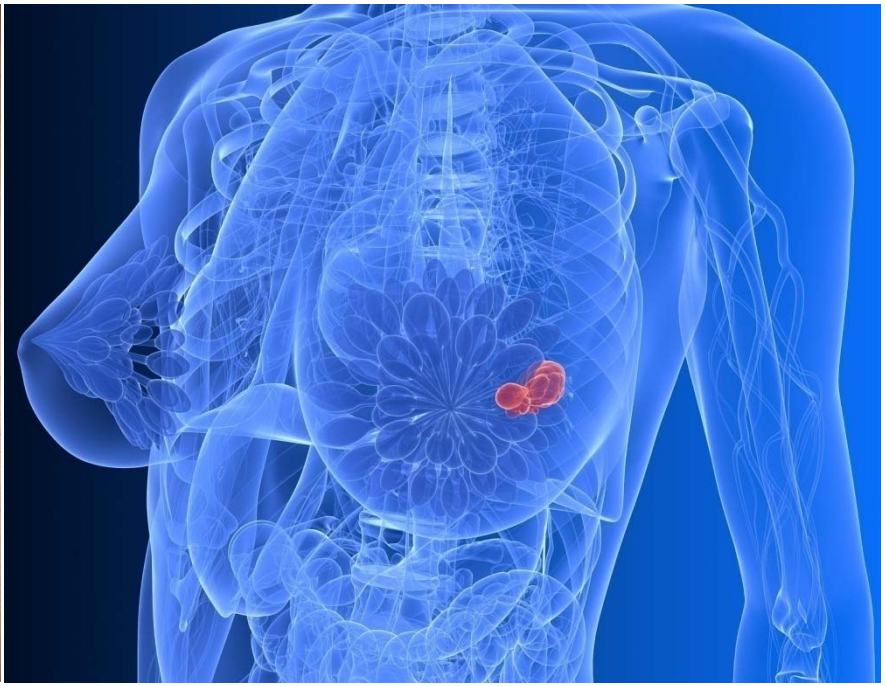
KCE REPORT 143S – 3rd EDITION

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

BREAST CANCER IN WOMEN: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX



KCE REPORT 143S – 3rd EDITION
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BREAST CANCER IN WOMEN: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX

HANS WILDIERS, SABINE STORDEUR, JOAN VLAYEN, ROB SCHOLTEN, FLEUR VAN DE WETERING, CLAIRE BOURGAIN, BIRGIT CARLY, MARIE-ROSE CHRISTIAENS, VÉRONIQUE COCQUYT, ERIC LIFRANGE, JEAN-CHRISTOPHE SCHOBBENS, MIREILLE VAN GOETHEM, GEERT VILLEIRS, ERIK VAN LIMBERGEN, PATRICK NEVEN

COLOPHON

Title :	Breast cancer in women: diagnosis, treatment and follow-up – Appendix
Authors:	Hans Wildiers (UZ Leuven), Sabine Stordeur (KCE), Joan Vlayen (KCE), Rob Scholten (Dutch Cochrane Centre), Fleur van de Wetering (Dutch Cochrane Centre), Claire Bourgain (Imelda), Birgit Carly (CHU Saint-Pierre), Marie-Rose Christiaens (UZ Leuven), Véronique Cocquyt (UZ Gent), Eric Lifrange (CHU Liège), Jean-Christophe Schobbens (Ziekenhuis Oost-Limburg Genk), Mireille Van Goethem (UZ Antwerpen), Geert Villeirs (UGent), Erik van Limbergen (UZ Leuven), Patrick Neven (UZ Leuven)
Reviewers:	Kristel De Gauquier (KCE), Kirsten Holdt (KCE), Christian Léonard (KCE), Raf Mertens (KCE), Jo Robays (KCE)
Acknowledgements:	Patrice Chalon (KCE), Cécile Dubois (KCE), Jo Robays (KCE), France Vrijens (KCE)
External validators:	Jan Bosteels (Belgian Center for Evidence Based Medicine, CEBAM), Fabienne Liebens (ISALA, CHU Saint-Pierre, Bruxelles), Emiel Rutgers (The Netherlands Cancer Institute, NKI)
Stakeholders:	Martine Berlière (GGOLFB), Patrick Berteloot (VVOG), Frédéric Buxant (GGOLFB), Cécile Colpaert (BVP), Guy Jérusalem (BSMO), Kathleen Lambein (BVP), Ann Smeets (BSBS), Marian Van Hoeij (BSBS), Rudy Van den Broecke (VVOG) In addition 2 patients participated on the guideline development group. For privacy reasons their names are not mentioned in this colophon.
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Fabienne Liebens (Europa Donna Belgium, Fonds Pink Ribbon (managed by Fondation Roi Baudouin), Geert Villeirs (Consilium Radiologicum, Koninklijke Belgische Vereniging voor Radiologie) Fees or other compensation for writing a publication or participating in its development: Véronique Cocquyt A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Véronique Cocquyt, Patrick Neven, Guy Jérusalem (Novartis, Astra-Zeneca, Roche, GSK, MSD, Sanofi), Fabienne Liebens (Fondation contre le Cancer, Fonds Iris Recherche) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Guy Jérusalem (Novartis, Roche) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Véronique Cocquyt, Patrick Neven, Hans Wildiers, Guy Jérusalem (Novartis, Astra-Zeneca, Roche, GSK, Janssen Pharma), Rudy Van den Broecke (Astra-Zeneca, Novartis, Amgen), Fabienne Liebens (TEVA, Roche, Hologic, Novartis, Astra-Zeneca) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Jan Bosteels (Vlaamse Vereniging voor Obstetrie en Gynaecologie), Rudy Van den Broecke (Astra-Zeneca, Novartis), Fabienne Liebens (ISALA), Geert Villeirs (Consilium

Radiologicum, Koninklijke Belgische Vereniging voor Radiologie)

Participation in scientific or experimental research as an initiator, principal investigator or researcher: Véronique Cocquyt, Hans Wildiers, Marian Van Hoeij (Vlaamse Liga tegen Kanker), Fabienne Liebens (Everolinus study (Novartis))

Layout : Sophie Vaes

Disclaimer :

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE**

Publication date: 8 July 2013 (3rd edition; 1st edition 9 November 2010; 2nd edition 20 January 2012)

Domain: Good Clinical Practice (GCP)

MeSH : Breast Neoplasms; Carcinoma, Ductal, Breast; Neoplasm, Metastasis; Practice Guideline

NLM Classification : WP 870

Language : English

Format : Adobe® PDF™ (A4)

Legal depot : D/2012/10.273/39

How to refer to this document ?

Wildiers H, Stordeur S, Vlayen J, Scholten R, van de Wetering F, Bourgain C, Carly B, Christiaens M-R, Cocquyt V, Lifrange E, Schobbens J-C, Van Goethem M, Villeirs G, Van Limbergen E, Neven P. Breast cancer in women: diagnosis, treatment and follow-up – Appendix. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 143S – 3rd EDITION. D/2013/10.273/39.

This document is available on the website of the Belgian Health Care Knowledge Centre

APPENDIX REPORT

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

APPENDICES

1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

Clinicians	Field of expertise
Hans Wildiers, President of the GDG	Medical Oncology
Claire Bourgain	Pathology
Birgit Carly	Surgery
Marie-Rose Christiaens	Medical Oncology
Véronique Cocquyt	Medical oncology
Eric Lifrange	Gynaecology
Patrick Neven	Gynaecology
Jean-Christophe Schobbens	Surgery
Mireille Van Goethem	Medical imaging
Erik Van Limbergen	Radiotherapy
Geert Villeirs	Medical imaging

1.2. Composition of the KCE expert team

KCE member	Specific role
Kristel De Gauquier	Program Manager
Sabine Stordeur	Guideline Coordinator, responsible for the scientific content
Joan Vlayen	Scientific and methodological support

1.3. Researchers involved in the guideline update

Dutch Cochrane Centre (DCC)	Specific role
Rob JPM Scholten	Senior clinical epidemiologist
Fleur van de Wetering	Junior researcher
Geertjan van Tienhoven	Radiation oncologist (content expert)
JWR (Hans) Nortier	Medical oncologist (content expert)

1.4. Acknowledgements

KCE is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline:

Clinicians	Field of expertise
Fatima Cardoso, former President of the GDG	Medical Oncology
Pierre Scaillet	Radiotherapy

The Guideline Development Group acknowledges Cécile Dubois (KCE), France Vrijens (KCE) and Jo Robays (KCE) for their helpful comments and statistical support provided during the update.

2. AGREE SCORES OF IDENTIFIED GUIDELINES

Source	Title	Standardised Scores						Final Appraisal
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence	
NICE 2009	Early and locally advanced breast cancer: diagnosis and treatment	100%	75%	98%	96%	78%	83%	Recommended
NICE 2009	Advanced breast cancer: diagnosis and treatment	100%	75%	98%	96%	78%	83%	Recommended
ASCO 2007	American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer	89%	50%	67%	79%	28%	50%	Recommended with modifications
ASCO 2006	American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer	100%	67%	88%	75%	56%	50%	Recommended with modifications
ASCO 2006	American Society of Clinical Oncology 2006 Update of the Breast Cancer Follow-Up and Management Guidelines in the Adjuvant Setting	78%	67%	74%	83%	61%	50%	Recommended with modifications
CCO 2007	Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer: A Clinical Practice Guideline	100%	67%	93%	71%	50%	100%	Recommended
CCO 2006	Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline	100%	62%	95%	75%	17%	100%	Recommended

Source	Title	Standardised Scores						Final Appraisal
CCO 2008	The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations	100%	63%	98%	79%	11%	100%	Recommended
CCO 2007	The Role of Gemcitabine in the Management of Metastatic Breast Cancer: A Clinical Practice Guideline	100%	46%	93%	62%	0%	100%	Recommended
CCO 2006	The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer: A Clinical Practice Guideline	100%	38%	93%	67%	6%	100%	Recommended
Alberta Medical Association 2007	The Early detection of Breast Cancer	67%	29%	19%	83%	0%	0%	Not recommended
CCO 2006	The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer: A Systematic Review	100%	50%	83%	67%	0%	100%	Recommended with modifications
SOGC 2006	Progesterone-Only and Non-Hormonal Contraception in the Breast Cancer Survivor: Joint Review and Committee Opinion of the Society of Obstetricians and Gynaecologists of Canada and the Society of Gynecologic Oncologists of Canada	67%	0%	24%	58%	0%	0%	Not recommended

Source	Title	Standardised Scores						Final Appraisal
CCO 2006	Diagnostic Imaging in Breast Cancer	100%	33%	69%	71%	0%	100%	Recommended with modifications
NCCN 2009	Breast Cancer	83%	71%	62%	100%	17%	83%	Not recommended
ACR 2006	American College of Radiology Appropriateness Criteria – Stage I Breast Carcinoma	83%	25%	29%	46%	33%	0%	Not recommended
ACS 2007	American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography	94%	29%	38%	58%	33%	0%	Not recommended
ICSI 2008	Health Care Guideline: Diagnosis of Breast Disease	61%	42%	57%	96%	78%	50%	Not recommended
NHS HDL 2007	Scottish referral guidelines for suspected cancer	67%	25%	2%	29%	28%	0%	Not recommended
FNCLCC 2007	Recommandations pour la Pratique Clinique : Saint Paul de Vence 2007 «cancers du sein»	100%	54%	83%	75%	50%	100%	Recommended with modifications
FNCLCC 2006	Utilisation de la TEP-FDG dans les cancers du sein, de l'ovaire et de l'utérus - Bulletin de synthèse de veille 2005	100%	17%	86%	62%	0%	50%	Recommended with modifications
NICE 2006	Familial breast cancer - The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care	100%	50%	81%	79%	100%	0%	Recommended with modifications
ESMO 2008	Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	67%	17%	38%	58%	6%	25%	Not recommended

Source	Title	Standardised Scores						Final Appraisal
ESMO 2008	Locally recurrent or metastatic breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	67%	25%	33%	58%	11%	25%	Not recommended
ABS 2007	Oncoplastic breast surgery - A guide to good practice	78%	42%	17%	50%	72%	75%	Not recommended
CCO 2008	Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations	100%	54%	98%	75%	0%	100%	Recommended with modifications
UMHS 2007	Guidelines for clinical care : Common breast problems	89%	25%	21%	62%	33%	67%	Not recommended
ACP 2007	Screening Mammography for Women 40 to 49 Years of Age: A Clinical Practice Guideline from the American College of Physicians	100%	46%	64%	79%	11%	100%	Recommended with modifications
NSGC 2007	Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer: Recommendations of the National Society of Genetic Counselors	78%	54%	50%	54%	39%	50%	Not recommended
ADA 2007	Breast cancer and oncology nutrition	28%	21%	55%	71%	11%	0%	Not recommended
CECOG 2007	Second consensus on medical treatment of metastatic breast cancer	94%	21%	67%	62%	0%	8%	Recommended with modifications
EUSOMA 2006	The role of complementary and alternative medicine in the management of early breast cancer: Recommendations of the	83%	33%	0%	25%	0%	50%	Not recommended

Source	Title	Standardised Scores						Final Appraisal
	European Society of Mastology (EUSOMA)							
ASCO 2006	Recommendations From an International Expert Panel on the Use of Neoadjuvant (Primary) Systemic Treatment of Operable Breast Cancer: An Update	72%	21%	29%	21%	0%	50%	Not recommended
ASCO 2006	Breast Carcinoma during Pregnancy - International Recommendations from an Expert Meeting	78%	17%	36%	33%	0%	8%	Not recommended
NOS and NCRI Breast Cancer Study Group 2008	Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group	89%	46%	45%	67%	0%	100%	Not recommended
ISGO 2007	Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology	94%	37%	62%	42%	11%	50%	Not recommended
ASCO 2006	American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients	100%	75%	69%	50%	39%	50%	Recommended
CCO 2006	Management of Ductal Carcinoma in Situ of the Breast: A Systematic Review	100%	75%	100%	75%	28%	100%	Recommended

3. SEARCH STRATEGIES

3.1. Breast cancer

1. breast/ or breast diseases/
2. Neoplasms/
3. 1 and 2
4. exp Breast Neoplasms/
5. (breast$ adj5 neoplas$).tw.
6. (breast$ adj5 cancer$).tw.
7. (breast$ adj5 carcin$).tw.
8. (breast$ adj5 tumo$).tw.
9. (breast$ adj5 metasta$).tw.
10. (breast$ adj5 malig$).tw.
11. exp Carcinoma, Ductal, Breast/
12. or/4-11

3.2. Search filter systematic review

1. meta-analysis.pt,ti,ab,sh.
2. 1 or (meta anal$ or metaanal$).ti,ab,sh.
3. (methodol$ or systematic$ or quantitativ$).ti,ab,sh.
4. ((methodol$ or systematic$ or quantitativ$) adj (review$ or overview$ or survey$)).ti,ab,sh.
5. (medline or embase or index medicus).ti,ab.
6. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
7. or/3-6
8. 7 and review.pt,sh.
9. 2 or 8

3.3. Search filter Randomized Controlled Trials

1. Randomized controlled trials/
2. Randomized controlled trial.pt.
3. Random allocation/
4. Double blind method/
5. Single blind method/
6. Clinical trial.pt.
7. exp clinical trials/
8. or/1-7
9. (clinic$ adj trial$1).tw.
10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
11. Placebos/
12. Placebo$.tw.
13. Randomly allocated.tw.
14. (allocated adj2 random).tw.
15. or/9-14
16. 8 or 15
17. Case report.tw.
18. Letter.pt.
19. Historical article.pt.
20. Review of reported cases.pt.
21. Review, multicase.pt.
22. or/17-21
23. 16 not 22
24. 8 or 23

3.4. Diagnostic studies

1. exp "Sensitivity and Specificity"/
2. sensitivity.tw.
3. specificity.tw.
4. ((pre-test or pretest) adj probability).tw.
5. post-test probability.tw.
6. predictive value$.tw.

7. likelihood ratio$.tw.
8. Prospective Studies/
9. or/1-8

3.5. Histopathologic examination

1. "prognos*".ti,ab.
2. first.ti,ab.
3. episode.ti,ab.
4. 2 and 3
5. cohort.ti,ab.
6. 1 or 4 or 5
7. pathology.mp. or Pathology/ or Pathology, Clinical/ or Pathology, Surgical/
8. Lymph Nodes/
9. (resection adj margin$).mp.
10. Neoplasm Invasiveness/
11. Neoplasm Staging/ or TNM.mp.
12. Neoplasm Recurrence, Local/
13. R0.mp.
14. R1.mp.
15. Frozen Sections/
16. or/7-15
17. 6 and 16

3.6. Follow-up

1. Follow-Up Studies/
2. follow-up.ti,ab.
3. followup.ti,ab.
4. follow up.ti,ab.
5. monitoring.ti,ab.
6. surveillance.ti,ab.
7. or/1-6
8. office visit.ti,ab.
9. physician visit.ti,ab.
10. physical examination.ti,ab.
11. frequency.ti,ab.
12. length.ti,ab.
13. Office Visits/
14. Physical Examination/
15. or/8-14
16. 7 and 15

3.7. Recurrent disease

1. Recurrence/
2. Neoplasm Recurrence, Local/
3. recurren$.tw.
4. or/1-3

4. GUIDELINE UPDATE 2013

On 29 May 2012, an invitation was sent to all members of the GDG to elaborate a list of research questions and outcomes related to breast cancer diagnosis, treatment or follow-up in women that require an urgent update (e.g. themes of interest to clinical practice that require new or updated recommendations for clinicians). A final selection and prioritization of research questions and outcomes was made by the KCE in collaboration with the president of the GDG and validated by all members via email.

4.1. Research questions and PICO

Four research questions were finally retained after the identification and selection process (Table 1).

Table 1 – Research questions and PICOs

Research question	Description
Research question 1	Can axillary lymph node dissection (ALND) in women with breast cancer be avoided a. when the SN is positive for isolated tumor cells? b. when the SN is positive for micrometastasis? c. when the SN is positive for macrometastasis?
Population	Women with T1-T2 breast cancer who underwent surgery, and might receive postoperative radiotherapy and systemic treatment; 3 subgroups: isolated tumor cells, micrometastases or macrometastases in the SLN. If possible, consider separately 'breast conserving surgery and 'mastectomy'
Intervention	No axillary lymph node dissection
Comparator	Axillary lymph node dissection
Outcomes	Disease-free survival, local recurrence and overall survival (primary outcomes); arm morbidity and QoL (secondary outcomes)
Research question 2	The use of bisphosphonates in the adjuvant setting
Population	Postmenopausal or premenopausal women with early non-metastatic breast cancer
Intervention	Bisphosphonates (oral or IV)
Comparator	No bisphosphonates

Research question	Description
Outcomes	Overall survival, disease-free survival, adverse events
Research question 3	Use of bevacizumab for patients with HER-2 negative metastatic breast cancer
Population	Women with HER-2 negative metastatic breast cancer
Intervention	Bevacizumab in combination with chemotherapy
Comparator	Chemotherapy alone
Outcomes	Overall survival, disease-free survival, adverse events
Research question 4	Use of trastuzumab with non-anthracycline chemotherapy for patients with HER-2 positive breast cancer in the adjuvant setting
Population	Women with HER-2 positive invasive early (non-metastatic) breast cancer
Intervention	Adjuvant non-anthracycline chemotherapy regimen plus trastuzumab
Comparator	Adjuvant anthracycline–taxane chemotherapy regimen plus trastuzumab
Outcomes	Disease-free survival, overall survival, adverse events

4.2. Search strategies

Date	18-09-2012
Database	Cochrane Library: • Cochrane Database of Systematic Reviews (CDSR) • Technology Assessments • Other reviews (DaRe database)
Search Strategy	Breast Cancer
Note	Applies to systematic reviews for all four research questions. Limited from 2010 onwards, except for CDSR.

Date	Systematic reviews: 20-09-2012 RCTs: 01-11-2012
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Strategy (attention, for PubMed, check « Details »)	1. breast/ or breast diseases/ 2. Neoplasms/ 3. 1 and 2 4. exp Breast Neoplasms/ 5. (breast$ adj5 neoplas$).tw. 6. (breast$ adj5 cancer$).tw. 7. (breast$ adj5 carcin$).tw. 8. (breast$ adj5 tumo$).tw. 9. (breast$ adj5 metasta$).tw. 10. (breast$ adj5 malig$).tw. 11. exp Carcinoma, Ductal, Breast/ 12. or/4-11 13. (axillary adj3 lymph).ti,ab,ot. 14. 12 and 13 15. (diphosphonate or biphosphonate or bisphosphonate or diphosphanate* or diphosphonate* or bisphosphanate* or biphosphonate* or neridronate* or olpadronate* or incadronate* or zoledronate* or zoledronic acid or ibandronate* or tiludronate* or risedronate* or alendronate* or pamidronate* or clodronate* or etidronate*).mp. 16. Bevacizumab.mp. 17. Angiogenesis Inhibitors.mp. 18. Avastin.mp. 19. exp Angiogenesis Inhibitors/ 20. (VEGF adj4 therap*).ti,ab,ot. 21. ("Vascular endothelial growth factor" adj3 therap*).ti,ab,ot. 22. or/16-21 23. trastuzumab.mp. 24. Herceptin.mp.

25. 23 or 24
26. HER2.mp.
27. exp Receptor, Epidermal Growth Factor/
28. Neu.ti,ab,ot.
29. CD340.ti,ab,ot.
30. (erb-2 or erb2).mp.
31. or/26-30
32. exp Daunorubicin/ or exp Doxorubicin/ or anthracycline antibiotic agent.mp.
33. Anthracycline.mp.
34. exp Anthracyclines/
35. daunorubicin.mp.
36. Doxorubicin.mp.
37. Epirubicin.mp. or exp Epirubicin/
38. Idarubicin.mp. or exp Idarubicin/
39. or/32-38
40. 12 and 15
41. 12 and 22
42. 12 and 25 and 31
43. meta-analysis.pt,ti,ab,sh.
44. (meta anal$ or metaanal$).ti,ab,sh.
45. 43 or 44
46. (methodol$ or systematic$ or quantitativ$).ti,ab,sh.
47. ((methodol$ or systematic$ or quantitativ$) adj (review$ or overview$ or survey$)).ti,ab,sh.
48. (medline or embase or index medicus).ti,ab.
49. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
50. 46 or 47 or 48 or 49
51. review.pt,sh.
52. 50 and 51
53. 45 or 52
54. 14 and 53

55. 40 and 53
56. 41 and 53
57. 42 and 53
58. Randomized controlled trials/
59. Randomized controlled trial.pt.
60. Random allocation/
61. Double blind method/
62. Single blind method/
63. Clinical trial.pt.
64. exp Clinical Trial/
65. 58 or 59 or 60 or 61 or 62 or 63 or 64
66. (clinic$ adj trial$1).tw.
67. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
68. Placebos/
69. Placebo$.tw.
70. Randomly allocated.tw.
71. (allocated adj2 random).tw.
72. 66 or 67 or 68 or 69 or 70 or 71
73. 65 or 72
74. Case report.tw.
75. Letter.pt.
76. Historical article.pt.
77. Review of reported cases.pt.
78. Review, multicase.pt.
79. 74 or 75 or 76 or 77 or 78
80. 73 not 79
81. 80 and 14
82. limit 81 to yr="2010 -Current"
83. 80 and 40
84. limit 83 to yr="2010 -Current"

	85. 80 and 41 86. limit 85 to yr="2010 -Current" 87. 80 and 42 and 39 88. limit 87 to yr="2010 -Current"
Note	Research question 1: Systematic reviews = line 54; RCTs = line 82 Research question 2: Systematic reviews = line 55; RCTs = line 84 Research question 3: Systematic reviews = line 56; RCTs = line 86 Research question 4: Systematic reviews = line 56; RCTs = line 88
Date	Systematic reviews: 20-09-2012 RCTs: 01-11-2012
Database	Embase OVID
Search Strategy (attention, for PubMed, check « Details »)	1. breast/ 2. breast disease/ 3. neoplasm/ 4. exp breast cancer/ 5. (breast$ adj5 neoplas$).tw. 6. (breast$ adj5 cancer$).tw. 7. (breast$ adj5 carcin$).tw. 8. (breast$ adj5 tumo$).tw. 9. (breast$ adj5 metasta$).tw. 10. (breast$ adj5 malig$).tw. 11. 1 or 2 12. 3 and 11

13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 12
14. (axillary adj3 lymph).ti,ab,ot.
15. 13 and 14
16. (diphosphonate or biphosphonate or bisphosphonate or diphosphanate* or diphosphonate* or bisphosphanate* or biphosphonate* or neridronate* or olpadronate* or incadronate* or zoledronate* or zoledronic acid or ibandronate* or tiludronate* or risedronate* or alendronate* or pamidronate* or clodronate* or etidronate*).mp.
17. 13 and 16
18. Bevacizumab.mp.
19. Avastin.mp.
20. Angiogenesis Inhibitors.mp. or exp angiogenesis inhibitor/
21. (VEGF adj4 therap*).ti,ab,ot.
22. ("Vascular endothelial growth factor" adj3 therap*).ti,ab,ot.
23. 18 or 19 or 20 or 21 or 22
24. 13 and 23
25. trastuzumab.mp.
26. Herceptin.mp.
27. 25 or 26
28. 13 and 27
29. limit 15 to "reviews (best balance of sensitivity and specificity)"
30. limit 29 to yr="2010 -Current"
31. limit 17 to "reviews (best balance of sensitivity and specificity)"
32. limit 31 to yr="2010 -Current"
33. limit 24 to "reviews (best balance of sensitivity and specificity)"
34. limit 33 to yr="2010 -Current"
35. limit 28 to "reviews (best balance of sensitivity and specificity)"
36. limit 35 to yr="2010 -Current"
37. HER2.mp. or exp epidermal growth factor receptor 2/
38. Neu.ti,ab,ot.
39. CD340.ti,ab,ot.
40. (erb-2 or erb2).mp.

	41. 37 or 38 or 39 or 40 42. 36 and 41 43. 34 and 41 44. exp anthracycline antibiotic agent/ or Anthracycline.mp. or exp anthracycline/ 45. Daunorubicin.mp. or exp daunorubicin/ 46..mp. or exp doxorubicin/ 47. Epirubicin.mp. or exp epirubicin/ 48. Idarubicin.mp. or exp idarubicin/ 49. 44 or 45 or 46 or 47 or 48 50. 42 and 49 51. exp randomized controlled trial/ or exp single blind procedure/ or exp double blind procedure/ or exp crossover procedure/ 52. (random* or placebo* or allocat* or crossover* or "cross over").ab,ti. or trial.ti. or (doubl* adj1 blind*).ab,ti. 53. 51 or 52 54. animal/ not human/ 55. 53 not 54 56. 15 and 55 57. limit 56 to yr="2010 -Current" 58. 17 and 55 59. limit 58 to yr="2010 -Current" 60. 24 and 55 and 41 61. limit 60 to yr="2010 -Current" 62. 28 and 55 and 41 and 49 63. limit 62 to yr="2010 -Current"
Note	Research question 1: Systematic reviews = line 30; RCTs = line 57 Research question 2: Systematic reviews = line 32; RCTs = line 59 Research question 3: Systematic reviews = line 34; RCTs = line 61

	Research question 4: Systematic reviews = line 36; RCTs = line 63
Date	20-09-2012
Database	CENTRAL
Search Strategy (attention, for PubMed, check « Details »)	#1 (breast* near/5 neoplas*):ti,ab,kw #2 (breast* near/5 cancer*):ti,ab,kw. #3 (breast* near/5 carcin*):ti,ab,kw #4 (breast* near/5 tumo*):ti,ab,kw #5 (breast* near/5 metast*):ti,ab,kw #6 (breast* near/5 malig*):ti,ab,kw #7 #1 or #2 or #3 or #4 or #5 or #6 #8 (axillary near/3 lymph):ti,ab,kw #9 #8 and #7
Note	RCTs RQ 1
Date	03-10-2012
Database	CENTRAL
Search Strategy (attention, for PubMed, check « Details »)	#1 (breast* near/5 neoplas*):ti,ab,kw #2 (breast* near/5 cancer*) .ti,ab,kw #3 (breast* near/5 carcin*) .ti,ab,kw #4 (breast* near/5 tumo*):ti,ab,kw #5 (breast* near/5 metast*):ti,ab,kw #6 (breast* near/5 malig*):ti,ab,kw #7 #1 or #2 or #3 or #4 or #5 or #6 #8 (diphosphonate or biphosphonate or bisphosphonate or diphosphanate* or diphosphonate* or bisphosphanate* or biphosphonate* or neridronate* or olpadronate* or incadronate* or zoledronate* or zoledronic acid or ibandronate* or tiludronate*

	or risedronate* or alendronate* or pamidronate* or clodronate* or etidronate*):ti,ab,kw #9 #8 and #7
Note	RCTs RQ 2
Date	29-10-2012
Database	CENTRAL
Search Strategy (attention, for PubMed, check « Details »)	#1 (breast* near/5 neoplas*):ti,ab,kw #2 (breast* near/5 cancer*):ti,ab,kw #3 (breast* near/5 carcin*):ti,ab,kw #4 (breast* near/5 tumo*):ti,ab,kw #5 (breast* near/5 metast*):ti,ab,kw #6 (breast* near/5 malig*):ti,ab,kw #7 #1 or #2 or #3 or #4 or #5 or #6 #8 (Bevacizumab):ti,ab,kw #9 (Angiogenesis Inhibitors):ti,ab,kw #10 (Avastin):ti,ab,kw #11 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees #12 (VEGF* near/4 therap*):ti,ab,kw #13 ("Vascular endothelial growth factor" near/3 therap*):ti,ab,kw #14 #8 or #9 or #10 or #11 or #12 or #13 #15 #7 and #14
Note	RCTs RQ 3

Date	01-11-2012	
Database	CENTRAL	
Search Strategy (attention, for PubMed, check « Details »)	#1	(breast* near/5 neoplas*):ti,ab,kw
	#2	(breast* near/5 cancer*):ti,ab,kw
	#3	(breast* near/5 carcin*):ti,ab,kw
	#4	(breast* near/5 tumo*):ti,ab,kw
	#5	(breast* near/5 metast*):ti,ab,kw
	#6	(breast* near/5 malig*):ti,ab,kw
	#7	#1 or #2 or #3 or #4 or #5 or #6
	#8	(trastuzumab):ti,ab,kw
	#9	(Herceptin):ti,ab,kw
	#10	#8 or #9
	#11	(HER2):ti,ab,kw
	#12	(Neu):ti,ab,kw
	#13	(CD340):ti,ab,kw
	#14	(erb2):ti,ab,kw
	#15	#11 or #12 or #13 or #14
	#16	MeSH descriptor: [Anthracyclines] explode all trees
	#17	(anthracycline antibiotic agent):ti,ab,kw
	#18	(Daunorubicin):ti,ab,kw
	#19	MeSH descriptor: [Daunorubicin] explode all trees
	#20	(Doxorubicin):ti,ab,kw
	#21	MeSH descriptor: [Doxorubicin] explode all trees
	#22	(Epirubicin):ti,ab,kw
	#23	MeSH descriptor: [Epirubicin] explode all trees
	#24	(Idarubicin):ti,ab,kw
	#25	MeSH descriptor: [Idarubicin] explode all trees
	#26	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
	#27	#7 and #10 and #15 and #26 from 2010 to 2012 (Word variations have been searched)

Note	RCTs RQ 4
Date	10 January 2013
Database	Medline (OVID)
Search Strategy (attention, for PubMed, check « Details »)	1 breast/ or breast diseases/ (33579) 2 ((breast or breast diseases) and Neoplasms).af. (224307) 3 1 and 2 (17627) 4 exp Breast Neoplasms/ (198059) 5 (breast$ adj5 neoplas$).tw. (2716) 6 (breast$ adj5 cancer$).tw. (157710) 7 (breast$ adj5 carcin$).tw. (34337) 8 (breast$ adj5 tumo$).tw. (27048) 9 (breast$ adj5 metasta$).tw. (19144) 10 (breast$ adj5 malig$).tw. (8158) 11 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (236204) 12 Lymph Nodes/ or Lymphatic Metastasis/ (114202) 13 Axilla/ (9341) 14 12 and 13 (4617) 15 exp Lymph Nodes/ and (sentinel or SLN).mp. (3930) 16 micrometastas$.mp. (4047) 17 macrometastas$.mp. (386) 18 occult metastas$.mp. (777) 19 isolated tumor cell$.mp. (553) 20 isolated tumour cell$.mp. (129) 21 exp Sentinel Lymph Node Biopsy/ (7041) 22 AMAROS.mp. (8) 23 ACOSOG Z0011.mp. (10)

	24 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (15039) 25 11 and 24 (7231) 26 limit 25 to (english language and yr="2000 -Current") (4558)
Note	Observational studies RQ1
Date	10 January 2013
Database	Embase
Search Strategy (attention, for PubMed, check « Details »)	#4. 'breast'/exp OR 'breast disease'/exp AND 'neoplasm'/exp OR 'breast tumor'/exp OR (breast* NEAR/5 neoplas*):ab,ti OR (breast* NEAR/5 cancer*):ab,ti OR (breast* NEAR/5 carcin*):ab,ti OR (breast* NEAR/5 tumo*):ab,ti OR (breast* NEAR/5 metasta*):ab,ti OR (breast* NEAR/5 malig*):ab,ti AND ('lymph node metastasis'/exp AND 'axillary lymph node'/exp OR ('lymph node'/exp AND (sentinel OR sln)) OR 'micrometastasis'/exp OR (occult AND metastasis) OR 'sentinel lymph node biopsy'/exp OR 'sentinel lymph node'/exp OR amaros OR acosog) AND ('lymph node dissection'/exp OR alnd) AND [2000-2013]/py 3,356 10 Jan 2013 #3. 'lymph node dissection'/exp OR alnd AND [2000-2013]/py 28,999 10 Jan 2013 #2. 'lymph node metastasis'/exp AND 'axillary lymph node'/exp OR ('lymph node'/exp AND (sentinel OR sln)) OR 'micrometastasis'/exp OR (occult AND metastasis) OR 'sentinel lymph node biopsy'/exp OR 'sentinel lymph node'/exp OR amaros OR acosog AND [2000-2013]/py 18,731 10 Jan 2013

	#1. 'breast'/exp OR 'breast disease'/exp AND 'neoplasm'/exp OR 'breast tumor'/exp OR (breast* NEAR/5 neoplas*):ab,ti OR (breast* NEAR/5 cancer*):ab,ti OR (breast* NEAR/5 carcin*):ab,ti OR (breast* NEAR/5 tumo*):ab,ti OR (breast* NEAR/5 metasta*):ab,ti OR (breast* NEAR/5 malig*):ab,ti AND [2000-2013]/py	226,523 10 Jan 2013
Note	Observational studies RQ1	

4.3. Studies selection and quality appraisal

4.3.1. Research question 1: Axillary surgery in breast cancer women with positive sentinel nodes (isolated tumour cells, micrometastases, macrometastases)

Selection of systematic reviews

On September 18, 2012 a search was performed to identify SRs comparing the effect of sentinel lymph node dissection (without further axillary surgery) versus axillary lymph node dissection in women with breast cancer and a positive sentinel lymph node. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched. Furthermore, all systematic reviews of the Cochrane Breast Cancer Group (CBCG) were browsed for their relevancy.

In MEDLINE and Embase 259 potential relevant references were identified (Figure 1). After de-duplication 229 references remained. Based on title and abstract 221 reviews were excluded. Two reviews were included[1, 2] (Table 2) and six were excluded with reason (Table 3). The searches in the Cochrane databases (Figure 2) resulted in two relevant systematic reviews which were already identified by the previous searches. No new reviews were identified by browsing the CBCG list of reviews.

The most extensive and recent review[2] included eight RCTs of which seven addressed the comparison ALND versus ALND only if the SLN was positive (which does not cover the research question of the guideline group) and one RCT that addressed the American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) trial that compared ALND versus no ALND in women with invasive breast cancer and sentinel node metastasis. The other review[1] included seven trials comparing three groups of interventions (SLND only, ALND only, SLND followed by ALND). Of those, only one included RCT (the same ACSOG Z0011 trial) applied to the research question. Because both included reviews addressed the one and only included RCT that addressed the research question, we processed only the original RCT[3].

Figure 1 – Study flow of selection of SRs (MEDLINE and Embase)

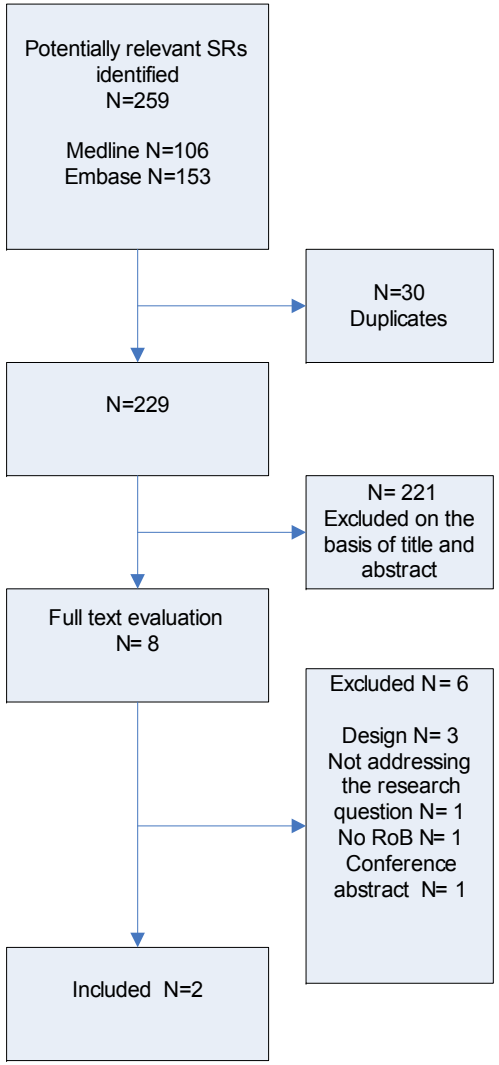


Figure 2 – Study flow of selection of SRs (CDSR, CLIB TA, CLIB DaRe)

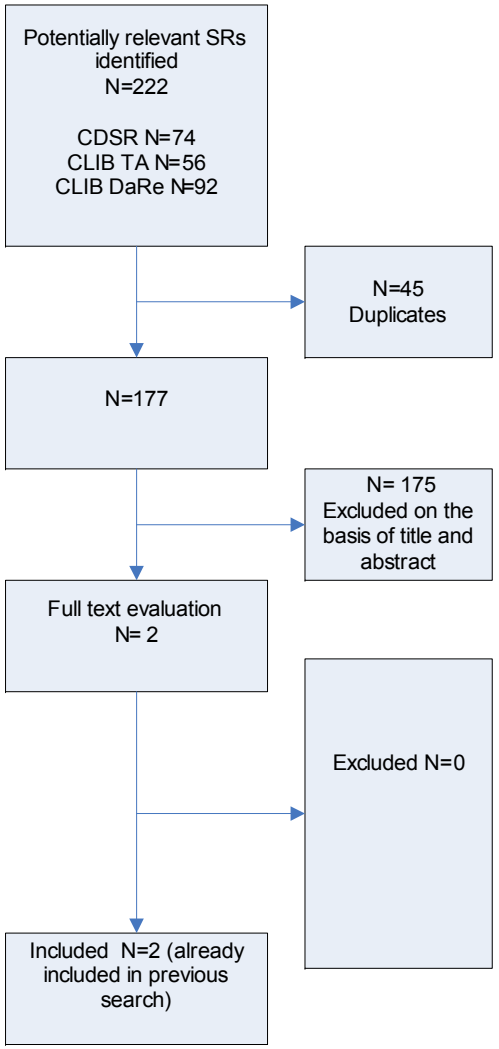


Table 2 – Included SRs

Reference	Interventions
Kell 2010[1]	Sentinel lymph node biopsy compared with axillary lymph node dissection
Wang 2011[2]	Sentinel lymph node biopsy compared with axillary lymph node dissection

Table 3 – Excluded SRs

Reference	Reason for exclusion
Barry 2012[4]	No systematic review
Barry 2012[5]	Editorial
Franco 2011[6]	No systematic review
Gerber 2011[7]	No risk of bias assessment.
Pepels 2011[8]	Population and/or design did not fit with our inclusion criteria (observational and comparative studies including node negative patients and observational studies including SN-positive patients without ALND (no control group))
Petrelli 2012[9]	Node negative patients only; conference abstract

Selection of RCTs

On September 20, 2012 a search was performed to identify RCTs comparing the effect of sentinel lymph node dissection (without further axillary surgery) versus axillary lymph node dissection in women with breast cancer and a positive sentinel lymph node. MEDLINE (including PreMedline), Embase and CENTRAL were searched, limited from 2010 onwards. Two hundred and eighty-six potential relevant references were identified (Figure 3). After de-duplication, 206 references remained. Based on title and abstract 192 studies were excluded. Of the remaining 14 studies, one study was included[3] and 13 studies were excluded with reason (Table 5). This publication is the more recent publication about ACOSOG Z0011 trial (see Giuliano 2010 and Lucci 2007).

Figure 3 – Study flow of selection of RCTs

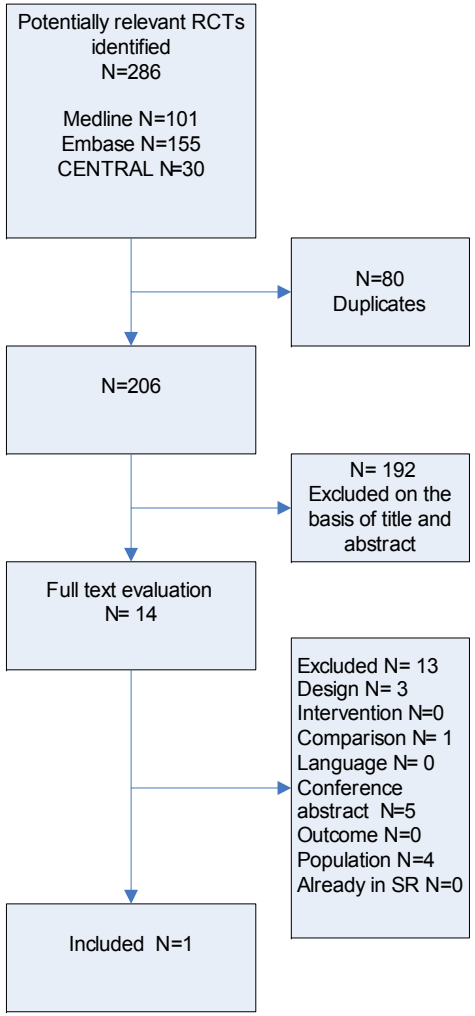


Table 4 – Included RCTs

Reference	Interventions
Giuliano 2011[3]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) metastasis of breast cancer

Table 5 – Excluded RCTs

Reference	Reason for exclusion
Ashikaga 2010[10]	Sentinel lymph node negative
Avril 2010[11]	No sentinel lymph node staging
Avril 2011[12]	No sentinel lymph node staging
Cody 2012[13]	Conference abstract
Dockx 2012[14]	Conference abstract
Franco 2011[6]	No randomized controlled trial (discussion of Z0011 en NSABP)
Glimberti 2011[15]	Retrospective study
Krag 2010[16]	If sentinel lymph node + then followed by axillary lymph node dissection
Kuwajerwala 2010[17]	Conference abstract
Petrelli 2012[9]	Conference abstract
Siso 2012[18]	Conference abstract
Sola 2010[19]	Conference abstract
Verry 2012[19]	Cost effectiveness analysis

Selection of observational studies

Since the only RCT retrieved (Giuliano et al. 2011)[3] did not differentiate the three subgroups of interest (isolated tumour cells, micrometastases and macrometastases), we completed the literature findings by a systematic review of observational studies. We focused on large observational studies (retrospective or prospective) conducted to assess the comparative benefits and harms of SLNB and ALND in women with T1 or T2 breast cancer and positive sentinel nodes. We restricted the search to the critical outcomes (overall survival, disease-free survival and axillary recurrence).

