6-year surveillance 2015 – Advanced breast cancer (2009; CG81.1 addendum 2014) NICE guideline CG81

Appendix A: decision matrix

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Diagnosis and assessment			
81-01 What are the investigations for (1) assessing disease extent and (2) monitoring the response to treatment, including positron emission tomography (PET)? (1.1.1 – 1.1.5)			
3-year surveillance (2011) **Imaging assessment** ***Comparisons between imaging strategies*** One study[1] was identified which compared the diagnostic performance of 18F-deoxyglucose (FDG)-positron emission tomography (PET), computed tomography (CT) and conventional imaging for detection of distant metastases in breast cancer. The study concluded that in breast cancer, FDG-PET was superior to conventional imaging procedures for detection of distant metastases. A systematic review[2] was identified which evaluated the accuracy of ultrasound (US), CT, magnetic resonance imaging (MRI), scintimammography (SMM) and PET in detecting recurrent breast cancer. The review concluded that MRI was the most useful imaging technique although FDG-PET could be performed in addition. One study[3] was identified which assessed the correlation between 18FDG-PET-CT, cancer antigen 27.29 and circulating tumour cell	**Imaging assessment** ***Positron emission tomography (PET)*** A meta-analysis[21] of 13 studies evaluated 18F-fluorodeoxyglucose (18F-FDG) PET in breast cancer recurrence detection in the presence of elevated tumour markers in patients with breast cancer. Sensitivity was 0.878 and specificity was 0.693. The study concluded that there was potential of 18F-FDG PET, and in particular of PET-CT, in detecting occult soft tissue and bone metastases in the presence of a progressive increase of serum tumour markers in patients with breast cancer. ***PET fused with computed tomography (PET-CT)*** A meta-analysis of 8 studies [22] (n=748) evaluated 18F-FDG PET-CT for diagnosing distant metastases in breast cancer patients, and also compared it with conventional imaging. The study concluded that 18F-FDG PET-CT has higher sensitivity than conventional imaging for diagnosing distant	None identified relevant to this question.	**PET-CT (assessment)** ***Bone metastases*** New evidence was identified which may change current recommendations. Among the evidence from the 3-year surveillance review were 2 studies that found FDG-PET-CT was equally specific but more sensitive and more accurate than bone scintigraphy for detecting bone metastases from breast and prostate cancers. A third study assessing the detectability of bone metastases found that lesions with sclerotic or mixed changes or located in bone cortex alone showed high uptake of18F-fluoride on PET-CT. Further evidence at the 6-year surveillance review from 2 meta-analyses found that 18-FDG PET-CT may have higher sensitivity and specificity than bone scintigraphy for detecting bone metastases in patients with breast cancer. Currently, the guideline recommendation 1.1.5 related to PET-CT is: 'PET-CT should only be used to make a new diagnosis of metastases

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
testing (CTC) in metastatic breast cancer. The study concluded that CA 27.29 and CTC had poor sensitivity and negative predictive value to detect metastatic disease observed on PET-CT scan. The diagnostic accuracy of diffusion-weighted whole body signal suppression (DWIBS) with skeletal scintigraphy for the detection of bone metastases was evaluated in a study[4]. The study concluded that the DWIBS was not superior to scintigraphy for staging in breast cancer. A study[5] was identified which compared whole body FDG-PET-CT with bone scintigraphy for the detection of bone metastases in breast cancer patients. The study concluded that on a lesion-basis whole-body FDG-PET-CT was more sensitive and equally specific for the detection of bone metastases compared with bone scintigraphy. A meta-analysis[6] compared the diagnostic value of 18FDG-PET, MRI and bone scintigraphy in detecting bone metastases in patients with breast cancer. The meta-analysis concluded that MRI was better than 18FDG-PET and bone scintigraphy in diagnosis of bone metastases in patients with breast cancer on a per-patient basis. The sensitivity of MRI and scintigraphy for detecting metastatic bone disease involving the axial skeleton was assessed in one study[7]. The study concluded that MRI was more sensitive than scintigraphy in the detection of bone metastases.	metastases in breast cancer. A meta-analysis of 7 studies[23] (n=668) compared 18F-FDG PET-CT and bone scintigraphy for detecting bone metastases in patients with breast cancer. The study concluded that 18F-FDG PET-CT may have higher sensitivity and accuracy for detection of bone metastases in breast cancer patients than bone scintigraphy. A meta-analysis of 41 studies[24] (n=4305) examined whole-body PET-CT for detecting distant malignancies in various cancers. The study concluded that whole-body PET-CT has excellent diagnostic performance for the overall assessment of distant malignancies in patients with various cancers, especially head and neck cancer, breast cancer, and lung cancer.		for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease'. Together, the studies from the 3 and 6-year surveillance reviews suggest PET-CT may be superior to bone scintigraphy in the initial detection of bone metastases, which may have an impact on the current recommendation 1.1.2 (which does not mention the use of PET-CT as first-line imaging): '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.' ***Other (visceral) metastases*** New evidence was identified which may change current recommendations. At the 3-year surveillance review, a study found that: sensitivity of detecting cerebral metastases using PET-CT was unsatisfactory, however another study found that PET-CT could improve staging and alter therapeutic options in patients suspected to have breast cancer recurrence. At the 6-year surveillance review, 3 meta-analyses found that 18-FDG PET-CT has high sensitivity and specificity for detecting distant metastases in breast cancer, and has higher sensitivity than conventional imaging. Currently, the guideline recommendation 1.1.5 related to PET-CT is: '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'. Together, the studies from the 3 and 6-year surveillance reviews suggest PET-CT may be superior to conventional imaging in

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
In summary, due to the heterogeneity between 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)*** One study[8] concluded that PET-CT could improve staging and alter therapeutic options in patients suspected to have breast cancer recurrence. One study[9] was identified which compared the diagnostic value of whole-body diffusion weighted imaging (DWI) and 18Fdeoxyglucose (FDG) PET-CT for breast cancer staging. However, the study concluded that further study was required to determine whether whole-body DWI could be used as an alternative to FDG PET-CT for whole-body breast cancer staging. The accuracy of whole-body PET-CT for detecting brain metastases from non-central nervous system tumours was evaluated in a study[10]. The results of the study indicated that the sensitivity of cerebral metastases using PET-CT was unsatisfactory. One study[11] aimed to assess the detectability of bone metastatic lesions and evaluate the correlation between 18F-fluoride uptake patterns on PET and morphologic changes on CT using integrated PET-CT. The results of the study indicated that lesions with sclerotic or mixed changes or located in bone cortex alone tended to show high maximum standard uptake value (SUVmax).			the initial detection of visceral metastases, which may have an impact on the current recommendation 1.1.1 (which does not mention the use of PET-CT as first-line imaging): 'Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI).' **Other strategies for assessment and monitoring** At the 3-year surveillance review, evidence was found for other imaging strategies including: US, MRI, SMM, DWIBS, scintigraphy, PET and CT. 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 3-year surveillance review 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 new evidence was found for any of these strategies at the 6-year surveillance review therefore conclusions of the 3-year surveillance review remain valid. **Surveillance decision** ***PET-CT (assessment): Bone metastases;***

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
One study[12] evaluated the accuracy of 18F-fluoride PET-CT to detect bone metastases in patients with breast or prostate cancer. The results indicated that 18F-fluoride PET-CT was more accurate than bone scintigraphy for detecting bone metastases from breast and prostate cancers. In summary, as the identified new evidence was variable it was considered unlikely to change the direction of the current guideline recommendation 1.1.5 which states: 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. ***Scintigraphy*** One study[13] was identified which aimed to determine the feasibility of detecting metastatic lesions with scintigraphy using the alpha(v)beta(3)-avid imaging agent (99m)Tc-NC100692. The results of the study indicated that this imaging strategy was feasible for detection of lung and brain metastases from breast cancer. **Monitoring disease status** ***Positron emission tomography fused with computed tomography (PET-CT)*** One study[14] concluded that PET-CT was useful in staging metastatic disease and assessing response to treatment. One study[15] was identified which indicated that 18F-FDG PET-CT was a useful tool for			***Other (visceral) metastases*** 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 first line treatment except in certain circumstances. The current recommendation covers that scenario and the experts agreed that it did not need to be changed This review question should not be updated. ***Other strategies for assessment and monitoring*** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
monitoring in patients with bone metastases from breast cancer. A retrospective study[16] compared morphologic and metabolic changes in bone metastases in response to systemic therapy in patients with metastatic breast cancer with integrated PET-CT. The study concluded that a decrease in SUV after treatment was an independent predictor of response duration in patients with bone metastases. Overall, two 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 a retrospective study[17]. The study concluded that CEA and CA 15-3 could be used as potential tools to monitor treatment response. One study[18] indicated the usefulness of CA15-3 kinetics in monitoring chemotherapy response in patients with metastatic breast			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
cancer. One study[19] was identified which compared a bone scan with CA15-3 titres in patients with breast cancer for evaluation of bone metastases. The results of the study indicated that the mean level of CA15-3 was higher in patients with bone metastases than those without but there was no significant relation between serum CA15-3 levels and the extent of bone metastases. Further study was warranted. New evidence was identified 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. ***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[20]. The study concluded that MRI was superior to PET-CT and ultrasound in monitoring the effect of neoadjuvant chemotherapy in advanced breast cancer. **Summary** In summary, new literature was identified at the 3 year surveillance review relating to diagnosis and assessment of advanced breast cancer however, due to the heterogeneity between the reported results there was insufficient evidence to support the choice of one imaging modality over another. New			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
evidence was identified relating to the use of carcinoembryonic antigen and cancer antigen 15-3 in monitoring disease status however, it was decided at the 3 year surveillance review that it would be pertinent to await further evidence before this was considered within the guideline.			
81-02 Reassessment of endocrine and HER2 status on disease progression. (1.1.6 – 1.1.8)			
3-year surveillance (2011) **Tumour biopsy to assess receptor status of the primary tumour and metastases** One study[25] evaluated whether confirmatory tumour biopsy altered the management of breast cancer patients with distant metastases. The study concluded that there could be discordance in hormone and human epidermal growth factor receptor 2 (HER2) receptor status between primary tumour and metastases, which led to altered management in 20% of cases.	No relevant studies identified.	**Topic expert comments received:** 'Currently, the Advanced Guideline states that patients should not have a second biopsy when their disease recurs or metastasises to re-assess their oestrogen receptor (ER) or human epidermal growth factor receptor 2 (HER2) status. However, since the last full update to the guideline in 2009, cumulative evidence has shown that when breast cancer recurs, the subtype can change from what it was in the primary site, and a second biopsy is needed to determine the most appropriate course of treatment. We accept that it is currently unrealistic to make a rebiopsy mandatory, but we believe that the recommendation not to take a second biopsy should be reviewed in light of this evidence, so that where clinically appropriate, patients are able to have their metastatic receptor status assessed.' The following evidence was supplied in support of these comments: A pooled analysis[26] of individual patient data from 2 prospective studies (n=289) examined discordance between receptor expression of	**Tumour biopsy to assess receptor status of the primary tumour and metastases** At the 3-year surveillance review, one study found there could be discordance in hormone and HER2 receptor status between primary tumour and metastases, which led to altered management in 20% of cases. At the 6-year surveillance review, topic expert feedback indicated that cumulative evidence has shown that when breast cancer recurs, the subtype can change from what it was in the primary site, and a second biopsy is needed to determine the most appropriate course of treatment. Results from a pooled analysis of individual patient data from 2 prospective studies supported this feedback, in that biopsy results showing discordance in ER, PgR or HER2 between primary and recurrent breast cancer altered management in 14.2% of patients. This evidence may have an impact on the current recommendations 1.1.6 and 1.1.7: 'Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
		primary and recurrent breast cancer. Recruiting clinicians assessed whether or not receptor discordance affected subsequent systemic treatment. Discordance in ER, progesterone receptor (PgR) or HER2 between confirmed primary and recurrent breast cancer was 12.6%, 31.2% and 5.5% respectively (all p<0.001). Biopsy results altered management in 14.2% of patients undergoing biopsy (p≤0.0001). The duration between primary and recurrent disease, the site of recurrence and the receptor profile of the primary tumour did not affect discordance rates.	reassess ER status.' And 'Patients with tumours of known human epidermal growth factor receptor 2 (HER2) status whose disease recurs should not have a further biopsy just to reassess HER2 status.' **Surveillance decision** The topic experts agreed with the need to reassess receptor status on disease recurrence. They noted that the NICE quality standard on breast cancer already states that 'People with newly diagnosed invasive breast cancer and those with recurrent disease (if clinically appropriate) have the ER and HER2 status of the tumour assessed'. The topic experts felt that there is evidence to update the recommendation which would then align the guideline (which currently states that, if disease recurs, further biopsy just to reassess ER and HER2 status should not be done) with the quality standard. This review question should be updated
Providing information and support for decision making			
81-03 The use of (1) decision aids and (2) information tools to improve treatment outcomes and quality of life (1.2.1 – 1.2.4)			
3-year surveillance (2011) No relevant studies identified.	**Providing information** ***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	None identified relevant to this question.	**Providing information** The new evidence is unlikely to impact on guideline recommendations. The evidence for using technology in cancer follow-up (mainly via telephone) only concluded that it did not compromise patient satisfaction or safety, rather than that it provided a better alternative to other types of follow-up. The evidence for risk of recurrence testing

