Appendix A: Summary of evidence from surveillance

8-year surveillance (2018) – Advanced breast cancer: diagnosis and treatment (2009) NICE guideline CG81

Summary of evidence from surveillance

Diagnosis and assessment

Q – 01 What are the investigations for (1) assessing disease extent and (2) monitoring the response to treatment, including positron emission tomography (PET)?

Recommendations derived from this review question

Imaging assessment

1.1.1 Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI). [2009]

1.1.2 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. [2009]

1.1.3 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. [2009]

1.1.4 Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases encroaching on the spinal canal). [2009]

1.1.5 Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease. [2009]

Monitoring disease status

1.1.7 Do not use bone scintigraphy to monitor the response of bone metastases to treatment. [2009]

1.1.8 Do not use PET-CT to monitor advanced breast cancer. [2009]

Surveillance decision

This review question should not be updated.

The section on imaging assessment should list a cross-referral to NICE diagnostics guidance DG5 SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver (2012).

Imaging assessment

Previous surveillance summary

Comparisons between imaging strategies

Eight studies(1–8) were identified investigating comparisons between imaging strategies for detection of metastases. However, due to the heterogeneity of the reported results there was insufficient evidence to support the choice of one imaging modality over another.

Positron emission tomography fused with computed tomography (PET-CT)

Nine studies(9–17) were identified investigating the diagnostic accuracy of PET-CT in detecting distant metastases. In summary, some evidence was found for improved sensitivity and specificity for detecting distant metastases with 18F-fluorodeoxyglucose (18F-FDG)-PET-CT when compared to conventional imaging or bone scintigraphy.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

The topic experts stated that in the UK, metastatic disease tends to be investigated only when it is suspected, and that PET-CT shouldn't be offered as a first-line investigation except in certain circumstances. The current recommendation covers that scenario and the experts agreed that it did not need to be changed.

Further topic expert feedback suggests that bone scintigraphy has a useful role in mapping disease at baseline so should be an option.

Impact statement

PET-CT (assessment)

Although there is some evidence to suggest superiority of PET-CT for the initial detection of metastases, the evidence identified at the previous surveillance reviews identified heterogeneity and variability between the reported results. It was also found that not all studies had a population relevant to advanced breast cancer.

Topic expert feedback highlighted the limitations of using PET-CT only in certain circumstances and also suggests the use of bone scintigraphy as an option. The current recommendations cover these scenarios and the experts agreed that they did not need to be changed.

No new evidence was found for any of these strategies at the 8-year surveillance review.

The results from the evidence are not sufficiently conclusive to impact on current recommendations.

Recommendations on imaging assessment of the liver for metastases can be found in NICE diagnostics guidance DG5 SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver (2012), which is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway.

New evidence is unlikely to change guideline recommendations.

Monitoring disease status

Previous surveillance summary

Positron emission tomography fused with computed tomography (PET-CT)

Three studies(18–20) were identified investigating the efficacy of PET-CT in monitoring disease status.

Two of these studies indicated that PET-CT was useful in monitoring disease status which differed from the current guideline recommendation which states that PET-CT should not be used to monitor advanced breast cancer. However, it was decided that further evidence was required comparing PET-CT with other imaging modalities for monitoring disease status to determine whether imaging with PET-CT improves management.

Carcinoembryonic antigen (CEA) and cancer antigen (CA) 15-3

The correlation between carcinoembryonic antigen (CEA) and cancer antigen (CA) 15-3 and imaging of the effectiveness of chemotherapy for metastatic breast cancer was assessed in 3 studies(21–23). Results generally found increased CEA or CA levels in

people with metastatic disease. Results also suggested that CEA and CA could be used as markers to predict treatment response. However, the studies were primarily of retrospective design with small sample sizes.

Comparisons between imaging strategies

The role of PET-CT, compared with ultrasound and MRI, in evaluating the response to neoadjuvant chemotherapy in advanced breast cancer was evaluated in one study(24). The study concluded that MRI was superior to PET-CT and ultrasound in monitoring the effect of neoadjuvant chemotherapy in advanced breast cancer.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

In the previous surveillance reviews, evidence was found for imaging strategies to monitor disease status. It was concluded that due to the heterogeneity between the reported results there was insufficient evidence to support the choice of one imaging modality over another and evidence was unlikely to change current guideline recommendations.

Evidence was also found at the previous surveillance reviews relating to the use of carcinoembryonic antigen and cancer antigen 15-3 in monitoring disease status, however, it was decided it would be pertinent to await further evidence before this was considered within the guideline.

No further evidence was identified at the 8-year surveillance review to change these conclusions.

New evidence is unlikely to change guideline recommendations.

Q – 02 Reassessment of endocrine and HER2 status on disease progression

Recommendations derived from this review question

Pathological assessment

1.1.6 On recurrence, consider reassessing oestrogen receptor (ER) and human epidermal growth factor 2 receptor (HER2) status if a change in receptor status will lead to a change in management. [2017]

Surveillance decision

This review question should not be updated.

Receptor status assessment

Previous surveillance summary

This review question was updated in 2017. Evidence(25,26) identified in 3- and 6-year surveillance was available for consideration in the update.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Evidence from topic expert feedback identified in 3- and 6-year surveillance was available for consideration in the update.

Further topic expert feedback at the 8-year review suggested that the wording in the recommendations on repeat biopsy should be amended. The suggestion is to consider

immunohistochemistry when making treatment decisions.

Impact statement

Tumour biopsy to assess receptor status of the primary tumour and metastases

The surveillance decision at the 6-year review prompted an update of the pathological assessment section of the recommendations.

Recommendation 1.1.6 has been updated to now advise consideration of reassessment of ER and HER2 status.

No further new evidence was found at the 8-year review to impact this area. The topic expert feedback from the 8-year surveillance review has been addressed by the update to recommendation 1.1.6.

New evidence is unlikely to change guideline recommendations.

Providing information and support for decision making

Q – 03 The use of (1) decision aids and (2) information tools to improve treatment outcomes and quality of life

Recommendations derived from this review question

Providing information and support for decision making

1.2.1 Assess the patient's individual preference for the level and type of information. Reassess this as circumstances change. [2009]

1.2.2 On the basis of this assessment, offer patients consistent, relevant information and clear explanations, and provide opportunities for patients to discuss issues and ask questions. [2009]

1.2.3 Assess the patient's individual preference for how much they wish to be involved in decision making. Reassess this as circumstances change. [2009]

1.2.4 Be aware of the value of decision aids and the range available. Make the most appropriate decision aid available to the patient. [2009]

Surveillance decision

This review question should not be updated.

Providing information

Previous surveillance summary

Technology for delivering structured cancer follow-up

A systematic review(27) of 17 papers (based on 13 RCTs) examined new technology for delivering structured cancer follow-up. Most studies involved women with breast cancer and included telephone follow-up. Results suggested that interventions comprising technology had not compromised patient satisfaction or safety, as measured by symptoms, health related quality of life or psychological distress. There was insufficient evidence to comment on the cost effectiveness of technological cancer follow-up interventions.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

No relevant evidence was identified.

Impact statement

The evidence for using technology in cancer follow-up (mainly via telephone) only concluded that it did not compromise patient satisfaction or safety. It is unclear from the evidence whether the use of technology is a better alternative to other types of follow-up.

This evidence is unlikely to impact current recommendations 1.2.1 and 1.2.2: 'Assess the patient's individual preference for the level and type of information. Reassess this as circumstances change' and 'On the basis of this assessment, offer patients consistent, relevant information and clear explanations, and provide opportunities for patients to discuss issues and ask questions.'

New evidence is unlikely to change guideline recommendations.

Systemic disease-modifying therapy

Q – 04 What is the choice of 1st line treatment for patients with metastatic breast cancer, endocrine therapy or chemotherapy?

Recommendations derived from this review question

Systemic disease-modifying therapy

1.3.1 Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer. [2009]

1.3.2 Offer chemotherapy as first-line treatment for patients with ER positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity. [2009]

1.3.3 For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy. [2009]

Surveillance decision

This review question should not be updated.

The section on first-line treatment should include a list of cross-referrals to NICE technology appraisals:

TA214 bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (2011)

TA257 Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (2012)

TA263 bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (2012)

First-line treatment

Previous surveillance summary

No relevant evidence was identified.

8-year surveillance summary

Endocrine therapy modulation

An RCT(28) (n=668) found significant improvement in progression-free survival for ribociclib plus letrozole compared to placebo plus letrozole as first-line treatment in postmenopausal women with hormone receptor

positive and HER2-negative metastatic breast cancer.

Topic expert feedback

A topic expert stated that recommendation 1.3.1 needs to be expanded to take account of ER-positive and HER2-positive disease where endocrine therapy would not be offered to the majority.

Further topic expert feedback stated there have been substantial changes in systemic treatment approaches for metastatic breast cancer in terms of chemotherapy, endocrine therapy modulators and biological therapies since 2009. Whilst many have been subject to NICE technology appraisals there is a need to consider the multiple technologies within a guideline to help healthcare professionals. They suggest that whilst evidence is more limited there are also changes in radiotherapy approaches with localised therapy such as SABR or gamma knife, along with surgery or localised ablative techniques for isolated metastases being considered in clinical practice.

Further topic expert feedback suggested that multiple areas could be reviewed although some will be/are being appraised through NICE Technology Appraisals (TA) and may therefore be outside of guideline scope. Examples are:

- Endocrine therapy modulation including CDK 4/6 inhibitors (palbociclib and ribociclib), everolimus and use of fulvestrant.
- Chemotherapy – the 2009 guideline describes a 'sequence' of treatment. Clinicians usually consider multiple treatment options but not necessarily in one sequence. Newer drugs have been through the TA process, e.g. eribulin but other drugs such as carboplatin for triple negative breast cancer have not been considered.
- Anti-HER2 therapies – since 2009 Trastuzumab emtansine and pertuzumab have been appraised in the TA process. Treatment with trastuzumab beyond progression remains uncertain and some trials have reported since 2009.
- Local therapies – e.g. SABR, gamma knife, ablation, surgery for solitary or limited metastases. However, quality of evidence is limited.
- Electrochemotherapy for skin metastases – again evidence is limited but some centres are offering within the NHS.