On January 10, 2013 a search was performed to identify observational studies comparing the effect of sentinel lymph node dissection (without further axillary surgery) versus axillary lymph node dissection in women with breast cancer and a positive sentinel lymph node. MEDLINE, PreMedline and Embase were searched.

Globally, 8 214 potential relevant references were identified (4 558 In MEDLINE, 300 in Pre-Medline and 3 356 in Embase) (Figure 4). After de-duplication 6 634 references remained. Based on title and abstract 6 606 papers were excluded. Of the remaining 28 studies, ten studies were included (Table 6) and 18 studies were excluded with reason (Table 7).

Figure 4 – Study flow of selection of observational studies

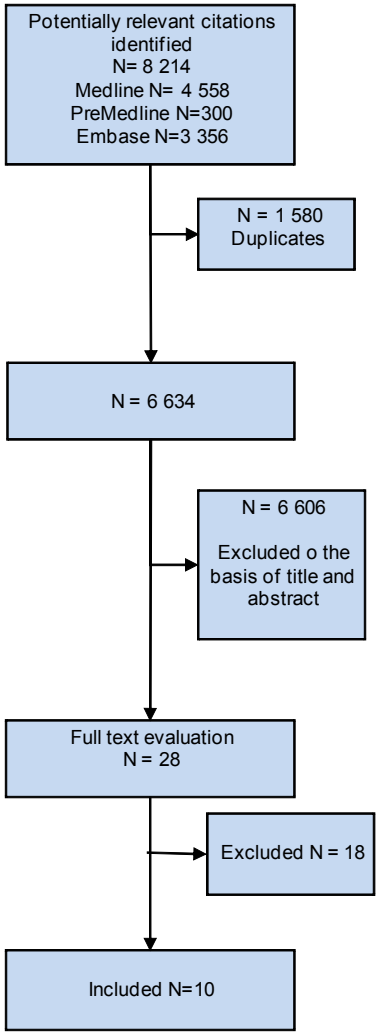


Table 6 – Included observational studies

Reference	Interventions
Bilimoria 2009[20]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micro- or macrometastasis of breast cancer
Bulte 2009[21]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micrometastasis of breast cancer
Calhoun 2005[22]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) isolated tumour cells of breast cancer
Cortesi 2012[23]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micrometastasis of breast cancer
Fan 2005[24]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micro- or macrometastasis of breast cancer
Giobuin 2009[25]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) isolated tumour cells of breast cancer
Pepels 2012[26]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micrometastasis or isolated tumour cells of breast cancer
Wasif 2010[27]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micrometastasis of breast cancer
Yi 2010[28]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micro- or macrometastasis of breast cancer
Yi 2013[29]	Axillary dissection vs. no axillary dissection in patients with sentinel lymph node (SLN) micro- or macrometastasis of breast cancer

Table 7 – Excluded observational studies

Reference	Reason for exclusion
Christiansen 2008[30]	SLNB vs ALND (not preceded by SLNB in 100% of cases)
Cox 2008[31]	No data reported
De Boer 2009[32]	Adjuvant systemic therapy vs. No adjuvant systemic therapy
Francissen 2012[33]	Review - No control group (ALND), only Pubmed, no QA of retrieved papers
Giard 2005[34]	Does not correspond to the PICO
Giuliano 2011[3]	RCT already included
Giuliano 2012[35]	Discussion paper
Haid 2006[36]	Outcome not reported by subgroup of positive SN
Helms 2009[37]	All positive SN received ALND (no ALND if negative SN)
Jakub 2002[38]	Outcomes not clearly defined and short follow-up
Jeruss 2008[39]	Outcome not reported by subgroup of positive SN
Joyce 2012[40]	No outcome measured (prognostic study)
Liang 2001[41]	No outcome measured (+ short follow-up, very small sample size)
Loong Chong 2012[42]	Survey about surgeons practices
Martelli 2011[43]	Negative SN
Naik 2004[44]	Negative SN vs. Positive SN without distinction between ITC, MicroM+, MacroM+
Schulze 2006[45]	Mix of negative and positive SN; unclear if ALND followed positive SLNB
Sola 2013[46]	ALND vs. Clinical follow-up

Quality appraisal

Figure 5 shows the results of the risk of bias assessment for the one included study[3]. Due to the lack of blinding a high risk of performance bias and detection bias was scored for all outcomes, except for survival outcomes, which are unlikely to be influenced by the lack of blinding. For the remaining items, a low risk of bias was scored. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), the study was considered of high risk of bias, except for the survival outcomes.

Table 8 reports the critical appraisal for the observational studies.

Figure 5 – Risk of bias summary of RCT

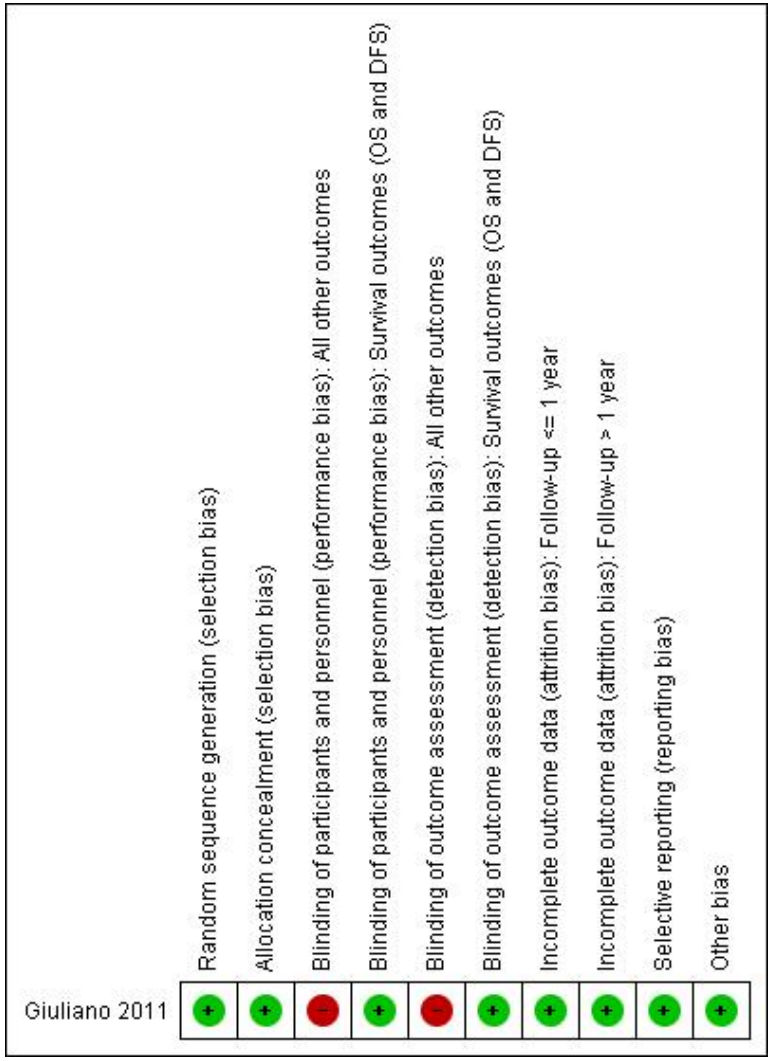


Table 8 – Critical appraisal for observational studies

Checklist COHORT studies: Bilimoria 2009

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: patients with T1 to T3 non-metastatic primary breast cancer, not treated with neoadjuvant chemotherapy

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

Yes

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

Yes: only extent of surgery not

Overall assessment of the study

Are the results of the study:
- valid? **Partly: large and relevant cohort, but methodological flaws (retrospective design, no blinding)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Bulte 2009

Internal validity

The study addresses an appropriate and clearly focused question
Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation
Yes: patients with T1-2 breast cancer, not treated with neoadjuvant chemotherapy

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis
Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up
No

The outcomes are clearly defined
Yes

The assessment of outcome is made blind to exposure status
No

The measure of assessment of exposure is reliable
Yes

The main potential confounders are identified and taken into account in the design and analysis
No

Overall assessment of the study
Are the results of the study:
- valid? **Partly: relevant cohort, but methodological flaws (no blinding, no risk adjustment)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Calhoun 2005

Internal validity

The study addresses an appropriate and clearly focused question
Partly: it is more a hypothesis that is stated

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation
Yes: patients with invasive breast cancer and SLNs positive for ITC

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis
Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up
No

The outcomes are clearly defined

Partly : axillary recurrence rate was identified as outcome

The assessment of outcome is made blind to exposure status

Probably not

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

No

Overall assessment of the study

Are the results of the study:
- valid? **Partly: methodological flaws (no information on blinding, no risk-adjustment, outcomes not clearly defined)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Cortesi 2012

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: patients with T1–T2 invasive breast cancers and clinically negative (N0–N1) axillary nodes who underwent surgery and SLNB

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

No subjects had the outcome at the time of enrolment

Comparison by exposure status is made between full participants and those lost to follow up

No patient was lost to follow up

The outcomes are clearly defined

Yes

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

Yes: the main potential confounders were identified but not taken into account in the analysis

Overall assessment of the study

Are the results of the study:

- valid? **Partly: large and relevant cohort, but methodological flaws (Retrospective analysis of prospective database [population-based study using regional cancer registry implying a high probability of heterogeneous treatments between centres], no blinding)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Fan 2005

Internal validity

The study addresses an appropriate and clearly focused question

Partly: it is more a hypothesis that is stated

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: patients with histologically confirmed primary breast cancer, not treated with neoadjuvant treatment

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Recurrent breast cancer is exclusion criterion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

Partly : axillary recurrence rate was identified as outcome

The assessment of outcome is made blind to exposure status

Probably not

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

No

Overall assessment of the study

Are the results of the study:

- valid? **Partly: large and relevant cohort, but methodological flaws (retrospective study, no blinding, no clear definition of outcomes, no risk-adjustment)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Giobuin 2009

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: patients with invasive breast cancer and clinically negative nodes that underwent SLNB

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Not clear, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

No

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

No

Overall assessment of the study

Are the results of the study:
- valid? **Partly: methodological flaws (no blinding, outcomes not clearly defined, no risk-adjustment)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Pepels 2012

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: patients with early-stage breast cancer who underwent surgery and SLNB (tumor size of ≤1 cm, irrespective of grade, or tumor size 1 to 3 cm and grade 1 or 2)

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

Yes

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

Yes: Adjusted HR for age, tumor size, histological grade, hormone receptor status, adjuvant systemic therapy, and irradiation of the breast

Overall assessment of the study

Are the results of the study:

- valid? **Partly: large and relevant cohort, but methodological flaws (Retrospective analysis of prospective database, no blinding, multicentre study implying a high probability of heterogeneous treatments)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Wasif 2010

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: patients with a diagnosis of infiltrating ductal carcinoma and infiltrating lobular carcinoma of the breast, who underwent SLNB

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

Yes

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

Yes

Overall assessment of the study

Are the results of the study:

- valid? **Partly: methodological flaws (retrospective study, no blinding)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Yi 2010

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: women older than 18 years diagnosed with primary breast cancer, with positive lymph node on SLNB

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

Yes

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

No

Overall assessment of the study

Are the results of the study:

- valid? **Partly: large and relevant cohort, but methodological flaws (retrospective design; no blinding; as cancer registries did not contain data regarding recurrence, the use of ipsilateral regional events after surgery were considered as one of the outcomes instead of axillary recurrence)**
- applicable to the patient group targeted in the search question? **Yes**

Checklist COHORT studies: Yi 2013

Internal validity

The study addresses an appropriate and clearly focused question

Yes

The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation

Yes: women diagnosed with primary breast cancer (T1/T2), with positive 1-2 lymph nodes on SLNB and who underwent surgery (BCS or mastectomy)

The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

Not clearly, but probably no recurrences at inclusion

Comparison by exposure status is made between full participants and those lost to follow up

No

The outcomes are clearly defined

Yes

The assessment of outcome is made blind to exposure status

No

The measure of assessment of exposure is reliable

Yes

The main potential confounders are identified and taken into account in the design and analysis

No

Overall assessment of the study

Are the results of the study:

- valid? **Partly: large and relevant cohort, but methodological flaws (retrospective design; no blinding)**
- applicable to the patient group targeted in the search question? **Yes**

4.3.2. Research question 2: The use of bisphosphonates in the adjuvant setting

Selection of systematic reviews

On September 20, 2012 a search was performed to identify SRs comparing bisphosphonates versus no bisphosphonates in women with early non-metastatic breast cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched. Furthermore, all systematic reviews of the Cochrane Breast Cancer Group (CBCG) were browsed for their relevancy.

In MEDLINE and Embase 405 potential relevant references were identified (Figure 6). After deduplication 390 references remained. Based on title and abstract 377 reviews were excluded. Of the remaining 13 reviews three reviews were included (Huang et al., 2012;Mauri et al., 2010;Wong et al., 2012)[47-49] (Table 9) and 10 were excluded with reason (Table 10).

The searches in the Cochrane databases resulted in four relevant systematic reviews (of which two were included) which were already identified by the previous searches (Figure 7). No new reviews were identified by browsing the CBCG list of reviews.

Because the most recent and complete review of Wong includes all RCTs that were included in Mauri (2010) and Huang (2012), only the results of the review of Wong (2012) will be discussed.

Figure 6 – Study flow of selection of SRs (MEDLINE and Embase)

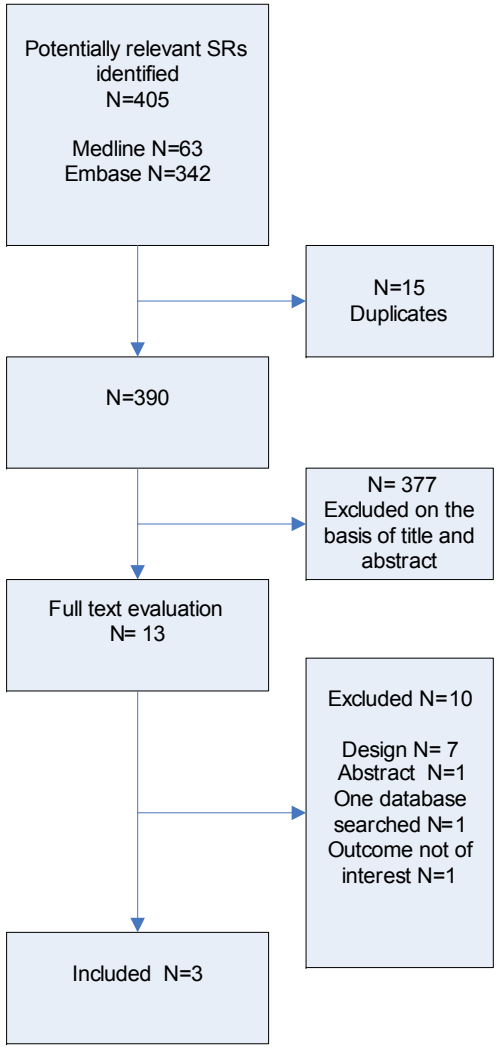


Figure 7 – Study flow of selection of SRs (CDSR, CLIB TA, CLIB DaRe)

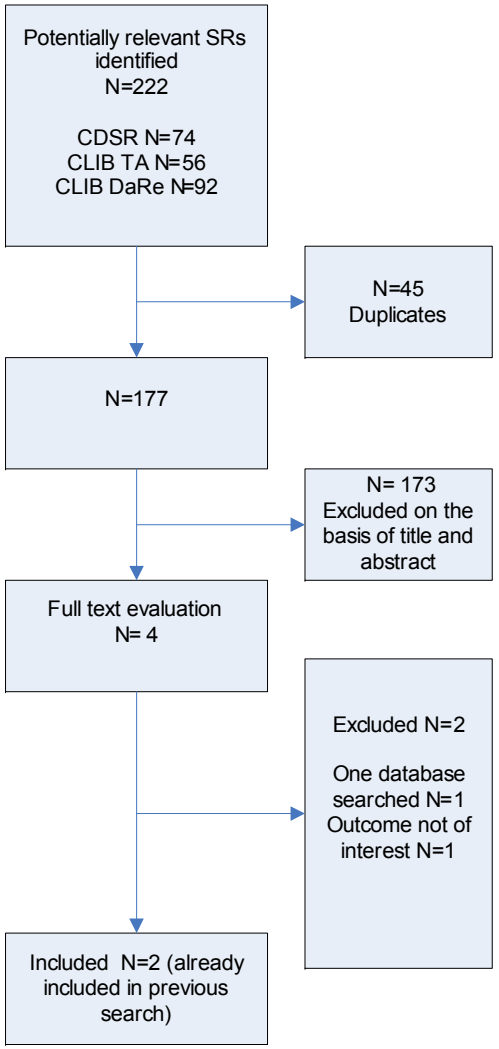


Table 9 – Included SRs

Reference	Interventions
Huang 2012 [47]	Zoledronic acid as an adjuvant therapy in patients with breast cancer
Mauri 2010 [48]	Bisphosphonates in the adjuvant setting of breast cancer
Wong 2012 [49]	Bisphosphonates versus control in women with early breast cancer

Table 10 – Excluded SRs

Reference	Reason for exclusion
Aapro 2012 [50]	No systematic review
Hadji 2011 [51]	No systematic review
Liu 2012 [52]	Systematic review of observational studies
Luis 2010 [53]	No systematic review
Perrin 2012 [54]	No systematic review
Tonyali 2010 [55]	No systematic review
Valachis 2010 [56]	Outcomes did not fit with the inclusion criteria (fractures)
Valachis 2011 [57]	Conference abstract
Yan 2012 [58]	Only one database was searched
Zhou 2011 [59]	No risk of bias assessment

Selection of RCTs

On October 12, 2012 a search was performed to identify RCTs comparing bisphosphonates versus no bisphosphonates in women with early non-metastatic breast cancer. MEDLINE (including PreMedline) Embase and CENTRAL were searched (from 2010 onwards) and 403 potential relevant references were identified (Figure 8). After deduplication, 301 references remained. Based on title and abstract 245 studies were excluded. Of the remaining 56 studies, four were included (Aft 2012; Coleman 2011; Gnant 2011; Paterson 2012) [60-63] (Table 11), three were already included in the SR of Wong (2012) and 49 were excluded with reason (Table 12).

Figure 8 – Study flow of selection of RCTs

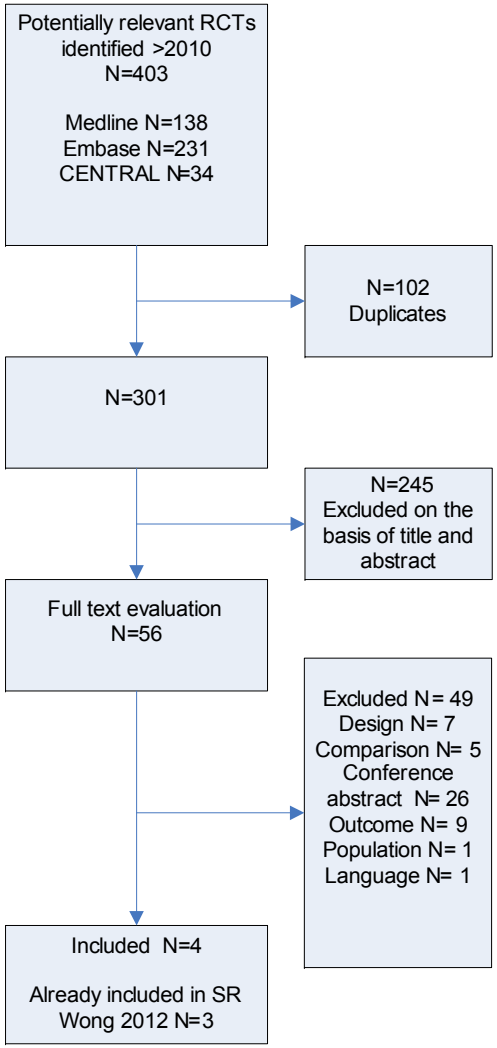


Table 11 – Included RCTs

Reference	Interventions
Aft 2012 [60]	Intravenous zoledronic acid 4mg every 3 weeks for 1 year vs. no zoledronic acid (control).
Coleman 2011 [61]	Zoledronic acid in the adjuvant therapy of women with stage II/III breast cancer vs. no additional treatment.
Gnant 2011 [62]	Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial
Paterson 2012 [63]	Oral clodronate (1600 mg daily for 3 years) vs. Placebo
Already included in SR Wong 2012	
Aft 2010 [64]	Already included in systematic review of Wong 2012
Coleman 2011 [65]	Already included in systematic review of Wong 2012
Leal 2010 [66]	Already included in systematic review of Wong 2012

Table 12 – Excluded RCTs

Reference	Interventions
Barret-Lee 2011 [67]	Conference abstract
Bell 2011 [68]	Conference abstract
Bell 2011 [69]	Conference abstract
Body 2010 [70]	No randomized controlled trial
Body 2010 [71]	Conference abstract
Body 2010 [72]	Conference abstract
Body 2010 [73]	Conference abstract
Body 2010 [74]	No randomized controlled trial
Bouganim and Clemons 2011 [75]	No randomized controlled trial
Brufsky 2012 [76]	Comparison not of interest to KCE (upfront versus delayed zoledronic acid)

Reference	Interventions
Coleman 2011 [77]	Conference abstract
Coleman 2011 [78]	Conference abstract
Coleman and Giordano 2011 [79]	Conference abstract
de Boer 2011 [80]	Conference abstract
Eidtmann 2010 [81]	Comparison did not fit with the inclusion criteria (immediate versus delayed zoledronic acid)
Fehm 2011 [82]	Conference abstract
Gnant 2010 [83]	Conference abstract
Gnant 2010 [84]	Conference abstract
Gnant 2011 [85]	Conference abstract
Gnant 2011 [86]	Conference abstract
Gnant 2012 [87]	Conference abstract
Goss 2011 [88]	Conference abstract
Greenberg 2011 [89]	Conference abstract
Hellriegel 2011 [90]	Conference abstract
Henry 2011 [91]	Women with advanced breast cancer
Hershman 2010 [92]	Conference abstract
Kim 2011 [93]	Outcomes not of interest for RQ2
Lipton 2010 [94]	Conference abstract
Lipton 2010 [95]	Review
Markopoulos 2010 [96]	Outcomes not of interest for RQ2
McCloskey 2010 [97]	Outcomes not of interest for RQ2
Morgan 2010 [98]	Conference abstract

Reference	Interventions
Morgan and Lipton 2010 [99]	Review
Neville-Webbe 2010 [100]	Review
Nuzzo 2012 [101]	Outcomes not of interest for RQ2
Perrone 2011 [102]	Conference abstract
Pfeiler 2011 [103]	Conference abstract
Pivot 2011 [104]	Outcomes not of interest for RQ2 / metastatic disease
Poznak 2010 [105]	Outcomes not of interest for RQ2
Rhee 2010 [106]	Conference abstract
Safra 2011 [107]	Outcomes not of interest for RQ2
Shapiro 2011 [108]	Comparison did not fit with the inclusion criteria (upfront versus delayed zoledronic acid)
Solomayer 2012 [109]	Outcomes not of interest for RQ2
Takahashi 2011 [110]	Conference abstract
Takahashi 2012 [111]	Comparison did not fit with the inclusion criteria (upfront versus delayed zoledronic acid)
Theriault 2010 [112]	Review
Van Londen 2010 [113]	Outcomes not of interest for RQ2
Von Minckwitz 2010 [114]	Conference abstract
Xu 2010 [115]	Language did not fit the inclusion criteria (Chinese)

Quality appraisal

Table 13 shows the results of the risk of bias assessment for the one included systematic review [49], using AMSTAR criteria. The review scored positively on all items, except indicating whether there was a conflict of interest for the included studies. Overall, the SR is considered as having a 'low risk' of bias (Table 13). Figure 9 reports the risk of bias summary for the four included RCTs [60-63]. Due to lack of blinding a high risk of performance bias and detection bias for adverse events was scored in three studies. For the remaining items, a low risk of bias was scored in all four studies. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), only one study scored a low risk of bias on all items (Figure 9).

Table 13 – Methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appropr-iate methods to combine findings	Likelihoo d of publica-tion bias assessed	Conflict of interest stated
Wong 2012 [49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No

Figure 9 – Risk of bias summary of RCTs

4.3.3. Research question 3: Use of bevacizumab for patients with HER-2 negative metastatic breast cancer

Selection of systematic reviews

On September 20, 2012 a search was performed to identify systematic reviews comparing bevacizumab in combination with chemotherapy versus chemotherapy alone in women with HER-2 negative metastatic breast cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched. Furthermore, all systematic reviews of the Cochrane Breast Cancer Group (CBCG) were browsed for their relevancy.

In MEDLINE and Embase 347 potential relevant references were identified (Figure 10). After deduplication 339 references remained. Based on title and abstract 316 reviews were excluded. Of the remaining 23 reviews five reviews were included (Table 14) (An 2010; Mackey 2012; Ranpura 2010; Valachis 2010; Wagner 2012) [116-120] and 18 were excluded with reason (Table 15).

The searches in the Cochrane databases resulted in five possibly relevant systematic reviews of which three were included (Wagner 2012; Valachis 2010; Ranpura 2011) [119-121]. Two of those reviews [119, 120] were already identified by the previous searches (Figure 11). No new reviews were identified by browsing the CBCG list of reviews. Therefore, the total number of included reviews was six [116-121] (Table 14).

As the most recent and complete review of Wagner 2012 overlaps all RCTs (and outcomes) that were included in the other reviews, only the results of the latter will be discussed.

Figure 10 – Study flow of selection of SRs (MEDLINE and Embase)

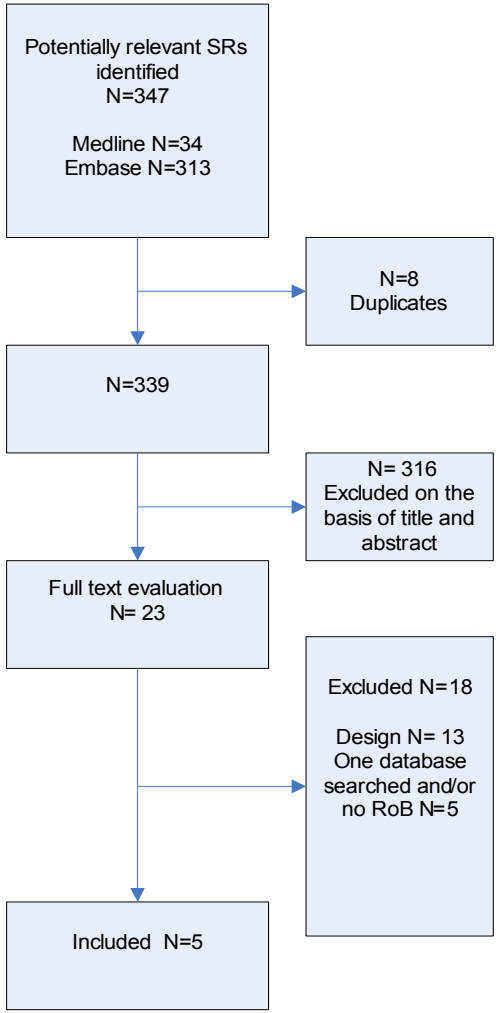


Figure 11 – Study flow of selection of SRs (CDSR, CLIB TA, CLIB DaRe)

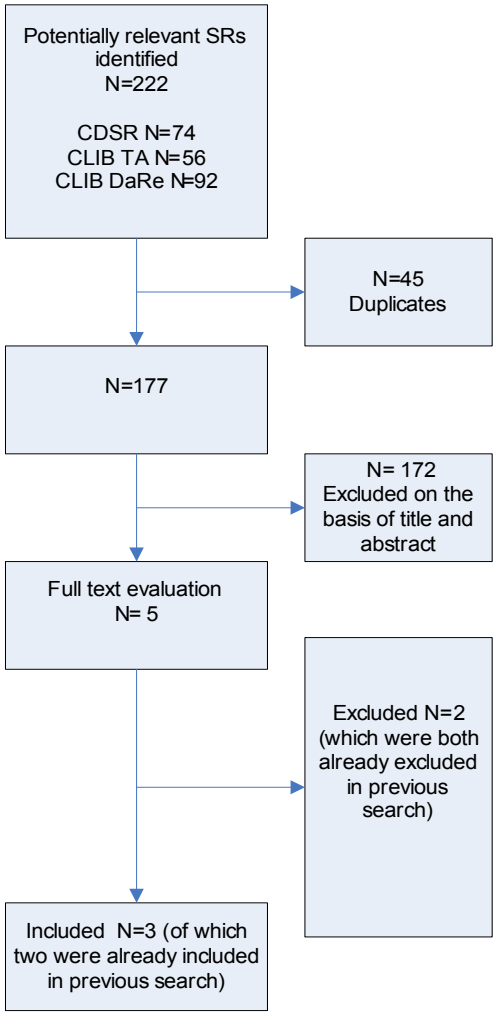


Table 14 – Included SRs

Reference	Interventions
An 2010 [116]	Chemotherapy, with versus without bevacizumab
Mackey 2012 [117]	Chemotherapy, with versus without bevacizumab
Ranpura 2010 [118]	Concurrent antineoplastic therapy, with versus without bevacizumab
Ranpura 2011 [121]	Bevacizumab in combination with chemotherapy or biological therapy versus chemotherapy or biological therapy alone
Valachis 2010 [119]	Chemotherapy, with versus without bevacizumab
Wagner 2012 [120]	First-and second line chemotherapy, with versus without bevacizumab

Table 15 – Excluded SRs

Reference	Reason for exclusion
Alvarez 2010 [122]	No systematic review
Bhinder 2010 [123]	No systematic review
Blank 2010 [124]	Cost effectiveness analysis
Brufsky 2010 [125]	No systematic review
Chan 2010 [126]	No systematic review
Choueiri 2011 [127]	Only one database searched
Cortes 2012 [128]	Only one database searched; no risk of bias assessment
Croom 2011 [129]	No systematic review
Cuppone 2011 [130]	Only one database searched; no risk of bias assessment
Dienstmann 2012 [131]	No systematic review
Dirix 2010 [132]	No systematic review
Garcia 2010 [133]	No systematic review

Hamilton 2011 [134]	No systematic review
Kumler 2012 [135]	Only one database searched; no risk of bias assessment
Lee 2011 [136]	No risk of bias assessment
Miles 2012 [137]	No systematic review
Petrelli 2012 [138]	No systematic review
Rodgers 2011 [139]	No systematic review

Selection of RCTs

On November 1, 2012 a search was performed to identify RCTs comparing bevacizumab in combination with chemotherapy versus chemotherapy alone in women with HER-2 negative metastatic breast cancer. MEDLINE (including PreMedline), Embase and CENTRAL were searched (from 2010 onwards) and 363 potential relevant references were identified (Figure 12).

After deduplication, 306 references remained. Based on title and abstract 265 studies were excluded. Of the remaining 41 studies, five were included (Brufsky 2011; Martin 2011; Miles 2010; Pivot 2011; Robert 2011) (Table 16) and 36 were excluded with reason (Table 17). All identified RCTs were already included in the SR of Wagner.

Figure 12 – Study flow of selection of RCTs

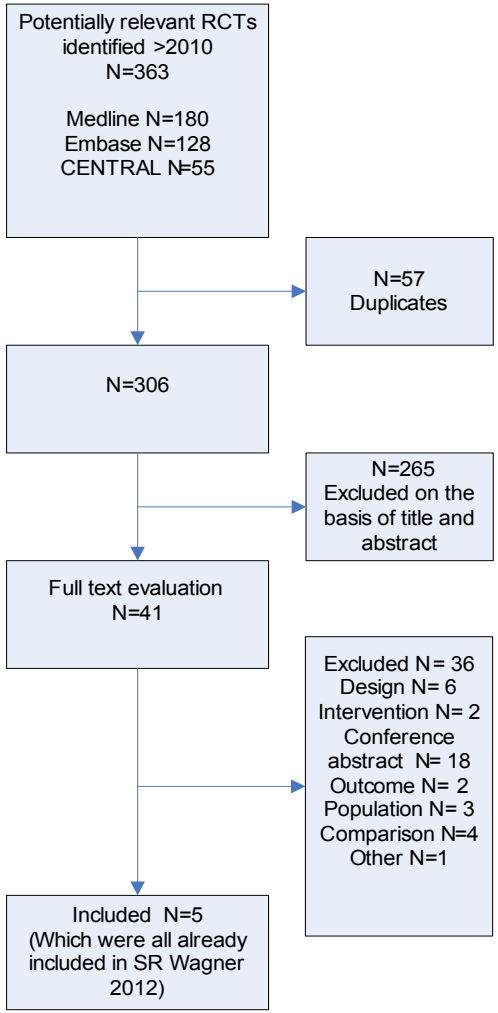


Table 16 – Included RCTs

Reference	Interventions
Already included in SR of Wagner 2012	
Brufsky 2011 [140]	Chemotherapy with bevacizumab versus chemotherapy with placebo
Martin 2011 [141]	Paclitaxel plus bevacizumab versus paclitaxel plus motesanib versus paclitaxel plus placebo
Miles 2010 [142]	Docetaxel with bevacizumab versus docetaxel with placebo
Pivot 2011 [143]	Docetaxel in combination with bevacizumab 7.5 mg/kg or bevacizumab 15 mg/kg or placebo (subgroup analysis of elderly of an already included RCT [Miles 2010] in Wagner 2012)
Robert 2011 [144] [Ribbon-1]	Chemotherapy plus bevacizumab versus chemotherapy plus placebo

Table 17 – Excluded RCTs

Reference	Reason for exclusion
Bear 2011 [145]	Conference abstract
Bear 2012 [146]	Population not of interest for RQ3
Bidard 2010 [147]	Outcomes not of interest for RQ3
Biganzoli 2012 [148]	No randomized controlled trial (ATHENA study)
Bondarenko 2010 [149]	Conference abstract
Brufsky 2010 [150]	Conference abstract
Brufsky 2010 [151]	Conference abstract
Brufsky 2010b [152]	Conference abstract
Brufsky 2011 [153]	Editorial (no original RCT)
Brufsky 2012 [154]	Population not of interest for RQ3
Cella 2011 [155]	Outcomes not of interest for RQ3 (Quality of Life results of an already included RCT in Wagner 2012)
Cortes 2012 [156]	Outcomes not of interest for RQ3
Dieras 2010 [157]	Conference abstract / population not of interest for RQ3
Dieras 2011 [158]	Comparison not of interest for RQ3

Forster 2010 [159]	Conference abstract
Glaspy 2010 [160]	Conference abstract
Hardy-Bessard 2012 [161]	No randomized controlled trial (ATHENA study)
Hegewisch-Becker 2011 [162]	Comparison not of interest for RQ3
Lang 2010 [163]	Conference abstract
Lang 2010 [164]	Conference abstract
Lindman 2010 [165]	Conference abstract / population not of interest for RQ3
Masuda 2010 [166]	Conference abstract
Mayer 2010 [167]	Conference abstract
Mayer 2010 [168]	Intervention not of interest for RQ3
Miles 2010 [169]	Conference abstract
Miles 2011 [170]	Conference abstract / no randomized controlled trial
Miller 2012 [171]	Comparison not of interest for RQ3
Robert 2011 [172]	Comparison not of interest for RQ3
Rugo 2010 [173]	Conference abstract / intervention not of interest for RQ3
Shaughnessy 2010 [174]	Conference abstract
Smith 2011 [175]	No randomized controlled trial (ATHENA study)
Smith 2011 [176]	No randomized controlled trial (ATHENA study)
Thomssen 2012 [177]	No randomized controlled trial (ATHENA study)
Von Minckwitz 2012 [178]	Population not of interest for RQ3
Wachter 2011 [179]	Conference abstract
Xu 2012 [180]	No randomized controlled trial (ATHENA study)

Risk of bias summary of SR

Of the included review (Wagner 2012), quality appraisal through the AMSTAR criteria was performed. The review scored positively on all items, therefore, the SR is considered as having a 'low risk' of bias (Table 18).

Table 18 – Methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Wagner 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies Yes

4.3.4. Research question 4: Use of trastuzumab with non-anthracycline chemotherapy for patients with HER-2 positive breast cancer in the adjuvant setting

Selection of systematic reviews

On September 20, 2012 a search was performed to identify systematic reviews comparing adjuvant non-anthracycline chemotherapy regimen plus trastuzumab with adjuvant anthracycline–taxane chemotherapy regimen plus trastuzumab in women with HER-2 positive invasive early (non-metastatic) breast cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched. Furthermore, all systematic reviews of the Cochrane Breast Cancer Group (CBCG) were browsed for their relevancy. In MEDLINE and Embase 365 potential relevant references were identified (Figure 13). After deduplication 349 references remained. Based on title and abstract 334 reviews were excluded. Of the remaining 15 reviews, none were included after full text evaluation (Table 19). Also the searches in the Cochrane databases did not result in any relevant systematic reviews: of the four potential relevant reviews two were excluded and two had been already excluded in the previous search (Figure 14).

Figure 13 – Study flow of selection of SRs (MEDLINE and Embase)

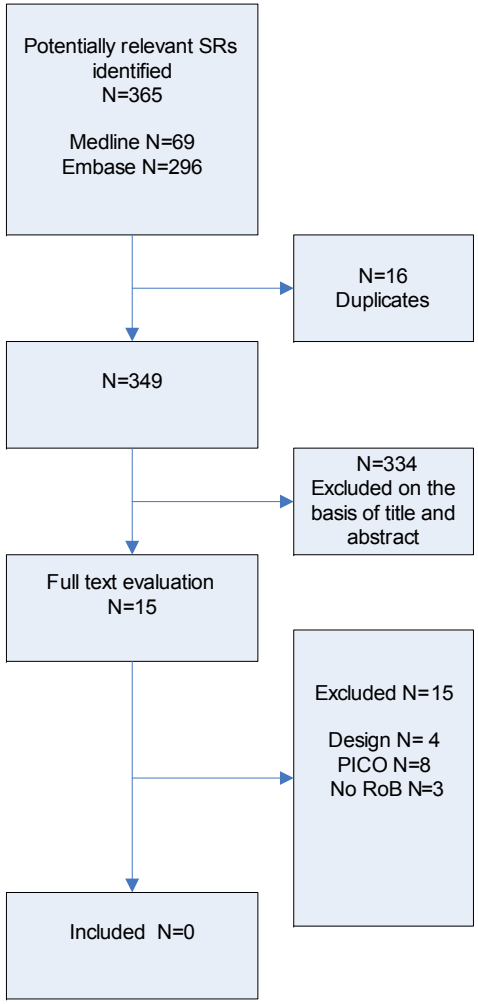


Figure 14 – Study flow of selection of SRs (CDSR, CLIB TA, CLIB DaRe)

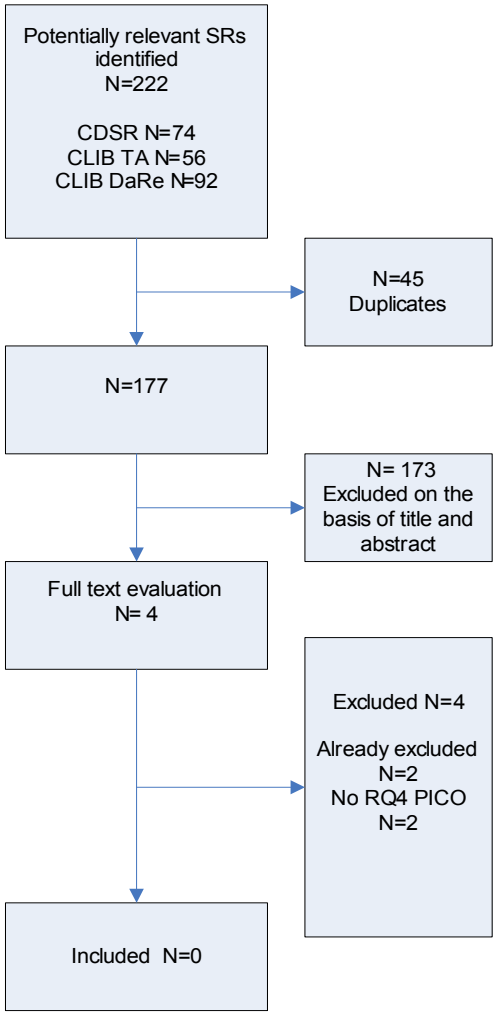


Table 19 – Excluded SRs

Reference	Reason for exclusion
Bayoudh 2012 [181]	No risk of bias assessment
Chang 2010 [182]	Pico not of interest / no systematic review
Chen 2011 [183]	Pico not of interest
Costa 2010 [184]	No systematic review/ indirect comparisons
Garnock-Jones 2010 [185]	No risk of bias assessment
Gines 2011 [186]	Pico not of interest
Grude 2010 [187]	No systematic review
Hysing 2011 [188]	Pico not of interest / no systematic review
Mateu 2011 [189]	Pico not of interest / no systematic review
Moja 2012 [190]	Pico not of interest
Mukohara 2011 [191]	No systematic review
Patani 2010 [192]	No risk of bias assessment
Pienkowski 2010 [193]	Pico not of interest / no systematic review
Tagliabue 2010 [194]	No systematic review
Valachis 2011 [195]	Pico not of interest
Valachis 2012 [196]	Pico not of interest
Yin 2011 [197]	Pico not of interest / only one database was sought

Selection of RCTs

On November 1, 2012 a search was performed to identify RCTs comparing adjuvant non-anthracycline chemotherapy regimen plus trastuzumab with adjuvant anthracycline–taxane chemotherapy regimen plus trastuzumab in women with HER-2 positive invasive early (non-metastatic) breast cancer. MEDLINE (including PreMedline), Embase and CENTRAL were searched (from 2010 onwards) and 232 potential relevant references were identified (Figure 15). After deduplication 184 references remained. Based on title and abstract 163 studies were excluded. Of the remaining 21 studies, one was included (Table 20) and 20 were excluded with reason (Table 21).

Figure 15 – Study flow of selection of RCTs

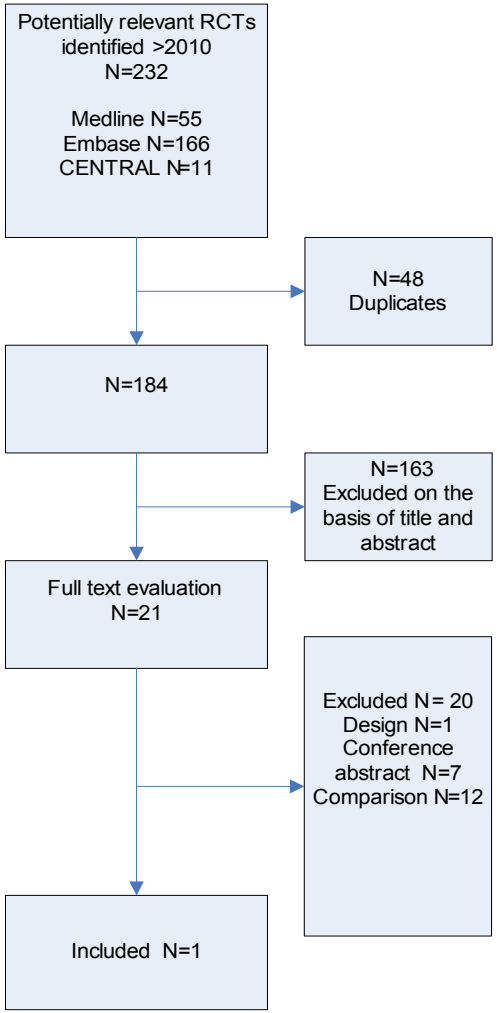


Table 20 – Included RCTs

Reference	Interventions
Slamon 2011 [198]	Doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH).