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
	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. ***Testing for risk of recurrence*** A systematic review[28] of 10 studies (reporting on 8 populations) examined testing for risk of recurrence in women with breast cancer. Key themes that emerged included: experience with the testing process; influence testing has on treatment; and comprehension of results. It was found that testing for breast cancer recurrence can have a negative impact on women – most frequently because of poor understanding of test results, and anxiety/distress. However despite these drawbacks, women consistently reported that they would recommend testing to others. The literature was considered to be limited, and heterogeneous.		suggested it could have a negative impact on women, although they would recommend testing to others. However the evidence was limited. Neither of these studies are likely to affect 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.' **Surveillance decision** This review question should not be updated.
Systemic disease-modifying therapy			
81-04 What is the choice of 1st line treatment for patients with metastatic breast cancer, endocrine therapy or chemotherapy? (1.3.1 – 1.3.3)			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant evidence identified **Surveillance decision** This review question should not be updated.
81-05 What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer? (1.3.4 – 1.3.7)			
3-year surveillance (2011)	**Endocrine therapy – monotherapies**	**Endocrine therapy – monotherapies**	**Fulvestrant (women)**

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Endocrine therapy – monotherapies ***Fulvestrant*** Five studies were identified relating to fulvestrant for treatment of advanced breast cancer[29-33]. However, at the 3 year surveillance review recommendations on the use of fulvestrant for breast cancer could be found in TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011. ***Aromatase inhibitors*** A systematic review[34] 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. A Cochrane review[35] 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. Lastly, a third systematic review[36] 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. In summary, the identified new literature relating to aromatase inhibitors for treatment of advanced breast cancer indicated a benefit of this therapy. As such, the identified new	***Fulvestrant (women)*** A meta-analysis[48] of 4 RCTs (n=1226) compared efficacy and tolerability of fulvestrant 250 mg once monthly with anastrozole 1 mg daily in postmenopausal women with advanced breast cancer. A cost-effectiveness review[49] examined fulvestrant 500 mg versus generic nonsteroidal aromatase inhibitors (anastrozole and letrozole) in first progression or recurrence of advanced breast cancer in postmenopausal patients in the UK. However, guidance on fulvestrant can be found in the 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. It is on the static list. ***Fulvestrant (men)*** A meta-analysis[50] of 5 studies (n=23; mean age=63.1 years) examined efficacy and safety of fulvestrant in male breast cancer. Adjuvant hormonal treatment was administered in 87.5 % of cases. Fulvestrant was first or second line in 40% of patients, and third line or beyond in 60% of patients. Visceral metastases were evident in 79.0% of patients at fulvestrant administration. Best responses were: partial response in 26.1% of patients; stable disease in 47.8% of cases; progressive disease in 26.1% of patients. Median progression free survival was 5 months. No grade 3 and 4 adverse events were recorded,	***Fulvestrant (women)*** A final analysis of overall survival in the CONFIRM trial[54] of 736 women, comparing fulvestrant 500mg vs 250 mg, reported data once 75% of patients had died. However, guidance on fulvestrant can be found in the 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. It is on the static list – the new evidence was considered during the decision to move TA239 to the static list. ***Toremifene*** The NICE Medicines and Prescribing team 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	***Monotherapy*** At the 3-year surveillance review, 8 studies were identified relating to fulvestrant monotherapy (5 generally, 2 versus exemestane, and 1 versus anastrazole). At the 6-year surveillance review, a meta-analysis compared fulvestrant with anastrozole, a cost-effectiveness review examined fulvestrant versus nonsteroidal aromatase inhibitors (anastrozole and letrozole), and an analysis of an RCT comparing fulvestrant 500mg vs 250 mg reported overall survival once 75% of patients had died . However, recommendations on the use of fulvestrant can be found in 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. It is on the static list. As such, the identified new evidence is unlikely to impact on guideline recommendations. ***Combined therapy*** No evidence was identified at the 3-year surveillance review. At the 6-year surveillance review, a meta-analysis examined anastrozole plus fulvestrant versus anastrozole alone in postmenopausal women, which concluded that the combined treatment was no better than anastrozole alone. This evidence is consistent with the current recommendation 1.3.4: 'Offer an aromatase inhibitor (either non-steroidal or steroidal) to postmenopausal women with ER-positive breast cancer and no

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
evidence was deemed unlikely to change the direction of guideline recommendation 1.3.4 which states that steroidal or non-steroidal aromatase inhibitors should be offered to postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy or previously treated with tamoxifen. ***Exemestane*** Two RCTs[37,38] compared exemestane with exemestane plus celecoxib in postmenopausal women with advanced breast cancer concluding that time to progression was similar in both groups. ***Estradiol*** One RCT[39] was identified which aimed to determine whether estradiol (6 mg daily versus 30 mg) was a viable therapy for postmenopausal women with advanced aromatase inhibitor-resistant hormone receptor-positive breast cancer. The study concluded that 6 mg of estradiol provided a similar clinical benefit as 30 mg with fewer serious adverse effects. **Endocrine therapy versus endocrine therapy** ***Fulvestrant versus exemestane*** Two studies[40,41] comparing fulvestrant with exemestane in patients with advanced breast cancer indicated similar clinical benefit of both therapies. ***Fulvestrant versus anastrazole*** The clinical activity of fulvestrant compared	but hot flashes were reported in 18.2% of patients. 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. ***Exemestane*** 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 flashes. Limited evidence showed non-adherence in 23%-32% of patients. However, the technology appraisal TA295 provides guidance on Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy	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.'	prior history of endocrine therapy or previously treated with tamoxifen.' **Fulvestrant (men)** No evidence was identified at the 3-year surveillance review. At the 6-year surveillance review there was evidence of efficacy of fulvestrant in men, but more research is needed. As such, this new evidence is unlikely to impact on guideline recommendations. **Exemestane** ***Monotherapy*** At the 3-year surveillance review: a systematic review comparing letrozole, exemestane and anastrazole concluded that further research was needed; 2 studies of fulvestrant versus exemestane indicated similar benefit of both therapies; a study of exemestane versus tamoxifen showed no longer-term PFS benefit of exemestane; and 1 RCT of anastrazole versus exemestane indicated similar efficacy in both groups. At the 6-year surveillance review, there was evidence that exemestane is superior to megestrol acetate, and noninferior to fulvestrant and to nonsteroidal aromatase inhibitors. Taken together, the evidence is consistent with the current recommendation 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 or previously treated with

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
with anastrazole as a first-line endocrine therapy for postmenopausal women with advanced breast cancer was assessed in an RCT[42]. 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[43] also indicated that fulvestrant and anastrazole were similarly effective. ***Exemestane versus tamoxifen*** The efficacy and safety of exemestane compared with tamoxifen in postmenopausal women with metastatic breast cancer was assessed in an RCT[44]. Exemestane demonstrated significant early improvement compared with tamoxifen although no longer-term benefit in progression-free survival was observed. ***Letrozole versus tamoxifen*** One RCT[45] 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. ***Aromatase inhibitor versus tamoxifen*** A meta-analysis[46] 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.	(August 2013), which is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. ***Toremifene versus tamoxifen*** A Cochrane review[52] 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 peri-menopausal women), and most patients were either ER-positive or of unknown status. The median time to progression (TTP) was 6.1 months for toremifene and 5.8 months for tamoxifen. The median overall survival (OS) was 27.8 months for toremifene and 27.6 months for tamoxifen. Most adverse events were similar in the 2 groups, while headache seemed to occur significantly less with toremifene group than tamoxifen. 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 post-menopausal 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 for some reason. **Combined endocrine therapy versus endocrine monotherapy** ***Anastrozole plus fulvestrant versus anastrozole*** A meta-analysis[53] of 2 RCTs examined anastrozole plus fulvestrant versus		tamoxifen.' ***Combination therapy*** The 3-year surveillance review found 2 RCTs of exemestane plus celecoxib versus exemestane and concluded that TTP was similar in both groups. This is consistent with the current recommendation: 'Offer an aromatase inhibitor (either non-steroidal or steroidal) to postmenopausal women with ER-positive breast cancer.' At the 6-year surveillance review, a systematic review found that exemestane was more effective when combined with everolimus than exemestane alone. This was based on the results of the BOLERO-2 trial which is discussed in a later section of the table [Question 81-08 'What is the most effective treatment for (1) women and (2) men with metastatic breast cancer? (combination therapies and comparisons between therapies)']. The combination of everolimus plus exemestane is covered, the technology appraisal TA295: 'Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy' (August 2013), which is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. As TA295 was based on evidence from the BOLERO-2 trial, the new evidence from the systematic review for this drug combination (which comprised only results from the BOLERO-2 trial) is unlikely to impact

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Anastrazole versus exemestane One RCT[47] 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. **Summary** In summary, for some treatments only single trials were identified therefore, at the 3 year surveillance review, it was considered that further study was warranted to confirm the results obtained. Some new evidence was identified which compared the efficacy and safety of endocrine therapies for advanced breast cancer however, it was decided it would be pertinent to await additional evidence to confirm the results.	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 250 mg monthly to anastrozole is no better than anastrozole alone.		on guideline recommendations. **Toremifene** No evidence was identified at the 3-year surveillance review. At the 6-year surveillance review, a Cochrane 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 post-menopausal patients with ER-positive advanced breast cancer. 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: 'Offer an aromatase inhibitor (either non-steroidal or steroidal) to postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy or previously treated with tamoxifen.'; '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.' And 'Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.' The new evidence identified may therefore change current recommendations. 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.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
			Aromatase inhibitors (general) The 3-year surveillance review concluded that the literature relating to aromatase inhibitors for treatment of advanced breast cancer indicated a benefit of this therapy. As such, the identified new evidence was deemed unlikely to change the direction of guideline recommendations which state that steroidal or non-steroidal aromatase inhibitors should be offered to postmenopausal women with ER-positive breast cancer. No new evidence (other than that already discussed for specific drugs above) was identified at the 6-year surveillance review therefore conclusions of the 3-year surveillance review remain valid. **Other endocrine therapies** At the 3-year surveillance review, evidence was found for other endocrine therapies including estradiol, anastrazole, letrozole and tamoxifen. It was concluded that further study was warranted to confirm the results obtained No new evidence (other than that already discussed for specific drugs above) was found for any of these strategies at the 6-year surveillance review therefore conclusions of the 3-year surveillance review remain valid. **Surveillance decision** ***Toremifene*** 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

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
			impact on the guideline. This review question should not be updated. ***Aromatase inhibitors*** The Medicines and Prescribing Centre raised a query 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. No change is needed to the guideline ***Other areas (Fulvestrant; Exemestane; Combination therapy; Other endocrine therapies)*** This review question should not be updated.
81-06 What is the most effective chemotherapeutic treatment for (1) women and (2) men with metastatic breast cancer? (1.3.8 –1.3.11)			
3-year surveillance (2011) **Health economics studies** A systematic review[55] (focusing on the economic impact of metastatic breast cancer) and 5 cost-effectiveness analyses[56-60] (evaluating the costs of different chemotherapy treatment regimens) were identified. The studies evaluated the cost impact of different treatment regimens with several studies suggesting that docetaxel treatment was the least costly which was	**Chemotherapy – monotherapies** ***Eribulin*** A systematic review[126] found 1 phase III trial of eribulin in previously treated patients with metastatic breast cancer. A pooled analysis[127] of 2 phase III studies (n=1864) was requested by the European Medicines Agency to assess whether specific patient subgroups, previously treated with an anthracycline and a taxane, benefited from	None identified relevant to this question.	**Eribulin** At the 3-year surveillance review, an RCT found that compared with currently available treatments, overall survival was improved in women with metastatic breast cancer receiving eribulin. At the 6-year surveillance review, two studies were found of eribulin in previously treated patients with metastatic breast cancer. The first study (a systematic review) found only the EMBRACE RCT (women with 2-5 lines of