Impact statement

One study was identified at the 8-year review which suggests benefit of endocrine therapy modulation with ribociclib. NICE have published a technology appraisal (TA496) on the use of ribociclib with an aromatase inhibitor.

A topic expert commented that recommendation 1.3.1 should take into account populations where endocrine therapy is not offered. However, treatment options taking into account ER and HER2 status are already covered in the NICE pathway for advanced breast cancer.

Topic experts suggested that developments in treatment strategies have occurred since publication of the guideline. Specifically highlighted are SABR or gamma knife, along with surgery or localised ablative techniques. However, no further evidence on these techniques was identified at any surveillance review and topic experts recognised the low quality of the limited evidence that is available currently.

Topic experts also identified developments in chemotherapy, endocrine and biological therapies. NICE Technology Appraisals generally cover these areas of treatment and they are discussed in the relevant sections below.

Recommendations on first-line treatment can be found in NICE technology appraisals:

TA214 bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (2011)

TA257 Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (2012)

TA263 bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (2012)

These TAs are not mentioned in the guideline but are included in the advanced breast cancer NICE pathway.

New evidence is unlikely to change guideline recommendations.

Q – 05 What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?

Recommendations derived from this review question

Endocrine therapy

1.3.4 Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]

1.3.5 Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. [2009]

1.3.6 Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. [2009]

1.3.7 Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. [2009]

Surveillance decision

This review question should not be updated.

The section on endocrine therapy should include a list of cross-referrals to NICE technology appraisals:

TA239 fulvestrant for the treatment of locally advanced or metastatic breast cancer (2011)

TA495 palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2017)

TA496 ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2017)

Endocrine therapy

Previous surveillance summary

Fulvestrant

Five studies(29–33) were identified relating to fulvestrant monotherapy and different dose regimens for treatment of advanced breast cancer in postmenopausal women. The results generally indicated comparable efficacy and safety profiles between the various dose regimens.

A final analysis of the CONFIRM trial(34) (n=736 women with ER-positive breast cancer) found significant improvement in overall survival for fulvestrant 500mg compared to 250mg.

A meta-analysis(35) of 5 studies (n=23; mean age=63.1 years) examined efficacy and safety of fulvestrant in male breast cancer. The review concluded that fulvestrant may potentially have a role in male patients with breast cancer but further clinical and pharmacokinetic investigations are warranted before fulvestrant use becomes a common practice.

Estradiol

One RCT(36) was identified which aimed to determine whether estradiol (6mg daily versus 30mg) was a viable therapy for postmenopausal women with advanced aromatase inhibitor-resistant hormone receptor-positive breast cancer. The study concluded that 6mg of estradiol provided a similar clinical benefit as 30mg with fewer serious adverse effects.

Aromatase inhibitors

A systematic review(37) assessed the use of steroidal (SAIs) and non-steroidal aromatase inhibitors (NSAIs) in metastatic breast cancer. The review concluded that switching from an NSAI to a SAI could be a reasonable option following failed initial treatment.

One RCT(38) was identified which evaluated the efficacy of anastrazole compared with exemestane in postmenopausal women with advanced breast cancer. The results of the study indicated that efficacy was similar in both treatment groups for all endpoints assessed.

A systematic review(39) evaluated the efficacy and safety of first-line aromatase inhibitors (letrozole, exemestane and anastrazole) in hormone sensitive advanced breast cancer concluding that additional head-to-head comparisons were warranted.

Two RCTs(40,41) compared exemestane with exemestane plus celecoxib in postmenopausal women with advanced breast cancer concluding that time to progression was similar in both groups. However, celecoxib is a non-steroidal anti-inflammatory drug and is not licensed in the UK for this indication.

Aromatase inhibitor versus other endocrine therapy

A Cochrane review(42) assessed evidence comparing aromatase inhibitors with other endocrine therapy in the treatment of advanced breast cancer in postmenopausal women. The review concluded that aromatase inhibitors showed a survival benefit compared to other endocrine therapy for advanced breast cancer.

Two studies(43,44) comparing fulvestrant with exemestane in patients with advanced breast cancer indicated similar clinical benefit of both therapies.

The clinical activity of fulvestrant compared with anastrazole as a first-line endocrine therapy for postmenopausal women with advanced breast cancer was assessed in an RCT(45). The clinical benefit rate and objective response rate (ORR) were similar for the two therapies although time to progression was longer for fulvestrant. The results of a second RCT(46) also indicated that fulvestrant and anastrazole were similarly effective.

A meta-analysis(47) of 4 RCTs (n=1226) found no significant differences in efficacy or tolerability between fulvestrant 250mg once monthly and anastrozole 1 mg daily in postmenopausal women with advanced breast cancer.

A meta-analysis(48) of 2 RCTs examined anastrozole plus fulvestrant versus anastrozole alone in first-line treatment of postmenopausal stage IV hormone receptor positive HER2-negative breast cancer. No significant difference was observed for progression free survival or overall survival. The review concluded that addition of fulvestrant 250mg monthly to anastrozole is no better than anastrozole alone.

An economic evaluation(49) found that fulvestrant 500mg was not a cost-effective option compared to generic nonsteroidal aromatase inhibitors (anastrozole and letrozole) in first progression or recurrence of advanced breast cancer in postmenopausal patients in the UK.

The efficacy and safety of exemestane compared with tamoxifen in postmenopausal women with metastatic breast cancer was assessed in an RCT(50). Exemestane demonstrated significant early improvement compared with tamoxifen although no longer-term benefit in progression-free survival was observed.

A systematic review(51) of 45 RCTs (42 on efficacy and safety, 3 on adherence) examined long-term efficacy and safety of exemestane in breast cancer in different clinical settings. In metastatic disease, exemestane was: superior to megestrol acetate after progression on tamoxifen; noninferior to fulvestrant (following a prior aromatase inhibitor) and to nonsteroidal aromatase inhibitors (e.g. anastrozole and letrozole) in the first-line setting; and was more effective when combined with everolimus than exemestane alone following previous aromatase inhibitor use. Exemestane was associated with myalgias and arthralgias, as well as reduced bone mineral density and increased risk of fracture, which did not appear to persist at follow-up, with subsequent return to pretreatment values. Compared with tamoxifen, there was a reduced incidence of endometrial changes, thromboembolic events, and hot flushes. Limited evidence showed non-adherence in 23%-32% of patients.

One RCT(52) was identified which compared serum tissue inhibitor of metalloproteinases-1 (TIMP-1) levels in advanced breast cancer patients receiving letrozole or tamoxifen.

Letrozole was superior to tamoxifen in both the normal serum TIMP-1 group and the elevated serum TIMP-1 group.

A meta-analysis(53) compared endpoints of aromatase inhibitors with tamoxifen in postmenopausal women with advanced breast cancer. Aromatase inhibitors were favourable over tamoxifen for overall response rate and clinical benefit whereas the trend towards improved overall survival was not significant.

Endocrine versus endocrine therapy

A Cochrane review(54) of 7 RCTs (n=2061) compared the efficacy and safety of toremifene with tamoxifen for advanced breast cancer (treatment was first line in six studies). Five studies were of postmenopausal women (only 2 studies included perimenopausal women), and most patients were either ER-positive or of unknown status. The review concluded that toremifene and tamoxifen are equally effective and the safety profile of the former is at least not worse than the latter in the first-line treatment of postmenopausal patients with ER-positive advanced breast cancer. Thus, toremifene may serve as a reasonable alternative to tamoxifen when anti-oestrogens are applicable but tamoxifen is not the preferred choice.

8-year surveillance summary

Aromatase inhibitor versus endocrine therapy

An RCT(55) (n=205) found a significant improvement in overall survival for fulvestrant compared to anastrozole in people with advanced breast cancer.

An RCT(56) (n=297) found no significant benefit in progression-free survival of adding abiraterone acetate to exemestane in postmenopausal women with ER-positive metastatic breast cancer compared to abiraterone acetate or exemestane monotherapies.

Endocrine versus endocrine therapy

An RCT(57) (n=222) found a 3-monthly goserelin 10.8mg regimen to be non-inferior compared to a monthly goserelin 3.6mg regimen when added to tamoxifen in premenopausal women with ER-positive advanced breast cancer. Outcome measures included progression-free survival and objective response rates.

Topic expert feedback

Toremifene

It is noted that there is an MHRA drug safety update from 2009 ('Toremifene (Fareston): risk of QT prolongation') which states that this medicine is not widely used in the UK, but remains a licensed option to treat hormone-dependent metastatic breast cancer in postmenopausal women.

The MHRA website states:

'Toremifene (Fareston) is an oestrogen receptor antagonist. Currently it is not widely used in the UK, but remains a licensed option to treat hormone-dependent metastatic breast cancer in postmenopausal women.

'A European assessment has concluded that toremifene is associated with a dose-dependent risk of increase in QT interval, which carries a risk of serious cardiac arrhythmia. The summary of product characteristics has been updated to include new contraindications and warnings. Do not prescribe toremifene with other drugs that prolong the QT interval.'

Impact statement

Fulvestrant monotherapy

At the previous surveillance reviews, 6 studies were identified relating to fulvestrant monotherapy and comparing different dose regimens in women with advanced breast cancer. The results generally indicated comparable efficacy and safety profiles between the various dose regimens. However, it is noted that many trials included treatment arms with a fulvestrant dose below the licensed dose of 500mg.

Also, a meta-analysis was found showing efficacy of fulvestrant in male breast cancer. However, this study included a small sample size and concluded that more research was needed to determine the effects of fulvestrant in this population. Currently, fulvestrant is not licensed in the UK for use in men.

Recommendations on the use of fulvestrant can be found in NICE technology appraisal TA239 Fulvestrant for the treatment of locally advanced or metastatic breast cancer (December 2011), which is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway.

Also, a further NICE technology appraisal related to fulvestrant is in development:

Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951].

Estradiol

At the previous surveillance reviews, evidence was found for estradiol. It was concluded at the time of review that further study was warranted to compare estradiol with other treatments. The identified study only compared dose regimens and on its own is unlikely to impact recommendations.

Aromatase inhibitors

The previous surveillance reviews found 5 studies investigating the efficacy of aromatase inhibitors in postmenopausal women. The results generally support recommendations to offer an aromatase inhibitor to this population.

