HER2)-positive status.

## Previous treatment

For both hormonal treatment and chemotherapy, the response diminishes with each line of treatment. If all endocrine options have been exhausted, chemotherapy may be considered. To avoid resistance caused by prior hormonal therapy or chemotherapy, patients who have relapsed should receive drugs they have not been exposed to previously.

continued

**Table 2. Hormonal treatment options in advanced breast cancer**

Hormonal treatment	Advantages	Disadvantages
<b>Premenopausal patients</b>		
Ovarian ablation: Surgical (often done via laparoscopy) Radiotherapy LHRH analogue (goserelin [Zoladex])	Permanent; immediate onset Low morbidity Reversible; allows patient to have 'trial' of menopause before surgical or radiation oophorectomy	Invasive; premature menopause Delayed onset; premature menopause Frequent injections to maintain menopausal status; costly
Tamoxifen	Well studied; oestrogen-agonist effect on bones potentially advantageous	Hot flushes; thromboembolic events; vaginal bleeding; small risk of endometrial cancer
<b>Postmenopausal patients</b>		
Tamoxifen	As above	As above
Aromatase inhibitors (anastrozole [Arimidex], exemestane [Aromasin], letrozole [Femara])*	More effective than tamoxifen; fewer thromboembolic events; less risk of vaginal bleeding; reduced risk of endometrial cancers	Osteoporosis; risk of fractures, musculoskeletal aches, pains
Progestins (e.g. medroxyprogesterone acetate)	May work in patients with cancers refractory to aromatase inhibitors	Weight gain; fluid retention; vaginal bleeding; venous thromboembolism; not as well tolerated as aromatase inhibitors

\*Aromatase inhibitors are not recommended for patients who are premenopausal because they affect mainly peripheral production of oestrogens, which is the predominant type of production in postmenopausal women but not in premenopausal women. In premenopausal women, the majority of oestrogen is produced by the ovaries and is unaffected by aromatase inhibitors.

**Disease bulk**

In patients with visceral involvement (liver, brain or lung lesions), more potent chemotherapy with anthracyclines or

taxanes may be preferred over better tolerated but less potent regimens or hormonal therapy because they are more likely to induce a rapid response.

**Patient comorbidities**

Elderly or frail patients tend to tolerate hormonal therapy better than chemotherapy. If chemotherapy is required, oral capecitabine (Xeloda) or weekly low-dose anthracycline (epirubicin), taxane (docetaxel) or vinorelbine (Navelbine) regimens are preferred, rather than the usual three-weekly regimens. The choice of chemotherapy drug may be influenced by organ dysfunction; for example, cardiac failure would contraindicate anthracycline chemotherapy.