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
considered to be in line with the current guideline. In addition, two economic analyses of albumin-bound paclitaxel concluded that this could be an economically reasonable alternative to docetaxel for advanced breast cancer. Currently the guideline recommendation 1.3.10 states single-agent docetaxel should be offered as first line treatment for advanced breast cancer whereas the use of paclitaxel as a monotherapy is not included in the guideline recommendations. **Chemotherapy – general studies** ***Chemotherapy regimens*** A systematic review[61] was identified which compared chemotherapy regimens for metastatic breast cancer. The review concluded that there was little evidence from published trials that major survival differences existed between commonly used chemotherapy regimens. Similarly, a systematic review[62] concluded that available clinical evidence did not suggest one conventional chemotherapy regimen as superior. A systematic review[63] was identified which evaluated the clinical efficacy of cytotoxic agents in patients with locally advanced or metastatic breast cancer pretreated with an anthracycline and a taxane however, limited evidence was identified. A retrospective analysis[64] was identified which carried out a long-term follow up of patients who had received chemotherapy for metastatic breast cancer. Improvement in	eribulin. One study compared eribulin with physician's choice of treatment in women after 2–5 lines of chemotherapy for advanced breast cancer. The other study compared eribulin with capecitabine in women after up to 2 prior chemotherapy regimens for advanced disease. However, guidance on eribulin is available in the following technology appraisals: The technology appraisal TA250: Eribulin for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease (April 2012) is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. A technology appraisal is in progress of eribulin mesylate for the treatment of locally advanced or metastatic breast cancer; second-line (see Topic selection technology appraisal decisions: January - March 2015). ***Gemcitabine*** A meta-analysis[128] of 9 trials (n=2651) compared gemcitabine-based and gemcitabine-free chemotherapy regimens in metastatic breast cancer. Compared with gemcitabine-free chemotherapy, gemcitabine-based therapy demonstrated no improvement in terms of ORR, TTP or OS. In a subgroup analysis of patients who received adjuvant chemotherapy containing anthracyclines or taxanes, gemcitabine-based doublets were significantly superior to monotherapy in ORR and TTP, but not OS. In the gemcitabine-		previous chemotherapy) upon which TA250 was based. The second study was a pooled analysis of 2 studies (EMBRACE and another similar trial but in women with up to 2 lines of previous chemotherapy). Recommendations on the use of eribulin can be found in TA250: Eribulin for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease (April 2012) 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 mesylate for the treatment of locally advanced or metastatic breast cancer; second-line (see Topic selection technology appraisal decisions: January - March 2015). **Gemcitabine** Various studies of gemcitabine were identified at the 3-year surveillance review. Similar outcomes were seen between treatment groups for gemcitabine in various different combinations. At the 6-year surveillance review, a meta-analysis concluded that gemcitabine-based chemotherapy was as effective as gemcitabine-free chemotherapy in patients with metastatic breast cancer with increased haematological toxicity. Adding gemcitabine to monotherapy might be more effective. The evidence is unlikely to affect the current recommendation 1.3.11 relating to gemcitabine: 'Gemcitabine in combination with

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
survival was observed in patients who had received an increased number of treatment regimens. One RCT[65] was identified which concluded that antiangiogenic treatment with sunitinib consolidation did not prolong remissions induced by taxane-based chemotherapy in women with metastatic breast cancer and led to significant toxicity. One meta-analysis[66] compared primary and secondary end points of taxane-based doublet with single-agent taxane chemotherapy in patients with advanced breast cancer and prior anthracycline treatment. The results of the meta-analysis indicated that taxane-based doublet appeared to improve progression free survival compared with single-agent taxane in this population. In summary, several studies were identified at the 3 year surveillance review which evaluated the efficacy of a variety of chemotherapy regimens for advanced breast cancer. However, due to heterogeneity among the studies above, it was concluded that further research was warranted to confirm the efficacy of a specific chemotherapy regimen over another. ***High-dose chemotherapy*** A systematic review[67] was identified which indicated that overall survival of metastatic breast cancer was not significantly improved by high-dose chemotherapy. One RCT[68] compared progression free survival and overall survival in women with	based arm, higher rates were seen of grade 3 and 4 anaemia, neutropenia, and thrombocytopenia. The review concluded that gemcitabine-based chemotherapy was as effective as gemcitabine-free chemotherapy in patients with metastatic breast cancer with increased haematological toxicity. Subgroup analysis indicated that adding gemcitabine to monotherapy might be more effective. However, the technology appraisal TA116 provides guidance on Gemcitabine for the treatment of metastatic breast cancer (January 2007), which is incorporated into the guideline and is included in the advanced breast cancer NICE pathway. It is on the static list. ***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 advanced/metastatic breast cancers, the clinical complete response (cCR), partial response (PR) and the disease control rates for the TNBC group were not significantly different compared with the non-TNBC group. The 6-month PFS rate for the TNBC group was significantly higher than that of the non-TNBC group in all patients. However, the 1- and 2-year PFS rates were not significantly different. Furthermore, the PFS rates were not significantly different between the groups in patients with advanced/metastatic breast cancer. In conclusion, platinum-based chemotherapy in the breast cancer patients		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'. This recommendation was incorporated from TA116 and is not likely to change as the Technology Appraisal has been placed on the static list. **Platinum-based chemotherapy** Various studies of platinum-based chemotherapy were identified at the 3-year surveillance review. Similar outcomes were seen between treatment groups for platinum-based therapy in various different combinations. 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. At the 6-year surveillance review, a meta-analysis concluded that platinum-based chemotherapy in triple-negative breast cancer has not yet been demonstrated to have an improved effect in advanced breast cancer. 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

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
metastatic breast cancer receiving high-dose chemotherapy plus autologous stem-cell (HDCT) transplantation. The results of the study indicated that HDCT did not improve overall survival in women with metastatic breast cancer when used as consolidation after response to induction chemotherapy. One systematic review[69] was identified which compared the effectiveness of high-dose chemotherapy and autologous bone marrow or stem cell transplantation with conventional chemotherapy for women with metastatic breast cancer. The review concluded that although there was evidence that high-dose chemotherapy and autograft significantly improved event-free survival compared to conventional chemotherapy there was no significant evidence of benefit in overall survival. An RCT[70] was identified which assessed the impact of first-line high-dose chemotherapy (cyclophosphamide and thiotepa) with stem cell support on overall survival, disease free survival and response rate in patients with metastatic breast cancer. The results of the study indicated that treatment improved disease free survival but not overall survival. In summary, some new evidence was identified at the 3 year surveillance 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	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. **Chemotherapy versus chemotherapy** ***Paclitaxel-based versus docetaxel-based regimens*** The technology appraisal TA116: Gemcitabine for the treatment of metastatic breast cancer (January 2007) recommends gemcitabine in combination with paclitaxel as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. It is incorporated into the guideline and is included in the advanced breast cancer NICE pathway. It is on the static list. A meta-analysis[130] of 7 trials (n=1694) compared paclitaxel-based and docetaxel-based regimens in metastatic breast cancer. In 3 trials patients received taxane-based regimens first-line and in 4 trials about half of patients had previously received anthracycline-based regimens. In 4 trials paclitaxel and docetaxel were given alongside gemcitabine, doxorubicin, carboplatin or capecitabine. A paclitaxel-based regimen was comparable to a docetaxel-based regimen in terms of OS, PFS, TTP, and ORR. But fewer grade 3 or 4 adverse events were observed in the paclitaxel-based regimen, including anaemia, neutropenia, febrile neutropenia, thrombopenia, mucositis, diarrhea and fatigue.		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.' **Paclitaxel-based versus docetaxel-based regimens** At the 3-year surveillance review, 4 RCTs of docetaxel were found and it was concluded that the evidence did not invalidate the guideline recommendation 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, further research was warranted to confirm these results. Three studies were identified relating to paclitaxel for advanced breast cancer. However, the literature was too heterogeneous to make a conclusion about the efficacy of paclitaxel as a monotherapy for advanced breast cancer. 5 studies also directly compared paclitaxel with docetaxel (with or without additional drugs – such as non-pegylated liposomal anthracycline, doxorubicin, carboplatin, and gemcitabine). The studies generally found that treatments were similarly effective (except 1 RCT that found weekly nab-paclitaxel had superior efficacy than docetaxel) but toxicity could differ. However due to the differing combinations of chemotherapies, further evidence was deemed to be required to further assess the choice of one

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
before considering for inclusion in the guideline. ***Monotherapy versus combination therapy*** One Cochrane review[71] was identified which compared single agent chemotherapy with combination therapy for the treatment of metastatic breast cancer concluding that combination chemotherapy regimens showed a significant advantage for survival, tumour response and time to progression although toxicity was higher. In addition, a Cochrane review[72] assessed the effects of adding chemotherapy drugs to an established regimen in women with metastatic breast cancer. The addition of chemotherapy drugs led to an advantage for tumour response but no difference in survival time or time to progression. The identified new evidence did not 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. ***Treatment duration*** One systematic review[73] 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 OS and	There was significant heterogeneity among included trials. The review concluded that both taxane-based regimens have comparable efficacy for patients with metastatic breast cancer, and the paclitaxel-based regimen is associated with less toxicity and better tolerability, especially in older patients and when used in weekly regimens. **Combination versus sequential single-agent chemotherapy** A Cochrane review[131] of 12 RCTs (n=2317) compared combination with sequential single agent chemotherapy for metastatic breast cancer in the first-, second- or third-line setting. There was no difference in OS, which was also seen in 4 subgroup analyses (risk of bias, line of chemotherapy, whether chemotherapy was given on disease progression or after a set number of cycles, and relative dose intensity). For PFS, risk of progression was higher in the combination arm than the sequential arm, which was consistent in all subgroups. Overall tumour response rates were higher in the combination arm. Treatment-related deaths did not differ between the 2 arms. The risk of febrile neutropenia was higher in the combination arm. Risk of neutropenia, nausea and vomiting, and overall quality of life did not differ. The review concluded that sequential single agent chemotherapy has a positive effect on PFS, whereas combination chemotherapy has a higher response rate and a higher risk of febrile neutropenia in metastatic breast cancer. There is no difference in overall survival time between		chemotherapy regimen over another At the 6-year surveillance review, the one meta-analysis that was found comparing paclitaxel-based and-docetaxel based regimens found significant heterogeneity among included trials. The review concluded that both taxane-based regimens have comparable efficacy, and the paclitaxel-based regimen is associated with less toxicity and better tolerability, especially in older patients and when used in weekly regimens. However, the variability of the regimens (such as the accompanying drugs, and whether or not it was first line) make firm conclusions difficult. Taken together, the evidence is unlikely to affect recommendations 1.3.10 and 1.3.11 that single-agent docetaxel should be used as a first-line chemotherapy, and that gemcitabine in combination with paclitaxel is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. **Combination versus sequential single-agent chemotherapy** At the 3-year surveillance review, a Cochrane review concluded that combination chemotherapy regimens had a significant advantage for survival, tumour response and time to progression although toxicity was higher. A further Cochrane review found adding chemotherapy drugs to an established regimen led to an advantage for tumour response but no difference in survival time or

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
longer PFS. ***Adverse effects*** One systematic review[74] 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. **Chemotherapy – monotherapies** ***Docetaxel*** Two RCTs[75,76] were identified which compared weekly docetaxel versus 3-weekly docetaxel for metastatic breast cancer concluding that the 3-weekly schedule was preferable. An additional RCT[77] compared weekly versus every three weeks docetaxel schedules among patients with metastatic breast cancer although no difference was observed between the two regimens in any measured outcomes. One RCT[78] aimed to determine whether concomitant administration of docetaxel plus zosuquidar.3HC1 could prolong PFS in patients with metastatic breast cancer. The study concluded that the treatment combination was safe but there was no difference in progression free survival or overall survival. In summary, the identified new evidence did not invalidate the guideline recommendation 1.3.10 at the 3-year surveillance review point that single-agent docetaxel should be used as a first-line chemotherapy. Two studies indicated that a 3-weekly schedule of	these treatment strategies, both overall and in the subgroups analysed. In particular, there was no difference in survival according to the schema of chemotherapy (giving chemotherapy on disease progression or after a set number of cycles) or according to the line of chemotherapy (first-line versus second- or third-line). Generally this review supports the recommendations by international guidelines to use sequential monotherapy unless there is rapid disease progression		time to progression. At the 6-year surveillance review, a Cochrane review concluded that sequential single agent chemotherapy has a positive effect on progression-free survival, whereas combination chemotherapy has a higher response rate and a higher risk of febrile neutropenia in metastatic breast cancer. There was no difference in overall survival time. Taken together, the evidence does not invalidate the current guideline recommendations1.3.8 and 1.3.9: '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.' **Other chemotherapy treatments** For all other chemotherapy treatments, no additional evidence was found by the 6-year surveillance review to change the conclusion of the 3-year surveillance review, namely that no conclusive new evidence was identified which would invalidate current guideline recommendation(s). **Surveillance decision** ***Eribulin*** Topic experts noted that other drugs such as eribulin are available but are not discussed by