Also, one of the above studies determined that switching from a steroidal to a non-steroidal aromatase inhibitor could be a reasonable option. This supports the current recommendation which states that either type can be used.

Recommendations on aromatase inhibitors can also be found in NICE technology appraisals:

- TA495 palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2017)
- TA496 ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (2017)

These TAs are not mentioned in the guideline but are included in the advanced breast cancer NICE pathway.

Aromatase inhibitor versus other endocrine therapy

In total, 13 studies were identified comparing efficacy between aromatase inhibitors and other endocrine therapies in mostly postmenopausal women samples. In general, a trend towards superiority was found in favour of aromatase inhibitors. A review found that fulvestrant was not a cost-effective option compared to aromatase inhibitors. These results generally support current recommendations to offer an aromatase inhibitor to this population.

The SPC for fulvestrant does not indicate a license for use in combination with an aromatase inhibitor.

Also, abiraterone acetate, as used in one of the studies, is not licensed for this indication.

Endocrine versus endocrine therapy

A Cochrane review found comparative efficacy and safety between toremifene and tamoxifen in postmenopausal patients with ER-positive advanced breast cancer. There are no recommendations for toremifene in NICE guideline CG81 and tamoxifen is only recommended for peri- or premenopausal women.

This evidence suggests toremifene may be an alternative to tamoxifen, and may add to current recommendations 1.3.4, 1.3.5 and 1.3.6. However, it should be noted that the MHRA have stated that toremifene is associated with a dose-dependent risk of increase in QT interval, which carries a risk of serious cardiac arrhythmia.

The topic experts agreed that they were not aware of toremifene being used in the UK and that there is no particular desire within the clinical community to use it. Therefore their opinion was that this Cochrane review had no impact on the guideline.

A study compared different dose regimens of goserelin when added to tamoxifen in premenopausal women with ER-positive advanced breast cancer. However, further studies are required to determine any benefit of adding goserelin compared to monotherapy with tamoxifen. Also, the 10.8mg dose as used in the study is not licensed for this indication.

It is also worth noting that a MHRA drug safety update (2010) had been issued on tamoxifen. Given the age of the safety update, it is likely that prescribers will already be aware of the associated risks.

A query was raised about whether the use of the wording ‘offer an aromatase inhibitor’ in recommendation 1.3.4 could be in conflict with TAs that provide guidance on named aromatase inhibitors – particularly if the TA recommendation was not to use a particular aromatase inhibitor. The topic experts felt that the guideline is purposely vague to allow use of whatever drug is the best available and should be kept nonspecific.

New evidence is unlikely to change guideline recommendations.

Q – 06 What is the most effective chemotherapeutic treatment for (1) women and (2) men with metastatic breast cancer?

Recommendations derived from this review question

Chemotherapy

1.3.8 On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. [2009]

1.3.9 Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. [2009]

1.3.10 For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment). [2009]

1.3.11 Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate*. [2009]

*This recommendation is from Gemcitabine for the treatment of metastatic breast cancer (NICE technology appraisal guidance 116; 2007). It was formulated as part of that technology appraisal and not by the guideline developers. It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendation is available.

Surveillance decision

This review question should not be updated.

The section on chemotherapy should list a cross-referral to NICE technology appraisal TA423 eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (2016).

Chemotherapy

Previous surveillance summary

Cost-effectiveness

Six studies(58–63) evaluated the cost-effectiveness of different chemotherapy regimens. Several studies suggested that docetaxel treatment was the least costly which was considered to be in line with the current recommendations.

High-dose chemotherapy

Four studies(64–67) were identified relating to high-dose chemotherapy. No recommendations are currently provided in the guideline relating to high-dose chemotherapy. However, due to heterogeneity among the identified new evidence it was decided it would be pertinent to await further evidence before considering for inclusion in the guideline.

Treatment duration

One systematic review(68) evaluated the effect of different first-line chemotherapy durations in patients with metastatic breast cancer indicating that longer first-line chemotherapy duration led to marginally longer overall survival and longer progression-free survival.

Chemotherapy – monotherapies

Docetaxel

In summary, the identified evidence(69–72) did not invalidate the guideline recommendation (1.3.10) that single-agent docetaxel should be used as a first-line chemotherapy. Two studies indicated that a 3-weekly schedule of docetaxel was preferable. However, it was considered that further research was warranted to confirm these results.

Paclitaxel

Three studies(73–75) were identified relating to paclitaxel for advanced breast cancer.

Paclitaxel is not currently recommended in the guideline except in combination with gemcitabine (recommendation 1.3.11).

However, the literature was too heterogeneous, including comparisons of different treatment regimens, to make a conclusion about the efficacy of paclitaxel as a monotherapy for advanced breast cancer.

Ixabepilone

Two systematic reviews(76,77) were identified which suggested that ixabepilone could be a potential treatment option for metastatic breast cancer.

This treatment was not then licensed for breast cancer. However, ixabepilone for breast cancer (locally advanced or advanced) had been referred for a single Technology Appraisal which may have an impact on the guideline recommendations in the future.

(Update September 2017: the technology appraisal has been suspended since 2008 when the manufacturer received a negative Committee for Medicinal Products for Human Use [CHMP] opinion).

Eribulin

In summary, 3 studies(78–80) were identified showing significant improvements in overall survival for eribulin in previously treated patients with metastatic breast cancer compared to other chemotherapy treatments.

Gemcitabine

A meta-analysis(81) of 9 trials (n=2651) compared gemcitabine-based and gemcitabine-free chemotherapy regimens in metastatic breast cancer. The review concluded that gemcitabine-free chemotherapy was as effective as gemcitabine-based chemotherapy in patients with metastatic breast cancer with increased haematological toxicity. Subgroup analysis indicated that adding gemcitabine to monotherapy might be more effective than therapy without gemcitabine.

Monotherapy versus combination therapy

Three studies(82–84) compared single agent chemotherapy with combination chemotherapy for the treatment of metastatic breast cancer.

The identified evidence was not considered to invalidate the current guideline recommendation (1.3.9) which states: ‘Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.’

Comparisons of mixed chemotherapy regimens

In summary, studies(85–128) were identified evaluating different chemotherapy regimens for treatment of advanced breast cancer. However, as the studies compared different combinations of mixed chemotherapies (and each different combination was generally only supported by one study), heterogeneity was found amongst studies and further evidence was deemed to be required to further assess the choice of one chemotherapy regimen over another.

Platinum-based chemotherapy

A meta-analysis(129) of 7 studies (n=717 of which 442 had advanced/metastatic breast cancer) examined platinum-based chemotherapy (cisplatin and carboplatin) in triple-negative breast cancer (TNBC). In conclusion, platinum-based chemotherapy in the breast cancer patients with TNBC showed an improved short-term efficacy compared with the non-TNBC group during neo-adjuvant chemotherapy, but has not yet been

demonstrated to have an improved effect in advanced breast cancer.

8-year surveillance summary

Chemotherapy – monotherapies

The PELICAN trial(130) (n=210) found no difference in time to disease progression in patients with metastatic breast cancer when comparing pegylated liposomal doxorubicin and capecitabine as first-line therapy.

A network meta-analysis(131) of 8 trials investigated the incidence of toxicity of different chemotherapy regimens. It found that capecitabine monotherapy had higher incidence of nausea or vomiting than other regimens. However, not all comparisons were reported in the abstract.

A trial(132) (n=212) found no significant differences in objective response rate, progression-free survival or overall survival between Genexol-PM formulation paclitaxel and conventional paclitaxel in HER2-negative metastatic breast cancer patients.

A trial(133) (n=200) found no significant differences in progression-free survival or overall survival rates with nab-paclitaxel compared with docetaxel in HER2-negative metastatic breast cancer.

A trial(134) (n=592) found the oral fluoropyrimidine S-1 to be non-inferior in overall survival to docetaxel or paclitaxel in HER2-negative metastatic breast cancer.

A trial(135) (n=142) found no significant differences in progression-free survival or objective response rates between oral fluoropyrimidine S-1 and capecitabine in metastatic breast cancer.

Combined chemotherapy

An RCT(136) (n= not stated in abstract) found no significant differences in progression-free survival between docetaxel plus YM155 compared with docetaxel alone in HER2-negative metastatic breast cancer.

An RCT(137) (n=236) found significantly improved progression-free survival for cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine in patients with triple-negative metastatic breast cancer.

A trial(138) (n=206) found no significant differences in progression-free survival, response duration or overall survival rates with docetaxel plus capecitabine compared to vinorelbine plus capecitabine in metastatic breast cancer.

A trial(139) (n=162) found a significant improvement in progression-free survival but not overall survival for capecitabine plus docetaxel compared to docetaxel alone in patients with HER2-negative metastatic breast cancer.

Capecitabine-based chemotherapy

A meta-analysis(140) of a total 9 trials found significant improvements in progression-free survival and overall response rate with capecitabine-based chemotherapy compared to capecitabine-free chemotherapy for advanced breast cancer. Overall survival was not significantly different between groups.

A meta-analysis(141) of 10 trials found similar progression-free survival and response rates between capecitabine-based and capecitabine-free chemotherapy in metastatic breast cancer. Overall survival was improved in the capecitabine-based treatment.

Platinum-based chemotherapy

An update to a previous systematic review and meta-analysis(142) found 15 new treatment comparisons of platinum-based chemotherapy compared to regimens without platinum in women with metastatic breast cancer. From the total of 28 comparisons, no significant differences in survival were found between treatments with and without platinum for this population.

A systematic review and meta-analysis(143) of 23 trials found significantly improved progression-free survival, overall survival and overall response rates for platinum-based treatments (cisplatin and carboplatin) compared with non-platinum treatments in advanced breast cancer patients.

Taxane versus non-taxane chemotherapy

An update to a Cochrane systematic review(144) included 28 studies and found significantly improved overall survival and time to progression for regimens containing taxanes in women with metastatic breast cancer.

Topic expert feedback

A topic expert suggested that many of the current recommendations on chemotherapy are obsolete (1.3.9, 1.3.10, 1.3.11) as combinations are rarely used and eribulin is standard therapy as recommended in TA423.

Further topic expert feedback suggested that there is published evidence showing that elderly women with breast cancer are less likely to be offered chemotherapy.