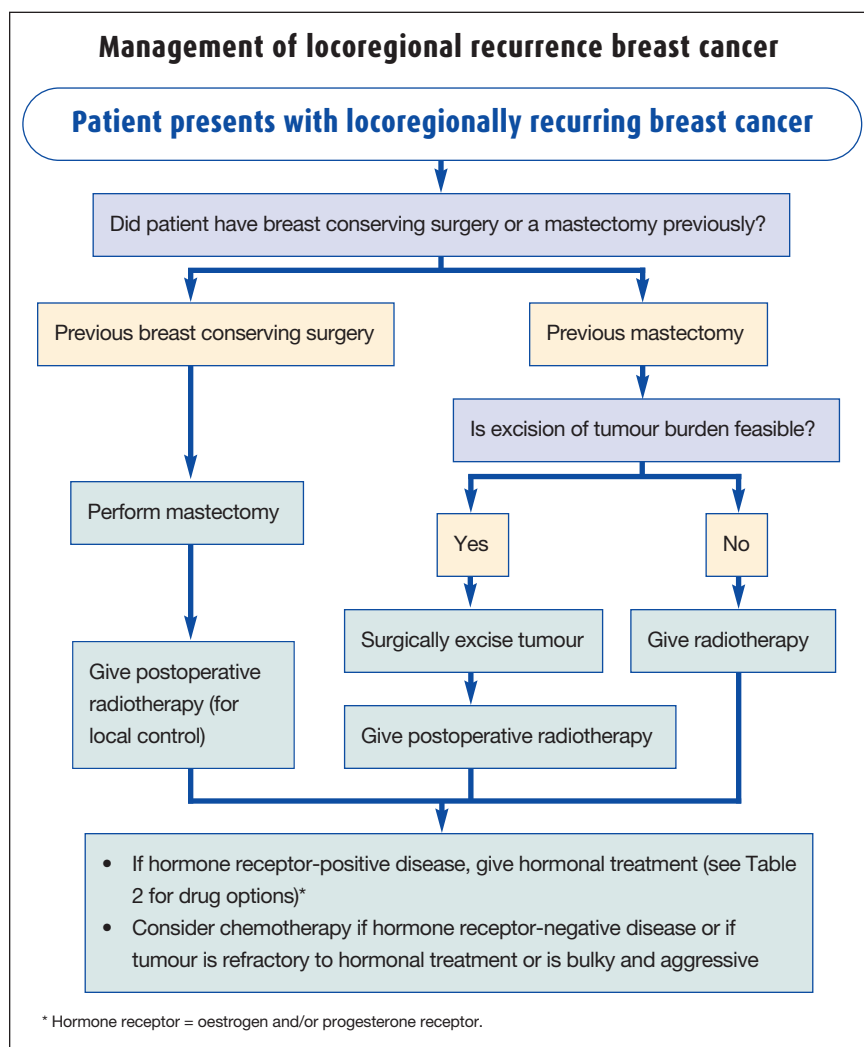
**Patient preferences**

Patients may have specific preferences relating to side effects and regimen for a particular treatment. For example, some patients would like to avoid cytotoxic drugs that cause alopecia and may prefer to be treated with drugs like capecitabine or vinorelbine that do not cause hair loss.



Figures 1a and b. Hand and foot syndrome secondary to capecitabine.

continued



### Choosing the right treatment – balancing risks and benefits

Optimal management of patients with advanced breast cancer often requires the use of multiple treatment modalities to achieve optimal outcome with minimal side effects. Management pathways for the various presentations are summarised in the flowcharts on pages 49, 52 and 55.

### Hormonal therapy

Hormonal treatment is usually well tolerated and effective in patients with tumours that are hormone receptor-positive, i.e. oestrogen receptor and/or progesterone receptor-positive. The treatment options are summarised in Table 2.

### Chemotherapy

Chemotherapy may be required in patients with hormone receptor-negative disease, those refractory to hormonal treatment or those with bulky, aggressive tumours. Efficacy and side effects need to be considered when choosing the regimen: efficacy may be higher in combination chemotherapy but at the cost of greater toxicity, and side effects may be of particular concern in elderly and/or frail patients (Figures 1a and b).

Cyclophosphamide (Cycloblastin, Endoxan), methotrexate (Ledertrexate, Methoblastin) and 5-fluorouracil (Efudix)

**Table 3. The newer cytotoxic agents used in advanced breast cancer**

Cytotoxic drug	Advantages	Disadvantages
Liposomal anthracycline formulation (liposomal doxorubicin [Caelyx])	Similar efficacy to standard anthracyclines but better tolerated with less cardiotoxicity, myelosuppression, hair loss and nausea	Hand and foot syndrome
Taxanes (docetaxel [Taxotere], paclitaxel [Anzatax Injection Concentrate, Taxol])	Very effective; additive effect with trastuzumab (Herceptin)	Fatigue; hair loss; neuropathy; lowered blood cell counts; myalgia; mouth ulcers; allergic reactions (paclitaxel)
Vinorelbine (Navelbine)	Better tolerated; no hair loss; additive effect with trastuzumab	Fatigue; lowered blood cell counts; neuropathy
Capecitabine (Xeloda)	Oral; well tolerated; no hair loss	Hand and foot syndrome; mouth ulcers; diarrhoea; nausea
Gemcitabine (Gemzar)	Well tolerated; little hair loss	Fall in blood count; fatigue

– that is, the CMF regimen – and anthracyclines (doxorubicin; epirubicin [Pharmorubicin]) are now supplemented by newer cytotoxic agents. These are listed in Table 3 and include the taxanes, vinorelbine, capecitabine and gemcitabine (Gemzar), and the less cardiotoxic formulation of doxorubicin, liposomal doxorubicin (Caelyx). The addition of these newer drugs has resulted in improved survival and, frequently, better tolerability of treatment.<sup>3</sup>