Table 21 – Excluded RCTs

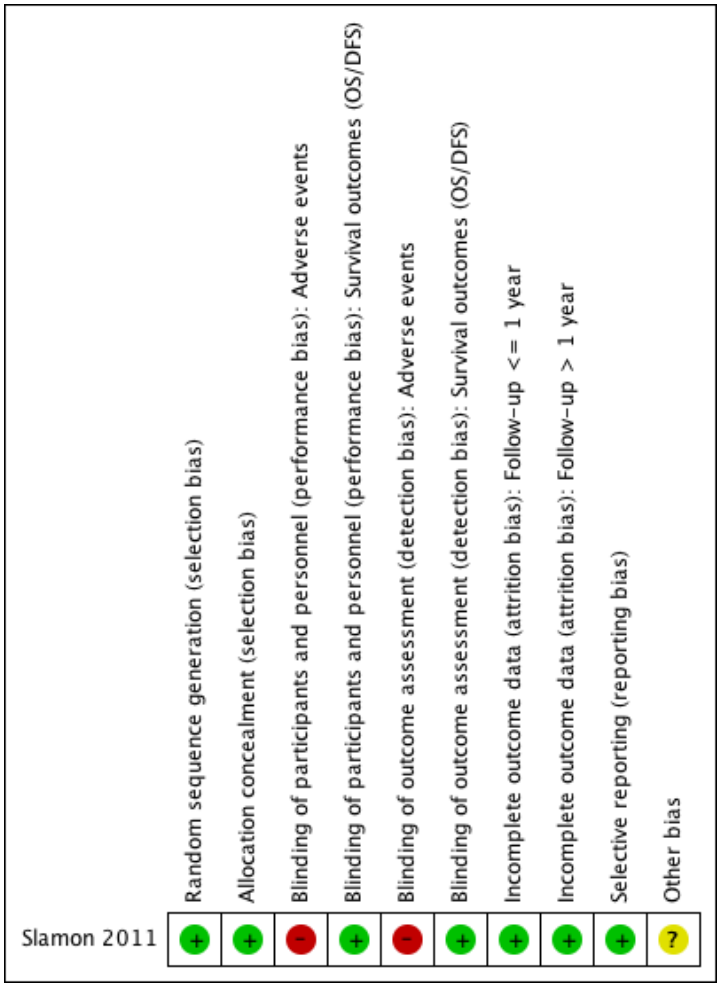
Reference	Reason for exclusion
Buzdar 2010 [199]	Conference abstract/comparison
Cameron 2010 [200]	Conference abstract/comparison
Gianni 2011 [201]	Comparison
Guarneri 2011 [202]	Conference abstract/comparison
Guarneri 2012 [203]	Comparison
Ismael 2012 [204]	Comparison
Jinno 2011 [205]	Conference abstract/no RCT
Masuda 2010 [206]	Conference abstract/protocol for relevant RCT
Moran 2010 [207]	No RCT
Nakamura 2012 [208]	Comparison
Perez 2011 [209]	Comparison
Perez 2011 [210]	Comparison
Procter 2010 [211]	Comparison
Rayson 2010 [212]	Conference abstract/comparison
Rayson 2012 [213]	Comparison
Romond 2012 [214]	Comparison
Sanchez-Munoz 2010 [215]	Comparison

Sawaki 2011 [216]	Comparison/population
Untch 2010 [217]	Comparison
Valero 2011 [218]	Conference abstract/comparison

Risk of bias summary of RCT

The risk of bias of the only included RCT (Slamon 2011) [198] was considered low for survival outcomes (overall survival and disease free survival) and high for adverse events (Figure 16).

Figure 16 – Risk of bias summary of RCTs



5. EVIDENCE TABLES BY CLINICAL QUESTION

5.1. Diagnosis

5.1.1. Triple assessment

No additional evidence found

5.1.2. Diagnosis with MRI

Table 22 – Diagnosis of breast cancer with MRI

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Peters et al. 2008[219]	July 2005	Women who have small lesions detected at mammographic screening (non palpable lesions)	CE-MRI Reference: Histologic analysis / mammographic and clinical follow-up > 2 years	Diagnostic performance of MR imaging	Pooled weighted estimates of : sensitivity: 0.90 (95% CI: 0.88, 0.92) specificity: 0.72 (95% CI: 0.67, 0.77) The performance of breast MRI was influenced by the prevalence of cancer in the studied population (23%-84%; p = 0.05) and the number of criteria used to differentiate benign from malignant lesions (p=0.02). For definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI.	Search strategy in Medline: January 1985 → March 2005 Search in PubMed, DARE, Cochrane database (July 2005) Quality appraisal with QUADAS 44 studies published between 1993 and 2004 were included in the meta-analysis	SR and meta-analysis	High

5.1.3. Diagnosis with scintimammography

Table 23 – Diagnosis of breast cancer with scintimammography

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
MAS 2007[220]	January 2007	Patients with palpable breast tumors OR patients with either palpable tumors or indeterminate or suspicious XMM findings OR patients with dense breast tissues	Scintimammography (SMM) versus US Standard: surgical histopathology	Se, Sp, PPV, NPV, adverse effects for SMM and US.	SMM alone : meta-analysis of 49 studies Se: 84% Sp: 81% PPV: 84% NPV: 76% SMM Versus US: Meta-Analysis on Paired Data (5 comparative studies) In the SROC plot, the area under the curve as a measure of discriminatory power showed minimal difference between the 2 techniques (94% for SMM and 93% for US). Conclusion: SMM is as effective as US in differentiating benign and malignant breast lesions. However, there may be a role for SMM as a third line adjunctive technique in the evaluation of breast abnormalities, in	Literature search for the period 1992-2002, since the potential use of SMM in breast cancer was discovered in 1992, and the first conducted study was published in 1994. The 2007 update included English- and French-language health technology assessments and English-language studies published from mid-October 2002 to January 31, 2007. Excluded were case reports, comments,	SR and meta-analysis of 49 studies on SMM published between 1994 and 1999 with data on 4 540 breast lesions	Moderate

			particular where breast US examination is inconclusive because of dense breast tissue or architectural distortion resulting from previous surgery or radiation treatment.	editorials, and letters.		

5.1.4. Diagnosis with PET scan

Table 24 – Diagnosis of breast cancer with PET scan

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009 [221]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	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.	2 SR (Shie 2008, Isasi 2005) and 15 small comparative studies or case series (Abe 2005, Altehoefer 2001, Bradley 2000, Bristow 2008, Cook 1998, Engelhard 2004, Eubank 2001, Eubank 2004, Fueger 2005, Haubold-Reuter 1993, Kamby 1987, Nakai 2005, Schirrmeister 1999, Schmidt 2008 and Ternier 2006)	Studies used to formulate these recommandation are based on PET and not on PET-CT→ non reliable	Very low

	Population	Index test	Results	Comments
HTA reports				
NCCHTA 2007[222]	Patients who have an abnormal mammogram or palpable breast mass and have been referred for breast biopsy	FDG-PET Reference standards: cytological aspiration and histopathology	One systematic review identified (AHRQ 2001): already included in previous KCE report. Additional primary study (Heinisch 2003) compared PET and MRI in 36 women with suspicious lesions on mammography or clinical examination. PET Se 76% (95% CI: 52% - 91%) Sp 73% (95% CI: 45% - 91%) MRI Se 95% (95% CI: 74% - 99%) Sp 73% (95% CI: 45% - 91%)	Good-quality HTA Search date: Aug 2005 Databases: Medline, EMBASE, Cochrane Library, HTA database, DARE, individual contacts through INAHTA Meta-analysis using random-effects Trials only include patients with suspicious mammograms or palpable masses, so prevalence is high and mean tumour size was large. Hence, report states that evidence is required in other patients.
AHRQ 2006[223]	Patients who have suspicious breast lesions (abnormal mammogram and/or physical examination and/or ultrasound examination)	FDG-PET Comparators: MRI, US, scintimammography Reference standard: biopsy	Objective: to determine if available non invasive diagnostic test (PET/MR/US/scintimammography) are sufficiently accurate to exclude malignancy, avoiding women with an abnormal mammogram to perform biopsy. 69 publications were included: - 9 of 18-FDG PET scanning (8 WBS, 1 gamma camera). - 45 of scintimammography (SCM) - 19 of MRI - 8 of ultrasound Some publications reported data for more than one technology For suspicious lesions Se: PET (82.2%); MRI (92.5%); US (86.1%)	High quality HTA Search date : April 2005 Databases: PubMed, EMBASE, Clinical Trials, Cochrane Databases, ECRI databases, CRISP, Controlled Trials, Database of Abstracts of Reviews of Effectiveness (DARE), U.S. Centers for Medicare & Medicaid Services. The quality of all of the studies was moderate.

Sp: PET (78.3%); MRI (72.4%); US (66.4%)

For non palpable lesions
Se: SCM (68.7%)
Sp: SCM (84.8%)

In USA, after an abnormal mammogram, women have a level of risk of cancer = 20%. All technologies could reduce the need for biopsy (a) but each would miss some cancers (b).

At this average risk level, in 1 000 women with:
- a negative PET scan, 924 (a) but 76 (b)
- a negative SCM, 907 (a) but 93 (b)
- a negative MRI, 962 (a) but 38 (b)
- a negative US, 950 (a) but 50 (b)

Future studies could overturn these findings.

Conclusion: MRI is a more valuable tool than PET to give a diagnosis (higher sensitivity and higher NPV). However, if a less than 2% risk of having breast cancer with a negative diagnostic test is considered an acceptable level of risk for a diagnostic test to reliably preclude biopsy, none of these tests was sufficiently accurate to replace biopsy for women at average risk of breast cancer.

For non palpable lesions, data were insufficient to estimate the accuracy of PET, MRI or US. SCM was not sufficiently accurate to avoid biopsy.
For palpable lesions, data were insufficient to estimate the accuracy of PET, MRI, US and SCM.

Systematic reviews				
Bourguet 2006[224]	Patients with suspicion of breast cancer	FDG-PET	No change since 2003. Standard: PET is not indicated in the diagnosis of breast cancer (evidence level A).	Update of a previous systematic review (2003) Literature search in Medline (2003-November 2005) + OVID alerts Language restrictions: French and English

5.1.5. Hormonal receptors assessment

Table 25 – Assessment of hormonal receptors

Hormonal receptors	Source	Recommendations	Supporting evidence	Level of evidence
Estrogen receptors and progesterone receptors (ER/PgR)				
Estrogen receptors and progesterone receptors (ER/PgR)	ASCO 2007[225]	ER and PgR should be measured on every primary invasive breast cancer and may be measured on metastatic lesions if the results would influence treatment planning. In both pre- and post-menopausal patients, steroid hormone receptor status should be used to identify patients most likely to benefit from endocrine forms of therapy in both the early breast cancer and metastatic disease settings. For patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PgR for therapy recommendations.	Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005 Clark et al. 1983 Ravdin et al. 1992 Diaz et al. 2005	Moderate-High

HER2				
HER2 evaluation in breast cancer	ASCO 2007[225]	HER2 expression and/or amplification should be evaluated in every primary invasive breast cancer either at the time of diagnosis or at the time of recurrence, principally to guide selection of trastuzumab in the adjuvant and/or metastatic setting.	Colomer et al. 1997, 2000 Fehm et al. 1997 Hayes et al. 1993 Leitzel et al. 1992, 1995 Lipton et al. 2000, 2002, 2003 Stender et al. 1997 Yamauchi et al. 1997	Moderate-High
HER2 to define prognosis for early stage breast cancer patients in the absence of systemic therapy	ASCO 2007[225]	Not recommended	Slamon et al. 1987 Pik et al. 1990 Van de Vijver et al. 1988 Stender et al. 1997 Kandl et al. 1994 Willsher et al. 1996 Mehta et al. 1998 Fehm et al. 1998 Leitzel et al. 2001	Moderate-High
HER2 to determine sensitivity to endocrine therapy	ASCO 2007[225]	There are insufficient data to support the use of HER2 in tissue (or serum) as a predictor of response to endocrine therapy : Not recommended	Berry et al. 2000 Bianco et al. 2000 Elledge et al. 1998 Love et al. 2003 Ellis et al. 2001 Dowsett et al. 2005, 2006	Moderate - High
	CCO 2006[226]	Tamoxifen: The evidence does not support a recommendation against tamoxifen therapy in HER2/neu-positive patients. While it	Tamoxifen: Knoop et al. 2001 De Placido et al. 2003	High

		is possible that tamoxifen is more effective in HER2/neu-negative patients, there is still sufficient evidence that it is effective in HER2/neu-positive patients as well.	Jakesz et al. 2002 Blanco et al. 1998 Rydén et al. 2005 Swedish Breast Cancer Cooperative Group 1996 Stal et al. 2000	
		Aromatase inhibitors: The current evidence does not support a definitive recommendation regarding aromatase inhibitor therapy and HER2/neu status.	Aromatase inhibitors: Lipton et al. 2003 Ellis et al. 2001 Smith et al. 2005 Eiermann et al. 2001	
		Ovarian ablation: The current evidence does not support a definitive recommendation regarding ovarian ablation and HER2/neu status.	Ovarian ablation: Jakesz et al. 2002 Love et al. 2002, 2003	
HER2 to determine sensitivity to chemoendocrine therapy	CCO 2006[226]	The current evidence does not support a definitive recommendation regarding chemoendocrine therapy and HER2/neu status.	Ravdin et al. 1998	Low
HER2 to predict response to taxane-based therapy	ASCO 2007[225]	It is not recommended to use HER2 guiding use of taxane chemotherapy in the adjuvant setting.	Baselga et al. 1997 Gianni et al. 1997 Hayes et al. 2006 Volm et al. 1999 Harris et al. 2006 Konecny et al. 2004	Moderate-High
	CCO 2006[226]	The current evidence does not support a definitive recommendation regarding taxane chemotherapy and HER2/neu status.	Sjostrom et al. 1999, 2002 Hamilton et al. 2000 Konecny et al. 2004 Paridaens et al. 2000	Moderate-High

			Luck et al. 2000 Learn et al. 2005 Lin et al. 2004 Martin et al. 2005	
HER2 to determine sensitivity to anti-HER2-based therapy	ASCO 2007[225]	High levels of tissue HER2 expression or HER2 gene amplification should be used to identify patients for whom trastuzumab may be of benefit for treatment of breast cancer in the adjuvant or metastatic disease settings.	Seidman et al. 2004 Buzdar et al. 2005 Joensuu et al. 2006 Piccart-Gebhart et al. 2005 Romond al. 2005 Slamon et al. 2005	High
HER2 to determine sensitivity to radiation therapy	CCO 2006[226]	The current evidence does not support a definitive recommendation regarding radiation therapy and HER2/neu status.	No paper found	Low
Utility of HER2 for predicting response to specific chemotherapeutic agents	ASCO 2007[225]	Level II evidence (prospective therapeutic trials in which marker utility is a secondary study objective) suggests that overexpression of HER2 (3+ by protein or > 2.0 FISH ratio by gene amplification) identifies patients who have greater benefit from anthracycline-based adjuvant therapy. If a clinician is considering chemotherapy for a patient with HER2 positive breast cancer, it is recommended that an anthracycline be strongly considered, assuming there are no contraindications to anthracycline therapy. In the context of trastuzumab therapy, there is Level I evidence (single, high-powered, prospective, randomized controlled trials specifically designed to test the marker or a meta-analyses of well-designed studies) that a non-anthracycline regimen may produce similar outcomes. At present, the Update Committee does not recommend that HER2 be used to guide use of taxane chemotherapy in the adjuvant setting.	- CMF-based regimens: Allred et al. 1992 Berns et al. 1995 Gusterson et al. 1992 Miles et al. 1999 - Anthracyclines : Baselga et al. 1997 Di Leo et al. 2002 Harris et al. 2004 Järvinen et al. 2000 Knoop et al. 2005 O'Malley et al; 2006 Carter et al. 2006 Mano et al. 2007	Moderate-High

			- CMF / anthracyclines Paik et al. 2000 Gianni et al. 1997 Pritchard et al. 2006	
	CCO 2006[226]	Patients with HER2/neu-positive breast cancer should be considered for chemotherapy containing an anthracycline instead of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or melphalan and 5-fluorouracil (PF) chemotherapy	Paik et al. 1998, 2000 Di Leo et al. 2001, 2002, 2005 Vera et al. 1999 Petruzelka et al. 2000 Moliterni et al. 2003 Fisher et al. 1989, 1990 Pritchard et al. 2002 Levine et al. 1998 De Laurentiis et al. 2001 De Placido et al. 1995 Knoop et al. 2005 Colozza et al. 2002, 2005 Del Mastro et al. 2004 Rodenhuis et al. 2003, 2005 Thor et al. 1998 Arnould et al. 2003 Bonneterre et al. 2003	High
Circulating extracellular domain of HER-2	ASCO 2007[225]	Measuring circulating extracellular domain of HER2 is not currently recommended for any clinical setting.	Nunes et al. 2001 Esteva et al. 2002 Volas et al. 1996 Leitzel et al. 1995 Yamauchi et al. 1997 Lipton et al. 2003 Burstein et al. 2003	Low

5.1.6. Tumour markers

Table 26 – Assessment of tumour markers

Tumour markers	Source	Recommendations	Supporting evidence	Level of evidence
uPA and PAI				
uPA and PAI as a marker for breast cancer (prognosis)	ASCO 2007[225]	uPA/PAI-1 measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer. IHC for these markers is not accurate, and the prognostic value of ELISA using smaller tissue specimens has not been validated. Low levels of both markers are associated with a sufficiently low risk of recurrence, especially in hormone receptor positive women who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit. Furthermore, CMF-based adjuvant chemotherapy provides substantial benefit, compared to observation alone, in patients with high risk of recurrence as determined by high levels of uPA and PAI-1.	Duffy 2002 Duffy et al. 1988 Foekens et al. 1994 Look et al. 2002 Jänicke et al. 2001 De Witte et al. 1998 Pedersen et al. 1999 Bouchet et al. 1994, 1999 Eppenberger et al. 1998 Harbeck et al. 2002 Zenzoum et al. 2003	Low
Multiparameter gene expression analysis for breast cancer				
Multiparameter gene expression analysis for breast cancer	ASCO 2007[225]	In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX™ assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX™ may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (CMF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint™	- Oncotype DX™ assay Paik et al. 2004, 2006 Hable et al. 2004 Hornberger et al. 2005 Esteva et al. 2005 - MammaPrint van ‘t Veer et al. 2002 van de vijver et al.2002 Dai et al. 2005 Breast International Group Buyse et al. 2006 Desmedt et al. 2007 Jenssen et al. 2005	Low

		assay, the “Rotterdam Signature,” and the ”Breast Cancer Gene Expression Ratio” are under investigation.	Ransohoff 2004 Espinosa et al; 2005 - Rotterdam Signature Wang et al. 2005 Foekens et al. 2006 - Breast Cancer Gene Expression Ratio Goetz et al. 2006 Jansen et al. 2007	
Markers of proliferation				
Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation	ASCO 2007[225]	Present data are insufficient to recommend measurement of Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation to assign patients to prognostic groupings. DNA low cytometry-based proliferation markers are not recommended for breast cancer	Colozza et al. 2005 Mandard et al. 2000	Low
Cyclin E				
Cyclin E as markers for breast cancer	ASCO 2007[225]	Present data are insufficient to recommend use of whole length or fragment measurements of cyclin E for management of patients with breast cancer.	Keyomarsi et al. 2002 Wang et al. 2006 Porter et al. 2006	Low
Proteomic analysis for breast cancer	ASCO 2007[225]	Present data are insufficient to recommend use of proteomic patterns for management of patients with breast cancer.	Hu et al. 2005 Fowler et al. 2004 Becker et al. 2004 Li et al. 2002 Vlahou et al. 2003 Pawlik et al. 2005, 2006 Sauter et al. 2005 Wulfkuhle et al. 2002 Jacquemier et al. 2005 Abd El-Rehim 2005 Makretsov et al. 2004 Nielsen et al. 2004	Low

Bone marrow micrometastases				
Bone marrow micrometastases as markers for breast cancer	ASCO 2007[225]	Present data are insufficient to recommend assessment of bone marrow micrometastases for management of patients with breast cancer.	Braun et al. 2005	Low
Circulating tumor cell assays				
Circulating tumor cell assays as markers for breast cancer	ASCO 2007[225]	The measurement of circulating tumor cells (CTC) should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in patients with breast cancer. Similarly, the use of the recently FDA-cleared test for CTC (Cell Search, Veridex) in patients with metastatic breast cancer cannot be recommended until further validation confirms the clinical value of this test.	Gaforio et al. 2003 Weigelt et al. 2003 Cristofanilli 2004, 2005 Hayes et al. 2006 Budd et al. 2006	Low
CA 15-3 and CA 27.29				
CA 15-3 and CA 27.29 as screening, diagnostic or staging tests or for detecting recurrence	ASCO 2007[225]	CA 15-3 and CA 27.29 are not recommended as Markers for Breast Cancer as screening, diagnostic or staging tests or for detecting recurrence.	Ebeling et al. 2002 Gion et al. 2002 Kumpulainen et al. 2002 Martin et al. 2006 Molina et al. 2003, 2005 Khatcheressian et al. 2006	Low
CA 15-3 and CA 27.29 to contribute to decisions regarding therapy for metastatic breast cancer	ASCO 2007[225]	For monitoring patients with metastatic disease during active therapy, CA 27.29 or CA 15-3 can be used in conjunction with diagnostic imaging, history, and physical exam. Present data are insufficient to recommend use of CA 15-3 or CA 27.29 alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure. Caution should be used when interpreting a rising CA 27.29 or CA 15-3 level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.	Ebeling et al. 2002 Gion et al. 2002 Kumpulainen et al. 2002 Martín et al. 2006 Molina et al. 2003	Low
Carcinoembryonic antigen				

CEA for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy	ASCO 2007[225]	CEA is not recommended for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy.	There is no change from the guideline published in 2000. No relevant studies were identified from the review of the review of literature conducted for this topic.	Low
CEA to contribute to decisions regarding therapy for metastatic breast cancer	ASCO 2007[225]	For monitoring patients with metastatic disease during active therapy, CEA can be used in conjunction with diagnostic imaging, history, and physical exam. Present data are insufficient to recommend use of CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CEA may be used to indicate treatment failure. Caution should be used when interpreting a rising CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.	Guadagni et al. 2001 Tondini et al. 1988 Basuyau et al. 2000 Cheung et al. 2001 Coveney et al. 1995 Deprés-Brummer et al. 1995 Lauro et al. 1999 Robertson et al. 1999 Söletormos et al. 2000 Yildiz et al. 2004	Low
P53				
P 53	ASCO 2007[225]	Present data are insufficient to recommend use of p53 measurements for management of patients with breast cancer. Note. p53 abnormalities are associated with either resistance or sensitivity to different therapeutic agents. However, most studies analyzing p53 have not taken therapy into consideration, and the results may be strongly biased in one direction or the other, depending on the agents in question.	Olivier et al. 2006 Pharoah et al. 1999	Low
Cathepsin D				
Cathepsin D	ASCO 2007[225]	Cathepsin D is not recommended as a marker for breast cancer	Foekens et al. 1994 Billgren et al. 2002	Low

Abbreviations. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; QA, quality assurance.

5.2. Staging

5.2.1. Magnetic Resonance Imaging (MRI)

Table 27 – Staging of breast cancer with MRI

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009 [227]	July 2008	Women and men with newly diagnosed invasive adeno-carcinoma of the breast of clinical stages 1, 2 and 3 who are candidates for breast cancer surgery	The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS).	There is insufficient evidence (a) to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes, and (b) on which to base any recommendation on the use of MRI in the assessment of the breast with a diagnosis of pure DCIS. MRI can complement mammography in guiding surgical treatment of DCIS by providing a better description of tumour size and detection of additional malignant lesions (Francescutti 2002; Shiraishi 2003; Menell 2005). However, data need to be interpreted with caution because of the limitations of the studies, low evidence levels and small sample sizes.	2 case control studies and 4 case series, with a relatively high degree of consistency in results.	Low
NICE 2009 [227]	July 2008	Women and men with newly diagnosed invasive adeno-carcinoma of the breast of clinical stages 1, 2 and 3 who	Offer MRI of the breast to patients with invasive breast cancer: if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment if breast density precludes accurate	Breast MRI: moderate to high sensitivity (75-100%) and specificity (82-100%) in detecting multicentric tumour foci in fibroglandular or dense breasts (BCBS-TEC Review 2004, Del et al. 2007). MRI will detect additional mammogram-occult foci greater than 2 cm from the	one SR, 9 case control studies and 11 case series, with a relatively high degree of consistency in results	Moderate

	are candidates for breast cancer surgery	mammographic assessment to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.	index cancer in +/- 10% of women (Schnall et al. 2005, Deurloo et al. 2006). Contrast enhanced MRI has the lowest FN rate in detecting invasive lobular carcinoma and has the highest accuracy in measuring the size of the invasive lobular carcinoma (Boetes et al. 2004). MRI has been shown to detect occult invasive breast cancers with the sensitivity of 97%-100%. Combined mammography, clinical examination and MRI were more sensitive than any other individual test or routine triad (Chung et al. 2005). Axillary lymph nodes can be evaluated as part of an MRI-mammography study (Kvistad et al. 2004). Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients (BCBS-TEC Review 2004, Blair et al. 2006, Bremner et al. 2007, Del et al. 2007, Schelfout 2004). Preoperative MRI of the breast is effective in patients with histopathologically verified breast cancer, for local staging (Fischer et al. 2004).

NICE 2009 [221]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI).	Two systematic reviews (Isasi et al. 2005 and Shie et al. 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium quality and many were retrospective studies.	Very Low
NICE 2009 [221]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	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.	Two systematic reviews (Isasi et al., 2005 and Shie et al., 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium quality and many were retrospective studies.	Very Low
NICE 2009 [221]	July 2008	Women and men with invasive adenocarcinoma of the breast	Assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone scintigraphy and/or plain	Two systematic reviews (Isasi et al. 2005 and Shie et al., 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008,	There was insufficient evidence to support the choice of one imaging modality over another	Very Low

		of clinical stage 4	radiography.	Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	Other than the SR, papers were of poor to medium quality and many were retrospective studies.	
NICE 2009 [221]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases encroaching on the spinal canal).	Two systematic reviews (Isasi et al., 2005 and Shie et al., 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium quality and many were retrospective studies.	Very Low
CCO 2006 [228]	September 2004	Candidates for breast cancer surgery	Subsets of patients that may benefit from MRI: - Women with clinically palpable and mammographically occult breast cancer. - Women with metastatic adenocarcinoma to axillary lymph nodes, with an unknown primary. - Extent of disease needs better	Five case series examined imaging of the breast with ultrasound or MRI to determine the extent of disease prior to surgery (Snelling 2004, Park 2003, Schelfout 2004, Liberman 2003, Zhang 2002). Snelling (2004; n=111; prev=24%) compared whole breast ultrasound with clinical measurement for differentiating tumours larger than 3 cm from smaller	Low evidence → consensus between panel members	Very Low

	delineation, e.g. women with lobular carcinoma. - Patients who require re-excision because of positive surgical margins. - Patients with a high risk of multifocal disease. MRI should not be used as a substitute for detailed mammographic or sonographic work-up of any abnormalities detected at a routine screening or as a substitute for the clinical or image-guided core biopsy of mammographic, sonographic, or clinical abnormalities	ones (gold standard: pathology). Low sensitivity for both modalities (26% vs. 30%) but higher overall accuracy using whole-breast ultrasound (94% versus vs. 83%). Park (2003; n=183) found high sensitivity (100%) but moderate (67%) specificity for breast sonography for the detection of multifocal or diffuse disease. Three case series examined imaging of the breast with MRI compared to other imaging modalities (Schelfout 2004, Liberman 2003, Zhang 2002) Schelfout (n=170) compared MRI, ultrasound and mammography in the detection of multifocal, multicentric, and bilateral disease. He found high specificity (100%) for all modalities, with high sensitivity for MRI (95% to 100%) but low to moderate sensitivity for ultrasound (9% to 56%) and mammography (18% to 56%). Liberman (n=70; prev=27%) reported only 53% positive predictive value of MRI in detecting cancer in the ipsilateral breast. Zhang (n=54; prev=37%) found the combination of ultrasound and mammography to have a low sensitivity (26%) but high specificity (100%) compared to the MRI high sensitivity (100%) and good specificity (85%).

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Houssami et al. 2008[229]	June 2007	Women diagnosed with breast cancer	MRI Reference: Histologic analysis	Accuracy of MRI in detection of additional tumour foci multifocal (MF) and/or multicentric (MC)	MRI detects additional disease in 16% of women with breast cancer. Se and Sp were only graphically provided per study, and were not meta-analysed. The accuracy differs according to the reference standard (p=0.16), from 99% to 86% as the quality of reference standard increases. The overall summary estimate for PPV was 66% (95% CI: 52% to 77%). TP:FP ratio was 1.91 (95% CI: 1.09 – 3.34) Due to MRI-detected lesions, conversion from wide local excision to mastectomy was 1.1% (95% CI: 0.3 – 3.6%), from WLE to more extensive surgery was 5.5% (95%CI: 3.1 – 18.3%). MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer. There is a need to reduce FP in MRI detection.	Search strategy in Medline: 1966 → June 2007 19 studies were included for a total of 2 610 patients; 8 of them were also included in Peters et al. 2008	SR and meta-analysis	High

5.2.2. Axillary ultrasonography

Table 28 – Staging of breast cancer with axillary ultrasonography

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 who are candidates for breast cancer surgery	Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered. Ultrasound-guided needle biopsy of abnormal lymph nodes using FNAC or core biopsy has the potential to provide the required definitive cytological or histological proof of a positive result on which to base treatment decisions.	The proportion of cases in whom it was possible to visualise axillary lymph nodes on ultrasound was of 76% (mean) but it varied widely, with a range 35% to 99%. The remaining proportion represents patients for whom ultrasound does not add any information (Altinyollar et al. 2005, Brancato et al. 2004, Damera et al. 2003, Deurloo et al. 2003, Dixon et al. 1992, Esen et al. 2005, Nori et al. 2005, Podkrajsek et al. 2005). The meta-analysis included only patients in whom it was possible to obtain biopsy material by ultrasound, the pooled sensitivity was 75.0% and the pooled specificity was 98.3%. The staging performance of 'grey scale' ultrasound alone showed a mean sensitivity of 62%, a mean specificity of 87% (Altinyollar et al. 2005, Bartonkova et al. 2006, Brancato et al. 2004, Chandawarkar and Shinde 1997, Esen et al. 2005, Heusinger et al. 2005, Lee et al. 1996, Hergan et al. 1996, Sato et al. 2004 and Van Rijk et al. 2006). The staging performance of 'grey scale' ultrasound plus colour doppler ultrasound showed a mean sensitivity of 65% and a mean specificity of 89% (Couto et al. 2004, Dixon et al. 1992, Esen et al. 2005, Lee et al. 1996, Nori	8 case series studies and one meta-analysis (Alvarez et al. 2006) which pooled estimates based upon 16 case series studies NICE (2009), Brancato et al. (2004), Davies et al. (2006) and Genta et al. (2007) conducted cost-effectiveness studies about pretreatment ultrasound plus needle biopsy in staging early breast cancer patients	Low

		et al. 2005, Perre et al. 1996, Podkrajsek et al. 2005, Walsh et al. 1994). The staging performance of ultrasound guided fine needle aspiration cytology (FNAC) showed a mean sensitivity of 43% and a mean specificity of 100%, a positive predictive value of 99% and a negative predictive value of 72% (Brancato et al. 2004, Damera et al. 2003, De Kanter et al. 2006, Deurloo et al. 2003, Lemos et al. 2005, Podkrajsek et al. 2005, Stewart et al. 2006, Van Rijk et al. 2006). Sahoo et al. (2007) reported that 70% of patients with positive ultrasound FNAC were spared the additional step of SLNB while Somasunder et al. (2006) reported that 47% of patients with positive ultrasound FNAC were spared SLNB. Cost-effectiveness studies (NICE 2009, Brancato et al. 2004, Davies et al. 2006 and Genta et al. 2007) concluded that ultrasound plus needle biopsy seemed to be a cost effective staging strategy when compared to SLNB, without translating their results in QALYs gains. However, this health gain is attainable because both the reduction in the number of patients undergoing SLNB and the fact that, ultrasound plus needle biopsy is a less invasive staging procedure when compared to SLNB, can translate in sufficient gains in quality of life.

5.2.3. Positron emission tomography (PET)

Table 29 – Staging of breast cancer with PET scan

	Population	Index test	Results	Comments
HTA reports				
NCCHTA 2007[222]	Extent of tumour in ALN in patients with confirmed primary breast malignancy, no palpable ALN metastases (cN0) and no evidence of distant metastases	FDG-PET Reference standards: ALND ALND + SNB	One systematic review (BCBSA 2003) already included in previous KCE report, and four additional primary studies (Fehr 2004, Lovrics 2004, Wahl 2004, Zornoza 2004). ALND as ref.: PET Se = 40–93% PET Sp = 87–100% ALND + SNB as ref.: PET Se = 20–50% PET Sp = 82–100% Prevalence of node-positive disease = 33–64%, so 36–67% patients with PET negative would have axillary disease undetected if further tests were not undertaken. Conclusion: PET cannot be used to avoid ALND in patients with clinically N0 axillae, because of unacceptably low sensitivity. With this level of false negatives, if patients did not go on to have standard diagnostic tests, modelling suggests that under-treatment would be associated with absolute difference in 10-year survival of 8.2%. Recommendation: PET cannot be reliably used to avoid ALND.	Good-quality HTA Search date: Aug 2005 Databases: Medline, EMBASE, Cochrane Library, HTA database, DARE, individual contacts through INAHTA Meta-analysis using random-effects
Systematic reviews				
Sloka 2007[230]	Patients with breast cancer	FDG-PET Reference standards: Histology via	19 studies for staging axillary lymph nodes were considered in this systematic review. In 3 high-quality studies (of which 2 were already included in previous KCE report: Wahl 2004, Zornoza 2004), i.e. studies	Literature search in December 2005 (MEDLINE, Current Contents and EMBASE)

		ALND / SNB / histology / histology + ALND / SNB +histo via ALND	with broad generalizability to a variety of patients and no significant flaws in research methods (Wahl 2004, Zornoza 2004, Greco 2001): sensitivity : 61 – 94% specificity : 80 – 98% Recommendation: Authors recommend that further studies be performed that control for contributory variables (patient position, etc) in order to explain the variability of study results. Avoid older studies (< 1992) due to the increased accuracy of new scanners.	restricted to English, Spanish and French language articles. Due to the high heterogeneity between studies, meta-analysis was not performed.
Bourguet 2006[224]	Patients with breast cancer	FDG-PET	1 primary study (Zornoza 2004): already included in previous KCE report. No change since 2003: PET is unable to detect microscopic lymph node metastasis. Option: PET enables documentation of loco-regional invasion and metastatic spread in the initial staging of invasive breast cancer (evidence level B2). Recommendation: the place of PET in the initial staging of invasive breast cancer remains to be established.	Update of a previous systematic review (2003) Literature search in Medline (2003-November 2005) + OVID alerts Language restrictions: French and English

	Population	Index test	Outcome	Results	Comments
FDG-PET					
Ueda 2008[231]	183 patients having primary breast cancer proven by core needle biopsy who are operable	FDG-PET/CT Comparator: axillary US Standard reference: ALND and/or SNB	Diagnostic performance of PET/ CT and AUS in assessing axillary status: Se and Sp	18-FDG PET/CT - visual assessment: Se: 58% (95% CI: 44% - 70%) Sp: 95% (95% CI: 89% - 98%) - SUV cut-off point 1.8 Se: 36% (95% CI: 24% - 49%) Sp: 100% (95% CI: 96% - 100%) AUS Se: 54% (95% CI: 31% - 55%) Sp: 99% (95% CI: 95% - 100%) Visual assessment of 18F-FDG uptake combined with AUS Se: 64% (95% CI: 51% - 76%) Sp: 94% (95% CI: 88% - 97%) Conclusion: performance of 18F-FDG PET/CT was almost equivalent to that of AUS for detecting of ALN involvement in patients with primary breast cancer. Sensitivity was low in both cases. The combination of these 2 exams slightly increased sensitivity. When it is difficult to judge the axillary staging using AUS alone, metabolic approach of 18F-FDG PET/CT for axillary staging would enable a much more	Prospective study Possibility of review bias: unclear

				confident diagnosis.	
Veronesi 2007[232]	236 patients with breast cancer and clinically negative axilla	FDG-PET Comparator: SNB Standard reference: ALND	Diagnostic performance of PET and SNB in assessing axillary status: Se and Sp	103 out of the 236 patients (44%) had metastases in axillary nodes 18 FDG-PET: Se: 37% (95% CI: 28% - 47%) Sp: 96% (95% CI: 91% - 99%) SNB: Se: 96% (95% CI: 90% - 99%) Sp: 100% (95% CI: 96% - 100%) Conclusion: The high specificity of PET indicates that patients who have a PET-positive axilla should perform an ALND rather than an SNB for axillary staging. In contrast, when FDG-PET is negative at the axilla, its reliability is very low and axillary SNB becomes imperative.	Prospective study conducted from September 2003 to April 2005 in Italy
Gil-Rendo 2006[233]	150 women with breast cancer: histologically proven carcinoma of the breast with clinically and ultrasonographically non-suspicious axillary lymph nodes, eligible for primary treatment by breast conservation or mastectomy	FDG-PET Standard reference: ALND	Diagnostic performance of PET in assessing axillary status: Se and Sp	In the first group of 150 women who had preoperative PET and ALND, the sensitivity and specificity for detecting axillary status were: Se: 90% (95% CI: 83% - 97%) Sp: 98% (95% CI: 93% - 99%) PET detected axillary involvement in 64 of 71 patients (7 false negatives) and correctly diagnosed 78 of 79 patients without axillary metastases. Conclusion: The high sensitivity and the high specificity of PET suggest that FDG uptake in the axilla could be an indication	Prospective study on 275 women (2 subgroups). In a first group (150 women), ALND was performed regardless of PET results with the aim of evaluating the Se and Sp of the technique. In a second group (125 women), the axillary examination was complemented by SLNB only in those with no pathological axillary

				for full ALND without previous SLNB	uptake on the FDG-PET scan.
Kumar 2006[234]	80 women with a histological diagnosis of breast cancer and clinically negative axillary nodes	FDG-PET Standard reference: SLNB or ALND	Diagnostic performance of PET in assessing axillary status: Se and Sp	36 out of the 80 patients (45%) had metastases in axillary nodes 18 FDG-PET: Se: 44% (95% CI: 28% - 62%) Sp: 95% (95% CI: 83% - 99%) Conclusion: FDG PET cannot replace histological staging using SLNB in patients with breast cancer. The high specificity of PET indicates that patients who have a PET-positive axilla should perform an ALND rather than an SLNB for axillary staging. In contrast, FDG-PET showed poor sensitivity in the detection of axillary metastases, confirming the need for SLNB in cases where PET is negative in the axilla.	Prospective study in USA

5.3. Treatment of non-invasive breast cancer : DCIS

5.3.1. Surgery and Sentinel lymph node biopsy

Table 30 – Surgery and Sentinel lymph node biopsy for DCIS

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 having breast conserving surgery	Do not perform SLNB routinely in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease. Patients at high risk include those with a palpable mass or extensive microcalcifications. Offer SLNB to all patients who are having a mastectomy for DCIS.	Ansari et al. (2008) conducted a meta-analysis (of observational studies) of the reported data on the incidence of SLN metastasis in patients with DCIS. This analysis reported SLNB results in patients with the diagnosis of DCIS. The analysis showed the frequency of sentinel lymph node positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. With an overall positivity incidence of 7·4%. Postoperative overall positivity incidence was 3.7%. There was no evidence to suggest that a pattern exists between the rate of positive sentinel lymph nodes and DCIS grade. There was no evidence to suggest that a pattern exists between the rate of positive sentinel lymph nodes and DCIS tumour size. It was not possible to reliably estimate the proportion of patients with DCIS and positive sentinel lymph nodes who have further axillary nodal involvement from the studies identified, because of small numbers of patients in the series. None of the selected studies (all retrospective) reported changes to treatment plans as a result of staging by SLNB.	GDG consensus	Moderate

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Women and men with newly diagnosed DCIS having breast conserving surgery	For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination. Re-excision should be considered if the margin is less than 2 mm after discussion of the risks and benefits with the patient.	Observational studies (Bijker et al. 2001; Boland et al. 2001 and 2003; Boyages et al. 1999; Cabioglu et al. 2007; Chan et al. 2001; Cheng et al. 1997; Denoux et al. 2001; Dillon et al. 2007; Goldstein et al. 1998, 1999, 2000; Hetelekidis et al. 1999; Holland et al. 1998; Kell and Morrow 2005; Macdonald et al. 2005 and 2006; Neuschatz et al. 2001 and 2002; Ratanawichitrasin et al. 1999; Rodrigues et al. 2002; Sahoo et al. 2005; Sigal-Zafrani et al. 2004; Silverstein et al. 1994, 1997 and 1999; Silverstein and Buchanan 2003; Solin et al. 2005; Tunon-de-Lara et al. 2001; Vargas et al. 2005; Vicini et al. 2001; Wong et al. 2006; Yau et al. 2006). There is no consistency regarding: the optimal tumour free tissue margin whether wide margins can and whether they should replace radiotherapy which of the two should most be avoided. There is consistency that the risk of local recurrence is reduced with very wide margins, e.g. more than 10 mm of tumour-free tissue.		Low
NICE 2009[227]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the	Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option.	These recommendations are based on limited clinical evidence from observational studies and on GDG consensus that immediate reconstruction is an acceptable procedure that does not disadvantage patients compared to delayed reconstruction.	GDG consensus	Low

	breast of clinical stages 1, 2 and 3 having mastectomy	All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.	Psychological outcomes SR (Fischbacher 2002): better psychological outcomes arise in patients treated with immediate reconstruction compared to delayed reconstruction. Observational studies (Drucker-Zertuche and Robles-Vidal 2007 and Gendy et al. 2003): psychological outcomes are generally good following immediate reconstruction. Cosmetic results Observational studies (Anderson et al. 2004; Drucker-Zertuche and Robles-Vidal 2007; Gendy et al. 2003; Cordeiro et al. 2004 and Vandeweyer et al. 2003) report high rates of acceptable cosmetic results between 80% and 96% whereas in one study (Knottenbelt et al. 2004) the reported rate is only 20%. Rate of complications Two SR (Fischbacher 2002 and Javaid et al. 2006): immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction. A third less rigorous review (Taylor et al. 2005) found similar rates of capsular contraction between immediate and delayed reconstruction with implants, but with a trend for unfavourable results with immediate autologous tissue reconstruction.

				Delay to start adjuvant therapy No reliable evidence was identified on whether immediate breast reconstruction following mastectomy delays the start of adjuvant chemotherapy or radiotherapy. Recurrence or survival No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction. Patients satisfaction Evidence from observational studies suggests that in general, patients are satisfied with their reconstructed breasts following either immediate reconstruction, or delayed reconstruction.		

5.3.2. Radiotherapy

Table 31 – Radiotherapy for DCIS

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Women with DCIS	Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery and discuss with them the potential benefits and risks.	4 RCTs: Bijker et al. 2006 (EORTC); Fisher et al. 1998 (NSABP); Emdin et al. 2006 (SweDCIS); Houghton et al. 2003 (UKCCCR); Holmberg et al. 2008 (update of the original SweDCIS RCT) Systematic reviews: Boyages et al. 1999; Fonseca et al. 1997; Shelley et al. 2006; Baxter et al. 2005; Smith et al. 2006 All ipsilateral breast recurrence 4 RCTS: pooled HR 0.49; 95%CI 0.41 to	A Cochrane SR (Goodwin et al. 2009) meta-analysed results obtained from these 4 RCTs Meta-analysis used Kaplan-Meier curves	High

		0.59; p<0.00001 → favoured RT Individual trial results were all consistent with the pooled HR Ipsilateral invasive recurrence 2 RCTS (NSABP and UKCCCR) HR 0.64; 95%CI 0.38 to 1.06; p<0.08 Ipsilateral DCIS recurrence 2 RCTS (NSABP and UKCCCR) HR 0.64; 95% CI 0.41 to 1.01; p=0.05 Lower rates of ipsilateral recurrence in the radiotherapy arm when considering either invasive ipsilateral recurrence or non-invasive ipsilateral recurrence (Bijker et al. 2006; Fisher et al. 1998; Houghton et al. 2003) Disease-free survival EORTC: 10-year metastasis free survival 96% in both groups Contralateral breast events were similar in both RT and control groups for all trials. Overall survival NSABP (8y FU): 94% (BCS) vs. 95% (BCS+RT) EORTC (10y FU): 95% in both groups SweDCIS: not reported UKCCCR: not reported

				No significant long-term toxicity from RT was found. No information about short-term toxicity from RT or quality of life data were reported.		