The topic experts suggested that in terms of drug sequencing, naming the drugs to be used without stipulating the order of use would make the recommendation less restrictive and potentially more useful.

Comments received from topic experts suggested that there is no single 'best treatment' for patients with recurrent/metastatic breast cancer. All appropriate options should be discussed with the patient who should be involved in choice of therapy. It was also suggested that treatment should be selected based on the following principles

- Endocrine therapy should be used prior to chemotherapy for invasive ER-positive disease except for immediately life-threatening disease.
- Single agent palliative chemotherapy is as effective as combination treatment and generally less toxic.
- No one type of chemotherapy has been shown superior to others, and selection should be based on previous treatments, toxicity, co-morbidities and patient choice (e.g. preference for oral therapy or wish to avoid alopecia).

No specific evidence was provided in support of these statements.

Impact statement

Literature was identified at the previous surveillance reviews relating to monotherapy and combination chemotherapy regimens as treatment for advanced breast cancer. Studies generally found taxane-based chemotherapy to be more effective than non-taxane regimens.

However, heterogeneity across studies in terms of treatment regimens and reported results was apparent. For most treatments only single trials were identified therefore further study was considered to be warranted to confirm the results obtained. As such, no conclusive new literature was identified which would change the direction of current guideline recommendations.

Eribulin

Recommendations on the use of eribulin can be found in TA423 Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (December 2016) which is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. Additionally, a technology appraisal is in progress of eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072].

Topic experts also noted that eribulin is the standard treatment and that combinations are rarely used.

The published TA on eribulin will be included in a list of relevant TAs within this section of the guideline.

Gemcitabine

The technology appraisal TA116 provides guidance on Gemcitabine for the treatment of metastatic breast cancer (January 2007), which is incorporated into the guideline in recommendation 1.3.11 and is included in the advanced breast cancer NICE pathway. It is currently on the static list.

Platinum-based chemotherapy

Various studies of platinum-based chemotherapy were identified at the surveillance reviews.

There are no recommendations in the current guideline specifically about platinum-based chemotherapy and the inconclusive evidence base is unlikely to affect the current generic recommendations 1.3.8 and 1.3.9 on chemotherapy in the guideline: 'On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy', and 'Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.'

Combination versus sequential single-agent chemotherapy

In summary, the evidence from previous surveillance reviews did not invalidate the current guideline recommendations:

- 1.3.8: 'On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.'
- 1.3.9: 'Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.'

No further studies on combination versus sequential single agent chemotherapy were identified at the 8-year surveillance review to change the conclusions of previous reviews.

The topic experts suggested that in terms of drug sequencing, naming the drugs to be used without stipulating the order of use would make the recommendation less restrictive and potentially more useful.

General issues around chemotherapy sequencing may be examined at the next surveillance review. No new evidence in this area was identified at the 8-year surveillance review.

Further topic expert feedback suggested that there is published evidence showing that elderly women with breast cancer are less likely to be offered chemotherapy. However, none of the surveillance reviews have identified studies supporting this view.

Topic expert feedback on involving patients in the treatment decision process is already covered in the current recommendations.

Feedback on selection of treatment based on ER or HER status and history of treatment is covered in the NICE pathway on advanced breast cancer.

New evidence is unlikely to change guideline recommendations.

Q – 07 What is the most effective biological treatment for (1) women and (2) men with metastatic breast cancer?

Recommendations derived from this review question

Biological therapy

1.3.12 For patients who are receiving treatment with trastuzumab** for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone. [2009]

**Recommendations on the use of trastuzumab are covered by Guidance on the use of trastuzumab for the treatment of advanced breast cancer (NICE technology appraisal guidance 34; 2002), which will be updated.

Surveillance decision

This review question should not be updated.

The section on biological therapy should include a list of cross-referrals to NICE technology appraisals:

TA34 Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2002)

TA421 everolimus with exemestane for treating advanced breast cancer after endocrine therapy (2016)

TA458 Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (2017)

The footnote relating to NICE technology appraisal TA34 Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2002) should be removed as it will be included in the list of cross-referrals instead.

Biological therapy

Previous surveillance summary

Monotherapies:

Lapatinib

Five studies(145–149) were identified focusing on the clinical efficacy of lapatinib as treatment for advanced breast cancer.

Trastuzumab

Through the review of the guideline, two studies(150,151) were identified relating to trastuzumab for advanced breast cancer.

Everolimus

The efficacy and safety of oral everolimus (10mg daily versus 70mg weekly) in minimally pretreated patients with metastatic breast cancer was investigated in an RCT(152). The response rate with daily therapy was 12% compared with 0% for weekly therapy.

Bevacizumab

A systematic review(153) examined bevacizumab efficacy in breast cancer. In 41 phase II trials in the metastatic setting, most trials found bevacizumab treatment feasible. The review concluded that despite an increased response rate in the metastatic setting, bevacizumab failed to show any OS benefit. The abstract provided no details of whether bevacizumab was used as monotherapy or in combination, or in what line, therefore firm conclusions on its impact were difficult to make.

Erlotinib

The efficacy and safety or erlotinib in advanced breast cancer was evaluated in a cohort study(154). However, the results indicated that this treatment had minimal activity in unselected previously treated women with advanced breast cancer.

Adecatumumab

One RCT(155) was identified which compared two doses (high-dose versus low-dose) of adecatumumab in patients with metastatic breast cancer. The results of the study indicated that the probability of tumour progression was lower in patients receiving the high-dose therapy although adverse events were higher in this group.

Pertuzumab

An RCT(156) compared two doses of pertuzumab in patients with human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer. Limited efficacy of pertuzumab was observed.

Pan-ErbB receptor tyrosine-kinase inhibitor CI-1033

The efficacy and safety of three different doses of a pan-ErbB receptor tyrosine-kinase inhibitor in metastatic breast cancer was evaluated in an RCT(157). The results of the study indicated that there was no clinically meaningful activity associated with treatment in heavily pretreated patients with metastatic breast cancer expressing more than one ErbB receptor.

Combined therapies:

Pertuzumab and trastuzumab

One single-arm, open-label trial(158) was identified which evaluated the efficacy and safety of pertuzumab in combination with trastuzumab in advanced breast cancer. The results of the study indicated that the ORR was 24.2% and the clinical benefit rate was 50% whilst combination treatment was well tolerated.

Lapatinib and trastuzumab

One RCT(159) was identified which compared the efficacy of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive metastatic breast cancer. The results of the study indicated that combination therapy was beneficial compared to lapatinib alone for progression free survival whilst a trend towards improved overall survival was also observed.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

During consultation, a stakeholder suggested that the recommendation to discontinue

trastuzumab at disease progression should change to mirror clinical practice as many oncologists continue with treatment at this point.

Impact statement

In summary, for some treatments only single trials were identified therefore the previous surveillance reviews concluded that further study was warranted to confirm the results obtained. No new evidence was identified at the 8-year surveillance review to impact recommendations.

In addition, the following NICE technology appraisals cover biological therapies, either as monotherapy or combination treatment, for advanced breast cancer:

- TA257 Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (June 2012)
- Lapatinib for breast cancer (first line use in advanced or metastatic hormone-sensitive breast cancer).
  (Update September 2017: TA now discontinued)
- Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer).
  (Update September 2017: Currently suspended)
- TA34 Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2002).
- TA263 Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012)
- TA214 Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011)
- Breast cancer (HER2 negative, metastatic) - bevacizumab (2nd line) [ID488] (TA currently suspended)
- Breast cancer (HER2 positive, metastatic) – pertuzumab (with trastuzumab and docetaxel) [ID523] (TA in progress)
- TA421 everolimus with exemestane for treating advanced breast cancer after endocrine therapy (December 2016)
- TA458 Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (July 2017)

The published TAs on biological therapies will be included in a list of relevant TAs within this section of the guideline.

Furthermore, several biological therapies discussed in the studies above that are not covered by the technology appraisals programme have the following noted in their SPCs:

- Erlotinib: not licensed for use in breast cancer
- Adecatumumab: not available in the UK
- Pertuzumab: not licensed as monotherapy. Only licensed for use in HER-positive metastatic breast cancer in combination with trastuzumab and docetaxel
- Lapatinib: licensed in combination with trastuzumab for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2); with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy

Combined biological therapies - adverse events

Technology appraisals of combined biological therapies are ongoing, and the risk of adverse events will be examined at the next surveillance review once these technology appraisals have completed.

On reviewing the stakeholder comment regarding recommendation 1.3.12 on trastuzumab, there is no anticipated impact. The recommendation specifies discontinuation when the disease has progressed outside the central nervous system. The recommendation is based on the evidence that the drug does not cross the blood-brain barrier and is therefore not effective in treating metastatic disease of the central nervous system. Guidance on the use of trastuzumab for the treatment of advanced breast cancer is covered in a NICE technology appraisal (TA34).

New evidence is unlikely to change guideline recommendations.

Q – 08 What is the most effective treatment for (1) women and (2) men with metastatic breast cancer? (combination therapies and comparisons between therapies)?

Recommendations derived from this review question

1.3.1 Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer. [2009]

1.3.2 Offer chemotherapy as first-line treatment for patients with ER positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity. [2009]

1.3.3 For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy. [2009]

Endocrine therapy

1.3.4 Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]

1.3.5 Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. [2009]

1.3.6 Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. [2009]

1.3.7 Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. [2009]

Chemotherapy

1.3.8 On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. [2009]

1.3.9 Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. [2009]

1.3.10 For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment). [2009]

1.3.11 Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate*. [2009]

Biological therapy

1.3.12 For patients who are receiving treatment with trastuzumab** for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone. [2009]

*This recommendation is from Gemcitabine for the treatment of metastatic breast cancer (NICE technology appraisal guidance 116; 2007). It was formulated as part of that technology appraisal and not by the guideline developers. It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendation is available.

**Recommendations on the use of trastuzumab are covered by Guidance on the use of trastuzumab for the treatment of advanced breast cancer (NICE technology appraisal guidance 34; 2002), which will be updated.

Surveillance decision

This review question should not be updated.

The footnote relating to NICE technology appraisal TA34 Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2002) should be removed as it will be included in the list of cross-referrals instead.