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
docetaxel was preferable however, further research was warranted to confirm these results. ***Paclitaxel*** Three studies were identified relating to paclitaxel for advanced breast cancer. One RCT[79] concluded albumin-bound paclitaxel (nab-paclitaxel) had greater efficacy compared with solvent-based paclitaxel (sb-paclitaxel) in patients with metastatic breast cancer. A meta-analysis[80] concluded that a weekly regimen of paclitaxel gave overall survival advantages compared with a standard every three weeks regimen. The results of one RCT[81] indicated that a 96-hour paclitaxel infusion schedule did not significantly improve response or time to progression. Paclitaxel is not currently recommended in the guideline except in combination with gemcitabine (recommendation 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. However, the literature was too heterogeneous, including comparisons of different treatment regimens, to make a conclusion about the efficacy of paclitaxel as a			the guideline. However eribulin would be managed through TAs. This review question should not be updated. ***Platinum-based chemotherapy*** Topic experts noted that platinum is an older drug and would be unlikely to be assessed in a TA. They highlighted the TNT trial – a UK-based study of carboplatin vs docetaxel first line in metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer. Results are not yet published but it may be useful for inclusion in a future surveillance review. Carboplatin may be examined at the next surveillance review once the TNT trial is published. ***Other areas (Gemcitabine; Paclitaxel-based versus docetaxel-based regimens; Combination versus sequential single-agent chemotherapy; Other chemotherapy treatments)*** 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.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
monotherapy for advanced breast cancer. ***Ixabepilone*** Two systematic reviews[82,83] 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) has been referred for a single Technology Appraisal which may have an impact on the guideline recommendations in the future. (Update April 2015: the technology appraisal has been suspended since 2008 when the manufacturer received a negative Committee for Medicinal Products for Human Use [CHMP] opinion) ***Doxorubicin*** A post-hoc analysis of an RCT[84] 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 was in progress at the time of the 3 year surveillance review: Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients (expected date of publication: August 2012). (Update April 2015: Now published as CG151)			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Everolimus The efficacy and safety of oral everolimus (10 mg daily versus 70 mg weekly) in minimally pretreated patients with metastatic breast cancer was investigated in an RCT[85]. The response rate with daily therapy was 12% compared with 0% for weekly therapy. ***Eribulin*** Overall survival in patients with metastatic breast cancer receiving eribulin compared with currently available treatments was assessed in an RCT[86]. The results of the study indicated that overall survival was improved in women receiving eribulin. At the time there was an ongoing Technology Appraisal 'Eribulin for the treatment of locally advanced or metastatic breast cancer' (publication date TBC) which was felt may have an impact on the guideline recommendations in the future. (Update April 2015: now published as TA250) **Chemotherapy – combined therapies** ***Capecitabine and ixabepilone*** Three studies[87-89] were identified which evaluated the efficacy of ixabepilone combined with capecitabine for metastatic breast cancer with variable results obtained. ***Doxorubicin and docetaxel*** One RCT[90] was identified which assessed maintenance therapy with pegylated liposomal doxorubicin (PLD) after induction chemotherapy (doxorubicin plus docetaxel) in patients with metastatic breast cancer. Time to			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
progression was improved in the PLD group although overall survival was not significantly prolonged. Similar results were obtained in a second RCT[91]. One RCT[92] compared the toxicity and efficacy of weekly versus 3-weekly administration of docetaxel in combination with doxorubicin. The study concluded that both treatment regimens were feasible although the 3-weekly application would be preferable. ***Gemcitabine and docetaxel*** Three studies[93-95] evaluated the efficacy of gemcitabine plus docetaxel in women with advanced breast cancer. Although different treatment regimens were used, no study observed statistically significant differences in time to disease progression or survival compared with the control group. ***Paclitaxel and epirubicin*** The efficacy and safety of two treatment regimens including epirubicin and paclitaxel for patients with metastatic breast cancer was assessed in an RCT[96]. The response rates and progression free survival for both treatment regimens were similar. One RCT[97] compared the effect on health-related quality of life of epirubicin plus paclitaxel (ET) versus epirubicin, paclitaxel and capecitabine (TEX) in women with metastatic breast cancer. At the nine month assessment, the TEX group scored significantly higher for global quality of life and physical functioning.			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Gemcitabine and paclitaxel One RCT[98] was identified which compared the efficacy of gemcitabine plus paclitaxel versus paclitaxel alone after prior anthracycline treatment in patients with advanced breast cancer. Median survival and time to progression was longer in the combination group although adverse events were more common compared with control. ***Vinorelbine and capecitabine*** The efficacy and safety of sequential versus simultaneous use of vinorelbine and capecitabine at the same dosage as first-line therapy in metastatic breast cancer was assessed in an RCT[99]. An improvement in clinical benefit rate was observed in the simultaneous group but this did not translate into long-term benefits such as progression free survival and overall survival. ***Capecitabine and enzastaurin*** One RCT[100] evaluated the efficacy of enzastaurin in combination with capecitabine in patients with metastatic or recurrent breast cancer. No progression free survival benefit was observed with combined therapy whilst median overall survival was lower compared with the control group. ***Vinorelbine and gemcitabine*** One RCT[101] was identified which compared gemcitabine and vinorelbine versus gemcitabine until disease progression followed by vinorelbine monotherapy in patients with metastatic breast cancer. The study concluded that both treatment regimens			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
were comparable in terms of efficacy and toxicity. ***Vinorelbine and chronomodulated 5-fluorouracil*** An RCT[102] was identified which aimed to determine the least toxic time of vinorelbine administration in patients with metastatic breast cancer however, no recommendation on optimal time of administration could be made. In summary, new literature was identified at the 3 year surveillance review relating to combined therapy for advanced breast cancer. The guideline recommendation 1.3.9 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. However, a meta-analysis was deemed necessary to support the use of a certain combination of chemotherapy over other combinations. **Chemotherapy versus chemotherapy** ***Comparisons of mixed chemotherapy regimens*** One RCT[103] compared four treatment regimens for advanced breast cancer. The study concluded that incorporation of docetaxel into anthracycline-based therapy resulted in an improvement in disease free survival and that sequential administration may provide more benefit compared with concurrent. One RCT[104] carried out comparisons between			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
doxorubicin plus cyclophosphamide, docetaxel and alternating cyclophosphamide and docetaxel as first-line chemotherapy for metastatic breast cancer however, no difference in time to survival was observed between the three treatment arms. One RCT[105] comparing anthracycline-based adjuvant chemotherapy (control arm) to anthracycline-docetaxel-based sequential or concurrent chemotherapy concluded that there was no evidence that adjuvant docetaxel treatment was associated with an increased frequency of CNS relapse. A meta-analysis[106] was identified which aimed to determine the efficacy of taxanes alone or in combination with anthracyclines as first-line therapy for metastatic breast cancer. The objective response to biweekly gemcitabine/paclitaxel, gemcitabine/carboplatin and gemcitabine/cisplatin as first line treatment for metastatic breast cancer was assessed in an RCT[107] with comparable activity and tolerability observed. In summary, the above studies evaluated 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 study), further evidence was deemed to be required to further assess the choice of one chemotherapy regimen over another. ***Paclitaxel versus docetaxel***			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
One RCT[108] assessed the efficacy and tolerability of weekly paclitaxel compared with weekly docetaxel in metastatic breast cancer patients concluding that administration of either treatment could be considered. Conversely, the results of one RCT[109] indicated that weekly nab-paclitaxel demonstrated superior efficacy and safety compared with docetaxel. The tolerability of weekly paclitaxel or docetaxel combined with non-pegylated liposomal anthracycline in first-line metastatic breast cancer patients was evaluated in an RCT[110]. The study concluded that combined weekly administration of taxane and non-pegylated liposomal anthracycline was well tolerated in this population. ***Docetaxel and gemcitabine versus docetaxel and capecitabine*** The efficacy and safety of docetaxel and gemcitabine compared with docetaxel and capecitabine in patients with advanced breast cancer was assessed in two RCTs[111,112] with both studies concluding that the treatment regimens had similar efficacy. ***Capecitabine versus vinorelbine*** One RCT[113] was identified which assessed the safety and efficacy of capecitabine compared with vinorelbine in patients with metastatic breast cancer following prior treatment with taxanes and anthracyclines. The results of the study indicated that both treatments had comparable efficacy. ***Docetaxel versus vinorelbine***			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
The efficacy of weekly vinorelbine compared with weekly docetaxel in patients with anthracycline-pretreated metastatic breast cancer was assessed in an RCT[114]. The study concluded that docetaxel demonstrated marginally better activity but did not improve time to progression compared with vinorelbine. ***Epirubicin and cyclophosphamide versus epirubicin and docetaxel*** One RCT[115] compared the safety and efficacy of epirubicin and cyclophosphamide with epirubicin and docetaxel in patients with metastatic breast cancer. The results of the study indicated that both treatments had comparable efficacy. ***Doxorubicin versus docetaxel*** The efficacy and safety of doxorubicin compared with docetaxel as first-line treatment for patients with metastatic breast cancer was evaluated in an RCT[116]. The results of the study indicated that both treatments had comparable efficacy and were both well tolerated. ***Doxorubicin and docetaxel versus doxorubicin and cyclophosphamide*** The efficacy of doxorubicin and cyclophosphamide compared with doxorubicin and docetaxel in women with invasive breast cancer that had metastasised was assessed in an RCT[117]. The results of the study indicated that both treatments had comparable efficacy although doxorubicin and docetaxel treatment was associated with more toxicity.			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Doxorubicin and docetaxel versus doxorubicin and paclitaxel One RCT[118] was identified which compared doxorubicin and docetaxel with doxorubicin and paclitaxel in patients with metastatic breast cancer. The results of the study indicated that both treatments had comparable efficacy although toxicity profiles differed between the two groups. ***Doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide*** The efficacy of doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide in women with advanced breast cancer was assessed through post-hoc analysis of an RCT[119]. The results of the study indicated that time to progression and overall survival was longer in the group receiving doxorubicin and paclitaxel therapy. ***Docetaxel and epirubicin versus docetaxel and capecitabine*** One RCT[120] was identified which compared docetaxel and epirubicin with docetaxel and capecitabine in women with advanced breast cancer. The results of the study indicated that both treatments had comparable efficacy although toxicity profiles differed between the two groups. ***Epirubicin/vinorelbine versus pegylated liposomal doxorubicin/vinorelbine*** One RCT[121] was identified which investigated the efficacy and tolerability of epirubicin plus vinorelbine compared with pegylated			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
liposomal doxorubicin plus vinorelbine in patients with advanced breast cancer. The study concluded that both treatment regimens were active with acceptable tolerability. ***Gemcitabine and vinorelbine versus gemcitabine and cisplatin versus gemcitabine and capecitabine*** An RCT[122] was identified which compared three treatment regimens (Gemcitabine plus vinorelbine; gemcitabine plus cisplatin and gemcitabine plus capecitabine) in patients with pretreated metastatic breast cancer. The study concluded that all treatment regimens evaluated were active with acceptable tolerability. ***Paclitaxel and carboplatin versus docetaxel plus gemcitabine versus paclitaxel*** One RCT[123] evaluated the effectiveness of paclitaxel plus carboplatin compared with docetaxel plus gemcitabine or paclitaxel alone in patients with metastatic breast cancer. No differences in time to progression or quality of life between the three treatment methods were observed although cost analysis favoured paclitaxel. In summary, 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			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
chemotherapy regimen over another. **Chemotherapy – management of chemotherapy-related adverse effects** ***Epoetin therapy*** One RCT[124] (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[125] concluded that antithrombotic therapy may have the potential to reduce the risk of thrombovascular events under epoetin therapy. **Summary** New literature was identified at the 3 year surveillance review relating to paclitaxel, doxorubicin, ixabepilone and eribulin as treatment for advanced breast cancer. However, heterogeneity across studies in terms of treatment regimens and reported results was apparent. For other 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. Relevant Technology Appraisals were in development at the time which it was felt may have an impact on the guideline recommendations in the future (see 6-year summary for updated			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
information on current technology appraisals). Limited evidence was identified focusing on gemcitabine. However, the recommendation relating to gemcitabine, which was incorporated from TA116, was deemed not likely to change as the Technology Appraisal had been placed on the static list.			
81-07 What is the most effective biological treatment for (1) women and (2) men with metastatic breast cancer? (1.3.12)			
3-year surveillance (2011) **Biological therapy – monotherapies** ***Lapatinib*** Five studies[132-136] were identified focusing on the clinical efficacy of lapatinib as treatment for advanced breast cancer. At the time of the 3-year surveillance there were three Technology Appraisals in progress (two suspended and one with publication date TBC) relating to lapatinib: • Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. (Update April 2015: Now published as TA257) • Lapatinib for breast cancer (first line use in advanced or metastatic hormone-sensitive breast cancer). (Update April 2015: TA now discontinued) • Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer).	**Biological therapy** ***Bevacizumab*** A systematic review[145] examined bevacizumab efficacy in breast cancer. In 41 phase II trials in the metastatic setting, most trials found bevacizumab treatment feasible. Response rates varied from 0% to 76.5%, TTP/PFS from 2.4 to 25.3 months and overall survival from 11.5 to more than 38 months. In 14 phase III trials (n>4400 patients with metastatic breast cancer) response rate and PFS unanimously increased, however no trials demonstrated an OS benefit. The review concluded that despite an increased response rate in the metastatic setting, bevacizumab failed to show any OS benefit. **Biological therapy – combined therapies** ***Adverse events*** A meta-analysis[146] of 7 studies examined risk of severe diarrhea with anti-HER2 combination therapy (pertuzumab plus trastuzumab or trastuzumab plus lapatinib) versus anti-HER2 monotherapy (lapatinib or trastuzumab or pertuzumab) in breast cancer. Incidence of severe diarrhea in the combined	None identified relevant to this question.	**Bevacizumab** No relevant studies were identified at the 3-year surveillance review. At the 6-year surveillance review, a systematic review concluded that despite an increased response rate in the metastatic setting, bevacizumab failed to show any OS benefit. The current guideline does not discuss bevacizumab. Several technology appraisals (published and in-progress) cover bevacizumab combination therapies, but 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. This evidence is unlikely to add to recommendations. **Combined biological therapies - adverse events** At the 3-year surveillance review, 1 single-arm, open-label trial evaluating the efficacy and safety of pertuzumab plus trastuzumab found that the combination was well tolerated. However at the 6-year surveillance review, a meta-analysis found an increased risk of