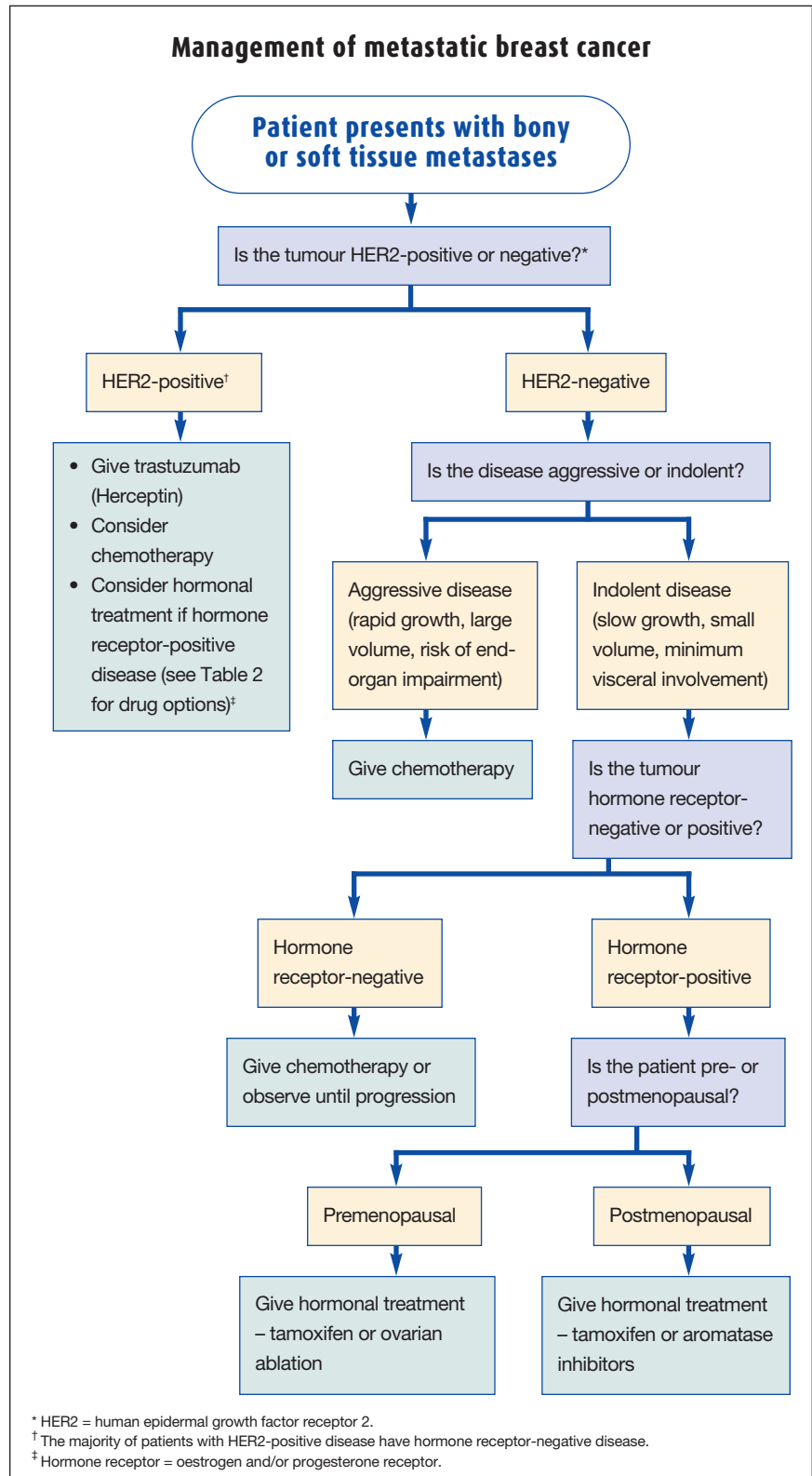
### Trastuzumab

Trastuzumab (Herceptin) is a humanised monoclonal antibody against HER2, a protein receptor on the surface of cells that is a key component in regulating cell growth. Approximately 20% of patients with breast cancer overexpress the receptor, making them suitable candidates for treatment with the drug.

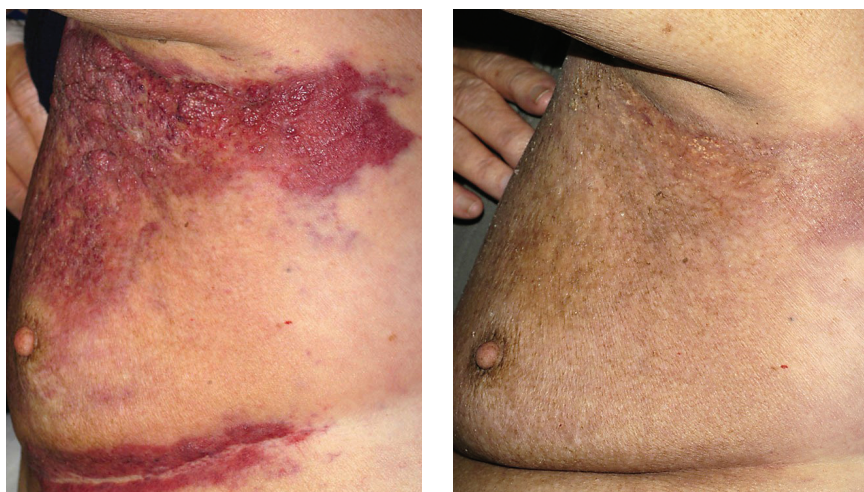
Addition of trastuzumab to chemotherapy improves response and survival.<sup>4</sup> Trastuzumab alone is also active as monotherapy in HER2-positive advanced disease, with response rates of approximately 20% and regressions lasting for more than a year (Figures 2a and b).<sup>5</sup> It is well tolerated, with the most common side effects observed during the infusion being chills and fever (usually mild). However, when given with doxorubicin in previous trials, increased rates of cardiac toxicity were noted.<sup>4</sup>