Treatment effectiveness

Previous surveillance summary

Combined chemotherapy and biological therapy

In summary, the previous surveillance reviews identified 37 studies(160–196) investigating multiple combinations of chemotherapy and biological therapy for advanced breast cancer.

Six studies(197–202) were identified specifically investigating bevacizumab plus a chemotherapy regimen.

Combined biological therapy and endocrine therapy

In summary, the previous surveillance reviews identified 10 studies(203–212) investigating multiple combinations of biological and endocrine therapies for advanced breast cancer.

Combined chemotherapy, biological therapy and endocrine therapy:

A meta-analysis(213) evaluated the efficacy of HER2-targeted therapy in addition to standard therapy (hormone or chemotherapy) in patients with metastatic breast cancer. The meta-analysis concluded that addition of HER2-targeted agents improved overall survival, time to progression and progression free survival.

Chemotherapy versus biological therapy

Three studies(214–216) investigating chemotherapy versus biological therapy were identified. These generally indicated inferiority of sunitinib either as monotherapy or in combination with other treatments.

Chemotherapy versus endocrine therapy

A systematic review(217) was identified which evaluated whether starting treatment with chemotherapy or endocrine therapy for metastatic breast cancer had a more beneficial effect on outcomes. The review concluded that first-line treatment with endocrine therapy was recommended for metastatic breast cancer where hormone receptors are present.

Vaccines

One RCT(218) was identified which evaluated time to progression and overall survival in women with advanced breast cancer who received a sialyl-TN (STn) keyhole limpet hemocyanin (KLH) vaccine. The results of the study indicated that the vaccine was well-tolerated however, no overall benefit in time to progression or overall survival was observed.

The immunogenicity and safety of a NeuGcGM3 based cancer vaccine in patients with advanced breast cancer who had received first line chemotherapy was investigated in an RCT(219). The study concluded that there was a trend towards a survival advantage in the vaccine treated group however, further study was required.

8-year surveillance summary

Combined chemotherapy and biological therapy

An RCT(220) (n=479) found no difference in progression-free survival between neratinib plus paclitaxel compared to trastuzumab plus paclitaxel as first-line treatment in groups of HER2 positive metastatic breast cancer. However, the onset and frequency of central nervous system metastases was significantly reduced in the neratinib group.

An RCT(221), the EMILIA trial, (n=991) found significant improvements in overall survival with trastuzumab compared to capecitabine plus lapatinib. Participants included people with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane.

A systematic review and meta-analysis(222) found that sunitinib in combination with chemotherapy did not show clinical benefit in terms of progression-free or overall survival compared to chemotherapy alone in people with advanced breast cancer. A similar result was found for sunitinib monotherapy. However, sunitinib is not licensed in the UK for breast cancer.

An RCT(223) (n=652) found significant improvements in progression-free survival with trastuzumab plus taxane compared to lapatinib plus taxane in people with HER2-positive advanced breast cancer. However, lapatinib is not licensed in the UK for use with taxanes.

The BOLERO-1 trial(224) (n=719) found no significant difference in progression-free survival between everolimus or placebo when added to treatment with trastuzumab plus paclitaxel in patients with HER2-positive advanced breast cancer. However, everolimus is not licensed in the UK for use in combination with trastuzumab and paclitaxel. It is also not licensed for use in HER-positive breast cancer.

An RCT(225) (n=1144) found no significant benefit of adding ramucirumab to docetaxel in patients with HER2-negative metastatic breast cancer. However, ramucirumab is not licensed in the UK for breast cancer.

An RCT(226) (n=175) found no significant differences in time to progression or overall survival between patients with HER2-positive advanced breast cancer when receiving trastuzumab followed by combination chemotherapy at disease progression compared to receiving the combination therapy upfront.

An RCT(227) (n=147) found no significant reductions in toxicity with metronomic chemotherapy (cyclophosphamide and capecitabine plus bevacizumab) compared to bevacizumab plus paclitaxel in patients with HER2-negative advanced breast cancer. However, this combination of treatments is not licensed for use in the UK.

An RCT(228) (n=783) found paclitaxel to be superior to both nab-paclitaxel and ixabepilone in patients already receiving bevacizumab as first-line therapy for advanced breast cancer. However, ixabepilone is not available in the UK.

A trial(229) (n=600) found no benefit in progression-free survival or overall survival rates when adding vinorelbine to capecitabine plus bevacizumab in advanced breast cancer. However, this is not a licensed combination in the UK.

A trial(230) (n=531) found bevacizumab plus paclitaxel was superior in overall survival but not progression-free survival compared to bevacizumab plus capecitabine for HER2-negative metastatic breast cancer.

Combined endocrine and biological therapy

An RCT(231) (n=666) found significantly increased rates of progression-free survival with palbociclib plus letrozole compared to placebo plus letrozole in post-menopausal women with ER-positive HER2 negative breast cancer.

A follow-up analysis(232) of the PALOMA-3 trial (n=521) found significantly improved patient-reported quality of life and pain scores for treatment with palbociclib plus fulvestrant compared to placebo plus fulvestrant in patients with HER2-positive metastatic breast cancer.

A further analysis(233) of the PALOMA-3 trial (n=521) found significant improvement in progression-free survival with fulvestrant plus palbociclib compared to placebo plus fulvestrant.

An RCT(234) (n=374) found no significant differences in progression-free survival with the addition of bevacizumab to endocrine therapy (letrozole or fulvestrant) in patients with advanced breast cancer. However, bevacizumab is not licensed in the UK in this combination.

An RCT(235) (n=80) found no significant improvement in progression-free survival with ridaforolimus plus dalotuzumab plus exemestane compared to ridaforolimus plus exemestane in ER-positive advanced breast cancer.

An RCT(236) (n=669) found significant improvements in progression-free survival and objective response rates with abemaciclib plus fulvestrant compared with placebo plus

fulvestrant in women with advanced breast cancer.

A trial(237) (n=521) found significantly improved progression-free survival with palbociclib plus fulvestrant compared with fulvestrant plus placebo in HR-positive advanced breast cancer. However, palbociclib is not licensed in the UK for HR-positive disease.

A trial(238) (n=165) found significantly improved progression-free survival with palbociclib plus letrozole compared to letrozole alone in advanced breast cancer.

Unspecified combined treatment

A meta-analysis(239) of a total of 9 trials found significant improvements in overall survival, progression-free survival and overall response rate with combination treatments compared to single agent treatment for metastatic patients pre-treated with a taxane or anthracycline. The abstract does not specify the treatments included in the trials.

Topic expert feedback

A topic expert stated that there is a need for additional information on biological therapies: pertuzumab in combination with trastuzumab, weekly paclitaxel as an option for first-line metastatic disease, and everolimus and fulvestrant for ER-positive disease.

Impact statement

Combined chemotherapy and biological therapy

It is noted that no recommendations are included in the guideline relating to combined biological therapy and chemotherapy. However, relevant Technology Appraisals are available:

- TA458 Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (July 2017)
- TA263 Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012)
- TA214 Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011)
- Breast cancer (HER2 negative, metastatic) - bevacizumab (2nd line) [ID488] (TA currently suspended)
- The technology appraisal TA34: Guidance on the use of trastuzumab for the treatment of advanced breast cancer (namely: trastuzumab plus paclitaxel in women with HER2 positive disease who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate; and trastuzumab monotherapy in women with HER2 positive disease who have received at least 2 chemotherapy regimens for metastatic breast cancer – including at least an anthracycline and a taxane where these treatments are appropriate, and hormonal therapy in suitable oestrogen receptor positive patients [March 2002]) is included in the CG81 recommendation footnotes and is also included in the advanced breast cancer NICE pathway. It is on the static list.

[Note: At the time the guideline was produced, there were not sufficient data for the guideline committee to make recommendations about the use of the combination of trastuzumab with docetaxel. It was agreed that TA34 would be updated by NICE and until such time the recommendations from TA34 will stand. The guideline committee requested that the update of TA34 investigate the clinical and cost-effectiveness of this new combination. The technology appraisal that would provide this update, ID345: Breast cancer (metastatic) - trastuzumab (as monotherapy and in combination with a taxane, is currently suspended since Oct 2011].

(Update September 2017: trastuzumab is now also licensed for use in combination with docetaxel and aromatase inhibitors)

- Breast cancer (HER2 positive, metastatic) – pertuzumab (with trastuzumab and docetaxel) [ID523] which is currently subject to the NICE Decision Support Unit (DSU) undertaking a discussion paper for assessing technologies that are not cost effective at a zero price.
- Guidance on everolimus plus trastuzumab plus vinorelbine was proposed for a technology appraisal, but a referral was not sought for this appraisal.

Two in-progress technology appraisals on sunitinib were identified which may have an impact on the guideline recommendations in the future:

- Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer. (Update September 2017: Technology appraisal is suspended)
- Sunitinib in combination with a taxane within its licensed indication for the first line treatment of advanced and/or metastatic breast cancer. Status: currently suspended. (Update September 2017: Technology appraisal is suspended)

However, the SPC for sunitinib notes that it is not licensed in the UK for use in breast cancer.

Combined biological therapy and endocrine therapy

It is noted that no recommendations are included in the guideline relating to combined biological therapy and endocrine therapy. However, relevant Technology Appraisals are available:

- TA257 Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (June 2012)
- TA421 Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (December 2016)

Although not mentioned in the guideline, they are included in the advanced breast cancer NICE pathway.

Sorafenib

Sorafenib is currently only licensed in the UK for hepatocellular carcinoma, renal cell carcinoma, and differentiated thyroid carcinoma. Given the adverse events associated with sorafenib-based therapy reported in the new evidence, further research is needed to examine this therapy outside of its currently licensed indications before considering for inclusion in the guideline. As such, the new evidence is unlikely to impact on guideline recommendations.

Vaccines

It is unclear whether the vaccines sialyl-TN (STn) keyhole limpet hemocyanin (KLH) and NeuGcGM3 are available in the UK. As such, the 2 studies investigating their effectiveness are unlikely to impact recommendations.