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
(Update April 2015: Currently suspended) ***Trastuzumab*** Through the review of the guideline two studies[137,138] were identified relating to trastuzumab for advanced breast cancer. Within the guideline, the recommendations on the use of trastuzumab are covered by TA34 (2002) however, a review of this guidance has been planned into the Technology Appraisal work programme and therefore may have an impact on guideline recommendations in the future. (Update April 2015: The review of TA34 has not yet been performed) ***Erlotinib*** The efficacy and safety or erlotinib in advanced breast cancer was evaluated in a cohort study[139] however, the results indicated that this treatment had minimal activity in unselected previously treated women with advanced breast cancer. ***Adecatumumab*** One RCT[140] 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[141] compared two doses of pertuzumab in patients with human epidermal	anti-HER2 therapy was 13.48% and with monotherapy was 8.68%. The following technology appraisals are of relevance: The in-progress technology appraisal ID523: Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy 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.		severe diarrhea with pertuzumab plus trastuzumab or trastuzumab plus lapatinib. The current guideline recommendation 1.3.9 about additional toxicity of combined therapy relates only to chemotherapy: '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*.' 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. **Other biological treatments** For all other biological treatments, no additional evidence was found by the 6-year surveillance review to change the conclusion of the 3-year surveillance review, namely that no conclusive new evidence was identified which would invalidate current guideline recommendation(s). **Surveillance decision** ***Trastuzumab*** The topic experts noted that some centres may not be following recommendation 1.3.12 to discontinue trastuzumab at the time of disease progression outside the central nervous system. However, it was noted that there is unlikely to be new evidence of a suitable standard to warrant any change to the guideline. It was noted by NICE that TA34 covers

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
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[142]. 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. **Biological therapy – combined therapies** ***Pertuzumab and trastuzumab*** One single-arm, open-label trial[143] 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[144] 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.			'Trastuzumab for the treatment of advanced breast cancer'. It was agreed at the time CG81 was developed that TA34 would be updated by NICE and until such time the recommendations from TA34 will stand. A new TA (ID345) was scheduled to examine 'Trastuzumab as monotherapy and in combination with a taxane for the treatment of metastatic breast cancer (to include a review of TA34)'. However this in-development TA is currently suspended. Updates on the use of trastuzumab are likely to remain within the remit of TAs ***Other areas (Bevacizumab; Combined biological therapies - adverse events; Other biological treatments)*** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Summary In summary, for some treatments only single trials were identified therefore the 3 year surveillance review concluded that further study was warranted to confirm the results obtained. In addition, new literature was identified relating to lapatinib, bevacizumab and trastuzumab as treatment for advanced breast cancer. In terms of bevacizumab, it was felt the guideline needed to cross refer to the technology appraisal (TA214) that was previously not mentioned in the guideline. In addition, other relevant Technology Appraisals were in development relating to lapatinib and trastuzumab and it was felt they may have an impact on the guideline recommendations in the future.			
81-08 What is the most effective treatment for (1) women and (2) men with metastatic breast cancer? (combination therapies and comparisons between therapies) (1.3.1 – 1.3.12)			
3-year surveillance (2011) **Combined chemotherapy and biological therapy** ***Bevacizumab plus paclitaxel; bevacizumab plus various chemotherapy regimens; and bevacizumab plus docetaxel*** Five studies[147-151] were identified which evaluated the efficacy of bevacizumab combined with paclitaxel for metastatic breast cancer. The treatment protocols differed between the studies and variable results were reported. The efficacy and safety of bevacizumab combined with docetaxel was evaluated in three studies[152-154]. In addition, 5 studies[155-159]	**Combined chemotherapy and biological therapy** ***Bevacizumab plus chemotherapy*** A meta-analysis[187] of 8 studies (n=3758) examined bevacizumab plus paclitaxel compared with other chemotherapy as first-line treatment for HER2-negative metastatic breast cancer. A Cochrane review[188] of 7 RCTs and 1 register (n=2886) examined vascular-endothelial-growth-factor targeting therapies for endocrine refractory or resistant metastatic breast cancer. All trials identified were of bevacizumab in combination with established chemotherapy regimens in either the first or	Several RCTs relevant to combination therapy for advanced breast cancer were highlighted through topic expert feedback. **Combined chemotherapy and biological therapy** ***Bevacizumab plus docetaxel plus trastuzumab*** An RCT [AVEREL][199] of 424 patients compared bevacizumab plus docetaxel plus trastuzumab with docetaxel plus trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer without prior trastuzumab or chemotherapy. Most patients had visceral metastases, 43% had a disease-free interval less than 12 months, and 85% had measurable disease. Median follow-	**Bevacizumab** ***Bevacizumab plus chemotherapy*** At the 3-year surveillance review: 5 studies evaluated the efficacy of bevacizumab plus paclitaxel; 3 studies evaluated the efficacy and safety of bevacizumab plus docetaxel; and 5 studies evaluated the efficacy of bevacizumab in combination with various chemotherapy regimens for advanced breast cancer. At the 6-year surveillance review, 4 meta-analyses and a Cochrane review examined bevacizumab plus various chemotherapy regimes. However, this new evidence is unlikely to impact on guideline recommendations as the

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
evaluated the efficacy of bevacizumab in combination with various chemotherapy regimens for advanced breast cancer. However, a Technology Appraisal was identified at the 3 year surveillance review which reviewed the use of bevacizumab in combination with a taxane for the treatment of metastatic breast cancer whilst a Technology Appraisal on bevacizumab in combination with capecitabine for metastatic breast cancer was in progress: • TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011. • Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer. (Update April 2015: Now published as TA263) ***Lapatinib and capecitabine*** Three RCTs and a systematic review[160-163] were identified which indicated a beneficial effect of lapatinib plus capecitabine versus capecitabine alone on the reported outcomes in patients with advanced breast cancer. Ongoing Technology Appraisals on lapatinib were in development at the 3 year surveillance review which were considered potentially to have an impact on the guideline recommendations in the future. ***Trastuzumab and capecitabine*** One study[163,164] was identified where patients with HER2-positive advanced breast cancer that progressed during treatment with	second line. A meta-analysis[189] of 4 RCTs (n=3131) examined bevacizumab plus chemotherapy versus chemotherapy alone as salvage treatment for HER-2 negative recurrent or metastatic breast cancer. A meta-analysis[190] of 10 RCTs (n=1546) compared biological agents and chemotherapy with chemotherapy alone in metastatic triple-negative breast cancer. Biological agents considered were bevacizumab, sunitinib, sorafenib, lapatinib, iniparib and cetuximab, but a meta-analysis was only reported for bevacizumab. A meta-analysis[191] of 12 RCTs (n=2054) compared targeted therapy (bevacizumab, sorafenib, cetuximab, lapatinib, and iniparib) plus chemotherapy with chemotherapy alone in triple-negative metastatic breast cancer. Progression free survival (PFS) was superior in previously untreated patients who received bevacizumab plus chemotherapy compared with chemotherapy alone. Also, PFS was significantly greater in 1 study of bevacizumab plus chemotherapy in previously treated patients. However, guidance on bevacizumab plus chemotherapy is covered by the following technology appraisals: The technology appraisal TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011) is not mentioned in the guideline but is included in the advanced	up was 26 months. For the primary analysis of investigator-assessed PFS, median PFS was less (though not significantly) in the non-bevacizumab than in the bevacizumab arm (13.7 vs 16.5 months). Grade ≥3 febrile neutropenia and hypertension were more common with bevacizumab-containing therapy. ***Pertuzumab plus trastuzumab plus docetaxel*** An RCT [CLEOPATRA][200] of 808 patients compared pertuzumab plus trastuzumab plus docetaxel (pertuzumab group) with placebo plus trastuzumab plus docetaxel (control group) as first-line treatment of HER2-positive metastatic breast cancer. An additional study[201] reported 1-year OS results of the CLEOPATRA trial. A further study[202] reported prespecified OS results of the CLEOPATRA trial at a median follow-up of 50 months. However, this drug combination is covered by the in-progress technology appraisal ID523: Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy 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. The new evidence will be passed on for consideration to the technology appraisals	combination of bevacizumab plus chemotherapy is covered by 2 published technology appraisals: TA214 Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011); and TA263 Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012). And is also covered by the in-progress technology appraisal ID488: Bevacizumab in combination with chemotherapy for the second line treatment of HER2 negative metastatic breast cancer . This guidance is captured in the advanced breast cancer pathway. ***Bevacizumab plus docetaxel plus trastuzumab*** No relevant studies were identified at the 3-year surveillance review. At the 6-year surveillance review, an RCT [AVEREL] found bevacizumab plus docetaxel plus trastuzumab did not significantly improve investigator-assessed PFS versus docetaxel plus trastuzumab. Some grade ≥3 adverse events were more common with bevacizumab-containing therapy. The lack of effect reported in the new evidence is unlikely to impact on guideline recommendations. **Sorafenib plus chemotherapy** No relevant studies were identified at the 3-year surveillance review. At the 6-year surveillance review, 2 meta-analyses found that sorafenib plus