5.3.3. *Endocrine therapy*

Table 32 – Endocrine therapy for DCIS

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Pre-menopausal women with ER-positive DCIS	Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS.	Ipsilateral local recurrence There is evidence from one placebo controlled RCT (NSABP B-24 trial-Fisher et al. 1999) that in patients treated for DCIS with lumpectomy and adjuvant radiotherapy, adjuvant tamoxifen reduces the risk of ipsilateral local recurrence by 30% and contralateral breast cancer by 50%. Any breast cancer event The risk at 5 years of any breast cancer event in the tamoxifen arm was 8% and in the placebo arm, 13%. One subsequent RCT with a less rigorous design found no similar benefit arising from tamoxifen (UKCCCR trial-Houghton et al., 2003). The UKCCCR trial examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS		High

				(without radiotherapy) and found no benefit arising from tamoxifen, except in terms of subsequent DCIS in either breast: this risk was reduced by 30%. The risk of any breast event in the tamoxifen arm at 56 months was 12% (UKCCCR) and in the control arm, 15%. Disease-free survival vs overall survival The NSABP B-24 trial found that Tamoxifen and radiotherapy improved disease-free survival at 5 years (87%) compared to placebo and radiotherapy (83%), but with no difference between groups for overall survival.	
CCO 2006	March 2006	Women with DCIS	Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen.	Two trials : the NSABP B-24 trial with a median follow-up of 6.9 years, and the UKCCCR trial (see above).	High

5.4. Treatment of non-invasive breast cancer: Paget's disease

5.4.1. Surgery for Paget's disease

Table 33 – Surgery for Paget's disease

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Women and men with Paget's disease of the nipple	Offer breast conserving surgery with removal of the nipple–areolar complex as an alternative to mastectomy. Offer oncoplastic repair techniques to maximise cosmesis.	11 observational studies (Sutton et al. 1999; Bijker et al. 2001; Dixon et al. 1991; Duff et al.1998; Howard et al. 1989; Nicolosai et al. 1996; Polgar et al. 2002; Zurrida et al. 1993; Estabrook et al. 1996 and Marshal et al. 2003) show higher rates of recurrence following breast conserving surgery compared to mastectomy, but no study provided a statistical analysis. In 3 out of 4 studies in which survival data were reported for both mastectomy and breast conserving surgery, post-mastectomy breast cancer-specific survival was superior (Dixon et al. 1991; Howard et al. 1989; Polgar et al. 2002 and Sutton et al. 1999). A single study statistically found no statistical difference in breast cancer-specific survival at 15 years following treatment (Chen et al. 2006). Cosmesis was assessed in one study only (Marshall et al., 2003) including 31 patients. These were rated as: excellent, 10 (32%; 4 patients underwent nipple reconstruction); good, 18 (58%); fair, 3 (10%).	There was no strong evidence that survival of these patients would be adversely affected by having breast conserving surgery rather than mastectomy	Low

5.5. Treatment of early invasive breast cancer

5.5.1. Neoadjuvant treatment

Table 34 – Neoadjuvant treatment for early invasive breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Early breast cancer						
NICE 2009[227]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast	Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery. Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation.	Three systematic reviews (Hind et al. 2006; Mieog et al. 2007 and Trudeau et al. 2005) and a review providing updated results of two RCTs (Rastogi et al. 2008). Primary endocrine therapy vs. surgery One SR (Hind et al., 2006) of RCTs in patients > 70 years. no significant difference in overall survival surgery + endocrine therapy vs. endocrine therapy alone: significant effect for breast cancer specific survival. Preoperative or postoperative chemotherapy A Cochrane SR (Mieog et al. 2007) and Rastogi et al. (2008) Overall survival rates HR of 0.98 (95% CI, 0.87 to 1.09; p= 0.67; no heterogeneity). Breast conservation rates	Mieog et al. (2007): Data were based on 1 139 estimated deaths in 4 620 women Women with operable breast cancer - TNM stage T1c, T2, T3, N0 to 2, and M0	High

				No difference as long as surgery remains part of the treatment even after complete tumour regression HR, 1.12; 95% CI, 0.92 to 1.37; p= 0.25; no heterogeneity. Adverse effects Preoperative chemotherapy was associated with fewer adverse effects.	
Locally Advanced or Inflammatory Breast Cancer					
NICE 2009[227]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast	Offer local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy.	A Cochrane review and two systematic reviews (Mieog et al. 2007; Shenkier et al. 2004; Pouillart et al. 1981). One RCT (Bucholz et al., 2006), retrospective studies (Huang et al. 2004; McGuire et al. 2007) and GDG consensus. No difference in overall survival was observed when comparing different radiotherapy regimens (Bucholz et al. 2006 and Shenkier et al. 2004) A higher rate of loco-regional recurrence was reported in patients who received radiotherapy without surgery after primary chemotherapy (Mieog et al. 2007 and Mauri et al. 2005).	High

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Preoperative aromatase inhibitor (AI) and cyclooxygenase-2 (COX-2) inhibitor								
Chow 2009[235]	NA	Postmeno-pausal women with invasive breast cancer (clinical size of tumor ≥3 cm) with ER- and/or PgR positive status	Group A: exemestane 25mg/d + celecoxib 400mg twice daily; n=30 Group B: exemestane 25mg/d; n=24 Group C: letrozole 2.5mg/d, n=28	Tumour size Clinical response (CR, PR, NR)	All groups showed clinical responses (58.6% for group A, 54.5% for group B and 62.0% for group C) and decrease in tumor area (61.8% for group A, 58.1% for group B and 55.7% for group C). → all of the three anti-aromatase therapies are effective and safe but the serum levels of CA15.3 dropped more significantly when anti-aromatase therapy was combined with celecoxib.	No precision about blinding No ITT	RCT	Moderate

5.5.2. *Surgery to the breast*

Table 35 – Surgery to the breast for early invasive breast cancer

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Lee et al. 2009[236]	July 2007	Breast cancer women	Mastectomy with (immediate or delayed) recontruction vs. mastectomy without reconstruction	Quality of life Body image Sexuality	Patient-reported outcomes of breast reconstruction after mastectomy are similar to outcomes of mastectomy without reconstruction. Results from high quality studies Equivalent or poorer quality of life, body image, or sexual outcomes in women who had	Search in Medline (using PubMed), PsycINFO, CINAHL and the Cochrane Library 28 studies were included The majority of the studies had limitations (study	SR	Low

					mastectomy with reconstruction, compared with women who had mastectomy only (Rowland 2000, Nissen 2001, Arora 2001, Janz 2005). Postoperative quality of life was poorer for women who had reconstruction, adjusted for preoperative quality of life (Nissen 2001).	design, methodology, selection bias, sensitivity of measures, power, and appropriateness of decisions).		
Yang 2008[237]	NA	Women with stage I or stage II breast cancer	Breast conserving surgery (BCS); n = 5 359 vs. Mastectomy (M); n = 4 038	Overall survival Locoregional recurrence	Three-year overall survival 9 RCTs: 92.8% (BCS) vs. 94.4% (MT) OR (fixed effect model) 0.84, 95% CI 0.63–1.12, p = 0.24 Five-year overall survival 12 RCTs: 82.6% (BCS) vs. 83.5% (MT) OR (fixed effect model) 0.97, 95% CI 0.84–1.11, p = 0.64 Ten-year overall survival 8 RCTs: 69.7% (BCS) vs. 69.3% (MT) OR (fixed effect model) 1.09, 95% CI 0.97–1.23, p = 0.16 Fifteen-year survival 6 RCTs: 56.2% (BCS) vs. 58.6% (MT) OR (random effects model) 0.90, 95% CI 0.80–1.02, p = 0.10	Among RCTs, some authors referred to adopted BCS as quadrantectomy plus axillary dissection, while others adopted tumourectomy plus axillary dissection The methodo-logical quality of several included RCTs was only moderate or poor.	SR and MA of 18 RCTs	Moderate

		Twenty-year OS 5 RCTs: 44.1% (BCS) vs. 45.0% (MT) OR (random effects model) 1.09, 95% CI 0.95–1.25, p = 0.23 Three-year locoregional recurrence rate 5 RCTs: 3.2% (BCS) vs. 1.9% (MT) OR (random effects model) 1.52, 95% CI 0.40–5.69, p = 0.54 Five-year survival locoregional recurrence 10 RCTs: 7.4% (BCS) vs. 7.1% (MT); OR (random effects model) 1.19, 95% CI (0.77–1.85), p = 0.44 Ten-year locoregional recurrence rate 8 RCTs: 10.4% (BCS) compared with 8.0% (MT); OR (random effects model) 1.55, 95% CI (1.05–2.30), p = 0.03 Fifteen-year locoregional recurrence rate 2 RCTs: 7.1% (BCS) vs. 3.6% (MT); OR (random effects model) 1.59, 95% CI (0.84–2.98), p = 0.15 Twenty-year locoregional

					recurrence rate 4 RCTs: 11.6% (BCS) vs. 10.1% (MT); OR (random effects model) 1.89, 95% CI (0.48–7.50), p = 0.37 The subgroup analysis showed that the overall survival in 3, 5, 10, 15 and 20 years and the locoregional recurrence rate in 3, 5, 10 and 20 years were not statistically significantly different between groups for patients with tumors up to 5 cm in diameter. Also the overall survival in 3, 5, 10, 15 and 20 years and the locoregional recurrence rate in 3, 5, 10 and 20 years were not statistically significantly different between groups for patients with tumors 2 cm or smaller			
Blichert-Toft 2008[238]	NA	Women with operable invasive breast carcinoma	Breast conserving surgery (BCS); n = 381 vs. Mastectomy (M); n = 350	Long-term efficacy of BCS vs. M Overall survival (OS) Recurrence free survival (RFS)	Patients with BCS received radiotherapy within 2-4 weeks after surgery In mastectomy group, only high-risk patients received radiotherapy All high-risk patients received adjuvant systemic therapy 10-year recurrence free survival and 20-year overall survival : no significant differences between groups (p=.95 and p=.10 respectively).	Median follow-up time : 19.6 years (17.1 – 23.3 years) Some problems with randomization No blinding	RCT	Moderate

					No differences in recurrences as a first event between groups (p=.27). BCS is as effective as mastectomy regarding tumour control, RFS and OS.			
Petit et al. 2008[239]	April 1997-December 2001	677 patients with invasive breast cancer	Total mastectomy and complete axillary dissection immediate breast reconstruction (IBR) in 518 patients Patey mastectomy without reconstruction (even delayed) in 159 patients (NoIBR)	Disease free survival (DFS) and overall survival (OS)	Median follow up was 70 months (range 15–114) for IBR group and 71 months (range 13–109) for NoIBR group. The local recurrence rate was 5.2% for the group of IBR and 9.4% for the mastectomy group (NoIBR). The regional metastases rate was 1.4 vs. 1.3%. The rate of distant metastases was 13.9 vs. 16.4%. Contra-lateral breast tumor was observed in 1.5 vs. 1.3%. Death rate was 10.4 vs. 16.4%. Overall survival IBR vs. NoIBR: HR 1.03 (95% C.I. 0.61–1.75) Disease-free survival IBR vs. NoIBR: HR 0.99 (95% C.I. 0.67–1.47).	An adjuvant medical treatment was given according to the biological characteristics of the tumor and lymph node status with the same protocol delivered to the two groups. No radiotherapy. Clinical follow up every 6 months (Rx/ year or more, mammo on the contra-lateral breast only and bilateral US examination). Liver, bone and thorax /year with the biological markers. Survival curves were estimated using the Kaplan-Meier method and the Log-rank test + Cox proportional	Case-control study	Low

				hazard regression model		

5.5.3. Surgery to the axilla

Table 36 – Sentinel lymph node biopsy

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 having breast conserving surgery	Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. SLNB is the preferred technique.	Invasive breast cancer SLNB versus axillary clearance or axillary sampling Evidence on SLNB comes both from RCTs and case series studies (Agarwal et al. 2005; Blanchard et al. 2003; BMJ Clinical Evidence 2005; Carlo et al. 2005; Clarke et al. 2004; Cody et al. 1999; Cox. et al. 2000; Cserni et al. 2002; Fleissig et al. 2006; Giuliano et al. 1997; Haid et al. 2002; Imoto et al. 2004; Julian et al. 2004; Katz et al. 2006; Kim et al. 2006; Kokke et al. 2005; Krag et al. 2001 and 2007; Langer et al. 2004, 2005; Leidenius 2004; Lucci et al. 2007; Mansel et al. 2006; Naik et al. 2004; Purushotham et al. 2005; Reitsamer et al. 2004; Rietman et al. 2003; Ung et al. 2004; Veronesi et al. 2003, 2006; Zavagno et al., 2005a, b and 2008). A well conducted systematic review and meta-analysis of 69 studies was undertaken by Kim, Giuliano and Lyman (2006) with data from over 8 000 patients. The overall sentinel lymph node localisation rate was 96.4%, the pooled estimate of FN rate was 7.0%, the mean proportion of patients with positive sentinal lymph nodes was 42% and the post			High

test probability negative was 4.6%.

From other studies, the sentinel lymph node localisation rate ranged from 81.4% to 100% (mean 94.0% and median 94.9%)

The false negative rate of SLNB ranges from 0% to 10.7% (mean 5.8%, median 5.9%)

The accuracy of SLNB ranges from 94.6% to 100% (mean 97.7% with a median of 98.3%)

The prevalence of axillary disease has a mean of 39.1%, median 35.4% and a range from 28.8% to 57.6%.

The evidence on morbidity, including lymphoedema, favours SLNB over axillary clearance.

The ALMANAC RCT and the RCT by Purushotham et al. (2005) found little evidence, by ITT, that a difference exists in psychological morbidity between patients treated by SLNB compared to axillary clearance.

Axillary sampling as staging surgery

15 studies evaluated axillary sampling as staging surgery in early breast cancer: two RCTs (Chetty et al., 2000 and Forrest et al., 1995) and 13 case series studies (Hadjiminas and Burke, 1994; Rampaul et al. 2004; Tanaka et al. 2006; Thompson et al. 1995; Mathew et al. 2006; Sato et al. 2001; Ishikawa et al. 2005; Narredy et al. 2006; Macmillan et al. 2001; Hoar and Stonelake, 2003; Gui et al. 2005; Cserni, 1999 and Kingsmore et al. 2003).

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Langer 2009[240]	January 2000 - December 2003	659 early stage breast cancer patients (pT1 and pT2 ≤ 3 cm, cN0)	SLNB frozen section Reference: Histopathology (H&E and ICT)	identification of SLN macro-metastases	SLN were identified in 98.3% of all patients. The accuracy of frozen section was 90.1%. Se: 70% (95% CI: 63.2% - 73.9%) Sp: 100% (95% CI: 98.9% - 100%) A delayed completion of ALND can be avoided in 98% of these patients. 96% of patients with SLN micro-metastases or isolated tumor cells undergoing delayed completion ALND did not benefit from the second operation as ALND specimens were free of macro-metastases. → the routine use of SLN frozen section in early stage breast cancer patients is recommended.		Prospective study	Low
Canavese 2009[241]	1998 - 2001	248 consecutive patients randomized in 2 arms	SLNB and ALND (ALND arm) SLNB + ALND if SLNB positive (SLNB arm)	Overall survival Axillary recurrence	Diagnostic accuracy of ALND Se: 45%; 95%CI: 25.1% - 67.3% Sp: 85%; 95%CI: 75.7% - 91.2% Risk ratio of SNB vs ALND RR=0.87; 95%CI 0.38 – 2.01	Non-inferiority trial having to analyze 2750 patients → underpowered study	RCT	Moderate

					5-year Event free survival ALND arm: 89.8% (95%CI: 86.9%-92.7%) SLNB arm: 94.5% (95% CI: 90.9% - 98.1%) Log rank p = 0.715 5-year overall survival ALND arm: 97.2% (95%CI: 95.4% - 92.7%) SLNB arm: 97.2% (95%CI: 95.4% - 92.7%) Log rank p = 0.697	The diagnostic accuracy is uncorrectly reported in the paper Median follow-up: 5.5 ± 1.4 years		
Motomura 2008[242]	January 2000 – September 2006	631 consecutive patients with clinical T1 breast cancer with clinically negative nodes	SLNB If positive intraoperatively → immediate ALND If positive by final pathologic results → subsequent ALND Reference: Histopathology (H&E / H&E and ICT)	Accuracy of imprint cytology for the intra-operative diagnosis of sentinel node metastases	Imprint cytology for the diagnosis of sentinel node metastases Se: 84.6% (95%CI: 77% - 90.1%) Sp: 96.6% (95%CI: 94.5% - 97.1%) Overall accuracy: 94.1% Only 20 (3.2%) patients required a second axillary operation in the present study.	Patients with multiple primary tumors, nonpalpable breast cancer, prior axillary surgery, or pregnancy were excluded.	Prospective study	Low

Table 37 – Evidence table of RCTs regarding the effect of sentinel lymph node dissection (without further axillary surgery) versus axillary lymph node dissection in women with breast cancer and a positive sentinel lymph node

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
The American College of Surgeons Oncology Group Z0011 trial, addressed by: Lucci 2007 Giuliano 2010 Giuliano 2011[3]	• **Design**: RCT • **Source of funding**: National Cancer Institute • **Setting**: Multicenter • **Sample size**: n=891 • **Duration**: patient enrollment from May 1999 to December 2004. Targeted enrolment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected. • **Follow-up** : Patients were assessed for disease recurrence by history and physical examination (every 6 months for the first 36 months and yearly thereafter) and annual mammography. Other testing was based on symptoms and investigator preference. Median follow-up of 6.3 years (last follow-up, March 4, 2010)	• **Eligibility criteria:** women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. • **Exclusion criteria:** women were excluded if they were pregnant or lactating, were treated with neoadjuvant chemo- or hormonal therapy, had bilateral breast cancer, multicentric disease, a history of ipsilateral axillary surgery, prepectoral implants, or medical contraindications to ALND. Patients with matted nodes or gross extranodal disease at the time of SLND were excluded as were patients with 3 or more involved SLNs. • **Patient**	**Group 1**: Sentinel lymph node dissection (SLND) only (no further axillary surgery) versus **Group 2** : SLND and axillary lymph node dissection (ALND) 1. SLND was performed with isosulfan blue, a radio-pharmaceutical or both. 2. All patients underwent breast conservation therapy and whole breast irradiation.	**Overall survival (OS) at a median follow-up of 6.3 years** (with a non-inferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is non-inferior to ALND) Group 1: 42 deaths Group 2: 52 deaths HR = 0.79 (90% CI 0.56 to 1.10), which did not cross the pre-specified boundary of 1.3 *NOTE: a 2-sided 90% CI corresponds to a 1-sided significance level of 0.05. If the 90% CI for the HR was below 1.3, this would indicate that patients undergoing SLND alone do not have an unacceptably worse overall survival than patients undergoing SLND plus ALND.* **5-year overall survival (OS)** Group 1 92.5% Group 2 91.8% HR (adjusted for adjuvant therapy (chemotherapy, endocrine therapy, and/or radiation therapy) and age) = 0.87 (90% CI 0.62 to 1.23) **5-year disease-free survival (DFS)** Group 1: 83.9% Group 2: 82.2% HR (unadjusted) = 0.82 (95% CI 0.58 to	**Results critical appraisal**: low risk of selection bias, attrition bias, reporting bias and other bias. High risk of performance bias and detection bias for all outcomes, except OS and DFS which are unlikely to be influenced by knowledge of the assigned treatment **Dropouts:** Of the 891, 70 were excluded: 26 withdrew consent before surgery; 11 had nodes not positive on examination of HE-stained samples; seven had too many positive SLNs; four had distant metastatic disease; three did not have clear margins; two had gross extracapsular invasion; and 17 others were excluded for unique reasons. However, ITT was used in result analysis

	characteristics: – Group 1: n= 436 – Group 2: n= 420 – Median age (range): 56 (24-92) vs. 54 (25-90); – Clinical T stage: T1: 284 (67.9%) vs. 303 (70.6%), T2: 134 (32.1%) vs.126 (29.4%) – Micrometastases in SLNs: 164/366 (44.8%) vs. 137/365 (37.5%) • Disease characteristics were well balanced between the 2 groups (T stage, tumour size, receptor status for estrogen and progesterone, LVI, Bloom-Richardson score, tumour type).	1.17) HR (adjusted for adjuvant therapy (chemotherapy, endocrine therapy, and/or radiation therapy) and age) = 0.88 (95% CI 0.62 to 1.25) **Local / regional recurrence** *Local recurrence after median follow-up of 6.3 years*: Group 1: 8/436 (1.8%) Group 2: 15/420 (3.6%) RR= 0.51 (95% CI 0.22 to 1.20) *At 5 years:* Group 1: 7/436 (1.6%) Group 2: 13/420 (3.1%) RR= 0.52 (95% CI 0.21 to 1.29) *Regional recurrences in ipsilateral axilla*: Group 1: 4/436 (0.9%) Group 2: 2/420 (0.5%) RR= 1.93 (95% CI 0.35 to 10.46) Median time of local recurrence-free survival and regional recurrence-free survival was not reached in either group and did not differ between the arms. *5-year locoregional recurrence–free survival* Group 1: 96.7% Group 2: 95.7% (P=0.28). Recurrence in 'Treatment received' sample*:

Locoregional recurrence:
Group 1: 12/425 (2.8%)
Group 2: 16/388 (4.1%)
RR= 0.68 (95% CI 0.33 to 1.43)

Local recurrence:
Group 1: 8/425 (1.9%)
Group 2: 14/388 (3.6%)
RR= 0.52 (95% CI 0.22 to 1.23)

Regional recurrence:
Group 1: 4/425 (0.9%)
Group 2: 2/388 (0.5%)
RR= 1.83 (95% CI 0.34 to 9.91)

Arm morbidity
Wound infections at 30 days
Group 1: 11/371
Group 2: 31/373
RR= 0.36 (95% CI 0.18 to 0.70)

Axillary seromas at 30 days
Group 1: 21/371
Group 2: 53/373
RR= 0.40 (95% CI 0.25 to 0.65)

Axillary paresthesias
At 30 days:
Group 1: 43/371
Group 2: 174/373
RR= 0.25 (95% CI 0.18 to 0.34)

At 6 months:
Group 1: 35/288
Group 2: 146/335
RR=0.28 (95% CI 0.20 to 0.39)

At 12 months:
Group 1: 24/268
Group 2: 113/287
RR= 0.23 (95% CI 0.15 to 0.34)

Lymphedema (reported subjectively)
At 6 months:
Group 1: 19/339
Group 2: 27/327
RR= 0.68 (95% CI 0.39 to 1.20)

At 12 months:
Group 1: 16/268
Group 2: 37/288
RR= 0.46 (95% CI 0.26 to 0.82)

After 12 months:
Group 1: 14/253
Group 2: 52/272
RR= 0.29 (95% CI 0.16 to 0.51)

Lymphedema (by arm measurements)
At 30 days:
Group 1: 17/272
Group 2: 23/255
RR= 0.69 (95% CI 0.38 to 1.27)

				At 6 months: Group 1: 21/271 Group 2: 29/270 RR= 0.72 (95% CI 0.42 to 1.23) At 12 months: Group 1: 14/226 Group 2: 26/242 RR = 0.58 (95% CI 0.31 to 1.08) *Brachial plexus injury (BPI)* "Eighteen BPIs were reported originally, but after each injury was re-evaluated, it was discovered that 10 would have been more accurately classified as axillary paresthesias. Three BPIs occurred after SLND alone, but all of these had resolved at last follow-up, as had 88% of all BPIs." **Quality of life** Not addressed.

** Thirty-two women in the ALND group did not have ALND and 11 women in the SLND-alone group had ALND. Therefore, the treatment-received sample consisted of 388 women who indeed did receive ALND and 425 women who indeed did receive SLND alone. The primary analyses were performed on the intent-to-treat sample, and all were repeated for the treatment received sample. Both analyses yielded similar results with no significant change in results.*

Table 38 – Evidence table of observational studies regarding the effect of sentinel lymph node dissection (without further axillary surgery) versus axillary lymph node dissection in women with breast cancer and a positive sentinel lymph node

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Bilimoria 2009[20]	• **Design**: Retrospective cohort study • **Source of funding**: Supported in part by the American College of Surgeons, the Commission on Cancer, and the American Cancer Society (National Cancer Data Base); and by the American College of Surgeons, Clinical Scholars in Residence Program • **Setting**: hospital (Commission on Cancer-approved hospitals, US) • **Sample size**: N=97 314 (macroM+=87 055; microM+=10 259) • **Duration**: 1998-2005 • **Follow-up**: 5 years after diagnosis • **Statistical analysis**: Cox proportional hazards models • Analysis for time to recurrence or death was adjusted for age, T classification, tumour grade, margin status, chemotherapy administration, radiation treatment, hormonal therapy administration, and hospital type.	• **Eligibility criteria**: o T1-3 non-metastatic primary breast cancer o No neoadjuvant chemotherapy o Surgically treated (BCS or mastectomy) o No clinically apparent nodal involvement or only internal mammary nodal M+ • **Exclusion criteria**: o Neo-adjuvant treatment o ALND only o no or unspecified LN evaluation • **Characteristics and group comparability of patients (entire cohort)** %T1: 63% vs. 49% %BCS: 81.% vs. 49.6% % mastectomy: 18.6% vs. 50.4%	**Group 1: SLNB alone (with reported nodal evaluation)** - microscopic M+: N=530 - macroscopic M+: N=1 673 vs. **Group 2: SLNB with completion ALND (with reported nodal evaluation)** - microscopic M+: N=2 357 - macroscopic M+: N=18 617	• **Survival (Kaplan-Meier)**: ***Macrometastases*** o Observed 5-year: ▪ N:1185 /1458 vs. 15229/18617 ▪ 81.3% (79.1-83.6) vs. 81.8% (81.2-82.4), p=0.63 o Unadjusted HR: 0.97 (95% CI 0.85-1.11) o Adjusted HR: 0.89 (95% CI 0.76-1.04) ***Micrometastases*** o Observed 5-year: ▪ N: 470/530 vs. 1 521/1 673 ▪ 88.6% (85.6-91.6) vs. 90.9% (89.3-92.4), p=0.16 o Unadjusted HR: 0.79 (95% CI 0.57-1.10) o Adjusted HR: 0.84 (95% CI 0.60-1.19) • **Axillary recurrence rate**: ***Macrometastases*** o 1.2% (0.5-1.8) vs. 1.0% (0.8-1.1), p=0.40 o Unadjusted HR: 0.79 (0.46-1.37), p=0.40 o Adjusted HR: 0.58 (0.32-1.06), p=0.076 ***Micrometastases*** o 0.6% (0.0-1.3) vs. 0.2% (0.0-0.4), p=0.0.063	**Results critical appraisal**: • Large and relevant cohort • Methodological flaws: retrospective design, no blinded evaluation of outcomes • Only patients diagnosed in 1998-2000 with follow-up reported in 2004-2006 were used in the outcomes analyses • Median follow-up was 64 months for the SLNB-alone cohort and 62 months for the SLNB-with–completion ALND cohort

				Sensitivity analysis for patients with T1 or T2 tumours who were undergoing breast conservation surgery with adjuvant radiation (with or without chemotherapy): no significant differences in axillary recurrence or survival for SLNB alone (five or fewer nodes) versus SLNB with completion ALND (nine or more nodes) (exact data not provided)	
Bulte 2009[21]	• **Design:** Prospective study • **Source of funding**: No information on funding • **Setting**: hospital (7 centres in the Netherlands) • **Sample size**: N=541 (micrometastasis: N=38) • **Duration**: 01/2002-12/2003	• **Eligibility criteria**: o T1-2 breast carcinoma o Staged with SLNB • **Exclusion criteria**: o only in situ carcinoma, tumours >5 cm, cN+, multifocal disease, neoadjuvant therapy, ALND • **Characteristics and group comparability of patients (entire cohort)** • Mean age: 58 years • %T1: 71% • %ER+/PgR+ = 60% • No adjuvant CT : 78% • No adjuvant hormonal therapy: 76% • After BCS, patients received RT (50 Gy) + boost if indicated	**Group 1:** SLNB alone (N=20) vs. **Group 2:** SLNB with completion ALND (N=18)	• **Axillary recurrence rate**: No axillary recurrences in group with micrometastasis	**Results critical appraisal**: • Large and relevant cohort but small subgroup with micronodal involvement • Multisetting study: uniform protocol for SN staging • Methodological flaws: no blinded evaluation of outcomes, no risk-adjustment • Median follow-up: 46 months (range 11-64 months)
Calhoun 2005[22]	• **Design**: Prospective cohort study • **Source of funding**: No information on funding • **Setting**: hospital (US) • **Sample size**: N=78 • **Duration**: 01/1995-	• **Eligibility criteria**: patients with invasive breast cancer and sentinel LNs positive for ITC • **Characteristics and group comparability** of patients with ITC not specified	**Group 1:** SLNB alone (N=17) vs.	• **Axillary recurrence rate**: After mean follow-up of 80.5 months, no patient with an ITC-positive SLN had experienced an axillary recurrence, regardless of whether or not ALND was performed	**Results critical appraisal**: • Methodological flaws: outcomes not clearly defined, no blinded

	12/1999	• %T1: SLNB alone 65%	**Group 2:** SLNB with completion ALND (N=61)		evaluation of outcomes, no risk-adjustment
Cortesi 2012[23]	• **Design:** Retrospective analysis of prospective database (Modena Cancer Registry - Italy) • **Source of funding**: not stated • **Setting**: multicenter ? • **Sample size**: 590 women with positive SLN (N0i+: 31; N1mi: 176; N1: 378; N2: 5) • **Duration**: 01/2000-12/2008 • **Follow-up**: median follow-up of 48.6 months after diagnosis (1 – 120 months) • **Statistical analysis**: Cox proportional hazards models •	• **Eligibility criteria**: T1–T2 invasive breast cancers and clinically negative (N0–N1) axillary nodes. • **Exclusion criteria:** patients with palpable lymph nodes in axilla and/or inflammatory breast cancer, pregnancy, feeding and neo-adjuvant treatments • **Comparability of the groups:** o SLNB alone: hormonotherapy 68.5%, chemo 9.7%, both 8.7%, none 13.1% o SLNB + ALND: hormonotherapy 36.1%, chemo 16%, both 45.1%, none 2.8%	**Group 1**: SLNB alone N1mi: 34/176 (19.3%) **Group 2**: SLNB + ALND N1mi: 142/176 (80.7%)	• **Survival (Kaplan-Meier)**: ***Micrometastases*** o Overall survival 5-year: 96% vs. 96% o No differences between patients who had only one positive node (114) and patients who had additional positive nodes (28) • **Axillary recurrence rate**: ***Micrometastases*** o 0 (0%) vs. 0 (0%)	**Results critical appraisal**: • Large cohort • Methodological flaws: retrospective analysis of population-based registry, no blinded evaluation of outcomes • Median follow-up was 48.6 months (range, 1–120).
Fan 2005[24]	• **Design**: Retrospective study • **Funding**: not stated • **Setting**: hospital (US) • **Sample size**: N=390 (114 with positive SLN: 45 patients with micrometastases and 69 with macrometastases) • **Duration**: 11/1997-11/2002	• **Patient eligibility criteria**: o Patients with histologically confirmed primary breast carcinoma undergoing SLNB • **Exclusion criteria**: neoadjuvant treatment, noninvasive cancer, recurrent disease, failed preoperative lymphoscintigraphy • **Characteristics of patients** (entire cohort): median age 51.7, mean tumor size 19.1 mm	**Group 1:** SLNB alone (N=38) MicroM+ : 27 MacroM+: 11 vs. **Group 2:** SLNB with completion ALND (N=76) MicroM+ : 18 MacroM+ : 58	• **Axillary Recurrence** ***Micrometastasis*** 1 vs. 0 (0.037% vs. 0%) ***Macrometastasis*** 0 vs. 6 (0% vs.10%)	**Results critical appraisal**: • Large and relevant cohort • Methodological flaws: retrospective design, no blinded evaluation of outcomes, no clear definition of outcomes, no risk-adjustment • Median follow-up: 34.7 months

Giobuin 2009[25]	• **Design**: Retrospective study • **Funding**: not stated • **Setting**: hospital (Ireland) • **Sample size**: N=1076 in total; N1mi: N=15; N0[i+]: N=34 • **Duration**: 01/2000-12/2006	• **Patients eligibility criteria**: patients with invasive breast cancer and clinically negative nodes that underwent SLNB • No group comparison for patients with N1mi • **Group comparison N0[i+]**: mean tumour size SLNB alone 18 mm, SLNB + ALND 32 mm • Mean tumour size N1mi: 19 mm	N0[i+]: **Group 1:** SLNB alone (N=18) vs. **Group 2**: SLNB with completion ALND (N=16) Note: All patients with N1mi underwent ALND	• **Axillary Recurrence** No axillary recurrence in the group of N0[i+], irrespective of treatment with ALND • **Cancer-related death** No cancer-related death in both groups	**Results critical appraisal**: • Methodological flaws: retrospective study, no blinded evaluation of outcomes, no risk-adjustment, outcomes not clearly defined • Median follow-up: 27 months (range 12-72 months)
Pepels 2012[26]	• **Design:** Retrospective analysis of prospective database (MIRROR Study) • **Source of funding**: • **Setting**: 113 hospitals (The Netherlands) • **Sample size**: 2680 women (negative SN: 857; N0[i+]: 795; N1mi: 1028 • **Duration**: 1997-2005	• **Eligibility criteria**: patients with early-stage breast cancer irrespective of their histology who underwent surgery and SLNB, with following characteristics: tumor size of 1 cm or smaller, irrespective of grade, or tumor size 1 to 3 cm and grade 1 or 2 • **Exclusion criteria**: SLN or non-SLN macrometastases	**Group 1**: SLNB alone N0[i+]: 345/795 (43.4%) N1mi: 141/1028 (13.7%) **Group 2**: SLNB + ALND N0[i+]: 396/795 (49.8%) N1mi: 793/1028 (77.1%) **Group 3** (not studied here) SLNB + RT	• **5 year regional recurrence rate** (involving axilla and infra- and supraclavicular sites) ***N0[i+]:*** 2% (7/345) vs. 1% (4/396) The adjusted HR for regional recurrence among SLNB only women was 2.39 (95% CI, 0.67–8.48) as compared with women who did receive axillary treatment (ALND or RT). ***N1mi:*** 5.6% (8/141) vs. 1% (8/793) The adjusted HR for regional recurrence among SLNB only women was 4.39 (95% CI, 1.46–13.24) as compared with women who did receive axillary treatment (ALND or RT).	**Results critical appraisal**: • Large cohort • Methodological flaws: retrospective analysis of prospective database, no blinded evaluation of outcomes • Median follow-up was 5.1 years (range, 0.04–9.3). • 3.5% patients were lost to follow-up 0.04 to 5.6 years after diagnosis • Adjusted HR for age, tumor size, histological grade, hormone receptor status, adjuvant systemic therapy, and irradiation of the breast

Wasif 2010[27]	• **Design:** Retrospective study • **Source of funding**: Gonda (Goldschmied) Research Laboratories of the John Wayne Cancer Institute at Saint John's Health Center; QVC and the Fashion Footwear Association of New York Charitable Foundation; the Margie and Robert E. Petersen Foundation; Mrs Lois Rosen; the Associates for Breast and Prostate Cancer Studies; the Family of Robert Novick; the Ruth and Martin H. Weil Fund; and the Wrather Family Foundation • **Setting**: hospital (population-based, US) • **Sample size**: N=5353 patients with micrometastases • **Duration**: 1998-2005 • **Median follow-up**: 36 months	• **Eligibility criteria**: o histologically confirmed infiltrating ductal carcinoma and infiltrating lobular carcinoma of the breast o SLNB performed o sentinel node micrometastasis o breast conserving surgery o no distant metastases o females • **Patient characteristics**: o Mean age: 58.1 years o Histology : invasive ductal 78.5%, invasive lobular 21.5% • **Group comparability**: significantly different as to age, grade and number of LN examined	**Group 1**: SLNB alone (N=2160) vs. **Group 2**: SLNB and completion ALND (N=3193)	• **5-year overall survival (Kaplan Meier)** 89% vs. 90%, p=0.98 (despite the 20.6% of patients with additional involved non-sentinel LN on ALND)	**Results critical appraisal**: • Large and relevant cohort • Methodological flaws: retrospective study, no blinded evaluation of outcomes • No multivariate correction of survival analysis
Yi 2010[28]	• **Design:** Retrospective analysis of prospective database (SEER database from 17 US cancer registries) • **Source of funding**: not stated • **Setting**: 17 US cancer registries • **Sample size**: 26 986 women (N1mi: 6838; macroM+: 20148)	• **Eligibility criteria**: women older than 18 years diagnosed with primary breast cancer, with positive lymph node on SLNB • **Exclusion criteria**: ALND only (without SLNB), no lymph node evaluation or evaluation status not specified in SEER data, no primary surgery, stage IV disease, follow-up time <24	**Group 1**: SLNB alone N1mi: 2240/6838 (32.7%) MacroM+: 2185/20148 (10.8%) **Group 2**: SLNB + ALND N1mi: 4598/6838	• **Survival (Kaplan-Meier)**: ***All positive SLN*** o Overall survival: HR: 1.0 (0.9-1.2), p=0.6 ***Micrometastases only*** o Overall survival: HR: 1.2 (0.90-1.7), p=0.3 • **Ipsilateral regional recurrence**	**Results critical appraisal**: • Large and relevant cohort • Methodological flaws: retrospective design, no blinded evaluation of outcomes • Patients diagnosed in 1998-2004 with follow-up reported on 30

	• **Duration**: 01/1998-11/2004 • **Follow-up**: median follow-up of 50 months after diagnosis • **Statistical analysis**: Cox proportional hazards models	months • Group comparability: o SLNB alone: median age 59 years; median tumor size: 16 mm; tumor grade: 21% low/intermediate; BCS: 78.8%; median number of lymph nodes removed: 3; %T1: 67.5%; Nmi: 50.6% o SLNB + ALND: median age 56 years; median tumor size: 20 mm; tumor grade: 13.3% high grade; median number of lymph nodes removed: 13; %T1: 52.1%; N1mi:20.4%	(67.3%) MacroM+: 17963/20148 (89.2%)	***Macrometastases*** o 0.2% vs. 0.08%; HR 0.30 (p=0.02) ***Micrometastases*** o no statistical difference	November 2006 were used in the outcomes analyses • Median follow-up was 50 months • Cancer registries did not contain data regarding recurrence; the use of ipsilateral regional events after surgery as one of our outcomes instead of axillary recurrence
Yi 2013[29]	• **Design**: Retrospective cohort study • **Source of funding**: not stated • **Setting**: hospital (MD Anderson Cancer Center, US) • **Sample size**: N=861 (macroM+=567; microM+=294) • **Duration**: 1994-2009 • **Follow-up**: 10 years after diagnosis • **Statistical analysis**: Cox proportional hazards models	• **Eligibility criteria**: o T1/T2, N0 patients with 1 or 2 positive SLNs identified by frozen section, touch preparation, or hematoxylin and eosin (H&E) staining of permanent sections o Surgically treated (BCS or mastectomy) • **Exclusion criteria**: o Patients with positive SLNs identified by immune-histochemistry (IHC) o Patients who were lost to follow-up within 1 year after surgery • **Characteristics and group comparability of patients (entire cohort)** %T1: 80.9% vs. 66.1%	**Group 1: SLNB alone** - microscopic M+: N=136 - macroscopic M+: N=52 vs. **Group 2: SLNB with completion ALND** - microscopic M+: N=158 - macroscopic M+: N=515	• **Survival (Kaplan-Meier)**: ***Entire cohort*** o Overall survival 5-year: 95.5% vs. 94.3% o Overall survival 10-year: 92.5% vs. 81.9% o Disease-free survival 5-year: 98% vs. 95.7% o Disease-free survival 10-year: 82.5% vs. 80.2% • **Axillary recurrence rate**: ***Entire cohort*** o 0 (0%) vs. 11 (1.6%) Sensitivity analysis for patients with Breast conserving surgery (n=449; SLNB:121 vs. ALND:328)	**Results critical appraisal**: • Large and relevant cohort • Methodological flaws: retrospective design, no blinded evaluation of outcomes • Median follow-up was 5.5 years (1.2-11.2) for the SLNB-alone cohort and 4.9 years (1-17.1) for the SLNB-with–completion ALND cohort

	%BCS: 64.4% vs. 48.7% % mastectomy: 35.6% vs. 51.3%	• **Survival (Kaplan-Meier)**: ***Entire cohort*** o Overall survival 5-year: 95.9% vs. 95.2% o Overall survival 10-year: 93.8% vs. 81.7% o Disease-free survival 5-year: 94.3% (91.1-98%) vs. 93.8% (91.4-95.5%) Unadjusted HR: 0.3 (0.1-1.01; p=0.052) Adjusted HR (T stage, age, adjuvant treatment): 0.3 (0.1-1.1; p=0.06) o Disease-free survival 10-year: 94% vs. 88.6% • **Axillary recurrence rate**: ***Entire cohort*** o 0 (0%) vs. 7 (2.1%)

Abbreviations: 95%CI: 95 percent confidence intervals; ALND: axillary lymph node dissection; CK-IHC: cytokeratin immunohistochemical staining; DFS: disease-free survival; HR: hazard ratio; IHC: immunohistochemical; ITC: isolated tumour cells; LN: lymph node; LVI: lymphovascular invasion; M+: metastases; N0[i+]: negative node by standard examination, but positive by CK-IHC staining; N0[i-]: negative node by standard examination and CK-IHC staining; N1mi: micrometastatic node by standard examination; OS: overall survival; SLNB: sentinel lymph node biopsy; US: United States

5.5.4. Adjuvant therapy

Table 39 – Sequencing of adjuvant planning

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
All patients with early invasive breast cancer						
NICE 2009[227]	July 2008	Women with early invasive breast cancer	Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded. Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient.	GDG consensus and expert position		Low
All patients with early breast cancer						
NICE 2009[227]	July 2008	Women with early breast cancer	Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments.	Sequencing of adjuvant therapies Concurrent adjuvant chemotherapy/ radiotherapy versus chemotherapy followed by radiotherapy: High-quality evidence from RCTs (Hickey et al. 2006; Calais et al. 2005) no difference in terms of local recurrence [OR (concurrent: sequential) 1.30; 95% CI 0.45 to 3.77; p=0.63], distant metastases [OR (concurrent:sequential) 1.43 95% CI 0.86 to 2.37, p=0.16] and overall survival. no difference with regard to some toxic		High

		effects [fever (OR 1.27, 95% CI 0.79 to 2.03, p=NS), cardiac complications (OR 1.73, 95% CI 0.50 to 5.96, p= NS), neutrophil toxicity (OR 0.89, 95% CI 0.63 to 1.27, p= NS) or platelet toxicity (OR 0.89, 95% CI 0.39 to 2.06, p=NS)]; oesophageal toxicity (OR 1.44, 95% CI 1.03 to 2.02, p=0.03), haematological toxicity (OR 1.43, 95% CI 1.01 to 2.03, p = 0.04) and skin toxicity (OR 1.46, 95% CI 1.00-2.14), p=0.05) were significantly lower with sequential therapy; nausea and vomiting was significantly less common with concurrent therapy (OR 0.70, 95% CI 0.50 to 0.98, p= 0.04) Late toxic effects (subcutaneous fibrosis, telengectasia, skin pigmentation, and breast atrophy) are more common following concurrent therapy than sequential therapy. in the subgroup of lymph node-positive patients, local recurrence-free survival is higher following concurrent therapy than sequential therapy (p<0.035). Subsequent RCT (Toledano et al., 2007): no statistically significant differences between the sequential therapy group and the concurrent therapy group in 5-year rates of disease-free survival (80% and 80% respectively; p=0.83, Log-rank test), recurrence-free survival (92% and 95% respectively; p=0.76, Log-rank test)	

and overall survival (90% and 91% respectively; p=0.76, Log-rank test).

no difference in local recurrence-free survival in the node-negative subgroup of patients between the sequential therapy group (93%) and the concurrent therapy group (93%; p=0.81, Log-rank test).

in the node-positive subgroup local recurrence-free survival was statistically significantly worse in the sequential therapy group (91%) compared to the concurrent therapy group (97%; p=0.02, Log-rank test; HR 0.61, 95% CI 0.38-0.93).

Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy:

RCT evidence (Hickey et al. 2006):

no difference in terms of distant metastases [HR (RT first:CT first) 0.82, 95% CI 0.49 to 1.36, p=0.44] and overall survival [HR (RT first:CT first) 0.85, 95% CI 0.51 to 1.40, p=0.52].

higher rate of neutropenic sepsis in patients who receive radiotherapy before chemotherapy [OR (RT first: CT first) 2.96, 95% CI 1.26 to 6.98, p=0.02]

no difference for other toxicity outcomes [skin toxicity [OR (RT first: CT first) 1.48, 95% CI 0.68 to 3.26, p=NS], subcutaneous toxicity [OR (RT first: CT first) 2.05, 95% CI 0.50 to 8.40, p=NS], pneumonitis [OR (RT first: CT first) 11.47, 95% CI 0.63 to 209.7,

p=NS], lymphoedema [OR (RT first: CT first) 0.11, 95% CI 0.01 to 2.02, p=NS] and brachial plexopathy [OR (RT first: CT first) 3.02, 95% CI 0.12 to 74.98, p=NS].

However, treatments in the included trials were given a decade ago on average (based on CMF) and the chemotherapy regimens may not be considered optimal today. Secondly, surgical outcomes in the trials might be considered unacceptable today. There is currently no information regarding the optimum sequencing of radiotherapy with taxanes or with trastuzumab.

Early versus late chemotherapy:

RCT evidence from the International Breast Cancer Study Group (1997) suggests there is no difference in 5-year disease-free survival or overall survival arising from early chemotherapy given over the first three months following surgery versus delayed chemotherapy given between 9 and 15 months following surgery.

Interval between surgery and start of adjuvant therapy

Interval from surgery to radiotherapy:

Disease-free and overall survival were not adversely affected by increasing delay to the start of radiotherapy in the first three months after surgery (Benchalal et al. 2005; Jobsen et al.

			2006 and Mikeljevic et al. 2004) whereas overall survival was adversely affected in those whose radiotherapy was delayed for at least 5 to 6 months after surgery (Mikeljevic et al. 2004). Interval from surgery to chemotherapy: Increasing delay to the start of adjuvant chemotherapy in the first 3 months after surgery was not associated with poorer disease-free or overall survival (Cold et al. 2005; Colleoni et al. 2000; Lohrisch et al. 2006; Sanchez et al. 2007 and Shannon et al. 2003). Colleoni et al. (2000) reported that disease-free survival was adversely affected by delays of three or more weeks in the sub-group of women with ERnegative disease. Another study reported that disease-free and overall survival were adversely affected only when the start of chemotherapy was delayed until at least three to six months after surgery (Lohrisch et al., 2006).

5.5.5. Radiotherapy

Table 40 – Radiotherapy for early invasive breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Breast conserving surgery						
NICE 2009[227]	July 2008	Women with early invasive breast cancer	Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.	Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Clarke et al. 2005) + additional data (Liljegren 2002; Rutqvist et al. 2003 and Vinh-Hung and Verschraegen 2004). One RCT (Ford et al. 2006) and one retrospective cohort study from the US SEER database (Vinh-Hung et al. 2003). *Cosmetic outcomes* Two systematic reviews reported (Liljegren 2002 and Mul et al. 2007), one RCT (Johansen et al. 2002) and one non-randomised study (Duetsch and Flickinger, 2003). *Quality of life outcomes* RCTs (Lee et al. 2008; Rayan et al. 2003 and Whelan et al. 2000), a survey (Back et al. 2005). Four guidelines: two Canadian (Shelley and Trudeau 2002 and Whelan et al. 2003), one American (Morrow et al. 2002) and one recent German DEGRO guideline (Sautter-Bihl et al. 2007). → postoperative radiation decreased the risk of local recurrence + moderate reduction in breast		High

				cancer deaths and overall mortality after 15 years.	
Post-Mamectomy Radiotherapy					
NICE 2009[227]	July 2008	Women with early invasive breast cancer	Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins. Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40 years. Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).	Meta-analyses of RCTs: EBCTCG (Clarke et al. 2005), Gebski et al. 2006; Killander et al. 2007; Kyndi et al. 2008 and Whelan et al. 2000. Danish Breast Cancer Cooperative Group (Nielsen et al. 2006 and Overgaard et al. 2007) Van de Steene et al. 2000; Bartelink 2000; Bellon et al. 2006; Fisher et al. 2002; Gustavsson et al. 1999; Hojris et al. 2000; Hojris et al. 1999; Recht et al. 2001; et al. Smith 2006 and Truong 2004. Loco-regional recurrence Reduction of locoregional recurrence. The absolute reduction in local recurrence was greater in lymph node-positive than lymph node-negative disease (17% versus 4%). Mortality Reduction in 15 year all cause mortality of 4.2% (for lymph node-negative) and 4.4% (for lymph node-positive). Prognostic factors for survival Significant factors reducing survival	High

				were a tumour size > 21 mm), number of involved lymph nodes, extracapsular invasion, and site of local recurrence (Nielsen et al. 2006).	
Dose fractionation					
NICE 2009[227]	July 2008	Women with early invasive breast cancer	Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.	Systematic reviews compared hypofractionated radiotherapy with no radiotherapy (EBCTCG 2002 and Gebski et al., 2006). RCT (Owen et al., 2006; START A and B 2008; Whelan et al., 2002 and Yarnold et al., 2005). Trials (Bates 1998; Goel et al., 2000 and Taher et al., 2004). Rates of local recurrence No difference between conventional 50 Gy fractions and hypofractionated schedules Distant relapse Lower in the hypofractionated schedules Rates of disease-free survival and overall survival Improved in the hypofractionated schedules Cosmetic outcomes Less consistent results	High

Breast boost					
NICE 2009[227]	July 2008	Women with early invasive breast cancer	Offer an external beam boost to the site of local excision to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy. If an external beam boost to the site of local excision following breast conserving surgery is being considered in patients with early invasive breast cancer, inform the patient of the side effects associated with this intervention, including poor cosmesis, particularly in women with larger breasts.	RCTs (EORTC 22881-10882; Poortmans et al. 2004) and non-randomised studies → a boost dose to the tumour bed reduced local recurrence but had little effect on overall survival A joint SR on cost effectiveness of radiotherapy + external beam radiotherapy boost to the site of local excision after breast conserving surgery. the addition of a radiotherapy boost after breast conserving surgery and radiotherapy on early breast cancer patients with stage 1 and 2 tumours and negative margins does not seem to be cost effective	High
Radiotherapy to nodal areas					
NICE 2009[227]	July 2008	Women with early invasive breast cancer	Do not offer adjuvant radiotherapy to the axilla or supraclavicular fossa to patients with early breast cancer who have been shown to be histologically lymph node negative. Do not offer adjuvant radiotherapy to the axilla after ALND for early breast cancer. If ALND is not possible following a positive axillary SLNB or four-node sample, offer adjuvant radiotherapy to the axilla to patients with early breast cancer. Offer adjuvant radiotherapy to the supraclavicular fossa in patients with early	Studies comparing surgery and regional lymph node irradiation with mastectomy and axillary dissection or mastectomy only (Fisher et al., 2002; Overgaard et al., 1999; Ragaz et al., 2005 and Wallgren et al., 1986); Studies comparing breast conserving surgery with or without axillary dissection or axillary radiotherapy (Louis-Sylvestre et al., 2004; Pejavar et al., 2006, and Veronesi et al., 2005);	

	breast cancer and four or more involved axillary lymph nodes. Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status. Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery.	Studies applying radiation to the internal mammary lymph nodes (Arriagada et al., 1988; Grabenbauer 2004; Kaija and Maunu 1995; Obedian and Haffty 1999; Vinod and Pendlebury, 1999); Retrospective studies (Livi et al. 2006; Grills et al. 2003; Fortin et al. 2006 and Tai et al. 2007).

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
James 2008[243]	June-November 2006	Women with early breast cancer who had undergone breast conserving surgery.	Unconventional versus conventional fractionation	(1) local-recurrence free survival (2) breast appearance (3) survival at five years (4) late skin toxicity at 5 years	Unconventional fractionation (delivering radiation therapy in larger amounts each day but over fewer days than with conventional fractionation) did not appear to affect: local-recurrence free survival (absolute difference 0.4%, 95% CI -1.5% to 2.4%), breast appearance (risk ratio (RR) 1.01, 95% CI 0.88 to 1.17), survival at five years (RR 0.97, 95% CI 0.78 to 1.19), late skin toxicity at five years (RR 0.99, 95% CI 0.44 to 2.22), late radiation toxicity in sub-cutaneous tissue (RR 1.0, 95% CI 0.78 to 1.28).	Two RCTs were included and reported on 2 644 women (Owen et al., 2006; Whelan et al., 2002) Both RCTs were included in NICE 2009	SR	High
Holli 2009[244]	NA	Women > 40 years having ≤20 mm, node negative, PgR positive (n=264)	Breast irradiation Vs. not after BCS and ALND		Time to local recurrence HR 0.36; 95%CI 0.20 - 0.65; p = 0.0007 Overall survival HR 0.63; 95% CI 0.35 to 1.12; p= 0.11	Randomisation computer program No blinding ITT analysis Median FU of 12.1 years (6 years follow-up: Holli 2001)	RCT	Moderate

5.5.6. Chemotherapy

Table 41 – Chemotherapy for early and locally advanced breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008		Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen. Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.	Cochrane review (Ferguson et al. 2007) HTA report (Ward et al. 2007) meta-analysis (De Laurentiis et al. 2008) pooled analysis (Bria et al. 2006) 2 RCTs (Kummel et al. 2006; Piedbois et al. 2007) 1 RCT from an abstract (Ellis et al. 2007) With taxanes Improved overall and disease-free survival With docetaxel More frequent (febrile) neutropenia	Sparano et al. (2008) showed that weekly paclitaxel was more effective than 3 weekly docetaxel. This trial also showed no difference between 3 weekly docetaxel and 3 weekly paclitaxel. This trial was found when updating the evidence searches.	High
CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast	The following taxane-containing regimens are considered reasonable treatment options for the target population: Six cycles of three-weekly docetaxel,	Randomized controlled phase III trials		High

		cancer.	doxorubicin, and cyclophosphamide (DAC) (75/50/500 mg/m2) Four cycles of doxorubicin and cyclophosphamide (AC) (60/600 mg/m2) followed by four cycles of paclitaxel (175 mg/m2 or 225 mg/m2 every three weeks or 175 mg/m2 every two weeks with granulocyte colony-stimulating factor [G-CSF]). Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m2) These regimens are recommended over their non–taxane-containing counterparts (six cycles of FAC, four cycles of AC, or six cycles of FEC-100), as they have been shown to be superior in efficacy.			
CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Six cycles of three-weekly DAC (75/50/500 mg/m2) is recommended over six-cycles of three-weekly FAC (500/50/500 mg/m2).	Breast Cancer International Research Group (BCIRG) 001 trial (Martin et al. 2005) Meta-analysis on 5 trials: Martin et al. 2005, Gianni et al. 2005, Goldstein et al. 2005, Kümel et al. 2006, Crown et al. 2006 Anthracycline–taxane regimens compared to their non-taxane containing counterparts. Disease free survival HR=0.82 (95% CI 0.71 to 0.94), with little statistical heterogeneity (χ2 test for heterogeneity p=0.16, I2 = 39.1%). Overall survival HR= 0.84 (95% CI 0.66 to 1.08), with evidence of statistical heterogeneity (χ2 test for heterogeneity p=0.02, I2 = 65.1%).	n=1 491 women	High

CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	The inclusion of a taxane in sequence with an anthracycline-based regimen should be considered. The following regimens have been specifically studied in comparison to their non–anthracycline-containing counterparts and are recommended. Four cycles of three-weekly AC (60/600 mg/m2) followed by four cycles of three-weekly paclitaxel (175 mg/m2 or 225 mg/m2) is recommended over four cycles of three-weekly AC alone (60/600 mg/m2). Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m2) is recommended over six cycles of FEC-100 alone.	Meta-analysis on 6 trials: Crown et al. 2006, Henderson et al. 2003, Martín et al. 2005, Rodriguez-Lescure et al. 2004, Buzdar et al. 2002, Mamounas et al. 2005, Roché et al. 2004 Disease free survival HR=0.80 (95% CI 0.75 to 0.86) Overall survival HR=0.83 (95% CI 0.76 to 0.91). No statistical heterogeneity in either estimate (I2=0% for both estimates).		High
CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Women in the target population should be considered for dose-dense therapy with doxorubicin and cyclophosphamide followed by paclitaxel. In practice, four cycles of two-weekly AC (60/600 mg/m2) followed by four cycles of two-weekly paclitaxel (175 mg/m2) (AC→ T) is more commonly used due to a shorter duration of treatment. G-CSF (days three to 10 of each cycle [a total of seven doses] at 5 µg/kg rounded to either 300 µg or 480 µg total dose) should be given in combination with four cycles of two-weekly AC→ T to prevent neutropenia.	Intergroup (INT) C9741 trial (Citron et al. 2003, Hudis et al. 2005) Disease free survival Significantly improved in women who received G-CSF and four cycles of two-weekly A→T→C or AC→T compared with women who received the same regimens every three weeks at a median follow-up of 69 months (HR 0.80, 95% CI 0.62 to 0.96, p=0.018). At a median follow-up of 36 months, the absolute difference in four-year DFS was 7% (p=0.010)	N = 1 973 women	High
CCO 2006[245]	May 2006	Women with T 1-3,	Four cycles of three-weekly docetaxel and cyclophosphamide (75/600	U.S. Oncology (USON) 9735 trial (Jones et al. 2001, 2005)	RCTs	High

		operable, node-positive breast cancer.	mg/m2) (DC) is recommended over four cycles of three-weekly AC (60/600 mg/m2).	Disease free survival: Significantly improved in women treated with DC versus those treated with AC (HR 0.67, absolute difference at five years 6%, p=0.015). Overall survival: No significant difference (HR 0.76, absolute difference at five years 3%, p=0.131).		
CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Prophylactic G-CSF (granulocyte colony-stimulating factor) should be considered in patients receiving concurrent anthracycline /taxane regimens.	Breast Cancer International Research Group (BCIRG) 001 trial (Martin et al. 2005): DAC versus FAC grade 3+ neutropenia 65.5% vs. 49.3%, p<0.001 grade 3+ anemia 4.3% vs. 1.6%, p=0.003 febrile neutropenia 24.7% vs. 2.5%, p<0.001	RCTs	High
CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia. In those who experience febrile neutropenia while receiving DAC, G-CSF (granulocyte colony-stimulating factor) should be administered with subsequent docetaxel infusions. Alternatively, a dose reduction should be considered.	GEICAM 9906 trial (Martín et al. 2005, Rodriguez-Lescure et al. 2004) : FEC→T vs FEC grade 3+ neutropenia 20.5% vs. 30%, p=significant grade 3+ leucopenia 7.4% vs. 10.6%, p=significant febrile neutropenia 5.1% vs. 9.3%, p=0.004 PACS 01 trial (Roché et al. 2004): FEC→D versus FEC febrile neutropenia 4.6% vs. 1%, p=0.001	RCTs	High

CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	The Breast Cancer DSG considers the following G-CSF regimen (granulocyte colony-stimulating factor) to be reasonable for either prophylaxis for or treatment of febrile neutropenia: day three to ten of each cycle (a total of seven doses) at 5 µg/kg rounded to either 300 µg or 480 µg total dose.	CALGB 9344 trial (Henderson et al. 2003): AC→T vs AC hematologic toxicity Fewer occurrences during the paclitaxel cycles of the AC→T arm than during the equivalent cycles of AC in the AC-only arm. INT C9741 trial (Citron et al. 2003, Hudis et al. 2005) : dose-dense AC→T versus standard AC→T grade 3+ neutropenia 5.9% vs. 12%, p not reported. grade 2+ anemia 23% 8%, p<0.0001) NB. patients receiving dose-dense therapy in this trial received G-CSF prophylaxis.	RCT	High
CCO 2006[245]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Women receiving a taxane regimen should also be monitored for other toxicities, including diarrhea, stomatitis, amenorrhea, asthenia, myalgia, paresthesia, and leukopenia.	USON 9735 trial (Jones et al. 2001, 2005): DC vs AC Febrile neutropenia 6% vs. 3%, p=0.03	RCT	High

Abbreviations: doxorubicin and cyclophosphamide [AC]; 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC]; 5-fluorouracil, epirubicin, and cyclophosphamide [500/100/500mg/m2] [FEC-100]; cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m2] [CEF].

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
EBCTCG 2008[246]	1985-2008	Pre-menopausal and post-menopausal women with ER-poor early breast cancer	Non-taxanes based polychemo-therapy vs. not Tamoxifen vs. not Chemotherapy denotes prolonged adjuvant trt with various standard combinations of older drugs: eg, about six courses of CMF (45% of randomised women) or about six courses of FAC or FEC (31% of randomised women) None of the regimens studied were taxane-based or deliberately myeloablative.	Recurrence Breast cancer mortality Death from any cause	Polychemotherapy vs not (with or without Tamoxifen) Recurrence (treatment versus control recurrence rate ratios) Age < 50 years (1 907 women, 15% node-positive) Ratio: 0·61 [SE 0·07] the 10-year risks were: recurrence 33% vs 45% (ratio of 10-year risks 0·73, 2p<0·00001), breast cancer mortality 24% vs 32% (ratio 0·73, 2p=0·0002), death from any cause 25% vs 33% (ratio 0·75, 2p=0·0003). Age 50-59 years Ratio: 0.68 [SE 0.06] Age 60–69 years Ratio: 0·82 [SE 0·07] In women aged 50–69 years (3 965 women, 58% node-positive), the 10-year risks were: recurrence 42% vs 52% (ratio	6 000 women with ER-poor breast cancer in 46 trials of polychemo-therapy versus not (typically about six cycles; trial start dates 1975–96, median 1984) 14 000 women with ER-poor breast cancer in 50 trials of tamoxifen versus not (in presence / absence of poly-chemotherapy; trial start dates 1972–93, median 1982).	SR et MA of RCTs	High

					0·82, 2p<0·00001), breast cancer mortality 36% vs 42% (ratio 0·86, 2p=0·0004), death from any cause 39% vs 45% (ratio 0·87, 2p=0·0009). Few were aged 70 years or older. Tamoxifen had little effect on recurrence or death in women who were classified in these trials as having ER-poor disease, and did not significantly modify the effects of polychemotherapy. → the older adjuvant polychemo-therapy regimens were safe (ie, had little eff ect on mortality from causes other than breast cancer) and produced substantial and definite reductions in the 10-year risks of recurrence and death.			
Albain 2009[247]	NA	1 558 post-menopausal women with hormone-receptor-positive, node-positive breast cancer	CAF followed by tamoxifen (CAF-T) Vs. CAF with concurrent tamoxifen (CAFT)	DFS OS Toxicity	Disease free survival HR 0·84, 0·70–1·01; p=0·061 Overall survival HR 0·90, 0·73–1·10; p=0·30 Toxicity Neutropenia, stomatitis,	13 years of follow-up Randomization : allocation by a central software program; 2:3:3 ratio to receive	Phase III RCT	Moderate

					thromboembolism, congestive heart failure, and leukaemia were more frequent in the combined CAF plus tamoxifen groups	tamoxifen alone, CAF-T, or CAFT Stratification by number of involved nodes (1−3 vs ≥4), PgR status (positive vs negative), and interval from surgery (≤6 weeks vs >6 weeks). Unblinded patients and treating physicians		
Amadori 2008[248]	NA	Women <70 y with node negative breast cancer after surgery (mammectomy or quadran-tectomy) + radiotherapy (n= 281)	Adjuvant CMF 6 cycles Vs. no further treatment	Relapse Death	Relapse HR 0.75 (95%CI 0.50-1.13) ; p =0.17 Death HR 0.80 (95%CI 0.48-1.33) p = 0.38 + retrospective subgroup analysis	FU 12 years Randomisation by permuted block No blinding ITT and per protocol analysis Previous publication in Amadori 2000 (same RCT)	RCT	Moderate
De Azambuja 2008[249]	NA	Women ≤70 y with node positive breast cancer after modified	6 cycles of CMF Vs. 8 cycles of EC (epirubicin	Event free survival Overall survival	15 years event free survival (EFS) CMF: 45% / EC: 39% / HEC 50%	Randomisation by central assignment No blinding ITT analysis	RCT	Moderate

		radical mastectomy or lumpectomy plus AND Tamoxifen if post menop and HER+ Radiotherapy mandatory for BCS Post-mastectomy optional (n=777)	low dose) Vs. 8 cycles HEC (high dose epirubicin + cyclophosphamide)	Toxicity	HEC vs EC: HR 0.77 (95%CI 0.60-0.98) HEC vs CMF HR 0.90 (NS) EC vs CMF HR 0.86 (NS) 15 years overall survival (OS) No difference Cardiac toxicity Significantly more frequent with HEC than CMF (p =0.006), but no more than EC (=0.21).	Follow up 15 years		
Eljertsen 2008[250]		1 224 women with reseceted unilateral invasive carcinoma of the breast and no signs of metastases	9 cycles of three-weekly IV CMF Vs. 9 cycles of three-weekly IV CEF	DFS OS Toxicity	10 years disease free survival (DFS) CEF vs. CMF HR 0.84 (95% CI 0.71–0.99) 10 years overall survival (OS) HR 0.79 (95% CI 0.66–0.94) Toxicity CEF: more nausea and vomiting (P < 0.01), conjunctivitis, stomatitis, alopecia Cardiac and thromboembolic events : similar incidence in the CEF (4.8%) and CMF (4.3%) groups.	ITT analysis 10 years follow-up and per protocol analysis	Phase III RCT	Moderate
Ellis 2009[251]	NA	4162 patients with node positive or high risk node	Experimental group: 4 cycles FEC followed by 4 cycles	DFS Toxicity	5-year disease-free survival Experimental group: 75·6% (95% CI 73·7–77·5)	Randomisation by computer-generated permuted block	RCT	Moderate

		negative early breast cancer Who underwent a mastectomy or wide local excision	docetaxel Vs. control group: -either FEC: 8 cycles FEC -either E-CMF: 4 cycles epirubicin followed by 4 cycles CMF		Control group: 74·3% (72·3–76·2) Absolute difference 1.3% (-2.2 to 4.8) HR 0·95, 95%CI 0·85–1·08; p=0·44. More patients with grade 3 or 4 adverse event in the experimental group (p<0·0001) The most frequent events were neutropenia (937 events vs 797 events), leucopenia (507 vs 362), and lethargy (456 vs 272).	randomisation No blinding ITT analysis Median follow up of 62 months		
Francis 2008[252]	NA	Patients with lymph node positive breast cancer T1-T3 who underwent mastectomy or BCS (n = 2887)	Sequential docetaxel (doxorubicin / docetaxel / CMF); concurrent docetaxel (doxorubicin + docetaxel / CMF) Vs. control: Sequential control (doxorubicin / CMF) concurrent control (doxorubicin + CMF);	Disease free survival	5-year disease free survival in control arms: 73% (95% CI 70% to 75%). docetaxel vs. Control : HR = 0.86, 95% CI = 0.7 -1.00; p = .05). sequential docetaxel vs. concurrent docetaxel : HR = 0.83, 95% CI = 0.69 - 1.00) sequential docetaxel vs. sequential control arm: HR = 0.79, 95% CI = 0.64 - 0.98.	Randomisation: minimization procedure with stratification No blinding ITT analysis Median follow up 5 years Reduced power of the study after 5 years and chance not excluded	RCT	Low (reduced power)

Gianni 2008[253]	NA	Operable breast cancer T2-T3, N0-N1, M0 (n= 1355) Surgery: mastectomy or BCS	Arm A: Surgery / doxirubin / CMF Arm B: Surgery / paclitaxel + doxorubin / CMF Arm C: paclitaxel + doxorubin / CMF / surgery	Disease free survival	Disease free survival at 76 months Arm B versus arm A HR = 0.73; 95% CI = 0.57 to 0.97 p = .03 Arm B versus arm C HR = 1.21; 95% CI = 0.92 to 1.60 P = .18	Randomisation: minimization procedure with stratification No blinding ITT analysis Median follow up 76 months	RCT	Moderate
Goldstein 2008[254]		Operable breast cancer with 1 to 3 involved lymph nodes or tumor > 1 cm with negative nodes (n= 2882) After surgery: lumpectomy or mastectomy and ALND	Doxorubicin + AC Vs. Doxorubicin + AT / hormone therapy for ER+ and/or PR+ tumors.	Disease free survival Overall survival	5 years disease-free survival 85% in both arms For AC versus AT: HR = 1.02 (95% CI 0.86 - 1.22; p = .78). 5 years overall survival 91% v 92% Grade 3 neutropenia associated with fever or infection occurred more often with AT (26% v 10%; p < .05).	Randomisation: permuted blocks No blinding ITT analysis Median follow-up of 79.5 months	RCT	Moderate
Jones 2009[255]	NA	Operable breast cancer > 1 cm and < 7 cm, T1-3, M0 (n = 1016) After lumpectomy + AND or	AC Doxorubicin + cyclophosphamide Vs. TC Docetaxel + cyclophosphamide	Disease free survival Overall survival	TC superior 7 years Disease free survival HR 0.74; 95% CI 0.56 to 0.98 7 years Overall survival (OS) HR 0.69; 95% CI 0.50 to 0.97	Randomisation (method not described) No blinding ITT analysis	RCT	Moderate

		modified radical mastectomy				(5 years follow-up: previous publication Jones 2006)		
Lee 2008[256]	NA	209 women with axillary node positive, stage II/III breast cancer	Docetaxel/capecitabine (TX) Vs. anthracycline-containing regimen, doxorubicin/cyclophosphamide (AC) followed by surgery and cross-over to the other treatment	Pathologic complete response (pCR) Disease free survival Overall survival Toxicity	pCR 21% TX vs. 10% AC, p = 0.024 Disease free survival (DFS) not significant Overall survival (OS) not significant TX was associated with less nausea and vomiting, but more stomatitis, diarrhea, myalgia, and skin/nail changes than AC.	Randomisation on block size No blinding ITT analysis Median follow-up of 37 months	RCT	Moderate
Martin 2008[257]	NA	Women with lymph node – positive disease after BCS (n= 1246)	FEC Vs. FEC / paclitaxel (FEC-P)	Disease free survival Overall survival	5-year disease-free survival (DFS) HR = 0.77, 95% CI = 0.62 to 0.95; p = 0.022 in favour of FEC-P Overall survival HR = 0.78, 95% CI = 0.57 to 1.06; p = 0.110	Randomisation by computer program No blinding ITT analysis Median follow-up of 66 months	RCT	Moderate
Muss 2009[258]	NA	Women ≥65 years; stage I, II, IIIA, or IIIB breast cancer (n = 600)	Standard chemotherapy (CMR or cyclophosphamide + doxorubicin)	Disease recurrence Death	Disease recurrence or death HR in the capecitabine group was 2.09 (95% confidence interval, 1.38 to 3.17; P<0.001) after a median FU	Randomisation (method not described) No blinding	RCT	Low

					of 2.4 years			
			Vs. capecitabine			ITT analysis Median follow-up of 66 months Test of the non inferiority of capecitabine		
Taucher 2008[259]	NA	High-risk endocrine non-responsive breast cancer patients (n= 203)	Pre- operative chemotherapy containing CMF Vs. postoperative chemotherapy CMF	Recurrence-free survival Overall survival	9 years recurrence-free survival HR 0.7, 0.51–0.95; P = 0.024 in favour of post op. 9 years overall survival HR 0.8, 0.56–1.13; p = 0.213.	Randomisation (method not described) No blinding No ITT analysis Median follow-up of 9 years	RCT	Low
Tokuda 2008[260]	NA	97 patients < 56 years with stage I to IIIB breast cancer involving 10 or more axillary lymph nodes	standard arm (STD): cyclophosphamide, oxorubicin, and 5-fluorouracil / tamoxifen Vs high-dose arm (HDC): cyclophosphamide, doxorubicin, and 5-	Recurrence-free survival Overall survival	5-year Relapse-free survival 37% (STD) and 52% HDC (P= 0.17) 5 year Overall survival 62% (STD) and 63% (HDC) (P=0.78).	Randomisation by minimisation No blinding ITT analysis Median follow-up of 63 months 31% of arm HDC did not undergo HDC	RCT	Low

			fluorouracil / tamoxifen + cyclophosphamide and thiotepa					
Watanabe 2009[261]	NA	Node negative high risk breast cancer (n= 773)	2 years UFT (uracil-tegafur) Vs. CMF	Recurrence-free survival Overall survival	5-year Relapse-free survival 88% (CMF) and 87.8% (UFT) HR 0.98, 0.66–1.45; P = 0.92 5 year Overall survival 96% (CMF) and 96.2% (UFT) HR 0.81, 0.44–1.48; P = 0.49	Randomisation by minimisation No blinding ITT analysis (?) Median follow-up of 6.2 years	RCT	Moderate
Zander 2008[262]	NA	307 patients with primary breast cancer and ≥10 axillary lymph nodes after mastectomy or BCS + AND	After four cycles of epirubicin and cyclophosphamide Standard-dose chemotherapy (SD-CT): CMF Vs high-dose chemotherapy (HD-CT): cyclophosphamide, thiotepa and mitoxantrone followed by stemcell transplantation	Recurrence-free survival Overall survival	Recurrence free survival (6.1 years) HR = 0.80 ; 95%CI 0.59-1.08, p = 0.15. for HD-CT versus SD-CT Overall survival (6.1 years) HR = 0.84 ; 95%CI 0.59 - 1.20, p = 0.33. for HD-CT versus SD-CT	Randomisation (method not described) No blinding No ITT analysis Median follow-up of 6.1 years	RCT	Low

Note. C=cyclophosphamide, M=methotrexate, F=5-fluorouracil, A=doxorubicin [also called adriamycin], and E=epirubicin.

5.5.7. Endocrine therapy for early and locally advanced disease

Table 42 – Ovarian suppression/ablation

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[227]	July 2008	Pre-menopausal women with ER-positive early breast cancer	Do not offer adjuvant ovarian ablation/ suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy. Offer adjuvant ovarian ablation/ suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.	Ovarian ablation or suppression versus none: One meta-analysis (EBCTCG 2005): ovarian ablation/suppression beneficial compared to none in terms of recurrence (respective rates 47% and 52%, p<0.0001) and breast cancer mortality (respective rates 40% and 44%, p<0.004), both assessed at 15 years follow-up. Ovarian ablation and the role of chemotherapy: One meta-analysis (EBCTCG 1998), randomised trials (Nomura et al. 1999; Thomson et al. 2002), and 1 RCT (Kaufmann et al. 2007): no benefit where adjuvant chemotherapy is given. LHRHa versus no systemic therapy: A meta-analysis (n=338; Cuzick et al. 2007): no difference in recurrence or survival, comparing LHRH agonists with no systemic therapy. A well conducted RCT (Love et al. 2008): 5 and 10 year disease free survival and overall survival rates improved following adjuvant oophorectomy and tamoxifen.	This guideline includes a Cochrane Systematic Review (Sharma et al. 2008)	High

		LHRHa versus chemotherapy: No difference in terms of recurrence and survival (Cuzick et al. 2007). LHRHa plus tamoxifen versus LHRH alone or tamoxifen alone: Reduction in recurrence and mortality with combined treatment (Sharma et al. 2008). No difference in a meta-analysis (Cuzick et al. 2007). LHRHa with or without tamoxifen in addition to chemotherapy: Cochrane Review (Sharma et al. 2008) and meta-analysis of randomised trials (Cuzick et al. 2007): recurrence and mortality are reduced. LHRHa with or without tamoxifen versus chemotherapy: Cochrane Review (Sharma et al. 2008) and meta-analysis of randomised trials (Cuzick et al. 2007): same effectiveness in terms of recurrence and mortality Side effects and quality of life: ovarian ablation, ovarian suppression and chemotherapy each have adverse side effects and each can induce menopausal symptoms, including amenorrhoea (Brunt et al. 2004; Groenvold et al. 2006; Schmid et al. 2007; Love et al. 1999; Sharma et al. 2008 and Celio et al. 2002).

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Hackshaw 2009[263]	NA	Pre-menopausal women or aged under 50 years with operable stage I or II breast cancer, confined to one breast; to have no evidence of distant metastases and regardless of ER status	- Goserelin and tamoxifen (n=1800) - Goserelin or not (n = 910; some received elective tamoxifen) for 2 years.	Event free survival Overall survival Risk of recurrence Risk of dying from breast cancer	Goserelin was associated with a risk reduction in all four endpoints EFS event HR 0.82; 95%CI 0.73-0.92; p=.001 Overall mortality HR 0.83; 95%CI 0.71-0.96; p=.013 Risk of recurrence HR=0.81; 95%CI 0.71-0.92;p=.001 Breast cancer mortality HR 0.82; 95% CI 0.70-0.96; p=.03 Goserelin without Tamoxifen EFS 33% of risk reduction Overall mortality 29% of risk reduction Recurrence 34% risk reduction	The ZIPP collaboration (Zoladex in pre-menopausal patients) includes four unblinded, randomised, multicentre trials Median follow-up: 12 years (26 545 persons-years)	RCT	Moderate

		Breast cancer mortality 29% risk reduction Goserelin with Tamoxifen EFS 8% of risk reduction Overall mortality 10% of risk reduction Recurrence 9% risk reduction Breast cancer mortality 11% risk reduction
		Tamoxifen vs Goserelin Two years of goserelin treatment was as effective as 2 years of tamoxifen treatment 15 years after starting therapy. In women who did not take tamoxifen, there was a large benefit of goserelin treatment on survival and recurrence (8.5 fewer breast cancer deaths vs no goserelin) In women who did take tamoxifen, there was a marginal potential benefit on these outcomes when goserelin was added (possibly 2.6 fewer deaths).

Table 43 – Aromatase inhibitors / Tamoxifen for premenopausal women

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Rossi 2008[264]	NA	Pre-menopausal women with early breast cancer	Tamoxifen (20mg daily) + triptorelin (3.75mg IM every 4 weeks) for 5 years; n=51 Letrozole (2.5 mg/d) + triptorelin (3.75 mg IM every 4 weeks) for 5 years; or Letrozole + triptorelin (as above) + zoledronic acid (4 mg by 15-minute IV every 6 months) for 5 years; n=30	Endocrine changes	Letrozole + triptorelin (± zoledronate) induced a stronger suppression of median E2 serum levels (P = .0008), LH levels (P = .0005), and cortisol serum levels (P < .0001) compared with tamoxifen + triptorelin. Median FSH serum levels were suppressed in both groups, but such suppression was lower among patients receiving letrozole, who showed significantly higher median FSH serum levels (P < .0001). No significant differences were observed for testosterone, progesterone, ACTH, androstenedione, and dehydroepiandrosterone between the two groups of patients. → letrozole could be more effective than tamoxifen as adjuvant hormonal treatment for premenopausal patients with endocrine responsive breast cancer	Triptorelin= gonadotropin releasing hormone (GnRH) agonists that produce post-menopausal-like plasma estrogen concentrations	RCT	High

Table 44 – Aromatase inhibitors / Tamoxifen for postmenopausal women

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Postmenopausal women with early invasive breast cancer						
NICE 2009[227]	July 2008	Post-menopausal women with ER-positive early invasive breast cancer	Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk* should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated. Offer an aromatase inhibitor, either exemestane or anastrozole instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low-risk* and who have been treated with tamoxifen for 2−3 years. Offer additional treatment with the aromatase inhibitor letrozole for 2−3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years. The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women. The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks	**Anastrazole** Boccardo et al. 2005; Buzdar et al. 2006; Buzdar and Cuzick 2006; Dowsett et al. 2005; Forbes et al. 2008; Hind et al. 2007; Howell et al. 2005; Jakesz et al. 2005; Kaufmann et al. 2007. Disease-free survival: significantly increased with anastrazole compared to tamoxifen either as first line adjuvant treatment or after tamoxifen. prior chemotherapy (CMF, anthracyclines or taxanes) reduces the disease-free survival advantage of anastrozole. in hormone receptor-positive patients: DFS favoured in the anastrozole group in the hormone receptor-negative subgroup: no difference (Forbes et al., 2008). Overall survival: no difference either as first adjuvant treatment or after tamoxifen. ><: Kaufmann et al. (2007b) showed a significant improvement in survival	High quality RCTs	High

	and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.	for patients in the anastrozole group when the benefits of switching to anastrozole after 2 years of tamoxifen treatment were compared with continuing on tamoxifen for 5 years. Risk of disease recurrence: significantly reduced in all ER-positive patients with anastrozole and independently of nodal status, tumour size or prior chemotherapy; 5 years of adjuvant tamoxifen (with or without the aromatase inhibitor, amino-glutethimide, for the first 2 years of therapy) + 3 years of anastrozole, DFS statistically improved with significantly fewer recurrences compared to no further treatment statistically fewer patients on anastrozole experienced distant disease recurrence (Forbes et al. 2008, Kaufmann et al. 2007). Risk of contralateral breast cancer: significantly reduced only if anastrozole is given as first line adjuvant treatment; not significantly different if given after tamoxifen. Time to progression: significantly increased for ER-	

positive/PR-negative tumours.

Adverse events:

significant increased risk of bone fracture with anastrazole compared to tamoxifen.

significant increased risk of endometrial cancer, deep venous and venous thromboembolic events and ischaemic cerebrovascular events with tamoxifen compared to anastrozole.