In progress NICE technology appraisals

The following NICE technology appraisals are currently in progress and may have a future impact on recommendations relating to combined therapies:

- Breast cancer (hormone-receptor positive, HER2-negative) - palbociclib [ID915]
- Palbociclib for treating hormone-receptor positive, HER2-negative breast cancer [ID916] (TA currently suspended)
- Ribociclib for breast cancer [ID1026]
- Breast cancer (brain metastases) - etirinotecan pegol [ID881]
- Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951]
- Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523]
- Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072]

These technology appraisals will be assessed at the next surveillance review following their publication.

New evidence is unlikely to change guideline recommendations.

Supportive care

Q – 09 What is the role of ongoing management of advanced breast cancer patients in the community setting?

Recommendations derived from this review question

1.4.1 Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in Improving outcomes in breast cancer: manual update (NICE cancer service guidance [2002]) and Improving supportive and palliative care for adults with cancer (NICE cancer service guidance [2004]), in particular the following two recommendations:

- 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis; at commencement, during, and at the end of treatment; at relapse; and when death is approaching).'
- 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.' [2009]

Surveillance decision

This review question should not be updated.

Supportive care

Previous surveillance summary

An observational study(240) involving 20 women with advanced breast cancer explored psychological reactions and coping on disease progression after first-line chemotherapy. Several coping strategies were assessed including work and social support with most women responding with acceptance.

A systematic review(241) identified five studies of group psychological therapies (including cognitive-behavioural or supportive-expressive) which demonstrated little evidence of psychological or survival benefit for women with metastatic breast cancer.

A post-hoc analysis(242) of an RCT assessing supportive-expressive group therapy for women with metastatic breast cancer was identified. The study concluded that decreasing depression symptoms over the first year were associated with longer subsequent survival in this population.

The impact of a mobile phone-based remote monitoring, advanced symptom management system (ASyMS) on the incidence, severity and distress of chemotherapy-related symptoms was assessed in a study(243). The results of the study indicated that reports of fatigue were lower in the intervention group.

The effect of emotionally expressive writing in women with metastatic breast cancer was evaluated in an RCT(244). The intervention was found to be more beneficial in women who had been recently diagnosed with metastatic breast cancer.

One RCT(245) was identified which evaluated the effect of a brief self-administered psychological intervention on the well-being of women with metastatic breast cancer and men with metastatic prostate cancer. An improvement in quality of life was observed whilst compliance was good.

The feasibility and acceptability of an online peer support group intervention for women with metastatic breast cancer was assessed in an RCT(246). The results of the study indicated that reported satisfaction with the intervention was high.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

A topic expert suggested a need for a designated key worker for metastatic disease and a need for procedures to be put in place for psychological intervention.

Feedback also highlighted the need for designated breast care nurses, especially at diagnosis, to improve care. It was also suggested that quality of life and satisfaction were low in women with metastatic breast cancer.

During consultation, a stakeholder suggested that the guideline should strengthen recommendations on providing information and support to patients with advanced breast cancer. The suggestion was to include advice on referrals to specific metastatic breast cancer support services, diagnosis with a holistic needs assessment, improve communication between services, recommend access to a clinical nurse specialist, and utilisation of multidisciplinary team meetings.

Impact statement

At the previous surveillance reviews, literature was identified focusing on a variety of supportive strategies which were generally effective. However, the previous surveillance reviews concluded that there was insufficient evidence at the time to support the choice of one intervention over another. As such, the identified new evidence was considered unlikely to change the direction of current guideline recommendations. No evidence was identified at the 8-year surveillance review to change this conclusion.

The topic expert suggestions for a key worker and psychological interventions are covered by recommendation 1.4.1.

Topic expert feedback suggested the need for further specialist staff to be involved during diagnosis to improve care. However, no further evidence was identified during the surveillance reviews to support this view.

On reviewing the comments provided by the stakeholder, there was no anticipated impact on the guideline as these areas are already adequately covered in recommendation 1.4.1, the NICE quality standard (QS12) on breast cancer, and in the cancer service guidance (2002 and 2004). NICE guideline CG81 cross-refers to the cancer service guidelines and incorporates the relevant advice within the recommendations.

New evidence is unlikely to change guideline recommendations.

Q – 10 What are the effective interventions used to support young families in which a parent has advanced breast cancer?

Recommendations derived from this review question

1.4.1 Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in Improving outcomes in breast cancer: manual update (NICE cancer service guidance [2002]) and Improving supportive and palliative care for adults with cancer (NICE cancer service guidance [2004]), in particular the following two recommendations:

- 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis; at commencement, during, and at the end of treatment; at relapse; and when death is approaching).'
- 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.' [2009]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Managing complications

Q – 11 What is the diagnostic accuracy of specific investigations to recognise lymphoedema early in patients with advanced (metastatic) breast cancer?

Recommendations derived from this review question

Lymphoedema

The guideline notes that there are no agreed diagnostic tests or assessment methods to detect lymphoedema. As such, there are no specific recommendations for this review question.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Q – 12 What is the best management strategy of lymphoedema?

Q – 13 In adults with breast cancer post-treatment (excepting ongoing home treatment), what is the role of exercise in relation to the safety of the exercise undertaken?

Recommendations derived from this review question

Lymphoedema

1.5.1 Discuss with people who have or who are at risk of breast-cancer related lymphoedema that there is no indication that exercise prevents, causes or worsens lymphoedema. [new 2014]

1.5.2 Discuss with people who have or who are at risk of breast cancer related lymphoedema that exercise may improve their quality of life. [new 2014]

1.5.3 Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme. [2009]

1.5.4 Offer all patients with lymphoedema complex decongestive therapy (CDT) as the first stage of lymphoedema management. [2009]

1.5.5 Consider using multilayer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery. [2009]

1.5.6 Provide patients with lymphoedema with at least two suitable compression garments. These should be of the appropriate class and size, and a choice of fabrics and colours should be available. [2009]

1.5.7 Provide patients with lymphoedema with clear, written information and the contact details of local and national lymphoedema support groups. [2009]

Surveillance decision

This review question should not be updated.

Management strategies

Previous surveillance summary

This review question was updated in 2014. Evidence(247–268) identified in 3- and 6-year surveillance was available for consideration in the update.

8-year surveillance summary

A meta-analysis(269) of 6 trials investigated manual lymphatic drainage (MLD) for breast cancer related lymphoedema. The analysis found significant reductions in swelling when manual lymphatic drainage is added to compression bandaging. However, mixed and inconclusive results were found when MLD was compared to other types of treatment.

Topic expert feedback

Topic experts noted that the opening narrative that describes lymphoedema and its management has marginally changed, along with some of the descriptive language e.g. Complex Decongestive Therapy (CDT) is now often referred to as Decongestive Lymphatic Therapy (DLT). Whilst such amendments do not directly impact or influence an update surrounding the specifics of the guideline i.e. diagnosis and treatment in advanced breast cancer; updating the language in the narrative would add credibility to CG81.

An additional comment noted that DLT is the preferred term. Some use the “L” to mean Lymphatic, while others to mean Lymphoedema. There was a suggestion that the latter is preferred.

Impact statement

Lymphoedema management

At the 3-year surveillance review, new evidence was identified on exercise in patients with breast cancer-related lymphoedema. This led to an update of the guideline in which 2 new recommendations (1.5.1 and 1.5.2) were added.

At the 6-year surveillance review, no further evidence on exercise was found. Nor were any further studies found to supplement evidence on various treatments identified at the 3-year surveillance review (bandaging, compression hosiery, laser therapy, complex decongestive therapy, aqua lymphatic therapy or hyperbaric oxygen therapy). All of which either showed no benefit, or required further validation.

However, new literature was identified at the 8-year review for manual lymphatic drainage and intermittent pneumatic compression pump, but neither intervention was better than standard treatment. As such, this new evidence is unlikely to impact on guideline recommendations.

Topic expert feedback indicated that some of the terminology used in the guideline has changed. For example, Complex Decongestive Therapy (CDT) is now often referred to as Decongestive Lymphatic [or Lymphoedema] Therapy (DLT).

The British Lymphology Society was contacted. They responded to say that the terms ‘decongestive lymphatic therapy’ and ‘decongestive lymphoedema therapy’ are interchangeable, noting that they are referred to by different groups by different names. The society felt that the UK has probably now moved to the term ‘decongestive lymphatic therapy’ but that is not reflected internationally. It was also noted that the term ‘complex physical therapy’ is also in use.

Because NICE has been made aware of a wide range of terms, without any strong preference for any of the terms in particular, the terminology should not be updated at this time.

New evidence is unlikely to change guideline recommendations.

Q – 14 What are the best management strategies for:

- Cancer-related fatigue

- Uncontrolled local disease

- Solitary or multiple bone-metastases

- Solitary or multiple brain-metastases

Recommendations derived from this review question

Cancer-related fatigue

1.5.8 Offer all patients with advanced breast cancer for whom cancer related fatigue is a significant problem an assessment to identify any treatable causative factors, and offer appropriate management as necessary. [2009]

1.5.9 Provide clear, written information about cancer-related fatigue, organisations that offer psychosocial support and patient led groups. [2009]

1.5.10 Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue. [2009]

Uncontrolled local disease

1.5.11 A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms. [2009]

1.5.12 A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team. [2009]

1.5.13 A palliative care team should assess all patients with uncontrolled local disease in order to plan a symptom management strategy and provide psychological support. [2009]

Bone metastases

1.5.14 Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain. [2009]

1.5.15 The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication. [2009]

1.5.16 Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain. [2009]

1.5.17 An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery. [2009]

Brain metastases

1.5.18 Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well controlled other metastatic disease. [2009]

1.5.19 Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis. [2009]

1.5.20 Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy. [2009]

1.5.21 Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate. [2009]

Surveillance decision

This review question should not be updated.

The section on cancer-related fatigue should list a cross-referral to NICE technology appraisal TA323 Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (2014)

The section on bone metastases should list a cross-referral to NICE technology appraisal TA265 Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (2012)

Management strategies for complications

Previous surveillance summary

Cancer-related fatigue

Five studies(270–274) were identified investigating the effects of exercise, psychosocial, and pharmacological treatments for cancer-related fatigue.

The literature on management of cancer-related fatigue was considered to be in line with the current guideline recommendation 1.5.10 that patients with advanced breast cancer should have access to an exercise programme. The literature on psychosocial and pharmacological interventions for cancer-related fatigue indicated that these interventions warranted further study.