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
trastuzumab were randomly assigned to receive capecitabine alone or in combination with trastuzumab. An improvement in overall response and time to progression was observed in the group continuing with trastuzumab plus capecitabine. A follow-up analysis[165] did not demonstrate a significant survival benefit for treatment beyond progression with trastuzumab. One RCT[166] was identified which evaluated trastuzumab and docetaxel with or without capecitabine as first-line combination therapy for HER2-positive advanced breast cancer concluding that treatment with trastuzumab, docetaxel and capecitabine was an effective and feasible first-line therapy. ***Trastuzumab and docetaxel*** One RCT[167] was identified which compared trastuzumab and docetaxel with sequential therapy of single-agent trastuzumab followed at disease progression by docetaxel alone for metastatic breast cancer. Progression free survival was similar in both groups whilst overall survival was nonsignificantly shorter in the group receiving sequential therapy of single-agent trastuzumab followed by docetaxel. One RCT[168] concluded that trastuzumab and docetaxel combination therapy as first-line treatment for metastatic breast cancer was superior to trastuzumab monotherapy followed by docetaxel at disease progression. ***Trastuzumab and paclitaxel*** One RCT[169] was identified which compared	breast cancer NICE pathway. It is on the static list The technology appraisal TA263: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012) is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. The technology appraisal ID488: Bevacizumab in combination with chemotherapy for the second line treatment of HER2 negative metastatic breast cancer is currently suspended (since Nov 2011) as the manufacturer decided not to apply for a centralised marketing authorisation for this indication. ***Sorafenib plus chemotherapy*** Two meta-analyses[192,193] compared the efficacy and safety of sorafenib plus chemotherapy with placebo plus chemotherapy in HER2-negative advanced breast cancer. The 2 studies both found the same 4 RCTs (n=844) and presented almost identical conclusions. Compared with chemotherapy (or with anti-hormone receptor therapy) alone, sorafenib-based therapy significantly increased PFS, TTP, and ORR but not OS. Grade 3/4 adverse events, including hand-foot syndrome, anaemia, fatigue, rash and stomatitis, were significantly increased with sorafenib-based therapy. A meta-analysis[191] of 12 RCTs (n=2054) compared targeted therapy (bevacizumab, sorafenib, cetuximab, lapatinib, and iniparib)	team. ***Trastuzumab emtansine versus lapatinib plus capecitabine*** An RCT [EMILIA][203] of 991 patients compared trastuzumab emtansine (an antibody-drug conjugate consisting of trastuzumab linked to the cytotoxic agent DM1) with lapatinib plus capecitabine for HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane. Additionally a study[204] analysed patient-reported outcomes from the EMILIA trial. The in-progress technology appraisal ID603: Trastuzumab emtansine for treating unresectable metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane is awaiting progress following an appeal hearing in which a complaint was upheld. ID603 was based on evidence from the EMILIA trial. Following the appeal against the Final Appraisal Determination for this appraisal, NICE has developed a position statement on the relevance of the 'PPRS Payment Mechanism' of the Pharmaceutical Price Regulation Scheme (PPRS) 2014 to the assessment of the cost effectiveness of branded medicines. The Committee will meet on 29th September 2015 to discuss the outcome of the appeal and to reconsider the relevance of the PPRS in the light of the position statement. Consultees and commentators have been invited to give their views on the relevance of	chemotherapy significantly increased PFS, TTP, and ORR but not OS. Grade 3/4 adverse events, including hand-foot syndrome, anaemia, fatigue, rash and stomatitis, were significantly increased with sorafenib-based therapy. Two further meta-analyses found that sorafenib plus chemotherapy increased PFS versus chemotherapy alone. 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. **Trastuzumab emtansine monotherapy** No new evidence was identified at the 3-year surveillance review for trastuzumab emtansine. At the 6-year surveillance review, an RCT [EMILIA] presented initial PFS results for trastuzumab emtansine versus lapatinib plus capecitabine, and an additional study reported 1-year OS results. The use of trastuzumab emtansine is covered by the in-progress technology appraisal ID603: Trastuzumab emtansine for treating unresectable metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane. As ID603 was based on evidence

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
treatment with paclitaxel weekly or every three weeks for metastatic breast cancer whilst after the first 171 patients all HER2 positive patients received trastuzumab in addition to paclitaxel. The results of the study indicated that, in the combined sample, weekly paclitaxel was superior to every three weeks administration. ***Lapatinib and paclitaxel*** The efficacy of lapatinib plus paclitaxel as first-line treatment for metastatic breast cancer was assessed in an RCT[170]. Patients with HER2-negative metastatic breast cancer did not benefit from the addition of lapatinib however improved clinical outcomes were observed in HER2-positive patients. ***Docetaxel and axitinib*** One RCT[171] assessed the safety and efficacy of axitinib plus docetaxel in metastatic breast cancer. No significant difference in time to progression compared with control was observed. ***Trastuzumab, epirubicin and cyclophosphamide*** One RCT[172] was identified which assessed the cardiac safety and efficacy of trastuzumab plus cyclophosphamide and epirubicin for HER2-positive metastatic breast cancer indicating this may be a promising treatment regimen in this population. ***Iniparib, gemcitabine and carboplatin*** One RCT[173] was identified which compared the efficacy and safety of gemcitabine and carboplatin with or without iniparib in patients	plus chemotherapy with chemotherapy alone in triple-negative metastatic breast cancer. In pooled data of sorafenib plus chemotherapy as first-line and second-line treatments, PFS was greater with sorafenib plus chemotherapy than chemotherapy alone. A meta-analysis[194] of 8 RCTs (n=2077) examined multitargeted antiangiogenic tyrosine kinase inhibitors plus chemotherapy in metastatic breast cancer. In a subgroup analysis, sorafenib improved PFS in patients with HER2 negative metastatic breast cancer in comparison to chemotherapy alone. ***Trastuzumab combination therapy*** A Cochrane review[195] of 7 RCTs (n=1497) examined trastuzumab-containing regimens in HER2-positive metastatic breast cancer. In 4 studies, trastuzumab was administered with chemotherapy (taxanes, doxorubicin, epirubicin, cyclophosphamide, capecitabine); 2 studies administered trastuzumab with endocrine therapy (anastrozole or letrozole); 1 study administered trastuzumab with lapatinib. Five studies administered trastuzumab until progression as first-line treatment and 2 studies considered trastuzumab beyond progression. However, guidance on trastuzumab combination therapy is covered by the following technology appraisals: 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	the PPRS and the position statement in relation to this appraisal. ***Everolimus plus trastuzumab plus vinorelbine*** An RCT [BOLERO-3][205] of 599 patients compared everolimus plus trastuzumab plus vinorelbine (everolimus group) with placebo plus trastuzumab plus vinorelbine (placebo group) for women with trastuzumab-resistant, HER2-positive, advanced breast cancer who had previously received taxane therapy. Median follow-up at the time of analysis was 20.2 months. Median PFS was significantly longer in the everolimus group than in the placebo group (7.00 vs 5.78 months). The most common grade 3-4 adverse event was neutropenia (73% in the everolimus group vs 62% in the placebo group). Serious adverse events were reported in 42% patients in the everolimus group and 20% in the placebo group; two on-treatment deaths due to adverse events occurred in each group. However, guidance on everolimus plus trastuzumab plus vinorelbine is covered by technology appraisal topic 5981, but a referral was not sought for this appraisal. **Combined biological and endocrine therapy** ***Everolimus plus exemestane*** An RCT [BOLERO-2][206] compared everolimus plus exemestane with exemestane plus placebo in 724 patients with hormone-receptor-positive advanced breast cancer who had recurrence or progression while receiving	from the EMILIA trial, the new evidence is unlikely to impact on guideline recommendations . **Trastuzumab combination therapy** At the 3-year surveillance review, several studies were found evaluating trastuzumab in combination with various other agents including: capecitabine; paclitaxel; epirubicin plus cyclophosphamide; anastrozole; docetaxel; docetaxel plus carboplatin. At the 6-year surveillance review, a Cochrane review examining various trastuzumab-containing regimens found that they performed better for OS and PFS but increased the risk of cardiac adverse events and neutropenia. However, currently the use of trastuzumab (alone or in combination) is covered by 2 published technology appraisals: TA34 Guidance on the use of trastuzumab for the treatment of advanced breast cancer [an update of which (ID345) has been suspended since 2011]; and 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. This information is reflected in the NICE advanced breast cancer pathway. **Pertuzumab plus trastuzumab plus docetaxel** No relevant studies were identified at the 3-year surveillance review. At the 6-year surveillance review, an RCT

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
with metastatic breast cancer. The results of the study indicated that the addition of iniparib to gemcitabine and carboplatin improved the rate of clinical benefit, the rate of overall response and the median overall survival. In summary, at the 3 year surveillance review it was noted that no recommendations were included in the guideline relating to combined biological therapy and chemotherapy. However, one relevant Technology Appraisal had been published (TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011) whilst other Technology Appraisals were in development (relating to bevacizumab and trastuzumab) which it was felt may have an impact on the guideline recommendations in the future. **Combined biological therapy and endocrine therapy** ***Lapatinib and letrozole*** Three RCTs[174-176] were identified which indicated enhanced progression free survival in patients with advanced breast cancer treated with letrozole plus lapatinib. ***Trastuzumab and anastrazole*** One RCT[177] was identified which compared the efficacy of anastrazole with or without trastuzumab in postmenopausal women with HER2/hormone receptor copositive metastatic breast cancer. The results of the study indicated that combined therapy improved outcomes for this patient population although adverse events were more frequent.	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 incorporated into the guideline and is 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 GDG 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 GDG 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]. The technology appraisal 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) is not mentioned in the guideline but is included in the advanced breast cancer NICE	previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). However, this drug combination is covered by the technology appraisal TA295: Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (August 2013), which is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. TA295 was based on evidence from the BOLERO-2 trial. This also addresses a research recommendation in CG81 which states: '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.' **Chemotherapy – general comments** Comments received from topic experts: '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 'Treatment should be selected based on the following principles • Endocrine therapy should be used prior to chemotherapy for invasive ER+ve disease except for immediately life-threatening disease. • Single agent palliative chemotherapy is	[CLEOPATRA] presented initial PFS results, an additional study reported 1-year OS results and a further study reported prespecified OS results at a median follow-up of 50 months. However, the combination of pertuzumab plus trastuzumab plus docetaxel for advanced breast cancer is covered by the in-progress technology appraisal: ID523 Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy. ID523 was based on evidence from the CLEOPATRA trial. Once the technology appraisal has published, this will be included in the NICE pathway for advanced breast cancer. **Everolimus** ***Everolimus plus trastuzumab plus vinorelbine*** No relevant studies were identified at the 3-year surveillance review. At the 6-year surveillance review, an RCT [BOLERO-3] compared everolimus plus trastuzumab plus vinorelbine with placebo plus trastuzumab plus vinorelbine. The addition of everolimus to trastuzumab plus vinorelbine significantly prolonged PFS, although more grade 3-4 adverse events were seen. Guidance on everolimus plus trastuzumab plus vinorelbine is covered by technology appraisal topic 5981, but a referral was not

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Gefitinib and anastrazole One RCT[178] was identified which assessed the efficacy and tolerability of anastrazole combined with gefitinib in women with HER2-positive metastatic breast cancer. Combination therapy was associated with improved progression free survival and was well tolerated. ***Tipifarnib and letrozole*** One RCT[179] evaluated the clinical efficacy of letrozole combined with tipifarnib versus letrozole plus placebo in patients with advanced breast cancer. The results of the study indicated no difference in response duration, time to disease progression or survival. In summary, it was noted at the 3 year surveillance review that no recommendations were included in the guideline relating to combined biological therapy and endocrine therapy. However, at the time there was a related Technology Appraisal in development: Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2 which was felt may have an impact on the guideline recommendations in the future. (Update April 2015: Now published as TA257) **Combined chemotherapy, biological therapy and endocrine therapy** ***HER2-targeted agents plus chemotherapy and endocrine therapy*** A meta-analysis[180] evaluated the efficacy of	pathway. ***Iniparib plus chemotherapy*** A meta-analysis[191] of 12 RCTs (n=2054) compared targeted therapy (bevacizumab, sorafenib, cetuximab, lapatinib, and iniparib) plus chemotherapy with chemotherapy alone in triple-negative metastatic breast cancer. A sub-analysis of 2 trials looked at iniparib plus chemotherapy versus chemotherapy alone, and found that iniparib plus chemotherapy significantly increased PFS. Increases were also seen in OS with this combination but were not significant when between-trial heterogeneity was accounted for. Of the 2 trials examined in the sub-analysis, 1 was a phase II trial and 1 was a 2011 conference abstract of a phase III trial. Full results of the phase III trial were published in 2014 and reported that the prespecified criteria for the coprimary endpoints of PFS and OSS in the ITT population were not met. **Combined biological and endocrine therapy** ***Lapatinib or trastuzumab in combination with an aromatase inhibitor*** A systematic review and economic analysis[196] of 3 trials examined an aromatase inhibitor plus either lapatinib or trastuzumab for the first-line treatment of hormone receptor-positive, HER2 positive metastatic breast cancer. A network meta-analysis[197] of 62 papers (from 18 RCTs) compared lapatinib plus letrozole with other first-line treatments for hormone	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.	sought for this appraisal. As topic 5981 was based on evidence from the BOLERO-3 trial, the new evidence is unlikely to impact on guideline recommendations. ***Everolimus plus exemestane*** No relevant studies were identified at the 3-year surveillance review. At the 6-year surveillance review, a network meta-analysis compared everolimus plus exemestane with fulvestrant. Additionally, an RCT [BOLERO-2] compared everolimus plus exemestane with exemestane plus placebo. The combination of everolimus plus exemestane is covered by technology appraisal TA295: Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (August 2013). TA295 was based on evidence from the BOLERO-2 trial. This information has been included in the NICE pathway for advanced breast cancer. This addresses the research recommendation: '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.' ***Lapatinib or trastuzumab in combination with an aromatase inhibitor*** At the 3-year surveillance review, 3 RCTs were identified of letrozole plus lapatinib, and