### Surgery

Apart from mastectomy and local excision for patients with local disease, patients may need mastectomy for fungating or painful breast lesions, decompression surgery for spinal cord compression, and internal fixation for impending or pathological fractures. Pleurodesis and pericardiocentesis or pericardial window may also be required for symptomatic pleural and pericardial effusions, respectively. Resection of isolated brain lesions may occasionally be performed in an attempt to achieve long term remission.



continued



Figures 2a and b. Treatment of advanced breast cancer with trastuzumab. a (left). Before treatment. b (right). Two weeks after starting treatment.

### Radiotherapy

Radiation therapy is used not only as the definitive or adjuvant treatment in local disease, but may also palliate specific symptomatic sites in the metastatic setting. Indications include: painful bony metastases; unresectable brain, meningeal or spinal cord metastases; bronchial obstruction; and painful or fungating breast or chest wall lesions. Radiotherapy should also be given following surgery

for decompression of intracranial or spinal cord metastases and following fixation of pathological fractures. The systemically administered radionuclides strontium-89 (Metastron) and samarium-153 (Quadramet) may be used for palliation of diffuse bony metastases.

### Supportive care

Good symptom control, psychosocial support (including counselling, support groups, psychiatric care, relaxation and meditation) and spiritual wellbeing are key factors in attaining optimal quality of life, especially for terminally ill patients.

Recent NHMRC guidelines offer recommendations regarding psychosocial support for patients with breast cancer.<sup>6</sup> Some of the many resources available to assist clinicians and patients are listed in the box on this page.

Supportive care measures include adequate pain relief, control of other symptoms such as nausea, fatigue, dyspnoea and constipation, intervention to address anxiety and depression, and advice on diet and exercise. In addition to these, patients with advanced breast cancer and evidence of bone metastases may benefit from bisphosphonates, which have been shown to reduce the morbidity of bone metastases, including hypercalcaemia, pain and fractures. Bisphosphonates are recommended for women with evidence of lytic bone metastases with bone destruction.<sup>7</sup> The advantages and disadvantages of the various bisphosphonates are given in Table 4.

### Palliative care

Early referral to the palliative care team allows strong links to be set up in advance rather than an abrupt transition of care having to be made when the terminal disease phase is reached. Oncologists and palliative care physicians and nurses may provide shared care while patients are still seeking active treatment in the pre-terminal phase.

### Useful internet resources

- The National Breast Cancer Centre <http://www.nbcc.org.au/>
- Cancer treatment guidelines <http://www.nccn.org/>
- NHMRC Clinical practice guidelines for the management of advanced breast cancer, 2001. <http://www.health.gov.au/nhmrc/publications/synopses/cp76syn.htm>
- NHMRC Psychosocial clinical practice guidelines: information, support and counselling for women with breast cancer, 2000. <http://www.health.gov.au/nhmrc/publications/synopses/cp61syn.htm>

**Table 4. Bisphosphonates used in the treatment of advanced breast cancer and bone metastases**

Bisphosphonate	Advantages	Disadvantages
Pamidronate (Aredia, Pamisol)	Well established efficacy	Intravenous administration every three to four weeks
Clodronate (Bonafos)	Oral administration convenient for rural patients or patients with poor intravenous access	Gastrointestinal side effects of nausea and cramps, discomfort
Zoledronate (Zometa)	More effective than pamidronate; given over 15 minutes only	Intravenous administration; contraindicated in patients with renal impairment

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## Conclusion

Advanced breast cancer should be treated with an emphasis on enhancing quality of life to achieve not just physical but also psychosocial wellbeing. Each patient's management plan should be tailored according to the disease status and the patient's preferences. A multidisciplinary approach with good communication between the patient and the different members of the team, including the GP, is important to achieve the optimal outcome. **MT**

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**DECLARATION OF INTEREST:** Dr Yap: None.  
Dr Koczwara has served on advisory boards for Aventis Pharma and Novartis.

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