Uncontrolled local disease

One Cochrane systematic review(275) was identified which evaluated the evidence relating to the effects of dressings and topical agents on quality of life in people with fungating malignant wounds. The review concluded that 6% miltefosine solution applied topically to people with superficial fungating breast lesions who have previously received radiotherapy, surgery, hormonal therapy or chemotherapy for their breast cancer, may slow disease progression. However, more research was needed on managing wound symptoms associated with fungating wounds.

Bone metastases

The efficacy and safety of high- or reduced-dose radiotherapy combined with zoledronic acid in breast cancer patients with bone metastases was assessed in an RCT(276). No significant differences were found in pain scores or bone scintigraphy results between the two groups indicating that reduced-dose radiotherapy produced a similar response rate to high-dose radiotherapy.

The incidence of adverse effects following administration of denosumab or intravenous bisphosphonate in patients with advanced breast cancer and bone metastases was evaluated in an RCT(277). The results of the study indicated that patients receiving denosumab had fewer adverse effects than those receiving intravenous bisphosphonate at three days and four weeks following treatment initiation.

In addition, the efficacy of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy was investigated in an RCT(278). The study concluded that denosumab appeared to reduce the risk of skeletal-related events in breast cancer patients who had not received prior bisphosphonate therapy.

An RCT(279) was identified which compared subcutaneous denosumab with intravenous zoledronic acid or placebo in patients with breast cancer and bone metastases. The results of the study indicated that denosumab was superior to zoledronic acid in delaying or preventing skeletal-related events in patients with bone metastases.

A Cochrane systematic review(280) was identified which evaluated the effect of bisphosphonates on skeletal events and bone pain in women with early or advanced breast cancer. The review concluded that in women with advanced breast cancer and bone metastases, bisphosphonates reduced the risk of developing skeletal events and the skeletal event rate.

One RCT(281) was identified which assessed the safety and efficacy of ibandronate in patients with advanced breast cancer and bone metastases. The results of the study indicated that treatment with intravenous ibandronate every four weeks for 24 months significantly reduced the number of patients experiencing a skeletal event compared with placebo.

The efficacy and safety of oral odanacatib, a cathepsin K inhibitor, compared with intravenous zoledronic acid in reducing markers of bone resorption in women with

breast cancer and bone metastases was evaluated in an RCT(282). The study concluded that odanacatib was generally well tolerated and could be a potentially novel therapeutic method for treating bone metastases.

A long-term follow-up of an RCT(283) was identified which evaluated whether adding oral clodronate to postoperative adjuvant breast cancer therapy improved survival in patients with bone metastases. The results of the study indicated that although a significant improvement in overall survival was maintained in the clodronate group at a median follow-up of 103 +/- 12 months, significant reductions in the incidence of bony and visceral metastases and improvement in duration of disease-free survival at 36- and 55-month follow-up periods were no longer seen with clodronate.

A Cochrane review(284) examined bisphosphonates and other bone agents for breast cancer. In breast cancer with bone metastases, bisphosphonates significantly reduced skeletal-related events versus placebo or no bisphosphonates. This benefit was most certain with zoledronic acid, pamidronate, and ibandronate. Denosumab significantly reduced skeletal-related events versus bisphosphonates.

A systematic review(285) to inform an evidence-based Canadian guideline examined bone health in patients with breast cancer. Zoledronate, pamidronate, clodronate, and denosumab were recommended for metastatic breast cancer patients; however, no one agent could be recommended over another.

Brain metastases

A small-scale clinical trial(286) evaluated the efficacy and safety profile of temozolomide using protracted low-dose and whole-brain radiotherapy (WBRT) for breast cancer patients with brain metastases. The results of the study indicated that the concomitant use of WBRT and protracted low-dose temozolomide appeared to be active and well-tolerated although further study was required.

The efficacy, safety and tolerability of concurrent cisplatin and vinorelbine chemotherapy and radiotherapy in patients with breast cancer and brain metastases was evaluated in a clinical trial(287). Progression-free survival was 3.7 months and overall survival was 6.5 months whilst overall toxicity was acceptable.

A clinical trial(288) was identified which assessed the use of trastuzumab concurrently with WBRT for patients with brain metastases from human epidermal growth factor receptor-2-positive breast cancer. The study concluded that although promising results were obtained further research was necessary.

The new literature relating to management of brain metastases was heterogeneous with the studies suggesting that further research was warranted. As such, the literature was deemed unlikely to change the direction of current guideline recommendations at the 3 year surveillance review.

Management of pain

One RCT(289) evaluated the effects of supportive-expressive group therapy plus education versus education-only control on pain over 12 months in women with advanced breast cancer. The results of the study indicated that the intervention group had less increase in the intensity of pain compared with controls but there was no difference in frequency of pain episodes or amount of constant pain.

Treatment of acute radiodermatitis

One RCT(290) was identified which evaluated treatment of acute radiodermatitis with an oil-in-water emulsion following radiotherapy. Compared with an untreated group, some beneficial effect of an oil-in-water emulsion on stratum corneum hydration was observed.

Chemotherapy – management of chemotherapy-related adverse effects

One RCT(291) (BRAVE study) was identified which evaluated whether epoetin beta could improve survival in patients with metastatic breast cancer. The results of the study indicated that median iron levels increased in the treatment group however no difference in overall survival, compared with control, was observed. Thromboembolic events were higher in the epoetin group. A post-hoc analysis of the BRAVE study(292) concluded that antithrombotic therapy may have the potential to reduce the risk of thrombovascular events under epoetin therapy.

One systematic review(293) evaluated the risk of early and late cardiotoxicity of anthracycline agents in patients treated for breast (mainly advanced) and other cancers however insufficient robust evidence was identified.

Doxorubicin

A post-hoc analysis of an RCT(294) was identified which aimed to develop a risk predication model for neutropenic complications during chemotherapy with doxorubicin. The study concluded that use of the model may improve patient care by targeting preventative therapies to patients most likely to experience neutropenic complications during chemotherapy. A related clinical guideline has now been published: NICE guideline CG151 Neutropenic sepsis: Prevention and management in people with cancer.

Liver metastases

(Note: The guideline did not cover management of liver metastases but it is very closely related to complications arising from advanced breast cancer so has been considered in the surveillance review).

A systematic review(295) of 19 studies (n=553) examined hepatic resection for metastatic breast cancer. The review concluded that hepatectomy is rarely performed for breast cancer liver metastases but studies indicate consistent results with superior 5-year survival for selected patients with isolated liver metastases and in those with well controlled minimal extra-hepatic disease.

8-year surveillance summary

Bone metastases

The OPTIMIZE-2 RCT(296) (n=416) found no differences in the safety profiles of every 4-week or every 12-week zoledronic acid regimens for breast cancer patients with bone metastases.

An RCT(297) (n=73) found no palliative improvements in patients with high-risk bone metastases when switching to zoledronic acid from pamidronate.

Brain metastases

An RCT(298) (n=51) found that prophylactic cranial irradiation did not significantly reduce the incidence of central nervous system metastases in HER2 positive metastatic breast cancer.

Topic expert feedback

A topic expert stated that the section on bone metastases should include the use of denosumab.

Further topic expert feedback suggested that patients should be discussed if possible at a metastatic multi-disciplinary team (MDT) meeting or neurosurgical MDT if brain metastases.

During consultation, a stakeholder commented that consideration should be given to a new recommendation supporting the use of stereotactic radiotherapy for brain metastases. This stakeholder also suggested that recommendation 1.5.14 should be updated to reflect the current practice of offering bisphosphonates to all patients with bone metastases.

Impact statement

Cancer-related fatigue

The evidence from previous surveillance reviews suggested that exercise improved cancer-related fatigue. This is considered to be in line with the current guideline recommendation 1.5.10: 'Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue'.

The literature on psychosocial and pharmacological interventions for cancer-related fatigue indicated that these interventions warranted further study.

It is noted that TA323: Erythropoiesis‐stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142) (November 2014) is now published, but is not mentioned in the guideline and is not included in the advanced breast cancer NICE pathway. The NICE pathway and the guideline section on cancer-related fatigue should cross-refer, at the earliest opportunity, to TA323.

Bone metastases:

Bisphosphonates

Taken together the evidence is consistent with the current guideline recommendations 1.5.14 and 1.5.15: 'Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain', and 'The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication.'

There are also a number of MHRA drug safety updates issued for bisphosphonates:

- Bisphosphonates: atrial fibrillation (2008)
- Bisphosphonates: osteonecrosis of the jaw (2009)
- Oral bisphosphonates: oesophageal cancer risk – insufficient evidence of a link (2010)
- Intravenous zoledronic acid: adverse effects on renal function (2010)
- Bisphosphonates: atypical femoral fractures (2011)
- Bisphosphonates: very rare reports of osteonecrosis of the auditory canal (2015)

Denosumab

A NICE technology appraisal already covers the use of denosumab and is in the advanced breast cancer pathway:

- TA265 Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012)

There are also a number of MHRA drug safety updates issued for denosumab:

- Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal (2017)
- Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk (2015)
- Denosumab: updated recommendations (2014)
- Denosumab 60 mg (Prolia▼) (2013)
- Denosumab: monitoring recommended (2012)

Liver metastases

(Note: The guideline did not cover management of liver metastases but it is very closely related to complications arising from advanced breast cancer so has been considered in the surveillance review).

At the previous surveillance reviews, a systematic review indicated hepatic resection for metastatic breast cancer led to superior 5-year survival for selected patients with isolated liver metastases and in those with well controlled minimal extra-hepatic disease. However, the review did not undertake a direct comparison with non-surgical patients; therefore evidence is currently unlikely to impact on guideline recommendations.

No evidence was identified at the 8-year surveillance review. This area will be monitored at the next surveillance review.

Uncontrolled local disease; Brain metastases; Pain; Acute radiodermatitis

In summary, no new evidence was identified which would impact on current recommendations.

For brain metastases, the evidence, at both 3- and 8-year reviews, was heterogeneous with the studies suggesting that further research was warranted. As such, the literature was deemed unlikely to change the direction of current recommendations.

The following NICE guideline is currently in progress and may have a future impact on recommendations relating to the management of brain metastases:

- Brain tumours (primary) and brain metastases in adults [GID-NG10003]

If appropriate, the NICE pathway on advanced breast cancer will cross-refer to the guideline on brain metastases when it publishes.