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
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** ***Sunitinib versus capecitabine*** One RCT[181] was identified which compared the efficacy of sunitinib with capecitabine with the study concluding that sunitinib should not be used as monotherapy for advanced breast cancer. ***Sunitinib plus paclitaxel versus bevacizumab plus paclitaxel*** One RCT[182] compared progression free survival following treatment with sunitinib plus paclitaxel versus bevacizumab plus paclitaxel for advanced breast cancer. The results of the study indicated that the sunitinib plus paclitaxel treatment regimen was clinically inferior to bevacizumab plus paclitaxel. ***Docetaxel and trastuzumab versus docetaxel, carboplatin and trastuzumab*** One RCT[183] was identified which compared the efficacy of trastuzumab plus docetaxel versus docetaxel, carboplatin and trastuzumab for metastatic breast cancer. Addition of carboplatin did not enhance the antitumour activity of trastuzumab and docetaxel. Two in-progress Technology Appraisals on sunitinib were identified which may have an	receptor positive and HER2 positive advanced or metastatic breast cancer. However, guidance in this area is covered by the following technology appraisal: 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) is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. ***Everolimus plus exemestane*** A network meta-analysis[198] of 6 studies compared everolimus plus exemestane with fulvestrant for hormone-receptor-positive advanced breast cancer following progression/recurrence after adjuvant or first-line endocrine therapy. The primary analysis was based on the local review of disease progression from BOLERO-2 [everolimus plus exemestane] with the data from the other studies). The BOLERO-2 trial was the basis of the following technology appraisal which provides guidance in this area: TA295: Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (August 2013) is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. Additionally, a research recommendation in		1 RCT of anastrazole plus trastuzumab versus anastrozole alone. At the 6-year surveillance review, a systematic review and economic analysis examined an aromatase inhibitor plus either lapatinib or trastuzumab, and a network meta-analysis compared lapatinib plus letrozole with other first-line treatments. The combination of lapatinib or trastuzumab plus an aromatase inhibitor is covered by technology appraisal 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). This information is reflected in the NICE pathway on advanced breast cancer. **Iniparib** At the 3-year surveillance review, 1 RCT compared the efficacy and safety of gemcitabine and carboplatin with or without iniparib in patients with metastatic breast cancer. At the 6-year surveillance review, a meta-analysis compared targeted therapy (bevacizumab, sorafenib, cetuximab, lapatinib, and iniparib) plus chemotherapy with chemotherapy alone in triple-negative metastatic breast cancer. A sub-analysis looked at iniparib plus chemotherapy versus chemotherapy alone, and found that iniparib plus chemotherapy significantly increased PFS. Because the phase III trial (which formed the

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
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 April 2015: 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 April 2015: Technology appraisal is suspended) **Chemotherapy versus endocrine therapy** ***Chemotherapy alone versus endocrine therapy alone*** A systematic review[184] 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[185] 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	CG81 states: '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.'		basis of the meta-analysis identified by the 6-year review) did not reach its primary endpoints, this evidence is unlikely to impact the guideline. **Other combination treatments/comparisons between treatments** For all other combination treatments/ comparisons between treatments, no additional evidence was found by the 6-year surveillance review to change the conclusion of the 3-year surveillance review, namely that no conclusive new evidence was identified which would invalidate current guideline recommendation(s). **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
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[186]. The study concluded that there was a trend towards a survival advantage in the vaccine treated group however, further study was required. **Summary** In summary, new evidence was identified at the 3 year surveillance review relating to combination systemic disease modifying therapy for advanced breast cancer, in particular combined chemotherapy plus biological therapy (bevacizumab or lapatinib combined with chemotherapy) and combined endocrine plus biological therapy (lapatinib and letrozole). However, a Technology Appraisal has been published (TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011) whilst another was in development at the time of the surveillance (Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer; Update April 2015: now published as TA263) therefore it was felt cross-referral to these in the guideline would be warranted. In addition, relevant Technology Appraisals were in development which were felt may have an impact on the guideline recommendations in the future. Only two studies were identified which evaluated vaccines for advanced breast cancer. Hence, more evidence was warranted before this			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
intervention could be considered within the guideline.			
Supportive care			
81-09 What is the role of ongoing management of advanced breast cancer patients in the community setting? (1.4.1)			
3-year surveillance (2011) **Supportive care** An observational study[207] 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. A systematic review[208] identified five studies of group psychological therapies (including cognitive-behavioural or supportive-expressive) which demonstrated little evidence of benefit. A post-hoc analysis[209] of an RCT assessing supportive-expressive group therapy 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[210]. The results of the study indicated that reports of fatigue were lower in the intervention group. The effect of emotionally expressive writing in	No relevant studies identified.	None identified relevant to this question.	**Management of advanced breast cancer in the community setting** At the 3-year surveillance review, no new evidence was identified which would invalidate the current guideline recommendations. No further evidence was found at the 6-year surveillance review. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
women with metastatic breast cancer was evaluated in an RCT[211]. The intervention was found to be more beneficial in women who had been recently diagnosed with metastatic breast cancer. One RCT[212] 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[213]. The results of the study indicated that reported satisfaction with the intervention was high. **In summary** In summary, new literature was identified focusing on a variety of supportive strategies which were generally effective however, the 3 year surveillance review 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.			
81-10 What are the effective interventions used to support young families in which a parent has advanced breast cancer? (1.4.1)			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant evidence identified **Surveillance decision**

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
			This review question should not be updated.
Managing complications			
81-11 What is the diagnostic accuracy of specific investigations to recognise lymphoedema early in patients with early, locally advanced and advanced (metastatic) breast cancer? (1.5.1 – 1.5.7)			
3-year surveillance (2011) One study[214] aimed to determine whether bioimpedance spectroscopy (BIS) could detect localised lymphoedema of the arm and to compare BIS measurements with equivalent measures of limb volume by perometry. The study indicated that BIS could be used for localised measurement of lymphoedema. BIS was more sensitive to localised lymphoedema than perometry because it was specific to extracellular fluid. The second study[215] evaluated circumference measurement (CM) and water displacement (WD) for volume measurements (VM) of the breast cancer-related lymphedema (BCRL) arm and the contralateral arm, comparing the results with regional dual energy X-ray absorptiometry (DXA). DXA was superior in repeatability when compared to CM and WD for VM, especially for the BCRL arm but also the contralateral arm. Lastly, one study[216] compared diagnostic accuracy of measures of breast cancer-related lymphoedema (BCRL). The results of the study supported the use of bioimpedance spectroscopy in the assessment of existing BCRL. The study also indicated that refining diagnostic cutoff values may improve	No relevant studies identified.	None identified relevant to this question.	**Early recognition of lymphoedema** At the 3-year surveillance review, no new evidence was identified which would invalidate the current guideline recommendations. No further evidence was found at the 6-year surveillance review. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
accuracy of diagnosis and warranted further investigation. **Summary** In summary, two studies showed bioimpedance spectroscopy (BIS) to be effective in detecting breast cancer-related lymphoedema (BCRL) but warranted further investigation. One study indicated that circumference measurement (CM) and water displacement (WD) may not be effective compared to X-ray absorptiometry (DXA). The 3 year surveillance review concluded that the identified new evidence did not support the use of one diagnostic tool over another for recognising lymphoedema early in patients with early, locally advanced or advanced (metastatic) breast cancer.			
81-12 What is the best management strategy of lymphoedema? (1.5.1 – 1.5.7)			
3-year surveillance (2011) **Systematic reviews** A systematic review[217] was identified which assessed the evidence relating to management of secondary lymphoedema following breast cancer. The review indicated that beneficial treatments included physiotherapy, exercise and complex decongestive therapy. One systematic review[218] concluded that combined physical therapy was an effective therapy for breast cancer-related lymphoedema although further research was required to determine the effectiveness of the	**Manual lymphatic drainage** A meta-analysis[237] of 10 RCTs (n=566) assessed manual lymphatic drainage for prevention and treatment of breast cancer-related lymphoedema in women after breast-cancer surgery. From 2 prevention studies, manual lymphatic drainage did not reduce the incidence of postoperative lymphedema versus standard treatment. From 7 management studies, manual lymphatic drainage did not reduce arm volume versus standard treatment. **Intermittent pneumatic compression pump** A meta-analysis[238] of 7 RCTs (n=287) assessed an intermittent pneumatic	**General comments** Comments received from topic experts noted: '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 /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	**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

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
individual components of the therapy. The effects and harms of physiotherapy methods and other treatment practices for lymphoedema in breast cancer patients were assessed in a systematic review[219]. The review concluded that evidence on physiotherapy methods was limited although compression bandages seemed to be beneficial in reducing lymphoedema. A systematic review[220] of physiotherapy treatments for breast cancer-related lymphoedema concluded that better results were obtained with combined treatments. Complex decongestive therapy combined with pneumatic compression was found to demonstrate efficacy. The systematic reviews showed some benefit of using physiotherapy, compression bandage, exercise, and complex decongestive therapy combined with pneumatic compression but it was considered that further evaluations were required to validate these interventions. **Compression therapy** ***Bandaging*** A randomised comparative study[221] evaluated whether there is a difference between low and high pressure bandaging in volume reduction for management of breast cancer-related arm lymphoedema. No statistically significant changes in volume were observed between the two groups in the first 24 hours after application although the low pressure bandages were better tolerated.	compression pump for breast cancer-related lymphoedema. No significant difference between routine management of lymphoedema with or without pneumatic pump was found (data not given).	preferred term. Some use the “L” to mean Lymphatic, while others to mean Lymphoedema. I think the latter is preferred.’	either showed no benefit, or required further validation. However, new literature was identified 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. However, 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). As such, the terminology used in the section of the guideline on lymphoedema and its management may need to be refreshed. **Surveillance decision** 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 reflective 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