Letrozole

BIG 1-98 trial: letrozole vs tamoxifen in the initial adjuvant setting (Crivellari et al. 2008; Coates et al. 2007; Hind et al. 2007; Thurlimann et al. 2005; Rasmussen et al. 2008) – Follow-up: 60 months

MA-17 trial: letrozole vs placebo in the extended adjuvant setting following standard adjuvant treatment with tamoxifen (Goss et al. 2005 and 2007; Hind et al. 2007; Ingle et al. 2006 and Muss et al. 2008)

Disease-free survival:

significantly improved with letrozole compared to tamoxifen for lymph node-positive tumours

significant improvement with letrozole compared to placebo. Over time (6 months to 4 years) the difference in

			the risk of progression significantly increased in the letrozole group compared to the placebo group improved in the placebo arm of the MA-17 trial who subsequently received letrozole Overall survival: not statistically different between letrozole and tamoxifen not statistically different between letrozole and placebo patients in the placebo arm of the MA-17 trial who subsequently received letrozole: the overall survival adjusted hazard ratio was 0.30 for the letrozole arm. Risk of contralateral breast cancer: did not report statistically significant results; letrozole vs tamoxifen: 0.4% vs 0.7% no difference for time to recurrence ; letrozole vs placebo. Adverse events: fewer thromboembolic events with letrozole compared with tamoxifen but higher risk of bone fracture and some cardiac events. Differences were not significant for thromboembolic or cardiac adverse events higher incidence of osteoporosis but no difference in the fracture rate with

			letrozole compared to placebo time to any disease recurrence was significantly decreased with letrozole compared to tamoxifen or placebo no significant difference between letrozole and tamoxifen with respect to quality of life disease-free survival for ER-positive/PR-positive tumours was significantly increased with letrozole compared with placebo. disease-free survival significantly improved with letrozole compared to placebo in lymph node-positive and lymph node-negative women. **Exemestane** Coombes et al. 2004 and 2007; Eisen et al. 2008 and Hind et al. 2007. Disease-free survival: significantly increased with exemestane compared with tamoxifen, and nodal status did not affect outcome. significantly increased for women with ER-positive histology regardless of PR status. Overall survival: not significantly different between exemestane or tamoxifen or between exemestane and placebo

				modest improvement in overall survival for patients who switch to exemestane after 2–3 years on tamoxifen Adverse events: significant increase in bone fractures with exemestane risk of contralateral breast cancer was significantly decreased with exemestane endocrine events decreased for all women with no difference between exemestane or tamoxifen.		
CCO 2008[265]	May 2007	Post-menopausal women with early-stage, hormone receptor-positive breast cancer.	Adjuvant tamoxifen (20 mg daily for five years) remains an acceptable option for the treatment of women with hormone receptor-positive, early-stage breast cancer. Adjuvant anastrozole (1.0 mg daily for five years) or letrozole (2.5 mg daily for five years) is an acceptable alternative to five years of adjuvant tamoxifen therapy. Adjuvant tamoxifen (20 mg for two to three years) followed by switching to either adjuvant exemestane (25 mg daily, to a total of five years of hormone therapy) or adjuvant anastrozole (1mg daily, to a total of five years) therapy is also an acceptable alternative to five years of tamoxifen. Adjuvant letrozole (2.5 mg daily for five years) should be considered for women	Nine randomized controlled trials (ATAC Trialists Group 2002, 2005; BIG 1-98 Collaborative Group 2005; Coates 2007; Coombes 2004, 2007; Boccardo 2005; Jakesz 2005; Goss 2005; Mamounas 2006) and one meta-analysis (Jonat 2006) ATAC study (n=9 366): tamoxifen versus anastrozole versus tamoxifen + anastrozole – FU: 68 months (5.7 years) disease-free surviva: significantly improved in the anastrozole group versus the tamoxifen group (HR: 0.87; 95% CI, 0.78 to 0.97; p=0.03). The absolute difference in four-year disease-free survival estimates was 2.4% (86.9% with anastrozole versus [vs.] 84.5% with tamoxifen). Additional benefit was seen for time to recurrence (TTR) and time to	All major trials under review were multicentre trials	High

			who have completed five years of adjuvant tamoxifen therapy.	distant recurrence (TDR) with anastrozole. Overall survival was not significantly different. A meta-analysis of the ABCSG-8, ARNO-95, and ITA trials : improvements for women who switched to anastrozole disease-free survival: HR, 0.59; 95% CI, 0.48 to 0.74; p<0.0001 distant recurrence-free survival: HR 0.61, 95% CI 0.45 to 0.83, p=0.002 overall survival: HR, 0.71; 95% CI, 0.52 to 0.98; p=0.04 Other RCTs: see NICE 2009		
CCO 2008[265]	May 2007	Post-menopausal women with early-stage, hormone receptor-positive breast cancer.	Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.	ATAC and BIG 1-98 trials TEAM International trial (Tamoxifen and Exemestane Adjuvant Multicenter substudy) IES ABCSG-8/ARNO-95 MA.17 trial See NICE 2009 (adverse events)	RCTs	High
CCO 2008[265]	May 2007	Post-menopausal women with early-stage, HR positive breast cancer.	Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on HER2/neu status can be made at this time.	No eligible trials on the efficacy of aromatase inhibitors according to HER2/neu status were identified.		Low

*Note. * Low-risk patients are those in the EPG (excellent prognostic group) or GPG (good prognostic group) in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. High-risk patients are those in groups PPG (poor prognostic group) with 53% or VPG (very poor prognostic group) with 39%.*

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Aromatase inhibitors in postmenopausal women with early breast cancer								
Big 1-98 2009[266]	NA	Post-menopausal women with ER-positive or PgR positive early breast cancer	5 years of tamoxifen 5 years of letrozole 2 years of treatment with one agent followed by 3 years of trt with the other.	DFS OS	Disease-free survival HR for tamoxifen followed by letrozole: 1.05 (99% CI: 0.84 to 1.32) HR for letrozole followed by tamoxifen: 0.96 (99% CI: 0.76 to 1.21). Overall survival HR for letrozole: 0.87 (95% CI: 0.75 to 1.02; p = 0.08). Safety thromboembolic events: higher incidence with tamoxifen regimens than with letrozole (4.1 to 4.9% vs. 2.4%, P<0.001). stroke and transient cerebral ischemic: similar rates between groups (1.7 to 1.9% and 1.4%, respectively; P = 0.74). cardiac events: similar rates (6.1 to 7.0% and 5.7%, respectively; P = 0.45). Vaginal bleeding, hot flashes and night sweats occurred more frequently with tamoxifen whereas arthralgia and myalgia were more frequent with letrozole.	71 months follow-up	RCT (phase 3, double-blind trial)	High

					Sequential treatment with letrozole and tamoxifen did not improve disease-free survival as compared with letrozole monotherapy. Update for monotherapy The 5-year overall survival was 91.8% in the letrozole group and 90.9% in the tamoxifen group (hazard ratio, 0.87; 95% CI: 0.75 to 1.02; P = 0.08)			
Eastell 2008	NA	Pos-tmenopausal women with localized early breast cancer	Anastrazole (1 mg/d): n=57 Tamoxifen (20 mg/d): n=51	Lumbar spine and total hip bone mineral density (BMD)	108 women included in the primary analysis. Follow-up: 5 years Anastrozole group Decrease in median BMD in lumbar spine (- 6.08%) and total hip (- 7.24%) Tamoxifen group Increase in median BMD in lumbar spine (+ 2.77%) and total hip (+ 0.74%). No patients with normal BMD at baseline became osteoporotic at 5 years. → Anastrozole is associated with	Comparison before and 5 years after treatment	Prospective substudy of the ATAC trial	High

					accelerated bone loss over the 5-year treatment period. However, patients with normal BMD would not appear to require specific monitoring			
Hadji 2009[267]	NA	Post-menopausal women with ER- and/or PgR positive invasive primary breast cancer (stage I, IIa, IIb, IIIa, T1-3, N0-2, M0)	Exemestane (25 mg/d): n=78 Tamoxifen (20 mg/d): n=83	Lumbar spine and total hip bone mineral density (BMD)	Exemestane group Decrease in median BMD in lumbar spine (- 2.8%) and total hip (- 2.2%) Tamoxifen group Increase in median BMD in lumbar spine (+ 0.5%) and total hip (0.4+%) No differences in BMD for neck femur. →The rapid increase of bone loss with exemestane then stabilized after 6- and 12 month treatment.	Blinding not reported Follow-up : 12 months	RCT	Moderate

5.5.8. Trastuzumab

Table 45 – Trastuzumab in women with HER2-positive early invasive breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Trastuzumab						
NICE 2009[227]	July 2008	Women with HER2-positive early invasive breast cancer	Neo adjuvant setting No recommendation in regards to neoadjuvant trastuzumab use can be made at this time. Adjuvant setting Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable. Dosage Prefer one of the following schedules: sequentially, after the completion of a minimum of four cycles of chemotherapy; concurrently with a taxane as part of an AC-paclitaxel (AC fi T + H), AC-docetaxel (AC fi D + H) or docetaxel and carboplatin regimen (D + Pla + H; weekly trastuzumab schedule only); concurrently with either: vinorelbine or docetaxel prior to FEC (V/D+H fi FEC), or	Two papers from the HERA trial (Herceptin Adjuvant) (Smith et al., 2007 and Suter et al., 2007) One joint-analysis of the NSABP B-31 trial (National Surgical Adjuvant Breast and Bowel Project), B-31 trial and the NCCTG N9831 trial (North Central Cancer Treatment Group) (Romond et al. 2005) Two papers which considered cardiac dysfunction in the NSABP B-31 (Tan-Chiu et al. 2005) and NCCTG N9831 (Perez et al. 2008) A meta-analysis of cardiotoxicity with adjuvant trastuzumab (Bria 2008) From the FinHer trial (Joensuu et al. 2006) From the ECOG E2198 trial (Budzar et al. 2007) One small trial (Buzdar et al. 2007)	A large volume of economic evidence was identified on the cost effectiveness of trastuzumab in the adjuvant setting. Ten economic evaluations were reviewed in detail (Garrison et al., 2007; Kurian et al., 2007; Lidgren et al., 2007; Liberato et al., 2007; Millar and Millward 2007; Dedes et al., 2007; Neyt et al., 2006; Neyt et al., 2008; Norum et al., 2007 and Shiroiwa et al., 2008).	High

	with paclitaxel prior to AC (T + H fi (AC)/(AC + H)). Favoured a weekly dosage schedule when trastuzumab offered concurrently with a taxane. A loading dose of 4 mg/kg of adjuvant trastuzumab should be offered on week one for all concurrent regimens. Target populations Trastuzumab should be offered for one year to all women with HER2/neu-positive, node-positive, and to a lesser extent, high-risk node-negative breast cancer (tumour size >1 cm) N.B. The definition of 'high-risk' node negative differed somewhat across trials Cardiac monitoring Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following: • a left ventricular ejection fraction (LVEF) of 55% or less • a history of documented congestive heart failure • high-risk uncontrolled arrhythmias • angina pectoris requiring medication • clinically significant valvular disease • evidence of transmural infarction on electrocardiograph (ECG)	Trastuzumab group Improved overall survival, disease free survival and distant recurrence event-free survival Higher incidence of cardiac end points (severe congestive heart failure (CHF), symptomatic CHF and confirmed left ventricular ejection fraction (LVEF) drop)	One SR (Mardanas et al. 2008) published after NICE guideline included same RCTs

			• poorly controlled hypertension. Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman. Single-agent trastuzumab therapy No recommendation follows for single-agent trastuzumab therapy as no trials under review addressed this choice of therapy.		
NICE[221] 2009	July 2008	Women with advanced breast cancer	For patients who are receiving treatment with trastuzumab for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.	A prospective post RCT study (Tripathy et al. 2004), five retrospective case series (Fountzilas et al. 2003; Gelmon et al. 2004; Garcia-Saenz et al. 2005; Montemurro et al. 2006 and Stemmler et al. 2005) and a phase II study (Bartsch et al. 2006). No significant improvements in survival, safety or efficacy for women with disease progression who continued TRZ combined with different chemotherapies.	Moderate

CCO 2006[268]	May 2006	Women with HER2/neu-overexpressing breast cancer	Trastuzumab should be offered for one year to all patients with HER2-positive node-positive or node-negative, tumour greater than 1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.	Herceptin Adjuvant (HERA) trial (Piccart-Gebhart et al. 2005): the addition of one-year trastuzumab following (neo)adjuvant chemotherapy vs observation after chemotherapy Significant improvement in terms of disease-free survival (DFS) (HR 0.54, 95% CI 0.43 to 0.67), recurrence-free survival (HR 0.50, 95% CI 0.40 to 0.63), and distant-disease-free survival (HR 0.40, 95% CI 0.40 to 0.66). National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trial (Romond et al. 2005): the addition of one-year trastuzumab concurrent with adjuvant paclitaxel following adjuvant doxorubicin and cyclophosphamide vs. no trastuzumab Significant improvement to in terms of DFS (HR 0.48, p-value 3x10-12), time-to-first-distant-recurrence (TTR) (HR 0.47, p-value 8x10-10), and overall survival (OS) (HR 0.67, p-value 0.015).	High

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Dahabreh 2008[269]	June 2007	(HER)-2 positive and resectable breast cancer women (early stage)	Adjuvant chemotherapy with trastuzumab vs. adjuvant chemotherapy without trastuzumab	Disease-free survival (DFS) Mortality (death from any cause) Locoregional recurrence Distant recurrence Central nervous system (CNS) recurrence Class III/IV congestive heart failure (CHF) Significant decline in left	Five eligible trials were identified, reporting outcomes on 13 493 women: NSABP B-31 trial, NCCTG 9831, HERA, FinHer and BCIRG 006 trial. Disease-free survival Longer for trastuzumab treated patients (risk ratio [RR], 0.62; 95% CI, 0.56–0.68). Mortality Lower for trastuzumab treated patients (RR, 0.66;95%CI, 0.57–0.77), Locoregional recurrence Lower for trastuzumab treated patients (RR, 0.58; 95% CI, 0.43–0.77) Distant recurrence Lower for trastuzumab treated patients (RR, 0.60; 95% CI, 0.52–0.68). Congestive heart failure Higher risk for patients receiving trastuzumab (RR, 7.60; 95% CI, 4.07–14.18)	Literature search in MEDLINE, the Cochrane central register of controlled trials, the online proceedings of the ASCO, and the online proceedings of the San Antonio Breast Cancer Symposium Meta-analyse used Mantel-Haenszel method with fixed-effects models to estimate pooled point estimates with their CIs. Random-effects models were used in a sensitivity analysis. All analyses were performed according to the intention-to-treat principle No evidence of significant	SR and MA of RCTs	High

				ventricular ejection fraction (LVEF)	Left ventricular ejection fraction decline Higher risk for patients receiving trastuzumab (RR, 2.09; 95%CI, 1.84–2.37). Central nervous system metastasis as the first recurrence event Higher risk for patients receiving trastuzumab (RR, 1.60; 95% CI, 1.06–2.40) A new trial was finally included in the analysis (PACS 04 trial) without modyfing the results. DFS 0.63 (0.59–0.69) p<.0001 Mortality 0.66 (0.57–0.77) p<.0001 Locoregional recurrence 0.60 (0.46–0.78) p=.0002 Distant metastasis 0.62 (0.55–0.70) p<.0001 CHF 7.32 (4.02–13.32) p<.0001 LVEF decline 2.09 (1.84–2.36) p<.0001	between-study heterogeneity or inconsistency for the primary outcome, DFS (I2 = 35.8%; Q = 4.67; p = .198)		
Untch 2008[270]	NA	HER2-positive breast cancer women	standard chemotherapy + trastuzumab (n=1703 women)	Magnitude of trastuzumab treatment effect on disease	The overall hazard ratio (HR) for trastuzumab versus observation was 0.64 [95% CI 0.54–0.76; P < 0.0001]. Three-year DFS (n; HR;	Analysis of subgroups from the HERA trial. Subgroup analyses must be interpreted	Sub-analyses of a RCT	Moderate

	vs. standard chemotherapy + observation (n= 1698 women)	free survival (DFS) in different subgroups identified by their nodal status and their hormone receptor status	95%CI) Nodal status Negative (1099; 0.59; 0.39-0.91) 1-3 positive nodes (976; 0.61; 0.43-0.87) ≥ 4 positive nodes (953; 0.64; 0.49-0.83) Hormone receptor status ER- / PgR- (1627; 0.63; 0.50-0.78) ER- / PgR+ (172; 0.77; 0.34-1.74) ER+ / PgR- (460; 0.82; 0.50-1.34) ER+ / PgR+ (984; 0.63; 0.43-0.93) Estimated improvement in 3-year DFS in subgroups ranged from +11.3% to +0.6%. Patients with the best prognosis (those with node-negative disease and tumors 1.1–2.0 cm) had benefit similar to the overall cohort (HR 0.53, 95% CI 0.26–1.07; 3-year DFS improvement +4.6%, 95% CI 24.0% to 13.2%).	with caution due to the increased likelihood of false-positive and false-negative results Median follow-up was 23.5 months.

Table 46 – Trastuzumab in women with HER2-positive early invasive breast cancer (update 2013)

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Slamon 2011[198]	• **Design:** RCT (BCIRG-006 ClinicalTrials.gov number, NCT00021255) • **Source of funding:** Sanofi-Aventis and Genentech; a Department of Defense Breast Cancer Innovator Award; Revlon/UCLA Women's Cancer Program; the Peter and Denise Wittich Breast Cancer Program; grants from the U.S. Army Medical Research and Development Command, the National Cancer Institute and the California Breast Cancer Research Program. • **Setting:** Multicenter (41 countries) • **Period :** 2001 - 2004 • **Sample size:** n=3222	• **Eligibility criteria:** Women with HER2-positive, invasive, high-risk, node-negative or node-positive adenocarcinoma (stage T1, T2, or T3). • **Exclusion criteria:** Prior systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy); prior anthracycline therapy, taxoids (paclitaxel, docetaxel) or platinum salts for any malignancy and prior radiation therapy for breast cancer; bilateral invasive breast cancer; Pre-existing motor or sensory neurotoxicity of a severity ≥ grade 2 by NCI criteria; cardiac disease that would preclude the	Group 1: standard therapy with doxorubicin (60 mg per m^2) and cyclophosphamide (600 mg per m^2) every 3 weeks for four cycles, followed by docetaxel (100 mg per m^2) every 3 weeks for four doses (AC-T) Group 2: AC-T plus trastuzumab, beginning with the first dose of docetaxel and continuing for 1 year (AC-T plus trastuzumab). Group 3: docetaxel (75 mg per m^2) plus carboplatin (area under the curve, 6 mg per millilitre per minute), given every 3 weeks for six cycles concurrently with trastuzumab, followed by trastuzumab for an additional 34 weeks	**Overall survival at median follow-up of 65 months** Group 1: 141 deaths /1073 Group 2: 94 deaths /1074 (HR for the comparison with AC-T = 0.63; P<0.001) Group 3: 113 deaths /1075 (HR for the comparison with AC-T = 0.77; P = 0.04) Group 3 vs. Group 2: RR 1.20 (95% CI 0.93 to 1.56)* **Disease-free survival at median follow-up FU of 65 months** Group 1: 257 events /1073 Group 2: 185 events /1074 (HR for the comparison with AC-T = 0.64; P<0.001) Group 3: 214 events /1075 (HR for the comparison with AC-T = 0.75; P = 0.04) Group 3 vs. Group 2: RR 1.16 (95% CI 0.97 to 1.38)* No significant difference in the rate of disease-free or overall survival was seen between the two trastuzumab-containing regimens. However, the study was not powered to detect	**Results critical appraisal:** low risk for survival outcomes, high for subjective outcomes (AEs). **Dropouts:** intention-to-treat analyses

• **Duration:** median follow-up 65 months	use of doxorubicin, docetaxel and Herceptin; and other serious illness or medical conditions . • **Patient characteristics:** Group 1: 1073 Group 2: 1074 Group 3: 1075 Age <50 yr: 562 (52) vs. 559 (52) vs. 577 (54); Karnofsky performance score of 100: 856 (80) vs. 853 (79) vs. 862 (80) • Specific demographic and clinical characteristics of patients were similar in the three study groups.	(TCH). In the two trastuzumab-containing regimens, trastuzumab was initially administered at a dose of 4 mg per kilogram of body weight, followed by 2 mg per kilogram per week during chemotherapy and then 6 mg per kilogram every 3 weeks to complete 1 year of trastuzumab treatment.	equivalence between these two regimens. **Cardiac safety** Cardiac related death: none Congestive heart failure (New York Heart Association grade 3 or 4): Group 1: 7 events/1073 Group 2: 21 events/1074 Group 3: 4 events/1075 Group 3 vs. Group 2: RR 0.19 (95% CI 0.07 to 0.55) >10% relative reduction in left ventricular ejection fraction: Group 1: 114 events/1073 Group 2: 194 events/1074 Group 3: 97 events/1075 Group 3 vs. Group 2: RR 0.50 (95% CI 0.40 to 0.63) **Adverse events (AEs) (graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0)** "A significant difference favoring the group receiving TCH (Group 3), as compared with the group receiving AC-T plus trastuzumab (Group 2), was noted for arthralgias, myalgias, the hand–foot syndrome, stomatitis, and vomiting. Significant differences in sensory and motor neuropathies, nail

				changes, and myalgias also favored the TCH group (Group 3). The incidences of neutropenia and leukopenia were significantly lower in the TCH group (Group 3) than in the group receiving AC-T plus trastuzumab (Group 2), whereas the incidences of anemia and thrombocytopenia were significantly lower in the group receiving AC-T plus trastuzumab (Group 2) than in the TCH group (Group 3). The rates of congestive heart failure and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group.”

** RR calculated by DCC ignoring the time to event*

5.5.9. Bisphosphonates

Table 47 – Use of bisphosphonates in women with early breast cancer (SR – update 2013)

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Wong 2012[49]	• SR • Funding: none • Search date: April 2011 • Databases: Cochrane Breast Cancer Group Specialised Register , MEDLINE, EMBASE, WHO International Cancer Trials Registry Platform (WHO ICTRP) + Handsearch in selected journals, proceedings of key meetings (American Society of Clinical Oncology, the European Society for Medical Oncology, the European Cancer Conference and the San Antonio Breast Cancer	Women with early breast cancer (EBC) (defined by stage I-III breast cancer with no distant metastases, locally advanced or recurrent disease) Total number of included studies: 12 trials with placebo groups and trials with open control groups (no treatment) (N = 10 124 patients with EBC) • Coleman 2010 • Diel 1998 • Gnant 2009 • Hershman 2008 • Kristensen 2008 • Powles 2002 • Saarto 2001 • Brufsky 2009 • Eidtmann 2010	Group 1: Treatment with a bisphosphonate administered orally or intravenously, in any dose and for any duration vs. Group 2: The same treatment without a bisphosphonate	**Overall survival (follow-up 1 to 10 years)** Any bisphosphonate versus control (N=7 studies) Group 1: 581 events/3 919 patients Group 2: 670 events/3 952 patients RR 0.84 (95% CI 0.68 to 1.04) (I^2 = 77%) *Overall survival by individual bisphosphonate drug at recommended dosing* IV Zoledronate 4 mg monthly (N=2 studies) Group 1: 134 events/2 580 patients Group 2: 161 events/2 582 patients RR 0.83 (95% CI 0.67 to 1.04) (I^2 = 0%) Oral clodronate 1600 mg daily (N=3 studies) Group 1: 194 events/826 patients Group 2: 243 events/827 patients RR 0.78 (95% CI 0.50 to 1.23) (I^2 = 86%) Oral pamidronate 150 mg (N=1 study) Group 1: 253 events/460 patients Group 2: 266 events/493 patients RR 1.02 (95% CI 0.91 to 1.14) Disease free survival (N=1 study)	Quality of SR: low risk of bias Quality of included studies: three studies: low risk of bias; eight studies: low-moderate risk of bias; one study: moderate-high risk of bias Overall conclusion of the authors (pertaining to all studies): "The use of bisphosphonates in EBC or ABC without bone metastases, outside of clinical research, is currently not supported by evidence. The benefit of bisphosphonates in women receiving aromatase inhibitors in EBC and/or targeted non-cytotoxic therapy such as treatment with monoclonal antibody to HER2-neu requires further study. The role of adjuvant bisphosphonates for women with EBC thus remains an open question for research."

	Symposium) + personal contacts with study sponsors and other bisphosphonates investigators to identify additional studies and results.	• Llombarto 2009 • Tevaarwerk 2007 • Aft 2010	IV Zoledronate 4 mg monthly in post-menopausal women HR 0.64 (P 0.0094) **Overall recurrence by menopausal status** Pre-menopausal (N=3 studies) RR 0.88 (95% CI 0.50 to 1.55) Post-menopausal (N=1 study) RR 0.75 (95%CI 0.59 to 0.95) Adverse events (obtaining to all studies included in SR of Wong 2012) "Reported toxicity was generally mild. Renal toxicity was the main issue with i.v. zoledronic acid and was related to the dose and infusion time. Mild gastrointestinal toxicity was themain toxicity with oral clodronate and oral ibandronate. There have been reports osteonecrosis of the jaw (ONJ) with long term bisphosphonate use, mainly with i.v. pamidronate or zoledronic acid. Denosumab appeared to have similar rates of ONJ as zoledronic acid, but less renal toxicity and acute phase reactions."	Comment: 6 ongoing studies were identified through the process of database searches of the WHO ICTRP, clinicaltrials.gov and contacting sponsors (Novartis Oncology and Amgen Oncology)

Table 48 – Use of bisphosphonates in women with early breast cancer (RCT – update 2013)

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Aft 2012 [60]	• **Design**: open-label, phase II RCT • **Source of funding**: KNW, St Louis Men's Group against Cancer; Novartis Pharmaceuticals Corporation. • Setting: single-centre • Sample size: n=120 • Duration: 1 year, 5 year FU	• **Eligibility criteria**: clinical stage II/III (≥T2 and/or ≥N1) newly diagnosed BC, Eastern Cooperative Oncology Group (ECOG) 0-1, normal cardiac, renal and liver function. • **Exclusion criteria**: evidence of distant metastasis by CT scan of the chest, abdomen, pelvis, or bone scan. Other exclusion criteria were prior malignancies, serious functional disorders of the heart, liver, or kidneys,	**Group 1**: 4 mg intravenous zoledronic acid (ZOL) every 3 weeks for 1 year (commencing with first dose of chemotherapy); N = 59 Vs. **Group 2**: No ZOL (chemotherapy alone); N = 58	**Disease-free survival (DFS) and overall survival (OS)** "After a median follow-up of 61.9 months, DFS (P=0.92) and OS (P=0.92) were similar in the ZOL and no-ZOL arms for the overall study population." "Hazard ratios (HRs) for disease recurrence and death were significantly less among patients with ER-negative tumours who received ZOL vs. no ZOL" OS: HR= 0.375 (95% CI 0.143 to 0.985) DFS: HR= 0.361 (95% CI 0.148 to 0.880) "There was no evidence that ZOL treatment altered DFS or OS vs no ZOL in patients with ER+ tumours" **Adverse events** "ZOL was generally well tolerated; toxicities were similar in the two treatment groups, with no observed cases of nephrotoxicity resulting in dose modifications. One of the 60 patients (1.7%) developed osteonecrosis of the jaw after receiving 11 infusions of ZOL." *Osteonecrosis of the jaw* Group 1: 1/60 Group 2: 0/59	**Results critical appraisal:** low risk of selection bias, attrition bias, reporting bias and other bias. Performance bias and detection bias: high risk for adverse events, low risk for OS and DFS which are unlikely to be influenced by knowledge of the assigned treatment. **Dropouts:** n=1

	pregnancy, or women below 18 years of age. • **Patient characteristics**: Group 1: n=60 Group 2: n=59 *mean age (range)*: Group 1: 50 (30–68) Group 2: 49.1 (32–69); *Race*, n(%) (Caucasian/African American): Group 1: 39(65)/20(33) Group 2: 45(76.3)/11(18.6); *Menopausal status*, n(%) (Premenopausal/ Postmenopausal): Group 1: 31(51.7)/ 29(48.3) Group 2: 33(55.9)/ 26(44.1); *Grade*, n(%): I/II/III: Group 1: 7(11.7)/ 20(33.3)/ 33(55)	RR 2.95 (95% CI 0.12 to 71.01)	

		Group 2: 2(3.4)/ 28(47.5)/ 29(49.2) • **Disease characteristics** were well balanced between the groups (age, race, menopausal status, type of carcinoma, mean tumour size, nodal status, grade, receptor status for estrogen and progesterone)	

Coleman 2011 (AZURE trial) [61]	• **Design**: Open-label phase III RCT • **Source of funding**: The study was sponsored by the University of Sheffield Grant support was provided by Novartis Pharmaceuticals and was supplemented in the United Kingdom by the infrastructure of the National Cancer Research Network **Setting**: multi-centre, international, open label, randomised parallel group trial • **Sample size**: n=3 360 • **Duration**: 5 years of treatment, median follow-up period 59.3 months	• **Eligibility criteria**: women aged ≥18 years, Karnofsky performance status of at least 80, a histologically confirmed breast cancer with axillary lymph-node metastasis (N1) or a T3–T4 primary tumor. • **Exclusion criteria**: patients were not eligible if there was clinical or imaging evidence of distant metastases or if complete treatment of the primary breast tumor and regional lymph nodes was not possible. Other exclusion criteria included a cancer	**Group 1**: Standard adjuvant treatment with the addition of zoledronic acid (ZOL) vs. **Group 2**: Standard adjuvant treatment without zoledronic acid ZOL was administered immediately after each cycle of adjuvant chemotherapy in a 4-mg dose by intravenous infusion every 3 to 4 weeks for 6 cycles and then every 3 months for 8 doses, followed by 5 cycles on a 6-month schedule for a total of 5 years.	**5 year overall survival** Group 1: 243/1 681 Group 2: 276/1 678 Adjusted HR= 0.85 (95% CI 0.72 to 1.01) <u>Postmenopausal (menopause more than 5 years earlier):</u> Adjusted HR= 0.74 (95% CI 0.55 to 0.98) <u>All other patients:</u> Adjusted HR= 0.97 (95% CI 0.78 to 1.21) **Disease free survival** (at a median follow-up of 59 months) Group 1: 377/1 681 Group 2: 375/1 678 Adjusted HR= 0.98 (95% CI 0.85 to 1.13) <u>Postmenopausal:</u> Adjusted HR= 0.75 (95% CI 0.59 to 0.96) <u>All other patients</u>: Adjusted HR= 1.15 (95% CI 0.97 to 1.36) **Adverse events** Osteonecrosis of the jaw Group 1: 17/1 681 (and 9 suspected cases) Group 2: 0/1 666 RR= 34.7 (2.1 to 576.0) “No significant differences between the groups with respect to neutropenia; pyrexia; vomiting; lower respiratory infection; central-	**Results critical appraisal:** low risk of selection bias, attrition bias, reporting bias and other bias. Performance bias and detection bias: high risk for adverse events, low risk for OS and DFS which are unlikely to be influenced by knowledge of the assigned treatment. **Dropouts:** n=1 (ITT analysis)

	diagnosis within the preceding 5 years, use of bisphosphonates during the previous year, or a diagnosis of osteoporosis or other bone disease likely to require bone targeted treatment. The serum creatinine level had to be less than 1.5 times the upper limit of the normal range. In 2005, after case reports of osteonecrosis of the jaw associated with bisphosphonates, an amendment was adopted to exclude patients with clinically significant, active dental problems or planned jaw surgery.	catheter infection; cellulitis and pulmonary embolus were found."

			• **Patient characteristics**: Group 1: n=1 681 Group 2: n=1 678 T1/2/3/4/X: 542/851/227/58 /3 vs. 523/867/228/59 /1; N0/1-3/≥4/unknown: 29/1041/604/7 vs. 32/1032/608/6 • Comparable groups			
Gnant 2011 (ABCSG-12 trial) [62]	• **Design**: RCT (2 by 2 factorial design) • **Source of funding**: Novartis provided zoledronic acid and AstraZeneca provided anastrozole and tamoxifen, but neither company was involved in data collection or analysis.	• **Eligibility criteria**: premenopausal women with stage I or II oestrogen-receptor-positive and/or progesterone-receptor-positive breast cancer, had fewer than ten positive lymph nodes, and were scheduled	Arm 1: Tamoxifen alone (20 mg per day orally) Arm 2: Tamoxifen and zoledronic acid Arm 3: Anastrozole alone Arm 4: Anastrozole and zoledronic acid All patients were	**Zoledronic acid vs. no zoledronic acid** (arm 2+4 vs. arm 1+3, stratified by endocrine therapy) **Overall survival** (at a median follow-up of 62 months) Arm 2+4: 30 deaths/900 women Arm 1+3: 43 deaths/903 women HR= 0.67 (95% CI 0.41 to 1.07) <u>OS node-positive</u> HR 0.62 (95% CI 0.34 to 1.15) <u>OS node-negative disease</u>	**Results critical appraisal:** low risk of selection bias, attrition bias, reporting bias and other bias. Performance bias and detection bias: high risk for adverse events, low risk for OS and DFS which are unlikely to be influenced by knowledge of the assigned treatment. No investigators, staff or patients were masked to treatment group; however, individuals analysing

	• **Setting**: Multicenter • **Sample size**: n=1803 • **Duration**: 3 years, follow-up is ongoing	to receive standard therapy with goserelin. • **Exclusion criteria**: T1a (except yT1a), T4d, and yT4 tumours; a history of other neoplasms; preoperative radiotherapy; pregnancy, lactation, or both; and contra-indications for study drugs. • **Patient characteristics**: Arm 1: n=450 Arm 2: n=450 Arm 3: n=453 Arm 4: n=450 median age (range) 45 (27-56), 45 (27-54), 44 (25-58), 44 (28-56); cancer stage T1/≥T2 341/98, 339/97; 352/93, 343/98	treated with goserelin 3.6 mg subcutaneously every 28 days	HR 0.70 (95% CI 0.33 to 1.52) **Disease-free survival** (at a median follow-up of 62 months) Arm 2+4: 76 events/900 Arm 1+3: 110 events/903 HR= 0.68 (95% CI 0.51 to 0.91) *Tamoxifen plus zoledronic acid vs. tamoxifen alone* Arm 2: 36/450 Arm 1: 53/450 HR= 0.67 (95% CI 0.44 to 1.03) *Anastrozole plus zoledronic acid vs. anastrozole alone* Arm 4: 40/450 Arm 3: 57/453 HR= 0.68 (95% CI 0.45 to 1.02) DFS node-positive HR 0.67 (95% CI 0.45 to 0.99) DFS node-negative disease HR 0.66 (95% CI 0.43 to 1.03) **Adverse events** “Treatments were generally well tolerated, with no reports of renal failure or osteonecrosis of the jaw.” “Patients in the zoledronic acid groups had a higher incidence of bone pain, arthralgia, and	disease recurrence from laboratory results were masked to treatment group. All events underwent double central medical review with masked source data, and only histopathology reports or appropriate imaging were regarded as acceptable for confirmation of disease recurrence. **Dropouts:** none (ITT analysis)

			• **Disease characteristics** were well balanced between the 4 groups (age, tumour stage, nodal status, hist. grading, receptor status for estrogen and progesterone, and preoperative chemotherapy)		pyrexia compared with the no zoledronic acid groups. Additionally, there were no reports of renal toxic effects or osteonecrosis of the jaw after 62 months' follow-up." *Bone pain* Arm 2+4: 349/900 Arm 1+3: 252/903 RR= 1.39 (95% CI 1.22 to 1.59) *Arthralgia* Arm 2+4: 145/900 Arm 1+3: 121/903 RR= 1.20 (95% CI 0.96 to 1.50) *Pyrexia* Arm 2+4: 85/900 Arm 1+3: 21/903 RR= 4.06 (95% CI 2.54 to 6.49) "As for other adverse events: no significant differences were found."	
Paterson 2012 (NSABP B-34 trial) [63]	• **Design**: RCT • **Source of funding**: National Cancer Institute's Department of Health and Human Services; Bayer Oy ("The sponsors of the study had no role	• **Eligibility criteria**: women with histologically confirmed operable breast cancer, no evidence of metastases. Every patient's hormone	**Group 1**: Oral clodronate (1600 mg daily for 3 years) vs. **Group 2**: Placebo NB: Low adherence to	**Overall survival** (at median follow-up of 90.7 months) Group 1: 140 deaths/1 655 women Group 2: 167 deaths/1 656 women HR= 0.84 (95% CI 0.67 to 1.05) **Disease-free survival** (at median follow-up of 90.7 months) Group 1: 286 events/1655	**Results critical appraisal:** low risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias **Dropouts:** Group 1: n=7 Group 2: n=5

	in study design, data collection, data analysis, data interpretation, or writing of this report, and had no access to the raw data").The first author declared to have received honoraria from Bayer, Novartis, Amgen, and Roche Diagnostics. • **Setting**: multicenter (162 centres in North America) • **Sample size**: n= 3 323 • **Duration**: January 2001 to March 2004; median follow-up was 90.7 months	receptor status (oestrogen [ER] and progesterone [PgR]) was required; testing for HER2 status was not routine in North America at the time this trial commenced accrual. • **Exclusion criteria**: women with any relevant renal, hepatic, or non-malignant bone disease and if they had a previous history of malignant disease or bisphosphonate use were excluded • **Patient characteristics**: Group 1: n=1 662 Group 2: n=1	treatment: "By the end of the 3-year therapeutic period, 60% (992/1647) of women assigned placebo and 56% (919/1640) of those allocated clodronate remained on study drugs"	Group 2: 312 events/1656 HR= 0.91 (95% CI 0.78 to 1.07) **Adverse events** "Reported side-effects [diarrhoea, alanine / aspartate aminotransferase, hypocalcaemia, creatinine, thrombosis or embolism, pancreatitis] were low in both arms and were similar between treatments. One possible case of osteonecrosis of the jaw arose in a woman assigned clodronate who had a 1 mm area of exposed bone on the maxillary taurus, which has since healed." "A slightly higher frequency of grade 3 diarrhoea was noted in the clodronate arm."	

	661 *age* (%): ≤49 years/≥50 years: 594(36%)/ 1068(64%) vs. 589 (35%)/1072 (65%); *Hormone receptor status* (%): both negative/ either or both positive: 368 (22%)/ 1294 (78%) vs. 368 (22%)/ 1293 (78%)	
	• **Disease characteristics** were well balanced between the groups (age, ethnic origin, no. of positive nodes, hormone receptor status, adjuvant therapy, and hist. grade)	

5.6. Treatment of metastatic breast cancer

5.6.1. Endocrine therapy

Table 49 – Use of aromatase inhibitors in pre-menopausal women

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[221]	July 2008	Premenopausal women with ER-positive advanced breast cancer	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. Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.	A moderate quality systematic review (Klijn et al. 2001) and one RCT (Klijn et al. 2000) reported a survival benefit for combination therapy over single agents in pre-menopausal patients with metastatic breast cancer. GDG consensus for peri-menopausal women.		Moderate
NICE 2009[221]	July 2008	Men with ER-positive advanced breast cancer.	Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer.	Two small retrospective case series (Ribeiro 1983 and Patterson et al. 1980) and GDG consensus		Low
CECOG 2007[271]	May 2005	Premenopausal women	Tamoxifen, ovarian function suppression, or a combination of both are suitable options for endocrine treatment of premenopausal patients.	Three small randomized studies have compared the combination of tamoxifen and LHRH agonist versus LHRH agonist alone (Boccardo et al. 1994; Jonat et al. 1995; Klijn et al. 2000). A small meta-analysis combined these data and suggested that combination of LH-RH agonist and tamoxifen may be superior to LH-RH agonist alone in all analyzed efficacy parameters (OS, PFS, RR) (Klijn et al. 2001).		Moderate

				At present, there are insufficient data on the use of aromatase inhibitors or fulvestrant in premenopausal patients. If aromatase inhibitors are considered, they definitely should be given in conjunction with some form of ovarian function suppression.		

Table 50 – Use of aromatase inhibitors in post-menopausal women

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[221]		Post-menopausal women with MBC	Offer an aromatase inhibitor (either non-steroidal or steroidal) to: postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.	The evidence base for this topic comprises one guideline (Eisen et al. 2004), five systematic reviews (Mauri et al. 2006; Gibson et al. 2007; Ferretti et al. 2006; Klijn et al. 2001 and Crump et al. 1997), five RCTs (Chia et al. 2008; Mouridsen et al. 2007; Taylor et al. 1998; Klijn et al. 2000 and Goss et al. 2007) a pooled analysis of RCT data (Howell et al. 2005) and a small, low quality comparative study (Catania et al. 2007a).		High
CECOG 2007[271]	May 2005	postmenopausal patients with hormone receptor-positive MBC	Based upon the more favorable toxicity profile, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) is recommended as first-line treatment for postmenopausal patients with hormone receptor-positive MBC, but tamoxifen remains a valuable option.	First-line endocrine therapy anastrozole versus tamoxifen Two randomized phase III trials compared anastrozole with tamoxifen (Bonneterre et al. 2000, 2001; Nabholtz 2000, 2003). →TTP : no difference between anastrozole and tamoxifen letrozole versus tamoxifen A randomized phase III trial compared		High

				letrozole to tamoxifen (Mouridsen et al. 2001, 2003). →TTP and ORR : better results with letrozole →OS : no difference between letrozole and tamoxifen exemestane versus tamoxifen A randomized phase III trial compared exemestane and tamoxifen (Paridaens et al. 2003) →TTP and ORR: better results with exemestane Fulvestrant versus tamoxifen A randomized phase III study compared fulvestrant and tamoxifen (Howell et al. 2004) → ORR and TTP : no difference between fulvestrant and tamoxifen → OS: better results with tamoxifen	
CECOG 2007[271]	May 2005	postmenopausal patients with hormone receptor-positive MBC	Following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for post-menopausal patients with hormone receptor-positive MBC based upon the more favorable side-effect profile.	Second line endocrine therapy Following failure of tamoxifen, the following studies have been performed: third generation aromatase inhibitors versus progestins or aminoglutethimide Randomized phase III studies showed the superiority of 3rd generation aromatase inhibitors versus progestins or aminoglutethimide (Buzdar et al.	High

			1996, 1998, 2001; Goss et al. 1999; Dombernowsky et al. 1998) anastrozole versus letrozole A phase III study found no difference in TTP and OS in the intent to treat analysis and ORR favored letrozol (Rose et al. 2003) anastrozole versus fulvestrant Two randomized phase III studies showed no significant difference in terms of ORR and TTP (Osborne et al. 2002; Howell et al. 2002, 2005).

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Campos 2009[272]	NA	Postmenopausal women with invasive breast cancer with visceral metastases (liver / lung)	Anastrozole (1mg/d); n=64 Exemestane (25 mg/d); n=64 ≥ 8 weeks	Response rate in visceral disease (CR / PR) Clinical benefit TTP Duration of clinical benefit Overall survival	Overall tumour response rate Anastrozole: 15.6% (95% CI: 7.8 – 26.9%) Exemestane: 10.9% (95% CI: 4.5 – 21.3%) Overall clinical benefit Anastrozole & Exemestane: 32.8% (95% CI: 21.6 – 45.7%) Median duration of overall response Anastrozole: 85.1 weeks (22.9 – 166.7) Exemestane: 109.9 weeks (21.6 – 131.3) Median TTP Anastrozole: 4.24 months Exemestane: 3.71 months Median survival Anastrozole: 33.3 months Exemestane: 30.5 months → efficacy and tolerability of AI in this group of patients	Blinding?	RCT	Moderate
Paridaens 2008[273]	NA	Postmenopausal women with ER- and/or PgR	Exemestane (25 mg/d): n=164	Overall response rate	Progression free survival HR: 0.84 (95% CI: 0.67 – 1.05)	Median follow-up: 29 months	RCT	Moderate

		positive metastatic or locally advanced breast cancer	Tamoxifen (20 mg/d): n=176	Progression free survival	in favour of exemestane Percentage of patients without disease progression Exemestane: 66% (95% CI: 59.3% - 73.1%) at 6 months; 41.7% (95% CI: 34.5% - 48.9%) at 12 months Tamoxifen: 49.5% (95% CI: 42.2% - 56.6%) at 6 months; 31.2% (95% CI: 24.4% - 37.9%) at 12 months Overall survival No differences between arms (log-rank p=.821) At 49 months, HR 1.13 (95% CI: 0.85 - 1.50) →Exemestane is an effective treatment for women with metastatic breast cancer and offers significant early improvement in TTP but without impact on OS	Update analysis at 49 months No evidence of blinding		
Dirix 2008[274]	NA	Postmenopausal patients with hormone-sensitive breast cancer and measurable	exemestane 25 mg/d; n=55 exemestane 25 mg/d + celecoxib 400 mg twice daily; n=56	Clinical benefit rate Tolerability Objective response	Clinical benefit rate Exemestane: 48.98% Exemetane + celecoxib: 47.06% Median TTP Exemestane: 20.0 weeks Exemetane+celecoxib: 23.4	Blinding?	Phase II RCT	Moderate

		disease who had progressive disease after treatment with tamoxifen		rate TTP Duration of clinical benefit	weeks Median survival time Exemestane: 74.1 weeks Exemetane+celecoxib: 73.9 weeks Duration of clinical benefit Exemestane: 49.1 weeks Exemetane+celecoxib: 96.6 weeks Both treatments were generally well tolerated.			
Johnston 2008[275]	NA	Postmenopausal women with ER-positive advanced breast cancer that had progressed after tamoxifen	letrozole (2.5 mg/d) + tipifarnib 300 mg (TL); n=80 letrozole (2.5 mg/d) + placebo (L); n=40	Response rate (CR / PR) TTP Tolerability Clinical benefit rate (proportion of patients who achieved response or stable disease for at least 24 weeks) Overall survival	Letrozole + tipifarnib Response rate: 30% (95% CI; 20–41%) Letrozole + placebo Response rate: 38% (95% CI; 23–55%) There was no significant difference in response duration, time to disease progression or survival. Clinical benefit rates were 49% (TL) and 62% (L). → Adding tipifarnib to letrozole did not improve objective response rate in this population of patients with advanced breast cancer	Tipifarnib = Farnesyltransferase inhibitors (FTIs) Tipifarnib has been shown to inhibit the growth of human breast cancer cell lines in vitro	phase II RCT	Moderate

Table 51 – Use of ER antagonists in post-menopausal women

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
ER antagonists						
CCO 2008[276]	June 2008	Post-menopausal women with locally advanced or metastatic breast cancer	Fulvestrant is NOT recommended as an alternative to tamoxifen for first-line therapy of locally advanced or metastatic breast cancer in post-menopausal women who have had no prior endocrine or cytotoxic therapy for advanced disease and no recent adjuvant endocrine therapy (within previous twelve months).	One superiority, Phase III, multicentre RCT (Howell et al. 2004) : fulvestrant 250 mg IM q (every) monthly vs. tamoxifen 20 mg daily for first-line metastatic therapy of locally advanced or metastatic breast cancer in postmenopausal women (n=587). no significant differences with respect to TTP, tumour response to treatment, or quality of life (QOL). no significant difference for TTP in ER+ and/or PgR + group. overall survival in favour of tamoxifen (38.7 vs. 36.5 months, HR 1.29, 95% CI 1.01-1.64, p=0.04). time-to-treatment-failure (TTF) in favour of tamoxifen (7.8 vs. 5.9 months, HR 1.24, 95% CI 1.03-1.50, p=0.026) tolerability: hot flashes (24.7% vs. 17.7%, p=0.0501, tamoxifen vs. fulvestrant).	A systematic review conducted by Flemming et al. (2009) reported the same results coming from the same trials	High
CCO 2008[276]	June 2008	Post-menopausal women with locally advanced or metastatic breast cancer	Fulvestrant may be considered as alternative therapy to anastrozole for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant tamoxifen therapy or progressed on prior tamoxifen therapy for advanced disease.	Two superiority, Phase III, multicentre RCTs (European Open-Label Trial 0020 and U.S. Double-Blind Trial 0021): fulvestrant 250 mg IM q monthly vs. anastrozole 1 mg daily in patients who had received prior adjuvant tamoxifen therapy, or tamoxifen for advanced disease.	The U.S. Double-Blind Trial 0021 used a double-dummy, double-blinding approach whereby patients were given both	Moderate