For pain and acute radiodermatitis, only single trials were identified therefore it was concluded that further study was warranted to confirm the results obtained. The same conclusion that more conclusive evidence is required applies to the management of uncontrolled local disease.

New evidence is unlikely to change guideline recommendations.

Areas not currently covered in the guideline

NQ – 01 What is the role of surgical resection of the primary tumour in stage IV breast cancer?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

Surgical resection

Previous surveillance summary

A meta-analysis(299) of 10 studies (n=28,693) examined the impact on survival of surgical resection of the primary tumour in stage IV breast cancer. Of the 10 included studies, 9 were retrospective cohort studies and 1 was case-control. Survival at 3 years was significantly higher at 40% in patients who underwent surgery versus 22% in those who had no surgery. In subgroup analyses, patients selected for surgery had significantly smaller primary tumours, less competing medical comorbidities and lower metastatic burden. There was no statistical difference between the two groups regarding location of metastatic disease, grade of tumour, or receptor status.

The authors concluded that in the absence of robust evidence, the meta-analysis provides an evidence base for primary resection in stage IV breast cancer for appropriately selected patients. It was however also noted by the authors that 5 RCTs in this area are underway, and preliminary results from 2 of these trials indicated no effect on overall survival of surgery to the primary tumour.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

The topic experts advised that surgical resection of the primary tumour in patients with established advanced or metastatic disease is not something that is done with regularity and is generally looked at on a case by case basis. They also commented that the studies in this area were of poor quality.

Impact statement

No evidence was identified at the 3- or 8-year surveillance reviews.

At the 6-year surveillance review, a meta-analysis indicated that surgical resection of the primary tumour in stage IV breast cancer can increase survival compared with no surgery.

As such, it may be appropriate to consider the evidence base for surgical resection of the primary tumour in the guideline, in appropriately selected patients. However, the retrospective nature of the current evidence base should be taken into account, and the future publication of results from ongoing RCTs may provide more robust data for analysis at the next surveillance review.

New evidence is unlikely to impact on the guideline.

NQ – 02 What are the predictors of treatment response?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

Predictors of response to treatment

Previous surveillance summary

Predictors of sensitivity to trastuzumab

A meta-analysis(300) of 10 studies (n=1889) examined the predictive role of phosphatase and tensin homolog (PTEN) loss, phosphoinositol-3 (PI3) kinase (PIK3CA) mutation, and PI3K pathway activation in sensitivity to trastuzumab in HER2-positive breast cancer. In patients with HER2-positive recurrent or metastatic breast cancer, PTEN loss was significantly correlated with poorer efficacy of trastuzumab-based salvage treatment. The authors noted the small sample size and the considerable heterogeneity in the chemotherapy treatment regimens, and that further research was needed.

8-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer

Topic expert feedback highlighted the following study:

A multicentre, prospective trial(301) identified genomic abnormalities with the aim of providing targeted therapy matched to individuals' genomic alterations. Of the 423 included patients, comparative genomic hybridisation array and Sanger sequencing were feasible in 283 and 297 patients respectively. A targetable genomic alteration was identified in 195 (46%) patients, most frequently in PIK3CA (25%), CCND1 (19%), and FGFR1 (13%). Other rare genomic alterations (defined as occurring in less than 5% of the general population) were seen in 39% of patients, including AKT1 mutations, and EGFR, MDM2, FGFR2, AKT2, IGF1R, and MET high-level amplifications. Therapy could be personalised in 13% of patients. Of the 43 patients who were assessable and received targeted therapy, 4 (9%) had an objective response, and 9 (21%) had stable disease for more than 16 weeks. The authors concluded that personalisation of medicine for metastatic breast cancer is feasible, including for rare genomic alterations.

Impact statement

Predictors of sensitivity to trastuzumab

No evidence was identified at the 3- or 8-year surveillance reviews.

At the 6-year surveillance review, a meta-analysis found that in patients with HER2-positive recurrent or metastatic breast cancer, PTEN loss was significantly correlated with poorer efficacy of trastuzumab-based salvage treatment. However, the small sample size and the considerable heterogeneity in the chemotherapy treatment regimens mean that further research is needed before considering this area for inclusion in the guideline.

Genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer

No evidence was identified at the 3- or 8-year surveillance reviews.

At the 6-year surveillance review, topic experts highlighted a multicentre, prospective trial suggesting that testing for genomic abnormalities in individual patients could provide a means of matching therapy to individuals' genomic alterations. However limited data on how the targeted therapy translated into beneficial outcomes for patients

means that an impact on the guideline is currently unlikely.	New evidence is unlikely to impact on the guideline.

Editorial and factual corrections identified during surveillance

During surveillance the following editorial or factual corrections were identified:

It is noted that TA323: Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142) (November 2014) is now published, but is not mentioned in the guideline and is not included in the advanced breast cancer NICE pathway. The NICE pathway on advanced breast cancer and the guideline section on cancer-related fatigue should cross-refer, at the earliest opportunity, to TA323.

Where appropriate, the guideline should list cross-referrals in the relevant sections to published NICE technology appraisals and NICE diagnostics guidance in alignment with those in the NICE pathway on advanced breast cancer. A statement will be added to the guideline noting that this is a clinical area in which new technologies are developed and assessed frequently and for clinicians to refer to the NICE pathway on advanced breast cancer in conjunction with the guideline.

Research recommendations

RR – 01 Clinical trials are needed to investigate the most effective endocrine therapy for postmenopausal women with ER-positive tumours who progress on treatment with an aromatase inhibitor.

See clinical questions 05 and 08 in the table above.

Although a number of endocrine therapies have been investigated, there is no clear indication as to the most effective in this population. Further studies, especially those with direct comparisons between endocrine therapies, are needed to address this research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 02 Randomised clinical trials should evaluate the clinical and cost effectiveness of different sequences of chemotherapy for advanced breast cancer.

See clinical question 06 in the table above.

The above studies evaluated different chemotherapy regimens for treatment of advanced breast cancer. However, as the studies compared different combinations of chemotherapies (and each different combination was only supported by one or two studies with inconclusive summaries), further evidence was deemed to be required to further assess the choice of one chemotherapy regimen over another. Also, topic experts suggested that in terms of drug sequencing, naming the drugs to be used without stipulating the order of use would make the recommendation less restrictive and potentially more useful.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 03 The use of continued trastuzumab in patients with progressive metastatic disease should be investigated as part of a randomised controlled trial. Trial design should incorporate collection of data required for prospective cost effectiveness analysis.

See clinical question 07 in the table above.

The use of trastuzumab has been covered by NICE Technology Appraisals TA34 and TA458.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 04 Randomised controlled trials are needed to assess whether patients who have had adjuvant trastuzumab should be offered further biological response modifiers. Trial design should incorporate collection of data required for prospective cost-effectiveness analysis.

See clinical question 07 in the table above.

The use of trastuzumab has been covered by NICE Technology Appraisals TA34 and TA458.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 05 **The relevant research organisations should be encouraged to address the topic of uncontrolled local disease and devise appropriate research studies. This might include development of a national register.**

See clinical question 14 in the table above.

No evidence in this area was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 06 **Clinical trials are needed to investigate the effectiveness of ovarian suppression in combination with an aromatase inhibitor compared with that of ovarian suppression in combination with tamoxifen in pre-menopausal women with ER-positive tumours.**

See clinical questions 05 and 08 in the table above.

Although a number of endocrine therapies have been investigated, there is no clear indication as to the most effective in this population. Further studies, especially those with direct comparisons between endocrine therapies, are needed to address this research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 **All randomised controlled trials of treatment after failure of all available treatments for which good quality evidence exists should either contain a placebo arm, or provide a valid justification for not doing so.**

See clinical questions 04 to 08 in the table above.

Not all trials contained a placebo arm and none provided justification for not doing so, from an assessment of the abstract.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 08 **An observational study examining levels of oestrogen suppression in men being treated with either single agent aromatase inhibitors or aromatase inhibitors in combination with a GNRH agonist are needed.**

See clinical questions 05 and 08 in the table above.

Although a number of endocrine therapies have been investigated, there is no clear indication as to the most effective in this population. Further studies, especially those in a male population, are needed to address this research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 09 **Research is needed to explore whether patients with advanced breast cancer would prefer intravenous therapies to be delivered at home, near home or in the hospital setting.**

No evidence identified in relation to this research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 10 Research is needed to identify the support needs specific to advanced breast cancer patients who are themselves carers. This research should identify which of these needs are currently met and where additional support resources are required.

No evidence identified in relation to this research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 11 Research is needed to compare the effectiveness of complex decongestive therapy with less intensive interventions in patients with advanced breast cancer. The research should incorporate both objective and quality of life measures.

See clinical question 12 in the table above.

Generally, the evidence identified at the 3-year surveillance review indicated effectiveness of complex decongestive therapy. However, no further evidence was identified at either the 6- or 8-year surveillance reviews.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 12 Randomised controlled trials are needed to assess the value of psychological interventions in the management of fatigue in patients with advanced breast cancer. Both short and long-term outcomes should be evaluated. An appropriate validated tool to measure fatigue should be used.

See clinical question 14 in the table above.

The evidence on psychological interventions was limited in number and generally showed little benefit. The literature on psychosocial interventions for cancer-related fatigue indicated that these interventions warranted further study.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 13 What is the role of arm and shoulder specific exercises compared with and/or used as an adjunct to established lymphoedema treatments (such as compression garments and complex decongestive therapy)?

See clinical questions 12-13 in the table above.

A number of studies identified a benefit of exercise especially for the management of lymphoedema. This evidence has resulted in the previous update to the guideline. No new evidence at the 8-year surveillance review was identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 14 A randomised controlled trial is needed to compare stereotactic radiotherapy with whole brain radiotherapy in patients with advanced breast cancer and solitary or a limited number of brain metastases.

See clinical question 14 in the table above.

A NICE guideline on the management of brain metastases is currently in development. The scope includes a review question related to the use of stereotactic radiotherapy. If appropriate, the NICE pathway on advanced breast cancer should cross-refer to the guideline on brain metastases when it publishes.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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