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
One RCT[222] was identified which compared alginate semi-rigid bandaging with conventional lymphologic-multilayered low-stretch bandaging for breast cancer-related lymphoedema. The study concluded that alginate bandages were a good alternative to conventional bandaging. ***Compression hosiery*** One small RCT[223] compared the efficacy of autologous stem cells in the treatment of postmastectomy lymphoedema with decongestive treatment with compression sleeves. An improvement in the volume of lymphoedema was observed in both groups. The effect of different intermittent pneumatic compression protocols (in particular, cycle time and number of sleeve chambers) on lymphoedema volume reduction was assessed in an RCT[224]. The study concluded that this was an effective method of reducing lymphoedema volume reduction regardless of the protocol used. One systematic review[225] was identified which evaluated the use of compression pumps for treatment of breast cancer-related upper extremity lymphoedema. The review concluded that there was no evidence to suggest that treatment with an intermittent compression pump was more beneficial than education about arm care and hygiene. One RCT[226] was identified which compared decongestive lymphatic therapy combined with pneumatic compression with Kinesio tape (K-tape) combined with pneumatic			time.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
compression for breast cancer-related lymphoedema. No significant differences between groups were observed for any measured outcomes. Some studies showed that alginate semi-rigid bandaging, autologous stem cells, and pneumatic compression protocols showed some effectiveness but further validation was required. Decongestive lymphatic therapy combined with pneumatic compression, compression pumps, and low and high pressure bandaging did not show any statistical significance. ***Therapeutic exercise*** One RCT[227] evaluated the effect of a mixed exercise programme on lymphoedema status among women who had completed treatment for breast cancer concluding that exercise did not exacerbate the lymphoedema. The results from one RCT[228] indicated that progressive weight lifting was safe for women following breast cancer who had, or were at risk of developing, lymphoedema. The effectiveness of complex decongestive physiotherapy with and without active resistive exercise for treatment of breast cancer-related lymphoedema was evaluated in an RCT[229]. The results of the study indicated that combination therapy did not cause additional swelling, reduced arm volume and improved quality of life. One systematic review[230] evaluating the role of exercise in lymphoedema care concluded that evidence was available on the safety of			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
resistance exercise without an increased risk of lymphoedema in breast cancer patients. An RCT[231] was identified which assessed the effect of twice-weekly weight lifting in women with breast cancer-related lymphoedema. The results of the study indicated that weight lifting had no significant effect on limb swelling and resulted in decreased incidence of exacerbations of lymphoedema. The studies showed some effectiveness of exercise, complex decongestive physiotherapy, and weight lifting in the treatment of lymphoedema. ***Laser therapy*** One RCT[232] was identified which compared the efficacy of an active laser with placebo in women with breast cancer-related lymphoedema. Limb volume tended to decline in both groups but significantly greater reduction was observed in the active laser group at 8 and 12 weeks. An RCT[233] comparing low-level laser therapy (LLLT) with no laser irradiation for managing postmastectomy lymphoedema concluded that LLLT was an effective management strategy with effects maintained at the 4 week follow-up. The studies showed some effectiveness of using active laser and low level laser therapies but further validation was required. ***Complex decongestive therapy*** One RCT[234] was identified which compared the efficacy of complex decongestive therapy			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
alone or in combination with intermittent pneumatic compression for breast cancer related lymphoedema. The results of the study indicated that complex decongestive therapy alone produced better results compared with combination therapy. ***Lymphatic therapy*** One RCT[235] compared aqua lymphatic therapy (ALT) with self-management therapy for management of breast cancer-related lymphoedema. ALT demonstrated an immediate effect on limb volume but no long-term effect. ***Hyperbaric oxygen therapy*** An RCT[236] of hyperbaric oxygen therapy (HBO) compared with best standard care for arm lymphoedema after radiotherapy for breast cancer demonstrated no beneficial effect of HBO. **Summary** In summary, through an assessment of the abstracts at the 3 year surveillance review it was not possible to determine if the studies addressed lymphoedema management in patients with advanced breast cancer. New literature was identified focusing on the safety and benefit of exercise for breast cancer-related lymphoedema. However, taking study heterogeneity into account and that this is a small area of the guideline, it was felt, at the 3 year surveillance review, that this new evidence may not be significant enough to warrant updating the guideline at this point. However, when this decision was made (April			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
2012) the Clinical Guidelines Update Team (CGUT) had recently been established and was looking to identify topics suitable for a pilot process. It was decided that the role of exercise in patients with breast cancer-related lymphoedema was suitable for an update via the CGUT. In July 2014 an update to CG81 in section 1.5 was published adding 2 recommendations about exercise in managing lymphoedema.			
81-13 What are the best management strategies for complications: • **Cancer-related fatigue** • **Uncontrolled local disease** • **Solitary or multiple bone-metastases** • **Solitary or multiple brain metastases** • **Pain** • **Acute radiodermatitis? (1.5.8 – 1.5.21)**			
3-year surveillance (2011) **Cancer-related fatigue** One RCT[239] evaluated the effect of a multimodal group exercise intervention, as an adjunct to conventional care, on fatigue, physical capacity, general wellbeing, physical activity, and quality of life in patients with cancer who were undergoing adjuvant chemotherapy or treatment for advanced disease. A reduction in fatigue was observed although no change in quality of life occurred. The clinical factors that may predict exercise training responses in patients with breast cancer were assessed in an RCT[240]. The results of the study indicated that patient	**Cancer-related fatigue** No relevant studies identified. However, the technology appraisal TA323: Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142) (November 2014) is relevant to this area but is not mentioned in the guideline and is not included in the advanced breast cancer NICE pathway. **Bone metastases** A Cochrane review[258] examined bisphosphonates and other bone agents for breast cancer. In breast cancer with bone metastases, bisphosphonates significantly	None identified relevant to this question.	**Cancer-related fatigue** At the 3-year surveillance review, the literature on management of cancer-related fatigue was 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. No further evidence was identified at the 6-year surveillance review, therefore

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
preference, medical variables and demographic variables moderated the effects of exercise training in breast cancer patients undergoing chemotherapy. In addition, the predictors of adherence to supervised exercise training during chemotherapy for breast cancer were evaluated in an RCT[241] and included disease stage, aerobic fitness and depression. A Cochrane systematic review[242] was identified which evaluated the effectiveness of psychosocial interventions in reducing cancer related fatigue. The review concluded that there was limited evidence that psychosocial interventions during cancer treatment are effective in reducing fatigue although this may be a promising intervention. An additional Cochrane systematic review[243] was identified which aimed to determine efficacy of pharmacological treatments on non-specific fatigue in palliative care with a focus on patients at an advanced stage of disease, including cancer. The review concluded that methylphenidate for fatigue in patients suffering from advanced cancer warrants further study. 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.	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. Bisphosphonates reduced the skeletal-related event rate in 12 studies and were associated with delays in the median time to skeletal-related events . Bisphosphonates improved bone pain versus placebo or no bisphosphonates in 6 out of 11 studies, improved global QoL versus placebo in 2 out of 5 studies (both ibandronate), but did not affect survival. Versus zoledronic acid, denosumab reduced the skeletal-related event rate, delayed the time to skeletal-related events and prolonged the time in developing pain for patients with no or mild pain at baseline, but did not affect survival. In women with advanced breast cancer without clinically evident bone metastases, bisphosphonates did not reduce bone metastases or improve survival (3 studies, n=320). Toxicity was generally mild. A systematic review[259] 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. Guidance on denosumab is available in the following technology appraisals: The technology appraisal TA265: Denosumab for the prevention of skeletal-related events in		conclusions of the 3-year surveillance review remain valid However, it was 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 should cross-refer, at the earliest opportunity, to TA323. **Bone metastases** ***Bisphosphonates*** Overall, the new evidence is consistent with guideline recommendations. At the 3-year surveillance review, literature was identified which indicated a beneficial effect of bisphosphonates in patients with bone metastases. At the 6-year surveillance review a Cochrane review again reported a beneficial effect of bisphosphonates (particularly zoledronate, pamidronate, ibandronate and clodronate) in patients with bone metastases. 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

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Uncontrolled local disease One Cochrane systematic review[244] 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. In terms of uncontrolled local disease, the new literature was thought unlikely to change the direction of the current recommendation 1.5.12 which states that a wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team. **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[245]. 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	adults with bone metastases from solid tumours (October 2012) is not mentioned in the guideline but is included in the advanced breast cancer NICE pathway. **Liver metastases** (Note: The original clinical question did not cover management of liver metastases but it is very closely related to this question so has been covered here). A systematic review[260] of 19 studies (n=553) examined hepatic resection for metastatic breast cancer. Hepatectomy was performed at a rate of 1.8 (range 0.7–7.7) cases per year in reported series. Time to liver metastases occurred at a median of 40 (range 23–77) months. Median mortality and complication rate were 0% (range 0–6%) and 21% (range 0–44%), respectively. Median overall survival was 40 (range 15–74) months and median 5-year survival rate was 40% (range 21–80%). Potential prognostic factors associated with a poorer overall survival included a positive liver surgical margin and hormone refractory disease. 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. **Uncontrolled local disease; Brain metastases; Pain; Acute radiodermatitis** No relevant studies identified.		limited to preparations licensed for this indication.' ***Denosumab*** The identified new evidence is consistent with guideline recommendations. At the 3-year surveillance review, studies were identified which suggested denosumab may be a beneficial option for managing bone metastases. At that time, denosumab was currently only licensed for treatment of postmenopausal osteoporosis in women at increased risk of fractures and for treatment of bone loss associated with hormone ablation in men with prostate cancer. Therefore, it was decided that it would be pertinent to await further evidence, particularly on the benefits, harms and cost-effectiveness of this treatment for managing bone metastases in advanced breast cancer before including in the guideline. At the 6-year surveillance review, new evidence from a Cochrane review found that denosumab reduces skeletal-related events versus bisphosphonates. However, the use of denosumab is covered by TA265 (October 2012) which recommends denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours. **Liver metastases** (Note: The original clinical question did not cover management of liver metastases but it is very closely related to this question so has been covered here).

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
evaluated in an RCT[246]. 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[247]. 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[248] 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[249] 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[250] was identified which assessed the safety and efficacy of ibandronate in patients with advanced breast cancer and bone metastases. The results of the study			No evidence was identified at the 3-year surveillance review. At the 6-year surveillance review, 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. 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. At the 3-year surveillance review: For uncontrolled local disease, the evidence was thought unlikely to change current recommendations. For brain metastases, the evidence 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. For pain and acute radiodermatitis, only single trials were identified therefore it was concluded that further study was warranted to confirm the results obtained. No new evidence was identified for any of these areas at the 6-year surveillance review,

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
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[251]. 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[252] 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. New literature was identified which indicated a beneficial effect of bisphosphonates in patients with bone metastases which supported the current guideline recommendations. In addition, new studies suggested denosumab could also be a beneficial option for managing bone			therefore conclusions of the 3-year surveillance review remain valid. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
metastases. However, at the 3-year review point, denosumab was currently only licensed for treatment of postmenopausal osteoporosis in women at increased risk of fractures and for treatment of bone loss associated with hormone ablation in men with prostate cancer. Therefore, it was felt it would be pertinent to await further evidence, particularly on the benefits, harms and cost-effectiveness of this treatment for managing bone metastases in advanced breast cancer before including in the guideline. **Brain metastases** A small-scale clinical trial[253] 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[254]. Progression-free survival was 3.7 months and overall survival was 6.5 months whilst overall toxicity was acceptable. A clinical trial[255] 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			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
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[256] 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[257] 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. In summary, only single trials were identified relating to management of pain and acute radiodermatitis therefore it was concluded that further study was warranted to confirm the results obtained. **Summary**			

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
In summary, the 3 year surveillance review concluded that no conclusive new evidence was identified relating to interventions for management of cancer related fatigue, uncontrolled local disease, bone metastases, brain metastases, pain or treatment of acute radiodermatitis which would invalidate current guideline recommendations.			
Research recommendations			
Systemic disease-modifying therapy			
RR1 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.			
3-year surveillance (2011) No relevant studies identified.	See 'Everolimus plus exemestane' under clinical question 81-08 in the table above.	See 'Everolimus plus exemestane' under clinical question 81-08 in the table above.	See summary for 'Everolimus plus exemestane' under clinical question 81-08 in the table above. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR2 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
RR3 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR4 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR5 Randomised clinical trials should evaluate the clinical and cost effectiveness of different sequences of chemotherapy for advanced breast cancer.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	No new evidence was identified from the GDG questionnaire, guideline issue log, or consultation on the 3-year surveillance decision.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR6 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
			point.
RR7 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
Supportive care			
RR8 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR9 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
Managing complications			
RR10 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR11 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR12 Further research is required into which exercise programmes are most effective for patients with advanced breast cancer and to identify the most efficient way to deliver these in an NHS service.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR13 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision**

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
			This research recommendation will be considered again at the next surveillance point.
RR14 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.			
3-year surveillance (2011) No relevant studies identified.	No relevant studies identified.	None identified relevant to this question.	No relevant studies identified. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
Areas not currently covered by CG81			
NQ-01 What is the role of surgical resection of the primary tumour in stage IV breast cancer?			
3-year surveillance (2011) No relevant studies identified.	**Surgical resection of the primary tumour** A meta-analysis[261] 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 smaller primary tumors, less competing medical comorbidities and lower metastatic burden ($p<0.01$). 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	None identified relevant to this question.	**Surgical resection of the primary tumour** No evidence was identified at the 3-year surveillance review. 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.

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
	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.		**Surveillance decision** 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 were of poor quality. This review question should not be added.
NQ-02 What are the predictors of treatment response?			
3-year surveillance (2011) No relevant studies identified.	**Predictors of sensitivity to trastuzumab** A meta-analysis[262] 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.	**Genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer** Topic expert feedback highlighted the following study: A multicentre, prospective trial[263] 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	**Predictors of sensitivity to trastuzumab** No evidence was identified at the 3-year surveillance review. 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-year surveillance review. At the 6-year surveillance review, a multicentre, prospective trial suggested that testing for genomic abnormalities in individual patients could provide a means of matching

Conclusions from previous surveillance	Summary of new evidence from 6-year surveillance (2015)	Summary of new intelligence from 6-year surveillance (2015)	Impact
		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.	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. **Surveillance decision** This review question should not be added.

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