			Factors that may influence the choice of fulvestrant versus anastrozole therapy include a slightly decreased, although still significant, incidence of joint disorders and the potential for improved compliance with fulvestrant.	Combined analyses (n=851) found: No significant difference for TTP, TTF, ORR, clinical benefit rate (CBR; the sum of complete response + partial response + stable disease) and OS (Howell et al. 2005). Superiority of Fulvestrant was not supported (Howell et al. 2005). No significant differences between therapy arms with respect to ORR or CB across subpopulations of patients with or without visceral metastases (Mauriac et al. 2003). Non-inferiority of fulvestrant to anastrozole (5.5 vs. 4.1 months, HR 0.95, 95% CI 0.82-1.10). The secondary endpoint of ORR also confirmed non-inferiority (Howell et al. 2005). Duration of response (DOR) was significantly longer for fulvestrant vs. anastrozole when analyzed for all randomized patients (ratio of average response durations = 1.30, p<0.01), or just for responders (16.7 vs. 13.7 months; p-value not reported) (Dodwell et al. 2006). Tolerability : higher incidence of joint disorders for those taking anastrozole (8.3% vs. 12.8%, p=0.0234, fulvestrant vs. anastrozole, respectively)	placebo and actual therapy simultaneously, whereas the European Open-Label Trial 0020 did not blind patients or investigators to therapy + Methodological weaknesses were reported 18.4% of patients in the combined population were ER/PgR unknown or ER/PgR-negative, but analyses were not stratified by hormone-receptor status	
CCO 2008[276]	June 2008	Post-menopausal women with locally advanced or	Fulvestrant may be considered as alternative therapy to exemestane for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has	Evaluation of Faslodex vs. Exemestane Clinical Trial (EFECT) is one superiority Phase III, multicentre, double-blind, double-dummy RCT (Chia et al. 2008) comparing a fulvestrant loading-dose regimen (500 mg IM day 0, 250 mg IM on	Only 10% of women enrolled received their previous AI as adjuvant	Moderate-High

		metastatic breast cancer	recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease. Factors that influence the choice of fulvestrant versus exemestane therapy include the potential for improved compliance in favour of fulvestrant.	days 14 and 28, and 250 mg IM injection q monthly thereafter) with exemestane 25 mg orally [po] daily in women with HR+ breast cancer that has recurred or progressed on prior NSAI therapy. At the time of a planned final analysis (median follow-up 13 months; n=693): The median TTP in both groups was 3.7 months (HR 0.93, 95% CI 0.819-1.133, p=0.65). Adjusting for covariates made little difference (HR 0.968, 95% CI 0.822-1.141). The ORR (7.4% vs. 6.7%, OR 1.12, 95% CI 0.578-2.186, p=0.736) and CBR (32.2% vs. 31.5%, OR 1.03, 95% CI 0.72-1.487, p=0.853) did not differ significantly between fulvestrant and exemestane treatment groups respectively. According to an abstract at the 2007 San Antonio Breast Cancer Symposium (SABCS), median OS was not significantly different between treatment arms (24.3 vs. 23.1 months, HR 1.012, 95% CI 0.833-1.229, p=0.9072 in favour of fulvestrant) at a median follow-up of 20.9 months (Chia et al. 2007). Good tolerability in both arms with no significant differences in the incidence of adverse events.	therapy, thus limiting the generalizability of results for this population	
CCO 2008[276]	June 2008	Post-menopausal women with locally	The recommended dose of fulvestrant for the treatment of locally advanced or metastatic breast cancer is 250 mg IM every month OR a loading dose	Two Phase III trials comparing fulvestrant vs. anastrozole (Trial 0020 and Trial 0021): fulvestrant was administered at 250 mg IM q monthly (28 +/- 3 days) as	Pharmacokinetic studies – no comparison with other	Moderate

	advanced or metastatic breast cancer	schedule of 500 mg IM day 0,250 mg IM on days 14 and 28, and 250 mg IM injection q monthly thereafter. Factors that may influence the choice of a loading dose include a shortened time to reach steady state (within one month vs. three to six months for standard dosage) although this may require further verification.	either two separate 2.5 ml injections (Trial 0020) or as a single 5 ml injection (Trial 0021). The latter approach was also used in the study by Howell et al. (2004). A randomized pharmacokinetic study (Robertson 2003) and a pharmaco-kinetic analysis of Trial 0020 and Trial 0021 (Robertson et al; 2004), both comparing a single 5 ml injection with two separate 2.5 ml injections for the delivery of a 250 mg fulvestrant dose, found no difference in pharmacokinetics or tolerability. In a Phase III trial comparing fulvestrant to exemestane (EFECT Trial; Chia et al. 2008), a loading dose schedule of fulvestrant was used (500 mg on day 0, 250 mg on day 14, 250 mg on day 28, and every 28 days thereafter). There are several currently active Phase III trials that are using this fulvestrant loading dose schedule (Southwest Oncology Group [SWOG]-S0226, Fulvestrant and Anastrozole Clinical Trial [FACT], Study of Faslodex, Exemestane and Arimidex [SOFEA];	dosages

5.6.2. Chemotherapy

Table 52 – Use of chemotherapy in women with metastatic breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Combination versus sequential chemotherapy						
NICE 2009[221]	July 2008		On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.	One large RCT (Sledge et al. 2003): combining anthracycline and taxane, rather than giving the drugs sequentially in either order, resulted in a better tumour response and superior time to progression but did not improve median overall survival. Consistently, adverse events due to combined therapy were reported as being more numerous or of greater severity.		High
CECOG 2007[271]	May 2005		The choice between polychemotherapy and sequential single agent chemotherapy should take into account the prognosis, performance status, symptom control and toxicity profiles with the ultimate goal of optimizing quality and quantity of life.	One Phase III RCT of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer (Sledge et al. 2003). →no gain in survival or quality of life with the combination despite increased response rates		High

Combined versus single chemotherapy regimes				
NICE 2009[221]	July 2008	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.	Evidence for comparing single chemotherapy with combined chemotherapy comprised one very high quality systematic review (n > 7,000 study participants) (Carrick et al. 2005) a systematic review (Takeda et al. 2007) three RCTs (Eijertsen et al. 2004; Pacilio et al. 2006 and Martin et al. 2007) and two post-study papers published from the pivotal trial by O'Shaughnessy et al. 2002 (Leonard et al. 2006 and Miles et al. 2004).	High
Optimal first-line chemotherapy				
CECOG 2007[271]	May 2005	No definitive recommendation for optimal first-line chemotherapy for patients with MBC can be given. Anthracycline- and/or taxane based regimens are to be preferred as first-line treatment in symptomatic patients and/or those with rapidly progressive disease. In patients who have received anthracyclines and/or taxanes in the adjuvant or neoadjuvant setting this strategy may have to be modified in the future. Reintroduction of anthracyclines and taxanes in patients relapsing more than a year after completion of adjuvant therapy or, alternatively, other regimens in patients with	Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer (Keller et al. 2004) Phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer (O'Brien et al., 2004) Pegylated liposomal doxorubicin (doxil) (Safra et	High

			shorter disease-free periods may be considered.	al., 2000) Two randomized studies have demonstrated improved OS (Jassem et al. 2001; Bonneterre et al. 2004). These benefits were achieved at the cost of higher treatment-related toxicity.		
Gemcitabine						
NICE 2009[221]	July 2008		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.	This recommendation is from 'Gemcitabine for the treatment of metastatic breast cancer', NICE technology appraisal guidance 116 (2007).		
CCO 2007[277]	August 2005	Women with metastatic breast cancer	The combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line chemotherapy in patients where the toxicity of the capecitabine and docetaxel regimen is a concern.	One randomized phase III study (Chan 2005) Combination of gemcitabine (1000 mg/m2 on days one and eight) and docetaxel (75 mg/m2 on day one) every 21 days vs. combination of capecitabine (1250 mg/m2 twice a day for 14 days) and docetaxel (as above) every 21 days No difference in terms of objective response rate (ORR), progression-free survival (PFS), duration of response, or time-to-progression (TTP).	Abstract form only	High

		However, patients receiving gemcitabine plus docetaxel experienced significantly less hand-foot syndrome, diarrhea, and mucositis than those receiving capecitabine plus docetaxel.	
CCO 2007[277]	For patients with metastatic breast cancer who have received prior (neo)adjuvant anthracycline therapy, the combination of gemcitabine plus paclitaxel is superior compared to paclitaxel alone as first-line chemotherapy.	One RCT (Albain et al. 2004, Moinpour et al. 2004, O'Shaughnessy et al. 2003) Combination of gemcitabine (1250 mg/m2 of on days one and eight) and paclitaxel (175 mg/m2 on day one) every 21 days to the same dosage and schedule of paclitaxel without gemcitabine in patients with metastatic breast cancer who had previously received adjuvant or neoadjuvant anthracycline chemotherapy. That trial found a significantly superior ORR (40.8% versus 22.1%, p<0.0001), median TTP (5.2 months versus 2.9 months, HR=0.650, 95% CI 0.524 to 0.805), and overall survival (18.5 months versus 15.8 months, HR 0.775, 95% CI 0.627 to 0.959) in patients treated with the combination regimen.	High
CCO 2007[277]	Single-agent gemcitabine is NOT recommended for women with metastatic	One randomized phase III study (Feher et al. 2005)	High

	breast cancer who are being considered for first-line single-agent anthracycline chemotherapy.	Epirubicin (35 mg/m2 on days one, eight, and 15) vs. gemcitabine (1200 mg/m2 on days one, eight, and 15) every 28 days in postmenopausal patients aged 60 or older. No significant differences in terms of time to response and duration of response. Epirubicin was significantly better than gemcitabine in terms of ORR (40.3% versus 16.4%, p<0.0001), TTP (6.1 months versus 3.4 months, p=0.0001), and overall survival (19.1 months versus 11.8 months, p=0.004).		
CCO 2007[277]	The combination of gemcitabine, epirubicin, and paclitaxel (GET) is NOT recommended as first-line chemotherapy for women with metastatic breast cancer who are being considered for anthracycline-based combination chemotherapy	One randomized controlled trial (Zielinski et al. 2005) Combination of gemcitabine (1000 mg/m2 on days one and four), epirubicin (90 mg/m2 on day one), and paclitaxel (175 mg/m2 on day one) vs. combination of 5-fluorouracil (500 mg/m2), epirubicin (90 mg/m2), and cyclophosphamide (500 mg/m2), all on day one. Both combinations used a 21-day cycle.	Patients were required to have had one prior non-anthracycline adjuvant chemotherapy.	High

			No significant differences in terms of ORR, TTP, or OS Significantly higher haematological toxicities, polyneuropathy, and mucositis in the gemcitabine-containing arm.	
Post-anthracycline-exposure (anthracycline resistance or failure)				
NICE 2009[221]	July 2008	For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contra-indicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence: first line: single-agent docetaxel second line: single-agent vinorelbine or capecitabine third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).	A health economic analysis that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens, for patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated Vinorelbine: 2C evidence Capecitabine: 2C evidence Taxanes: 1A evidence The most cost-effective treatment sequence based on a threshold of £30,000 per QALY was docetaxel-capecitabine- vinorelbine. The ICER for this sequence was estimated to be £23,332 per QALY. When applying a threshold of £20,000 per QALY, the most cost-effective sequence was docetaxel- capecitabine.	The costs considered in the analysis were those relevant to the NHS, and included; drug acquisition costs, administration costs, cost of assessment and follow-up, cost of treating adverse events, cost of supportive and palliative care.

CECOG 2007[271]	May 2005	In patients with anthracycline-resistance or failure, considered for further chemotherapy, taxane-based treatment (monotherapy or combination of a taxane with gemcitabine or capecitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration.	Paclitaxel Nabholtz et al. 1996; Winer et al. 2004; Perez et al. 2001 Seidman et al. 1998 Docetaxel Mouridsen et al. 2002; Jones et al. 2005; Kuroi et al. 2003 Nanoparticle albumin paclitaxel (ABI-007, Abraxane). Gradishar et al. 2005 Docetaxel plus capecitabine O'Shaughnessy et al. 2002 Paclitaxel plus gemcitabine Albain et al. 2004 Docetaxel plus gemcitabine vs docetaxel plus capecitabine Chan et al. 2005	Phase III RCTs	High

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Carrick 2009[278]	First search in 2003 Update in November 2008	Women with metastatic breast cancer	Single chemotherapy agents that include cyclophosphamide, fluorouracil, epirubicin, lomustine and ifosamide vs. polychemo-therapy	Overall survival Time-to-progression Response rate Toxicity	Overall survival HR 0.88; 95%CI 0.83-0.93, p<0.00001 in favour of multiple agents (vs. single agent) HR 0.82; 95%CI 0.75-0.89, p<0.00001 in favour of multiple agents (vs. single agent taxane) HR 0.94; 95%CI 0.86-1.02, p=0.15 (multiple agents vs. single agent anthracycline) No significant heterogeneity between trials (X2 = 48.56, 35 df, p=0.06). Time to progression HR 0.78, 95%CI 0.74 - 0.82, p<0.00001 in favour of multiple agents (vs. single agent) but Heterogeneity was statistically significant (X2= 71.88, 26 df, p<0.00001; I2=64%). Overall response RR 1.29, 95%CI 1.14 -1.45, p<0.0001 in favour of multiple agents (vs. single agent) but Heterogeneity was statistically significant (X2=177.93, 45 df,	Search in Cochrane Breast Cancer Group Specialised Register + conference proceedings Compared to the first review (2004), 6 new trials were added (Albain 2004, GEICAM 2007, Norris 2000; O'Shaughnessy 2001; Stockler 2006, Thomas 2008) as 2 trials previously classified as 'ongoing' (Ejlertsen 2004; Heidemann 2004). Two RCTs included in the first review (Keller 2004; Liu 1986) were excluded on the basis of further assessment during the update	SR including 43 RCTs (9 742 women)	High

				p<0.00001, I2 =75%). Toxicity Higher toxicity level for : white cell count: RR of 1.49; 95% CI 1.24 to 1.79, p<0.0001. There was evidence of heterogeneity (X2 = 607.34, 34 df, p< 0.00001, I2 = 94%) There was no statistically significant difference between the groups for alopecia (RR 1.12, 95%CI 0.81 to 1.54, p=0.48) or for nausea and vomiting (RR 1.29, 95% CI 0.96 to 1.74, p=0.09). There was evidence of heterogeneity (X2= 394.44, 20 df, p<0.00001, I2 = 95%) and (X2 = 172.40, 29 df, p< 0.00001, I2 = 83%) respectively. The findings of this review are not necessarily applicable to some of the more modern single agents including, docetaxel, paclitaxel and capecitabine for example.			
Chan 2009[279]	Patients with locally advanced breast cancer or MBC	Docetaxel plus gemcitabine (DG) with docetaxel plus capecitabine (DC)	Progressio n-free survival Tumour response rate	Progression-free survival median PFS was 8.05 months [95% CI, 6.60 to 8.71] for GD and 7.98 [95% CI, 6.93 to 8.77] for CD Tumour response rate	Blinding of randomization and assessment were not reported	Phase III RCT	Moderate

	Overall survival	32% in both arms
	Toxicity	Overall survival No difference : p=0.983 Time-to-failure Longer in the DG arm (p=0.053) Non-hematologic toxicity Significantly lower in the DG arm Hematologic toxicity Rates for grades 3 to 4 leukopenia were higher in DG group (78% vs. 66%; p=0.025) as transfusions (DG, 17%; CD, 7%; p=0.0051).

5.6.3. Trastuzumab

Table 53 – Use of Trastuzumab in women with HER2-positive metastatic breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CECOG 2007[271]	May 2005		The use of first-line trastuzumab as either monotherapy or in combination with non-anthracycline-based chemotherapy was strongly recommended in patients with HER-2/neu protein overexpressing (3+ by IHC) or Her-2/neu FISH positive MBC regardless of age, prior adjuvant chemotherapy, or sites of metastatic disease. For patients with newly diagnosed MBC that is both hormone receptor positive and HER-2/neu positive, hormonal options should be explored first.	Randomized phase III trial (Slamon et al. 2001): trastuzumab plus chemotherapy vs. chemotherapy alone → significantly higher ORR and prolonged OS A phase II trial (Marty et al. 2005): docetaxel with or without trastuzumab has shown benefit in OS. A series of phase II trials (Burstein et al. 2003; Jahanzeb et al. 2002; O'Shaughnessy et al. 2004; Sledge 2003; Pegram and Slamon 1999; Burris et al. 2004; Leyland-Jones et al. 2003): Trastuzumab + other cytotoxic drugs including vinorelbine, platinum compounds, capecitabine and gemcitabine		High

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Von Minckwitz 2009[280]	NA	Patients with HER-2–positive breast cancer that progresses during treatment with trastuzumab	Capecitabine alone (C group; n=78) OR Capecitabine with continuation of trastuzumab in 3-week cycles (C/T group; n=78)	Time-to-progression Overall survival Overall response rates Toxicity	Time to progression C group: median 5.6 months C/T group: median 8.2 months HR 0.69 (95% CI, 0.48 to 0.97; two-sided log-rank p= .0338). Overall survival rates C group: 20.4 months (95% CI, 17.8 to 24.7) C/T group: 25.5 months (95% CI, 19.0 to 30.7) (p= .257). Overall response rates C group: 27.0% C/T group: 48.1% odds ratio, 2.50; p= .0115). Toxicity Continuation of trastuzumab beyond progression was not associated with increased toxicity.	German Breast Group 26/Breast International Group 03-05 trial Random assignment was stratified by pretreatment No investigator blinding Kaplan-Meier product-limit method Sensitivity analyses Follow-up: 15.6 months	RCT	High

5.6.4. Bevacizumab

Table 54 – Use of Bevacizumab in women with metastatic breast cancer (Update 2013)

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Wagner 2012[120]	• SR • Funding: Wilhelm-Roux-Programme, University Halle-Wittenberg, Germany, Ministry for Education and Research Germany. • Search date: January 2011 (conference abstracts) and September 2011, starting in 2000 (electronic databases) • Databases: CENTRAL, MEDLINE, EMBASE, the Cochrane Breast Cancer Group's Specialised Register, registers of ongoing trials	Women with histologically or cytologically confirmed, endocrine refractory or resistant, locally advanced or metastatic breast cancer. Total number of included studies: seven RCTs, one register, and five ongoing trials. Five included RCTs addressed predominantly HER-2 negative patients (maximum of 4% HER-2 positive patients).	Systemic, oral or intravenous, vascular-endothelial-growth-factor (VEGF)- targeting therapies, in combination with chemotherapy, with or without trastuzumab. Only agents directly targeting VEGF, such as bevacizumab, were the subject of this review. Vs. Systemic chemotherapy, with or without trastuzumab, in the same dose, route and schedule of administration as in the experimental intervention.	Overall survival (OS) First-line chemotherapy with versus without bevacizumab, subgroup HER-2 negative (N=3; Miles 2010 [Avado]; Miller 2007 [E2100]; Robert 2011 [Ribbon-1 Cape Cohort and T+Anthra Cohort]) HR 0.93 (95% CI 0.84 to 1.04) Second-line chemotherapy with versus without bevacizumab, subgroup HER-2 negative (N=1; Brufski 2011 [Ribbon-2];) HR 0.90 (95% CI 0.71 to 1.14) Progression-free-survival (PFS) First-line chemotherapy with versus without bevacizumab, subgroup HER-2 negative (N=4; Martin 2011; Miles 2010 [Avado]; Miller 2007 [E2100; Robert 2011 [Ribbon-1 Cape Cohort and T+Anthra Cohort]) HR 0.67 (95% CI 0.61 to 0.73) Second-line chemotherapy with versus without bevacizumab, subgroup HER-2 negative (N=1; Brufski 2011 [Ribbon-2]) HR 0.78 (95% CI 0.64 to 0.93) Adverse effects	Quality of SR: low risk of bias Quality of included studies: of the five studies that addressed (predominantly) HER-2 negative patients, two were low risk of bias, two were high risk of bias and one was unclear risk of bias. Overall conclusion of the authors (pertaining to all studies): "Overall, the clinical value of bevacizumab in metastatic breast cancer can at best be considered as modest. Whether the observed benefit in time to progression, which does not translate into a benefit in overall survival, quality of life, or other patients-related outcomes is a clinically meaningful patient benefit is highly questionable. In any case, this benefit has to be weighed up against an increased risk of serious adverse events, such as hypertension, bleeding, and arterial thromboembolic events, which have previously been associated with bevacizumab. Nevertheless, treatment related

	and proceedings of conferences.		Applies to both first-line and second-line sample Grade 3/4 adverse events: OR 1.77 (95% CI 1.44 to 2.18) Serious adverse events: OR 1.41 (95% CI 1.13 to 1.75) Treatment-related deaths: OR 0.63 (95% CI 0.38 to 1.06) AE's previously shown to be associated with bevacizumab or chemotherapy: "The risk of hypertension grade > 3 (OR 14.75; 95% CI 8.14 to 26.70) and proteinuria grade > 3 (OR 10.55; 95% CI 3.59 to 30.99) were significantly higher for patients treated with bevacizumab. Furthermore, the risk of bleeding grade > 3 increased more than three-fold in patients treated with bevacizumab (OR 3.23; 95% CI 1.29 to 8.05). There was also increased frequencies of congestive heart failure (CHF), left ventricular systolic dysfunction or cardiomyopathy in those patients treated with bevacizumab compared to those patients without bevacizumab. The incidence of bevacizumab-specific adverse events were comparable or lower in Smith 2011 (ATHENA), compared to the bevacizumab groups from RCTs. Hypertension was reported in 4.4% (95% CI 3.6 to 5.4%) compared to 10.9% (95% CI 9.6 to 12.3%), proteinuria in 1.7% (95% CI 1.3 to 2.4%) compared to 2.7% (95% CI 2.1 to 3.5%), gastrointestinal (GI) perforation in 0.3% (95% CI 0.1 to 0.6%) and 0.7%	deaths were lower in patients treated with versus without bevacizumab. Therefore, the clinical relevance of bevacizumab in metastatic breast cancer remains controversial, as reflected by the different attitudes of health authorities in Europe and the United States."

				(95% CI 0.4 to 1.2%), bleeding in 1.4%(95%CI 1.0 to 2.0%) and 1.8%(95%CI 1.3 to 2.6%) and CHF in 0.4% (95% CI 0.2 to 0.8%) and 1.3% (95% CI 0.7 to 2.7%), respectively.	

5.6.5. *Treatment of metastases*

Table 55 – Treatment of bone and brain metastases

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Bone metastases						
NICE 2009[221]	July 2008	Women with advanced breast cancer	Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain. The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication. Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain. An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery	Three systematic reviews (Pavlakis et al. 2005; Martinez-Zapata et al. 2006 and Sze et al. 2002), a guideline (Warr et al. 2002), five RCTs (Tripathy et al. 2004; Hartsell et al. 2005; Salazar et al. 2001; Wardley et al. 2005 and Rasmusson et al. 1995), two comparative or cohort studies (Weinfurt et al. 2004 and Pecherstorfer et al. 2006) and six case series (Broos et al.1993; Gerszten et al. 2005; Gristina et al. 1983; Scarantino et al. 1996; Borojevic et al. 1999 and Durr et al. 2002). Bisphosphonates had little impact on overall survival, but could reduce pain and the occurrence of skeletal events. Four papers offered good evidence on the role of radiotherapy in bone		High

				metastases, including a Cochrane review (Sze et al., 2002) and three RCTs (Hartsell et al., 2005; Salazar et al., 2001 and Rasmussen et al., 1995)	
Brain metastases					
NICE 2009 [221]	July 2008	Women with advanced breast cancer	Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease. Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis. Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy. Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate.	Retrospective case series Surgery (Pieper et al. 1997 and Wroski et al. 1997), stereotactic radiosurgery (Combs et al. 2004; Lederman et al. 2001; Amendola et al. 2000; Firlik et al. 2000; Levin et al. 2002; Akyurek et al. 2007 and Muacevic et al., 2004), chemotherapy (Rivera et al. 2006; Rosner et al. 1986; Boogerd et al. 1992; Franciosi et al. 1999; Oberhoff et al. 2001; Lassman 2006 and Trudeau 2006) and whole brain radiotherapy (WBRT) (Bartsch et al. 2006; Fokstuen et al. 2000; Korzeniowski and Szpytma 1987; Lentzsch et al. 1999; Liu et al. 2006; Ogura et al. 2003 and Mahmoud-Ahmed et al. 2002; Viani et al. 2007 and Johansen et al. 2008).	Low

5.7. Management of Complications of Local Treatment

Table 56 – Management of complications of local treatment

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Lymphoedema						
NICE 2009[221]	July 2008	Women with early invasive breast cancer	Inform all patients with early breast cancer about the risk of developing lymphoedema and give them relevant written information before treatment with surgery and radiotherapy. Give advice on how to prevent infection or trauma that may cause or exacerbate lymphoedema to patients treated for early breast cancer. Ensure that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.	RCTs: Bendz and Fagevik, 2002; Box et al., 2002a and 2002b; Cave and Jones, 2006 and Cheema et al., 2008. Observational studies: Cordero et al., 2003; Coward, 1999; Karki et al., 2001, 2004; Lane 2005 and Sandel et al., 2005.		High
NICE 2009[221]	July 2008	Women with advanced breast cancer	Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme. Offer all patients with lymphoedema complex decongestive therapy (CDT) as the first stage of lymphoedema management. Consider using multi-layer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery. Provide patients with lymphoedema with at least two suitable compression garments. These should be of the appropriate class and size, and a choice of fabrics and colours should be available.	A guideline (Harris et al. 2001), one very high quality systematic review (Moseley et al. 2007), two systematic reviews of less quality (Kligman et al. 2004 and Rinehart-Ayres et al. 2007), four randomised trials (Didem et al. 2005; Irdesel and Kahraman 2007; Badger et al. 2004 and Johansson et al. 2005) and six case series or phase II studies (Vignes et al. 2007; Hamner and Fleming 2007; Sitzia et al. 2002; Kim et al. 2007; Koul et al. 2007 and Fiaschi et al. 1998).		

Arm mobility					
NICE 2009[221]	July 2008	Women with early invasive breast cancer	All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy regimens. Identify breast cancer patients with pre-existing shoulder conditions preoperatively as this may inform further decisions on treatment. Give instructions on functional exercises, which should start the day after surgery, to all breast cancer patients undergoing axillary surgery. This should include relevant written information from a member of the breast or physiotherapy team. Refer patients to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment.	RCTs: Wingate et al. 1989; Dawson et al. 1989; Gerber et al. 1992; Le Vu et al. 1997; Na et al. 1999; Bendz and Fagevik 2002; Box et al. 2002; Gordon et al. 2005; Johannsson 2005; Lauridsen et al. 2005; Sandel et al. 2005; Wang et al. 2005; Kilbreath et al. 2006; Beurskens et al. 2007; Cinar et al. 2008.	High
Cancer-related fatigue					
NICE 2009[221]	July 2008	Women with advancedbreast cancer	Offer all patients with advanced breast cancer for whom cancer-related fatigue is a significant problem an assessment to identify any treatable causative factors and offer appropriate management as necessary. Provide clear, written information about cancer-related fatigue, organisations that offer psychosocial support and patient-led groups. Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-	Two systematic reviews (Minton et al. 2007 and Cramp and Daniel, 2008) one on drug therapies and one on exercise regimes, together with two RCTs (Headley et al. 2004 and Bordeleau et al. 2003) and a poor quality case series (Carson et al. 2007). no significant effect of progestational steroids, including megesterol acetate.	High

			related fatigue.	Meta-analysis of data from 28 RCTs (Cramp and Daniel, 2008) highly significant effect of exercise		
Uncontrolled local disease						
NICE 2009[221]	July 2008	Women with advanced breast cancer	A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms. A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team. A palliative care team should assess all patients with uncontrolled local disease in order to plan a symptom management strategy and provide psychological support.	Low patient number case series (Bower et al. 1992; Kuge et al. 1996; Lund-Nielsen et al. 2005; Kumar et al. 1987; Kolodziejski et al. 2005; Faneyte et al. 1997 and Pameijer et al. 2005), the majority of which were retrospective		Low
Menopausal symptoms						
NICE 2009[221]	July 2008	Women with early invasive breast cancer	Discontinue HRT in women who are diagnosed with breast cancer. Do not offer HRT (including oestrogen/progestogen combination) routinely to women with menopausal symptoms and a history of breast cancer. HRT may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed.	Systematic reviews: Antoine et al. 2007; Bordeleau et al. 2007; Carpenter et al. 2007; Col et al. 2005; Deng et al. 2007; Ganz et al. 2000; Goodwin et al. 2008; Hickey et al. 2005; Kenemans et al. 2005; Kimmick et al. 2006; Kroiss et al. 2005; Loprinzi et al. 2007; MacLennan et al. 2004; Modelska et al. 2002; Mom et al. 2006; Nedrow et al. 2006;	Some SR included studies of women without breast cancer	

			Offer information and counselling for all women about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment. The selective serotonin re-uptake inhibitor antidepressants paroxetine and fluoxetine may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen. Clonidine, venlafaxine and gabapentin should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects. Soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended for the treatment of menopausal symptoms in women with breast cancer.	Nelson et al., 2006; Pritchard et al. 2002; Royal College of Obstetricians and Gynaecologists et al. 2006; Thompson et al. 2008; Tremblay et al. 2008; von Schoultz et al. 2005 and Walji et al. 2007.	
Anaemia					
CECOG 2007[271]	May 2005	Women with MBC	Supportive treatment with erythropoesis stimulating proteins can be considered for the maintenance of quality of life in the case of symptomatic anemia including disease- or treatment-associated fatigue. For acute symptoms and in the case of non responsiveness to erythropoesis stimulating proteins, erythrocyte transfusions should be administered. In contrast, in patients undergoing cytotoxic treatment, erythropoesis stimulating proteins	Leyland-Jones et al. 2005	Low

			should not be administered for the prevention of anemia or to reach high hemoglobin targets.		
Leukopenia					
CECOG 2007[271]	May 2005	Women with MBC	In the case of chemotherapy-associated myelosuppression or a history of recurrent febrile neutropenia following previous chemotherapy, the use of myeloid colony stimulating factors can be considered. If the anticipated febrile neutropenia rate is high (>20% according to NCCN guidelines, >40% according to ASCO guidelines, the primary prophylactic use of myeloid colony stimulating factors should be considered.	GDG consensus	Low
Psychosocial distress					
CECOG 2007[271]	May 2005	Women with MBC	Psychosocial support should be available to patients with MBC. No recommendation of an optimal type of intervention, an optimal timing or the duration of such interventions can be formulated.	GDG consensus	Low

5.8. Hormone replacement therapy

Table 57 – Hormone replacement therapy for post-menopausal women

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Holmberg 2008[281]	NA	Post-menopausal women previously treated for breast cancer	Hormone replacement therapy (n=221) vs. best management of menopausal symptoms without hormones (n=221)	New breast cancer event Distant Metastasis – Free and Overall Survival	New breast cancer event HT arm: 39 women experienced a new breast cancer event vs. 17 women in the control group HR = 2.4; 95%CI = 1.3 to 4.2. Cumulative incidences at 5 years were 22.2% in the HT arm and 8.0% in the control arm. Distant Metastasis – Free and Overall Survival HT arm: 6 deaths + 6 women with distant metastases. Control arm: 5 deaths + 4 women with distant metastases. The difference in distant metastasis – free survival was not statistically significant (p = 0.51, log-rank test). → After extended follow-up, there was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HT	More women in the HT arm than the control arm had had hormone receptor–positive cancer (62.3% vs 54.5%). No blinding Possibility of information bias related to possibly more vigorous follow-up and diagnosis of events in the HT arm. However, identical number of follow-up visits in the two groups Median follow-up: 4 years	Randomized, non-placebo-controlled noninferiority trial (HABITS)	Moderate

5.9. Psychological intervention

Table 58 – Psychological support for women with breast cancer

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Andersen 2008[282]	NA	Women with regional breast cancer surgically treated	Assessment + Psychologic intervention (n=114) Versus Assessment alone (n=113)	Breast cancer recurrence Breast cancer related death	Intervention: 26 sessions in small groups, led by 2 psychologists (39 hours over 12 months); muscle relaxation, problem solving for common difficulties, identifying supportive family members or friends, improving dietary habits, strategies to cope with treatment side effects… Median Follow-up: 11 years Breast cancer recurrence HR 0.55 (95%CI 0.32-0.96; p=0.034) Breast cancer related death HR 0.44 (95% CI 0.22-0.86; p=0.016) Overall survival HR=0.51 (95% CI 0.28-0.93; p=0.028)	No blinding Patients were paid per assessment Cox proportional Hazards analysis for survival	RCT	Moderate

5.10. Surveillance (Follow-Up)

Table 59 – Surveillance of women treated for a breast cancer

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
History/physical examination						
ASCO 2006[283]	March 2006	Patients with breast cancer	History/physical examination is recommended every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually	The GIVIO Investigators 1994 Rosselli et al. 1994	No recent prospective studies evaluating alternative clinical follow-up schedules for surveillance. The current recommendations are the same as the original 1997 guidelines.	Moderate
Patient education regarding symptoms of recurrence						
ASCO 2006[283]	March 2006	Patients with breast cancer	Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, abdominal pain, dyspnea or persistent headaches	A meta-analysis (De Bock et al. 2004) of 12 studies (n=5 045 patients): 40% (95% CI, 35% - 45%) of patients with locoregional recurrences were diagnosed during routine clinic visits or routine testing 60% developed symptomatic recurrences before their scheduled clinical visits.	SR and meta-analysis	Moderate
Referral for genetic counseling						
ASCO 2006[283]	March 2006	Patients with breast cancer	Women at high risk for familial breast cancer syndromes should be referred for genetic	US Preventive Services Task Force 2005	Recommendation statement	Low

			counselling. Criteria to recommend referral include the following: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before the age of 50 years; two or more first- or second degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative			
Breast self-examination (BSE)						
ASCO 2006[2] [83]	March 2006	Patients with breast cancer	All women should be counseled to perform monthly breast self-examination Women should be made aware that monthly BSE does not replace mammography as a breast cancer screening tool.	A large comparative study (Thomas et al. 2002; n > 260 000 Chinese women) BSE vs no surveillance Efficacy of BSE alone No survival benefit in the group BSE. Similar cumulative breast cancer mortality rates through 10 years of follow-up (risk ratio=1.04; 95% CI, 0.82 to 1.33; p=.72) More benign breast lesions diagnosed in the BSE group	Routine screening mammography was not available.	Moderate
Mammography						
NICE 2009[221]	July 2008	Women	Offer annual mammography to all patients with early breast cancer, including DCIS. Patients diagnosed with early breast cancer who are already eligible for screening should	Two systematic reviews of observational studies		Low

	have annual mammography for 5 years.	Ipsilateral local recurrence Proportion detected by follow-up mammography between 8%-50% (Grunfeld et al., 2002 and McGahan and Noorani 2000) and median values of 26% (McGahan and Noorani, 2000) and 27% (Grunfeld et al., 2002). Temple et al. 1999: Se: 38%-74%; Sp: 39%-60%. Contralateral breast cancer Proportion detected by follow-up mammography between 8%-80% (Grunfeld et al., 2002 and McGahan and Noorani, 2000) and median values of 36% (McGahan and Noorani, 2000) and 45% (Grunfeld et al., 2002). Physical examination plus mammography (Temple et al., 1999): Se: 81%-88% Sp: 96.5%-99.9% For DCIS, 2 retrospective studies (Liberman et al., 1997

				and Weng et al., 2000).		
ASCO 2006[283]	March 2006	Patients with breast cancer	Women treated with breast-conserving therapy should have their first post-treatment mammogram no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained every 6 to 12 months for surveillance of abnormalities. Mammography should be performed yearly if stability of mammographic findings is achieved after completion of locoregional therapy.	Grunfeld et al. 2002	Observational study (Included in NICE 2009)	Low
Coordination of care						
ASCO 2006[283]	March 2006	Patients with breast cancer	Continuity of care for breast cancer patients is encouraged and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormonal therapy for the particular patient; this may necessitate referral for oncology assessment if a patient is receiving adjuvant endocrine therapy.	Grunfeld et al. 1995, 1996, 1999, 2006; Gulliford et al. 1997 Institute of Medicine and National Research Council, Committee on Cancer Survivorship 2005	Well designed RCT involving 296 women receiving follow-up for breast cancer in specialist oncology and surgical clinics in Great Britain IoM proposed a shared-care model that could be integrated across different specialties	High
Pelvic examination						
ASCO 2006[283]	March 2006	Patients with breast cancer	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians	No	See literature on 'Tamoxifen'	Low

Intensive surveillance monitoring						
ASCO 2006[283]	March 2006	Patients with breast cancer	Intensive surveillance monitoring (CBC testing, chest x-ray, bone scans, liver ultrasound and computed tomography) is not recommended for routine breast cancer surveillance.	Intensive monitoring Meta-analysis of 2 well-designed RCTs (The GIVIO Investigators 1994; Rosselli et al. 1994) involving a total of 2 563 women: regular clinical visits vs intensive surveillance Overall Survival HR=0.96; 95% CI, 0.80 to 1.15 Disease-free survival HR=0.84;95%CI, 0.71 to 1.00 5-year mortality No statistical difference In The GIVIO Investigators (1994): higher percentage of asymptomatic metastases was found in the intensive surveillance group compared with the control group (31% v 21%, respectively) → no improvement in survival. Routine blood tests Palli et al. 1999 Rojas et al. 2005 CT scans 2 retrospective studies : Drotman et al. 2001 ; Hurria et al. 2003	Intensive surveillance includes clinical visits, bone scans, liver US, chest x-rays, and laboratory testing	High Low Low

FDG-PET scanning						
NCC-HTA 2007[222]		Patients with breast cancer and clinical suspicion of recurrence (with arm pain or other symptoms referable to the brachial plexus)	FDG-PET Reference standard: histopathology/follow-up	One systematic review (BCBS 2003) and one additional primary study (Goerres 2003) both included in previous KCE report.	See above	
ASCO 2006[283]	March 2006	Patients with breast cancer	FDG-PET scanning is not recommended for routine breast cancer surveillance	2 retrospective cohort studies (Vranjesevic et al. 2002, Kamel et al. 2003) 1 meta-analysis of 16 studies comprising 808 patients (Isasi et al. 2005): - pooled sensitivity: 90% (95% CI, 86.8% to 93.2%) - pooled false-positive rate: 11% (95% CI, 86.0% to 90.6%).		Low High
Breast MRI						
NICE 2009[227]	July 2008	Women with early invasive breast cancer or DCIS.	Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.	7 diagnostic studies of follow-up MRI (Aichinger et al., 2002; Bone et al., 1995; Buthiau et al., 1995; Coulthard et al., 1999; Heywangkobrunner et al., 1993; Preda et al., 2006 and Viehweg et al., 1998). Se MRI: 85.7%-100%. Sp MRI: 82%-100%		Low

ASCO 2006[283]	March 2006	Patients with breast cancer	There is no evidence that breast MRI improves outcomes when used as a breast cancer surveillance tool during routine follow-up in asymptomatic patients. Breast MRI is not recommended for routine breast cancer surveillance.	Kuhl et al. 2005 Leach et al. 2005	2 prospective cohort studies in women at high risk for breast cancer based on family history	Low
Re-assessment of ER and HER2 status						
NICE 2009[227]	July 2008	Patients with advanced breast cancer with ER/PR and HER2 status known in primary tumour	Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to reassess ER status. 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. Assess ER and HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER2 status.	17 observational studies all of which compared paired (from the same patient) biopsy or FNA samples from primary and locoregional or metastatic tumour tissue. HER2 (Niehans et al. 1993; Shimizu et al. 2000; Gancberg et al. 2002; Carlsson et al. 2004; Regitnig et al. 2004; Gong et al. 2005; Zidan et al. 2005; Lorincz et al. 2006; Rom et al. 2006; Pectasides et al. 2006; Tapia et al. 2007 and Santinelli et al. 2008) and/or ER (Spataro et al. 1992; Johnston et al. 1995; Lower et al. 2005; Rom et al. 2006; Shimizu et al. 2000 and Brankovic-Magic et al. 2002)	Papers were concerned with identifying the rate of status change but did not address overall survival, time to progression or quality of life. Approximately 15% of patients showed a change in ER status, from positive to negative, comparing primary with locoregional or metastatic tumour samples. 93% of patients tested for HER2 status showed no change between paired samples.	Low

Abbreviations; PCP, primary care physician; FDG-PET,18Ffluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging.

Study ID	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Beaver 2009[284]	NA	Women treated for breast cancer who were at low to moderate risk of recurrence.	Traditional hospital follow-up (consultation, clinical exam and mammo-graphy as per hospital policy) Versus Telephone follow-up by specialist nurses (consultation with structured intervention and mammography according to hospital policy).	Psychological morbidity (anxiety, general health), participants' needs for information, participants' satisfaction, clinical investigations ordered, and time to detection of recurrent disease.	No difference in anxiety and in number of investigations ordered but higher satisfaction in the telephone group (intention to treat P<0.001). Recurrences were few (4.5%), with no differences between groups for time to detection (median 60.5 (range 37-131) days in hospital group v 39.0 (10-152) days in telephone group; P=0.228).	Trial registration National Cancer Research Institute 1477.	Equivalence RCT	High

6. SUMMARY OF FINDINGS TABLES

6.1. Axillary surgery in early invasive breast cancer with a positive sentinel node

Table 60 – Clinical evidence profile: ALND vs. SLND in early invasive breast cancer with a positive sentinel node

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects** *Time frame is patients enrolled from May 1999 to December 2004*	
							With ALND	**With SLND only**		**Risk with ALND**	**Risk difference with SLND only** (95% CI)
5-year overall survival (CRITICAL OUTCOME)											
891 (1 study) 5 years	no serious risk of bias	serious[1]	no serious indirectness	serious[2,3,4]	undetected	⨁⨁⊖⊖ **LOW**[1,2,3,4] due to inconsistency, imprecision			**HR 0.87** (0.62 to 1.23)[5,6]		
5-year disease free survival (CRITICAL OUTCOME)											
891 (1 study) 5 years	no serious risk of bias	serious[1]	no serious indirectness	serious[2,3,4]	undetected	⨁⨁⊖⊖ **LOW**[1,2,3,4] due to inconsistency, imprecision			**HR 0.88** (0.62 to 1.25)[6]		
Axillary recurrence (CRITICAL OUTCOME)											
856 (1 study) 5 years	serious[7]	serious[1]	no serious indirectness	serious[3,4]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,3,4,7] due to risk of bias, inconsistency, imprecision	13/420 (3.1%)	7/436 (1.6%)	**RR 0.52** (0.21 to 1.28)	**31 per 1000**	**15 fewer per 1000** (from 24 fewer to 9 more)

Wound infections (IMPORTANT OUTCOME)											
744 (1 study) 30 days	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ **LOW**[3,7] due to risk of bias, imprecision	31/373 (8.3%)	11/371 (3%)	**RR 0.36** (0.18 to 0.7)	**83 per 1000**	**53 fewer per 1000** (from 25 fewer to 68 fewer)
Axillary seromas (IMPORTANT OUTCOME)											
744 (1 study) 30 days	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ **LOW**[3,7] due to risk of bias, imprecision	53/373 (14.2%)	21/371 (5.7%)	**RR 0.40** (0.25 to 0.65)	**142 per 1000**	**85 fewer per 1000** (from 50 fewer to 107 fewer)
Axillary paresthesias (IMPORTANT OUTCOME)											
555 (1 study) 12 months	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ **LOW**[3,7] due to risk of bias, imprecision	113/287 (39.4%)	24/268 (9%)	**RR 0.23** (0.15 to 0.34)	**394 per 1000**	**303 fewer per 1000** (from 260 fewer to 335 fewer)
Lymphedema (reported subjectively) (IMPORTANT OUTCOME)											
525 (1 study) 12 months	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ **LOW**[3,7] due to risk of bias, imprecision	52/272 (19.1%)	14/253 (5.5%)	**RR 0.29** (0.16 to 0.51)	**191 per 1000**	**136 fewer per 1000** (from 94 fewer to 161 fewer)
Lymphedema (by arm measurements) (IMPORTANT OUTCOME)											
468 (1 study) 12 months	serious[7]	no serious inconsistency	no serious indirectness	serious[3,4]	undetected	⊕⊕⊖⊖ **LOW**[3,4,7] due to risk of bias, imprecision	26/242 (10.7%)	14/226 (6.2%)	**RR 0.58** (0.31 to 1.08)	**107 per 1000**	**45 fewer per 1000** (from 74 fewer to 9 more)

Quality of life - not measured											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment

[1] *Heterogeneity assumed, because systemic therapy was at the discretion of the treating physician; survival can be influenced by the provided adjuvant systemic therapy*
[2] *This trial concerns a non-inferiority trial and the upper limit of the CI did not cross the pre-specified boundary of 1.3*
[3] *Optimal information size not reached*
[4] *CI includes both benefit and harm*
[5] *90% CI was used*
[6] *Adjusted HR; control risk not applicable*
[7] *No blinding*

Table 61 – 5 year-overall survival: SLND vs. ALND in early invasive breast cancer with positive sentinel nodes

Study design	Studies GRADE level of evidence	Median follow-up	N deaths (breast cancer related)	Sample size SLND	Sample size ALND	5-year survival Kaplan-Meier (95% CI) SLND	5-year survival Kaplan-Meier (95% CI) ALND	Unadjusted HR (CI) SLND vs. ALND *<1 favours SLND*	Adjusted HR (CI) SLND vs. ALND *<1 favours SLND*
Macrometastases and micrometastases combined									
RCT	Giuliano 2011[3] LOW	6.3 years	SLND: 42 ALND: 52	436	420	92.5% (90.0%-95.1%)	91.8% (89.1%-94.5%)	0.79 (90%CI 0.56-1.10)[π]	0.87* (90%CI, 0.62-1.23)[π]
Observa-tional study	Yi 2010[28] VERY LOW	50 months	Global: 1 460	4 425	22 561				1.0** (95%CI, 0.9-1.2)
Observa-tional study	Yi 2013[29] VERY LOW	SLND: 5.5 years ALND: 4.9 years		188	673	95.5%	94.3%		
Macrometastases only									
Observa-tional study	Bilimoria 2009[20] VERY LOW	SLND: 64 months ALND: 62 months		1 458	18 617	81.3% (79.1%-83.6%)	81.8% (81.2%-82.4%)	0.97 (95% CI 0.85-1.11)	0.89[¶] (95% CI 0.76-1.04)

Micrometastases only									
Observa-tional study	Bilimoria 2009[20] VERY LOW	SLND: 64 months ALND: 62 months		530	1 673	88.6% (85.6%-91.6%)	90.9% (89.3%-92.4%)	0.79 (95% CI 0.57-1.10)	0.84¶ (95% CI 0.60-1.19)
	Cortesi 2012[23] VERY LOW	48.6 months	Global: 34	34	142	96%	96%		
	Wasif 2010[27] VERY LOW	36 months		2 160	3 193	89%	90%		
	Yi 2010[28] VERY LOW	50 months		2 240	4 598				1.2** (95%CI, 0.9-1.7)

***** *Adjusted for age and adjuvant treatment; ** Adjusted for age and tumour size ;* ¶ *Adjusted for age, T classification, tumour grade, margin status, chemotherapy administration, radiation treatment, hormonal therapy administration, and hospital type.* ∏*A 90% power was set by the researchers to confirm the non-inferiority of SLND alone compared with ALND*

Table 62 – 5 year-disease free survival: SLND vs. ALND in early invasive breast cancer with positive sentinel nodes (who underwent BCS)

Study design	Studies GRADE level of evidence	Median follow-up	N deaths (breast cancer related)	Sample size SLND	Sample size ALND	5-year disease free survival (Kaplan-Meier) SLND	5-year disease free survival (Kaplan-Meier) ALND	Unadjusted HR (95% CI) SLND vs. ALND *<1 favours SLND*	Adjusted HR (95% CI) SLND vs. ALND *<1 favours SLND*
Macrometastases and micrometastases combined									
Observa-tional study	Yi 2013[29] VERY LOW	SLND: 5.5 years ALND: 4.9 years		188	673	94.3% (91.1% - 98.0%)	93.8% (91.4% - 95.5%)	0.3 (95% CI 0.1 to 1.01)	0.3* (95% CI 0.1 to 1.1)

** Adjusted for clinical T stage, age, and adjuvant treatment*

Table 63 – Axillary recurrence: SLND vs. ALND in early invasive breast cancer with positive sentinel nodes

Study design	Studies GRADE level of evidence	Recurrence SLND	Patients at risk SLND	Proportion of recurrence in patients at risk (SLND)*	Recurrence ALND	Patients at risk ALND	Proportion of recurrence in patients at risk (ALND)*	Difference in recurrence proportions (SLND vs. ALND) (95% CI) A positive % indicates a higher rate of recurrence in SLND-alone group
Macrometastases and micrometastases combined								
RCT	Giuliano 2011[3] VERY LOW	7	436	1.6%	13	420	3.1%	- 1.5% (-3.5% ; +0.5%)
Macrometastases only								
Observa-tional studies	Bilimoria 2009[20] VERY LOW	17	1 458	1.2%	187	18 617	1.0%	+0.2% (-0.4% ; +0.7%)
	Yi 2010[28] VERY LOW	5	2 185	0.2%	15	17 963	0.08%	+0.12% (-0.06% ; +0.35%)
	Fan 2005[24] VERY LOW	0	11	0%	6	58	10.3%	-10.34% (-24.2% ; +3.5%)
Micrometastases only								
Observa-tional studies	Bilimoria 2009[20] VERY LOW	3	530	0.6%	3	1 673	0.2%	+0.4% (-0.28% ; +1.06%)
	Bulte 2009[21] VERY LOW	0	20	0%	0	18	0%	0% (-9.71% ; +9.71%)
	Cortesi 2012[23] VERY LOW	0	34	0%	0	142	0%	0% (-4.05% ; +4.05%)
	Fan 2005[24] VERY LOW	1	27	0.04%	0	18	0%	+0.04% (-7.31% ; +14.72%)
	Pepels 2012[26] VERY LOW	8	141	5.7%	8	793	1.0%	+4.7% (+0.78% ; +8.55%)
	Yi 2010[28] VERY LOW	?	2 240	?	?	4 598	?	NS

Study design	Studies GRADE level of evidence	Recurrence SLND	Patients at risk SLND	Proportion of recurrence in patients at risk (SLND)*	Recurrence ALND	Patients at risk ALND	Proportion of recurrence in patients at risk (ALND)*	Difference in recurrence proportions (SLND vs. ALND) (95% CI) A positive % indicates a higher rate of recurrence in SLND-alone group
ITC only								
Observa-tional studies	Calhoun 2005[22] VERY LOW	0	17	0%	0	61	0%	0% (-7.91% ; +7.91%)
	Giobuin 2009[25] VERY LOW	0	18	0%	0	16	0%	0% (-10.78% ; +10.78%)
	Pepels 2012[26] VERY LOW	7	345	2.0%	4	396	1.0%	+1.0% (-0.77% ; +2.8%)

** Proportion computed as the number of recurrences observed on the number of patients at risk at the beginning of the study*

6.2. Trastuzumab in patients with HER-2 positive invasive (non metastatic) breast cancer

Table 64 – Clinical evidence profile: trastuzumab with adjuvant non-anthracycline chemotherapy vs. trastuzumab with adjuvant anthracycline-taxane chemotherapy in patients with HER-2 positive invasive (non metastatic) breast cancer

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** With Adjuvant anthracycline-taxane chemotherapy regimen plus trastuzumab	With Adjuvant non-anthracycline chemotherapy regimen plus trastuzumab	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with Adjuvant anthracycline-taxane chemotherapy regimen plus trastuzumab	Risk difference with Adjuvant non-anthracycline chemotherapy regimen plus trastuzumab (95% CI)
Overall survival (CRITICAL OUTCOME)											
2149 (1 study) 65 months	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to inconsistency, imprecision	94/1074 (8.8%)	113/1075 (10.5%)	**RR 1.20** (0.93 to 1.56)[3]	**88 per 1000**	**18 more per 1000** (from 6 fewer to 49 more)
Disease free survival (CRITICAL OUTCOME)											
2149 (1 study) 65 months	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to inconsistency, imprecision	185/1074 (17.2%)	214/1075 (19.9%)	**RR 1.16** (0.97 to 1.38)	**172 per 1000**	**28 more per 1000** (from 5 fewer to 65 more)
Congestive heart failure (New York Heart Association grade 3 or 4) (CRITICAL OUTCOME)											
2149 (1 study) 65 months	serious[4]	serious[1]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**[1,4] due to risk of bias, inconsistency	21/1074 (2%)	4/1075 (0.37%)	**RR 0.19** (0.07 to 0.55)	**20 per 1000**	**16 fewer per 1000** (from 9 fewer to 18 fewer)
>10% relative reduction in left ventricular ejection fraction (CRITICAL OUTCOME)											
2149 (1 study) 65 months	serious[4]	serious[1]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**[1,4] due to risk of bias, inconsistency	194/1074 (18.1%)	97/1075 (9%)	**RR 0.50** (0.4 to 0.63)	**181 per 1000**	**90 fewer per 1000** (from 67 fewer to 108 fewer)

[1] One multicentre trial without information about heterogeneity across sites; [2] CI includes no effect; [3] Results presented as RR for dying; [4] No blinding (high risk of bias)

6.3. Bisphosphonates in early breast cancer women without metastases

Table 65 – Clinical evidence profile: Bisphosphonates vs. no bisphosphonates in early breast cancer women without metastases

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects** *Time frame is Follow-up ranged from 59-120 months*	
							With Control	With Bisphosphonates vs. no bisphoshonates		Risk with Control	Risk difference with Bisphosphonates vs. no bisphoshonates (95% CI)
Overall survival (CRITICAL OUTCOME)											
11 198 (8 studies) 59-120 months	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⨁⨁⊖⊖ **LOW**[1,2] due to inconsistency, imprecision	995/5616 (17.7%)	860/5582 (15.4%)	**RR 0.85** (0.72 to 1)	**177 per 1000**	**27 fewer per 1000** (from 50 fewer to 0 more)
Overall survival - Zoledronate 4 mg i.v. monthly (CRITICAL OUTCOME)											
5 281 (3 studies) 59-62 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	319/2640 (12.1%)	273/2641 (10.3%)	**RR 0.86** (0.74 to 1)	**121 per 1000**	**17 fewer per 1000** (from 31 fewer to 0 more)
Overall survival - Oral Clodronate 1600 mg daily (CRITICAL OUTCOME)											
4 964 (4 studies) 67-120 months	no serious risk of bias	serious[1]	no serious indirectness	serious[3]	undetected	⨁⨁⊖⊖ **LOW**[1,3] due to inconsistency, imprecision	410/2483 (16.5%)	334/2481 (13.5%)	**RR 0.80** (0.6 to 1.08)	**165 per 1000**	**33 fewer per 1000** (from 66 fewer to 13 more)
Overall survival - Oral Pamidronate 150 mg (CRITICAL OUTCOME)											
953 (1 study) 120 months	no serious risk of bias	serious[4]	no serious indirectness	serious[3]	undetected	⨁⨁⊖⊖ **LOW**[3,4] due to inconsistency, imprecision	266/493 (54%)	253/460 (55%)	**RR 1.02** (0.91 to 1.14)	**540 per 1000**	**11 more per 1000** (from 49 fewer to 76 more)
Disease free survival (CRITICAL OUTCOME)											
8 874 (5 studies) 59-120 months	no serious risk of bias	serious[1]	no serious indirectness	serious[3]	undetected	⨁⨁⊖⊖ **LOW**[1,3] due to inconsistency, imprecision	797/4439 (18%)	739/4435 (16.7%)	**RR 0.90** (0.76 to 1.06)	**180 per 1000**	**18 fewer per 1000** (from 43 fewer to 11 more)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects *Time frame is Follow-up ranged from 59-120 months*	
							With Control	With Bisphosphonates vs. no bisphoshonates		Risk with Control	Risk difference with Bisphosphonates vs. no bisphoshonates (95% CI)
Disease free survival - Zoledronate 4 mg i.v. monthly (CRITICAL OUTCOME)											
5 281 (3 studies) 59-62 months	no serious risk of bias	serious[1]	no serious indirectness	serious[3]	undetected	⨁⨁⊖⊖ **LOW**[1,3] due to inconsistency, imprecision		485/2640 (18.4%)	453/2641 (17.2%)	**RR 0.85** (0.59 to 1.22)	**184 per 1000**	**28 fewer per 1000** (from 75 fewer to 40 more)
Disease free survival - Oral Clodronate 1600 mg daily (CRITICAL OUTCOME)											
3 593 (2 studies) 91-120 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⨁⨁⊖ **MODERATE**[3] due to imprecision		312/1799 (17.3%)	286/1794 (15.9%)	**RR 0.92** (0.79 to 1.06)	**173 per 1000**	**14 fewer per 1000** (from 36 fewer to 10 more)
Osteonecrosis of the jaw - Zoledronate (CRITICAL OUTCOME)											
5 269 (3 studies) 59-62 months	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	undetected	⨁⨁⨁⊖ **MODERATE**[5,6] due to risk of bias		0/2628 (0%)	18/2641 (0.68%)	**RR 18.79** (2.52 to 139.88)		**-**
Bone pain - Zoledronate (IMPORTANT OUTCOME)											
1 803 (1 study) 62 months	serious[7]	serious[4]	no serious indirectness	no serious imprecision	undetected	⨁⨁⊖⊖ **LOW**[4,7] due to risk of bias, inconsistency		252/903 (27.9%)	349/900 (38.8%)	**RR 1.39** (1.22 to 1.59)	**279 per 1000**	**109 more per 1000** (from 61 more to 165 more)
Arthralgia - Zoledronate (IMPORTANT OUTCOME)											
1 803 (1 study) 62 months	serious[7]	serious[4]	no serious indirectness	serious[3,8]	undetected	⨁⊖⊖⊖ **VERY LOW**[3,4,7,8] due to risk of bias, inconsistency, imprecision		121/903 (13.4%)	145/900 (16.1%)	**RR 1.20** (0.96 to 1.5)	**134 per 1000**	**27 more per 1000** (from 5 fewer to 67 more)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects** *Time frame is Follow-up ranged from 59-120 months*	
							With Control	With Bisphosphonates vs. no bisphoshonates		Risk with Control	Risk difference with Bisphosphonates vs. no bisphoshonates (95% CI)
Pyrexia - Zoledronate (IMPORTANT OUTCOME)											
1 803 (1 study) 62 months	serious[7]	serious[4]	no serious indirectness	serious[8]	undetected	⨁⊖⊖⊖ **VERY LOW**[4,7,8] due to risk of bias, inconsistency, imprecision		21/903 (2.3%)	85/900 (9.4%)	**RR 4.06** (2.54 to 6.49)	**23 per 1000**	**71 more per 1000** (from 36 more to 128 more)

[1] Vast statistical heterogeneity; [2] CI includes clinical irrelevant effect; [3] CI includes both benefit and harm; [4] One multicentre trial without information about heterogeneity across sites; [5] No blinding in all three studies; [6] Not downgraded (low event rate with high sample size); [7] No blinding; [8] Optimal information size not reached

6.4. Bevacizumab in women with HER-2 negative metastatic breast cancer

Table 66 – Clinical evidence profile: bevacizumab in combination with chemotherapy versus chemotherapy alone in women with HER-2 negative metastatic breast cancer

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	With Bevacizumab		Risk with Control	Risk difference with Bevacizumab (95% CI)
Overall survival (first-line chemotherapy) (CRITICAL OUTCOME)											
2 695 (3 studies)	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to inconsistency, imprecision			**HR 0.93** (0.84 to 1.04)		
Overall survival (second-line chemotherapy) (CRITICAL OUTCOME)											
684 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision			**HR 0.90** (0.71 to 1.14)		
Progression free survival (first-line chemotherapy) (CRITICAL OUTCOME)											
2 886 (4 studies)	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency			**HR 0.67** (0.61 to 0.73)		
Progression free survival (second-line chemotherapy) (CRITICAL OUTCOME)											
684 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**			**HR 0.78** (0.64 to 0.93)		
Adverse events (grade 3 or higher; first-line chemotherapy) (CRITICAL OUTCOME)											
1 950 (2 studies)	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency	170/634 (26.8%)	518/1316 (39.4%)	**OR 1.77** (1.44 to 2.18)	**268 per 1000**	**125 more per 1000** (from 77 more to 176 more)
Serious adverse events (first and second-line chemotherapy) (CRITICAL OUTCOME)											
2 084 (3 studies)	serious[3]	serious[1,4]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**[1,3,4] due to risk of bias, inconsistency	146/713 (20.5%)	362/1371 (26.4%)	**OR 1.41** (1.13 to 1.75)	**205 per 1000**	**68 more per 1000** (from 22 more to 118 more)

[1] The studies used different lengths of follow-up (from 15.6 months to a median follow-up of 43.5 months); [2] CI includes both benefit and harm; [3] One study high risk of bias; [4] First and second-line chemotherapy

7. FOREST PLOTS

Figure 17 – Axillary recurrence: SLND vs. ALND in early invasive breast cancer with positive sentinel nodes, by subgroups of LN metastases

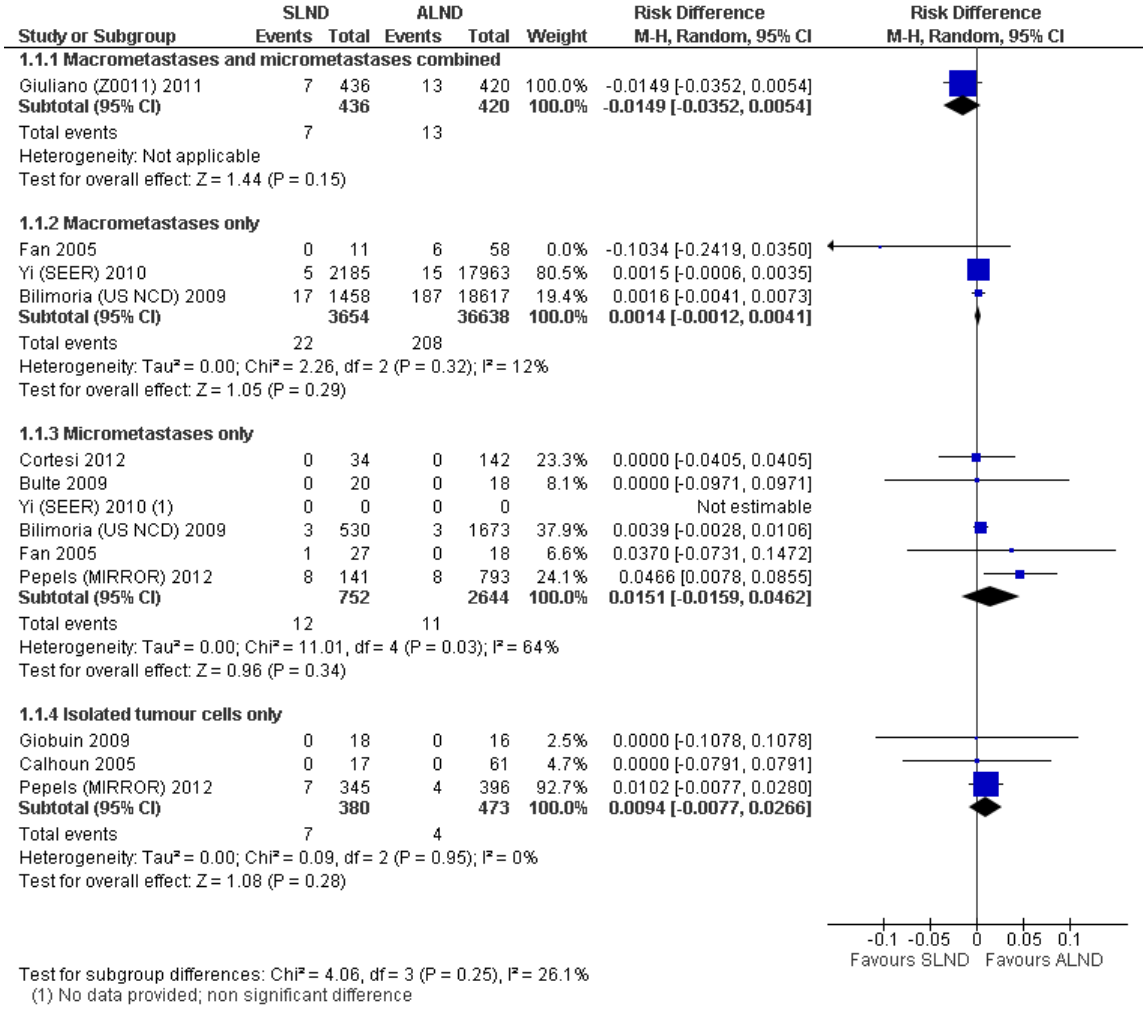
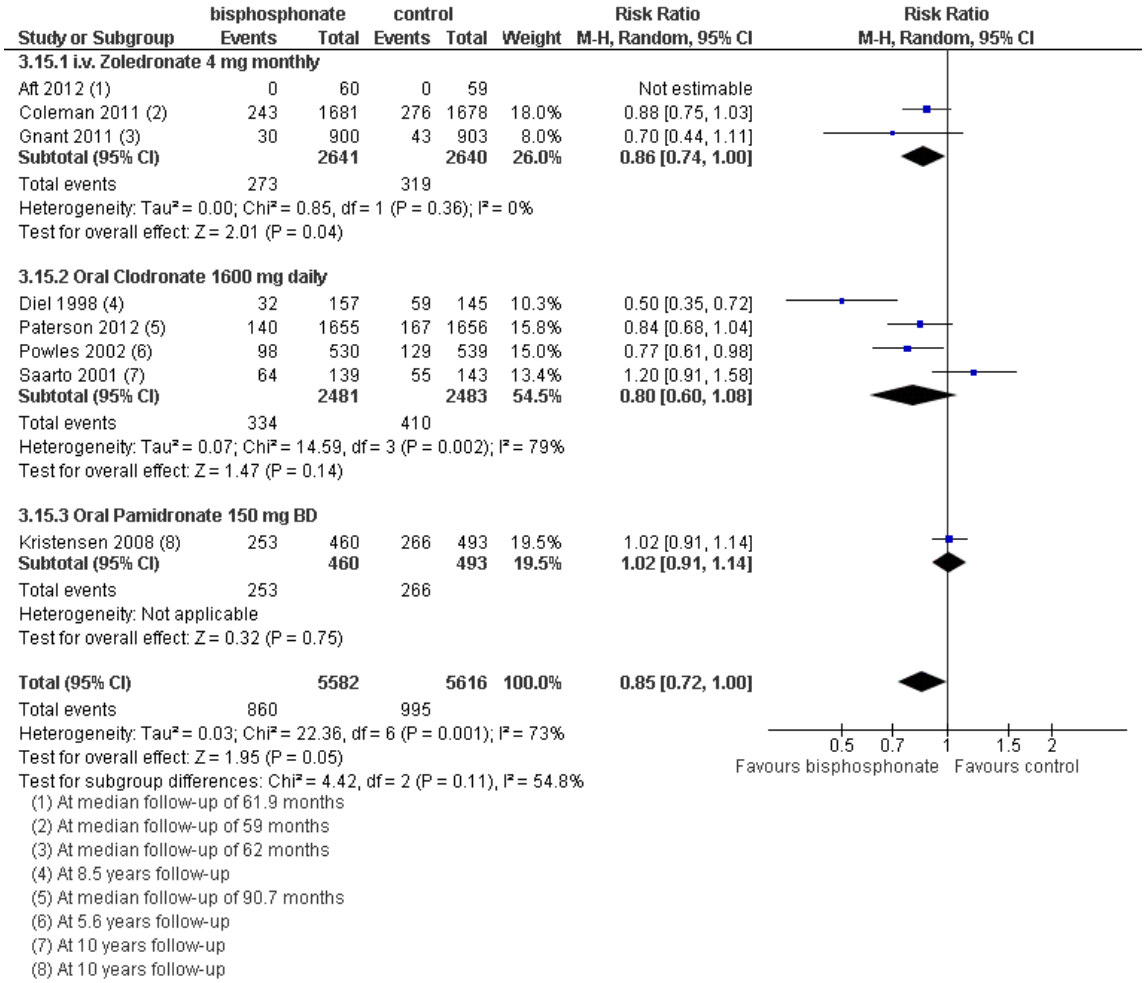
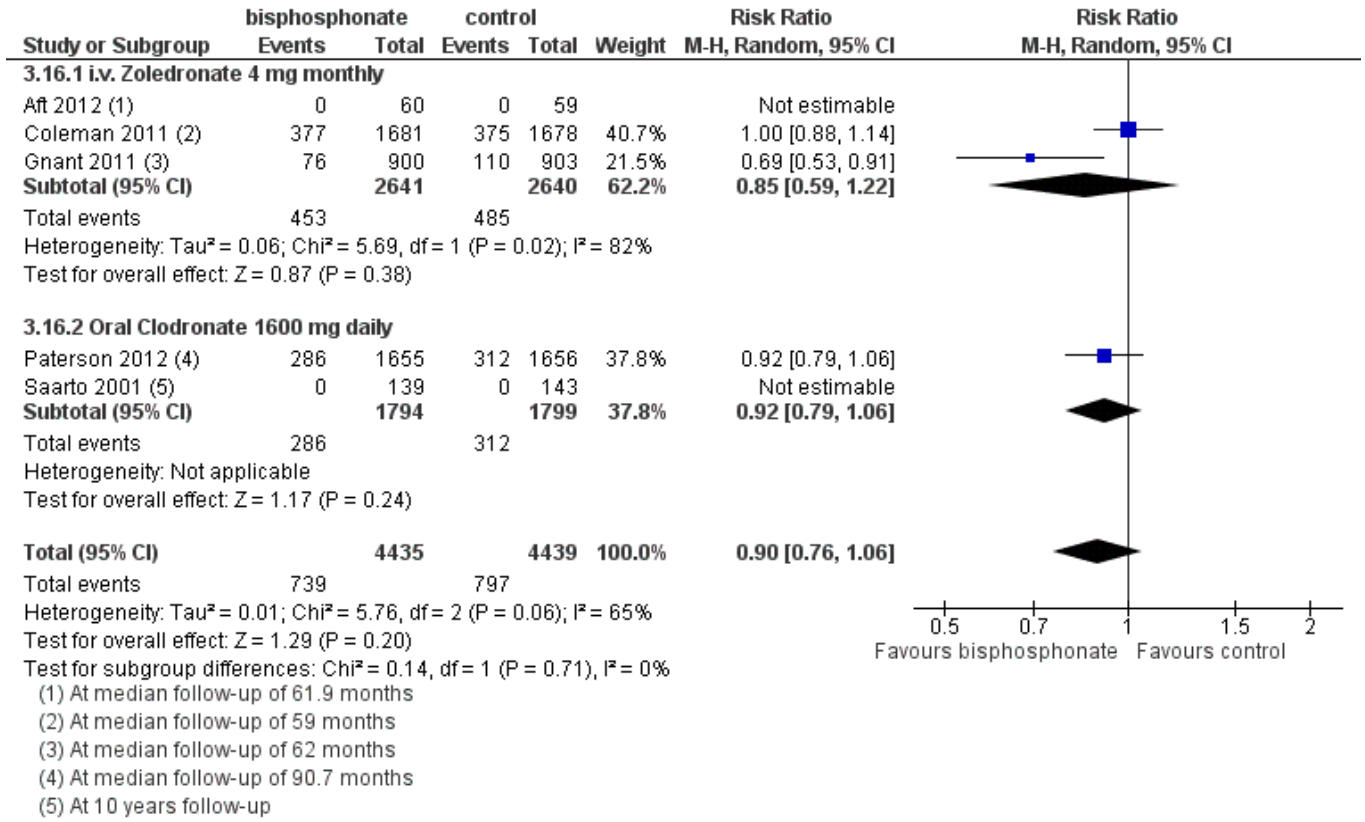


Figure 18 – Overall survival: bisphosphonates vs. control in early breast cancer women without metastases



(1) At median follow-up of 61.9 months
(2) At median follow-up of 59 months
(3) At median follow-up of 62 months
(4) At 8.5 years follow-up
(5) At median follow-up of 90.7 months
(6) At 5.6 years follow-up
(7) At 10 years follow-up
(8) At 10 years follow-up

Figure 19 – Disease-free survival: bisphosphonates vs. control in early breast cancer women without metastases



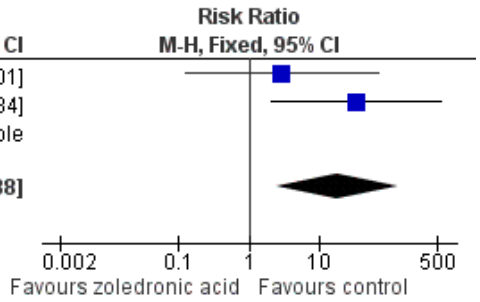
(1) At median follow-up of 61.9 months
(2) At median follow-up of 59 months
(3) At median follow-up of 62 months
(4) At median follow-up of 90.7 months
(5) At 10 years follow-up

Figure 20 – Osteonecrosis of the jaw: bisphosphonates vs. control in early breast cancer women without metastases

Study or Subgroup	Zoledronic acid Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aft 2012	1	60	0	59	50.1%	2.95 [0.12, 71.01]
Coleman 2011	17	1681	0	1666	49.9%	34.69 [2.09, 576.34]
Gnant 2011	0	900	0	903		Not estimable
Total (95% CI)		**2641**		**2628**	**100.0%**	**18.79 [2.52, 139.88]**
Total events	18		0			

Heterogeneity: $Chi^2 = 1.48$, $df = 1$ ($P = 0.22$); $I^2 = 33\%$

Test for overall effect: $Z = 2.86$ ($P = 0.004$)



8. TNM CLASSIFICATION

8.1. TNM Clinical classification

8.1.1. T – Primary tumour

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

- Tis (DCIS) Ductal carcinoma in situ
- Tis (LCIS) Lobular carcinoma in situ
- Tis (Paget) Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.

T1 Tumour 2 cm or less in greatest dimension

- T1mi Microinvasion 0.1 cm or less in greatest dimension

Microinvasion is the extension of cancer cells beyons the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion (do not use the sum of all individual foci). The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

- T1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
- T1b More than 0.5 cm but not more than 1 cm in greatest dimension
- T1c More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumour more than 5 cm in greatest dimension

T4 Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)

Note: Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostals muscles, and serratus anterior muscle, but not pectoral muscle

- T4a Extension to chest wall (does not include pectoralis muscle invasion only)
- T4b Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
- T4c Both 4a and 4b, above
- T4d Inflammatory carcinoma

Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

8.1.2. N – Regional lymph nodes

Nx Regional lymph nodes cannot be assessed (e.g. previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral Level I, II axillary lymph node(s)

N2 Metastasis in ipsilateral Level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary lymph nodes(s) in the absence of clinically evident axillary lymph node metastasis

- N2a Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
- N2b Metastasis only in clinically detected* internal mammary lymph nodes(s) and in the absence of clinically detected axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident Level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

- N3a Metastasis in infraclavicular lymph node(s)
- N3b Metastasis in internal mammary and axillary lymph nodes
- N3c Metastasis in supraclavicular lymph node(s)

*clinically detected = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination. Confirmation of clinically detected metastatic disease by fine-needle aspiration without excision biopsy is designated with an (f) suffix, e.g., cN3a(f).

Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g., cN1. Pathological classification (pN) is used for excision or sentinel lymph node only in conjunction with a pathological T assignment.

8.1.3. M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

8.2. pTNM Pathological Classification

pT- Primary tumour

A case can be classified pT if there is only microscopic tumour in a margin. The pT categories correspond to the T categories.

Note: When classifying pT the tumour size is a measurement of the invasive component. If there is a large in situ component (e.g., 4 cm) and a small invasive component (e.g., 0.5 cm), the tumour is coded pT1a.

pN – Regional Lymph nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (Level I). Such a resection will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

- pNx: Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathological study)
- pN0: No regional lymph node metastasis*.

*Isolated tumour cell clusters (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by immunohistochemistry or by routine HeE stains. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification and should be included in the total number of nodes evaluated.

- pN1: Micrometastasis; or metastasis in 1-3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastasis detected by sentinel lymph node biopsy but not clinically detected*
  - pN1mi: micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
  - pN1a metastasis in 1-3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
  - pN1b internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected*
  - pN1c metastasis in 1-3 axillary lymph nodes and internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected*
- pN2: Metastasis in 4-9 ipsilateral axillary lymph nodes, or in clinically detected* ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis
  - pN2a metastasis in 4-9 axillary lymph nodes, including at least one larger than 2 mm.
  - pN2b metastasis in clinically detected* internal mammary lymph node(s), in the absence of axillary lymph node metastasis

- pN3: Metastasis as described below:
  - pN3a metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes
  - pN3b metastasis in clinically detected* internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
  - pN3c metastasis in ipsilateral supraclavicular lymph node(s)
- *clinically detected is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination.
- Not clinically detected is defined as not detected by clinical examination or by imaging studies (excluding lymphoscintigraphy).

pM – Distant Metastasis

8.2.1. Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0, T1*	N1mi	M0
Stage II A	T0, T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1*, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*Note: *T1 includes T1m*

9. CONSULTATION OF STAKEHOLDERS

9.1. Evaluation of the recommendations : Delphi consultation, first tour

Item	Recommendation(s)	GOR	LoE	R VDB	A S	P N	M B	B C	P B	E L	G J	K L	C C	M VH	MR C	FB	HW	Comments
ALND vs. SLND	For women with a SLNB that shows isolated tumor cells, we recommend not performing a completion ALND regardless of the type of breast surgery	Strong	Very low	5	5	5	5	5	5	5	5	5	4	5	5	5	5	
	For women with one or two positive sentinel nodes (micrometastases or macrometastases) treated with breast conserving surgery, we suggest performing a completion ALND. However, for women with low risk of non-sentinel lymph node involvement and whole breast radiotherapy, completion ALND can be omitted	Strong	Low	3	2	5	5	2	4	4	5	5	4	4	5	4	5	M B: in many nomograms (MSKCC) authors take into consideration the number of negative SN. Is it important to use this parameter? ; B C: je propose de scinder SN positif pour ITC ou micromets et SN positif pour macromet.pour ITC et micromet, une ALND ne se justifie plus, pour les macromet, la formule est bien ; MVH : indicators of low risk should be defined ; FB : you have to indicate if you have also other negative sln and how much You have to define low risk patient
	For women with three or more positive SLNs (micro- or macrometastases), we recommend performing ALND	Strong	Very low	5	5	5	5	5	5	5	5	5	4	5	5	5	5	
	For women with one or two positive sentinel nodes (micrometastases or macrometastases) treated by mastectomy and chest wall radiotherapy, completion ALND remains the standard. However, for women with low risk of non-sentinel lymph node involvement, completion ALND can be omitted	Weak	Very low	3	2	5	5	5	3	4	5	5	4	4	4	4	4	MVH : indicators of low risk should be defined / FB: you have to indicate if you have also other negative sln and how much You have to define low risk patient
	Benefits and risks of each procedure have to be discussed with the patient	Strong	Very low	5	3	5	5	5	5	5	5	5	5	5	5	4	5	
Bisphosphonates	In women with early non-metastatic breast cancer, bisphosphonates cannot be recommended as an adjuvant breast cancer therapy	Strong	Low	5	5	5	5	5	3	5	5	NA	NA	NA	3	5	5	
Bevacizumab	In women with metastatic breast cancer, adding bevacizumab to a systemic chemotherapy, either in first-line or in second-line therapy, cannot be recommended	Strong	Low	5	4	4	5	4	3	5	1	NA	NA	NA	5	NA	4	A S : strong??? Recommendation; G J: Several months of PFS improvement is observed with paclitaxel (clinically meaningful); we can neither strongly recommend the use nor stronlgy argument against its use; the doctor should discuss with the patient; side effects and costs should be considered; several studies not yet published but presented reported similar long PFS with bevacizumab and paclitaxel not seen with any other drug combination in this patient population
Trastuzumab	One year treatment with adjuvant trastuzumab is indicated for women with HER2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 1 cm), having a left ventricular ejection fraction of ≥ 55% and without important cardiovascular risk factors who received chemotherapy	Strong	High	5	5	5	5	5	4	4	5	NA	NA	NA	5	5	5	E L: What about patients with a 5-9 mm aggressive tumor?
	Trastuzumab can be combined either with a taxane in an anthracycline containing regimen or with a non-anthracycline regimen (TCH)	Weak	Low	5	5	5	5	5	5	4	5	NA	NA	NA	5		5	

9.2. Evaluation of the recommendations: Delphi consultation, second tour

Item	Recommendation(s)	GOR	LoE	R VDB	A S	P N	B C	E L	G J	HW	Comments
Bevacizumab	In women with metastatic breast cancer, adding bevacizumab to a systemic chemotherapy, either in first-line or in second-line therapy, cannot be recommended	Weak	Low	5	5			5	5	5	
ALND vs. SLND	For women with a SLNB that shows isolated tumor cells, we recommend not performing a completion ALND regardless of the type of breast surgery	Strong	Very low	5	5	5	5	5	5		AS : regardless of the type of breast surgery can be omitted
	For patients with SLNB that shows micrometastases, a completion ALND is not warranted.	Weak	Low	5	4	1	4	4	5		PN: This is limited to inclusion criteria in ACOZOG and these were limited to breast conservative surgery and number of SLN with metastatic disease; EL: To be discussed case by case
	For women with three or more positive SLNs (micro- or macrometastases), we recommend performing ALND	Strong	Very low	4	5	5	5	3	5		
	For patients with one or two positive sentinel nodes (macrometastases), a completion ALND remains the standard treatment. However, for patients at low risk for axillary failure, a completion ALND can be omitted	Strong	Very low	5	5	1	5	5	5		PN: You should include that evidence following mastectomy is completly lacking from the 2 RCT/ this can not be a strong recommendation ; EL: To be discussed case by case (additional non sentinel nodes in initial biopsy?Pt age and general condition. Size of macromet etc…); RVDB: Low risk schould be defined. The total number of sentinelnodes removed durung the procedure schould be mentioned I could argee in full for one pos sentinel node, however i am in doubt for two pos nodes
	Benefits and risks of each procedure have to be discussed with the patient	Strong	Very low	5	4	5	5	5	5		

9.3. Evaluation of the recommendations: Delphi consultation, third tour

Item	Recommendation(s)	GOR	LoE	R VDB	A S	P N	MRC	HW	Comments
ALND vs. SLND	For women with a SLNB that shows isolated tumor cells, we recommend not performing a completion ALND	Strong	Very low	5	5	5	5	5	
	For patients treated with BCS and with one or two positive sentinel nodes (micrometastases), a completion ALND is not warranted.	Strong	Very low	5	5	5	5	5	
	For patients treated with ME and with one or two positive sentinel nodes (micrometastases), a completion ALND is not warranted.	Weak	Very low	5	5	5	5	5	
	For patients treated with BCS and with one or two positive sentinel nodes (macrometastases), a completion ALND remains the standard treatment. However, for patients at low risk for axillary failure, a completion ALND can be omitted	Strong	Low	5	5	5	5	5	
	For patients treated with ME and with one or two positive sentinel nodes (macrometastases), a completion ALND remains the standard treatment. However, for patients at low risk for axillary failure, a completion ALND can be omitted	Weak	Very low	5	5	5	5	5	
	For women with three or more positive SLNs (micro- or macrometastases), we recommend performing ALND	Strong	Very low	5	5	5	5	5	
	Benefits and risks of each procedure have to be discussed with the patient	Strong	Very low	5	5	5	5	5	

9.4. Meeting with patients representatives

Patients representatives found that the conclusions and recommendations were well written and sufficiently clear to support clinicians in interpreting these recommendations in the context of individual patient values and preferences, and to make appropriate decisions regarding all aspects of disease management, tailored to the patient with a breast cancer. However, for Trastuzumab, they would like to stress the importance of patients information about the cardio-toxicity of combining treatments. They emphasized that patients preferences towards treatments outcomes (survival, recurrence, quality of life) can be really different from one patient to another, leading to different therapeutic options.

10. SET OF QUALITY INDICATORS

Table 67 – Set of 32 quality indicators in breast cancer care.

	Indicator	Type of indicator	Level of evidence (GRADE)	Measurable with BCR-claims data
	Generic indicators			
BC1	Overall 5-year survival by stage	Outcome	A	Yes
BC2	Disease-specific 5-year survival by stage	Outcome	A	Yes
BC3	Disease-free 5-year survival by stage	Outcome	A	No
BC4	5-year local recurrence rate after curative surgery, by stage	Outcome	A	No
BC5	Proportion of breast cancer women discussed at the multidisciplinary team meeting	Process	C	Yes
BC6	Proportion of women with breast cancer who participate in clinical trials	Process	C	No
	Diagnosis and staging			
BC7	Proportion of women with class 3, 4 or 5 abnormal mammograms having an assessment with a specialist within 2 months of mammography	Process	C	No
BC8	Proportion of women with class 3, 4 or 5 abnormal mammograms who have at least one of the following procedures within 2 months after communication of the screening result: mammography, ultrasound, fine-needle	Process	C	No

	Indicator	Type of indicator	Level of evidence (GRADE)	Measurable with BCR-claims data
	aspiration, or percutaneous biopsy			
BC9	Proportion of newly diagnosed cstage I-III breast cancer patients who underwent two-view mammography or breast ultrasonography within 3 months prior to surgery	Process	C	Yes
BC10	Proportion of patients who received axillary ultrasonography with fine needle aspiration cytology of the axillary lymph nodes before any treatment	Process	C	No
BC11	Proportion of patients in whom human epidermal growth factor receptor 2 status was assessed before any systemic treatment	Process	B	No
BC12	Proportion of patients in whom a ER and PgR status assessment were performed before any systemic treatment	Process	B	Yes
BC13	Proportion of breast cancer women with cytological and/or histological assessment before surgery	Process	C	Yes
BC14	Proportion of sentinel lymph nodes biopsy in cN0 patients without contraindications	Process	A	No
	Treatment			
BC15	Proportion of operable cT2-T3 women who received neoadjuvant systemic therapy	Process	A	Yes
BC16	Proportion of breast cancer women who underwent an ALND after positive SNLB > 2 mm	Process	A	No

	Indicator	Type of indicator	Level of evidence (GRADE)	Measurable with BCR-claims data
BC17	Proportion of women with high-grade and/or palpable and/or large DCIS of the breast who had negative margins after surgery, whatever the surgical option (local wide excision or mastectomy)	Process	C	No
BC18	Proportion of cStage I and II women who undergo breast-conserving surgery / mastectomy	Process	A	Yes
BC19	Proportion of women with breast cancer recurrence after breast conserving surgery who are treated by a mastectomy	Process	C	Partly
BC20	Proportion of women with a breast cancer who are receiving intravenous chemotherapy for whom the planned chemotherapy regimen (which includes, at a minimum: drug[s] prescribed, dose, and duration) is documented prior to the initiation, and at each administration of the treatment regimen	Process	C	No
BC21	Proportion of women receiving adjuvant systemic therapy after breast surgery for invasive breast cancer	Process	A	Yes
BC22	Proportion of women with hormone receptor positive invasive breast cancer or DCIS who received adjuvant endocrine treatment (Tamoxifen/AI)	Process	A	No
BC23	Proportion of women with HER2 positive, node positive or high-risk node negative breast cancer (tumour size > 1 cm), having a left ventricular ejection fraction of > or= 50-55% who received chemotherapy and Trastuzumab	Process	A	No

	Indicator	Type of indicator	Level of evidence (GRADE)	Measurable with BCR-claims data
BC24	Proportion of women treated by Trastuzumab in whom cardiac function is monitored every 3 months	Process	A	Yes
BC25	Proportion of women who received radiotherapy after breast conserving surgery	Process	A	Yes
BC26	Proportion of women who underwent a mastectomy and having ≥ 4 positive nodes who received radiotherapy on axilla following ALND	Process	A	No
BC27	Proportion of women with HER2 positive metastatic breast cancer who received Trastuzumab with/without non-anthracycline based chemotherapy or endocrine therapy as first-line treatment	Process	A	No
BC28	Proportion of metastatic breast cancer women who receive systemic therapy as 1st and/or 2nd line treatment	Process	A	Yes
BC29	Proportion of women with metastatic breast cancer and lytic bone metastases who received biphosphonates	Process	A	No
	Follow-up			
BC30	Proportion of women who benefit from an annual mammography after a history of breast cancer	Process	C	Yes
	Histopathology			
BC31	Proportion of breast cancer resection pathology reports that include the tumour size (macro-and	Process	C	No

	Indicator	Type of indicator	Level of evidence (GRADE)	Measurable with BCR-claims data
	microscopically invasive and DCIS), the histologic type of the primary tumour, the pT category (primary tumour), the pN category (regional lymph nodes including numbers), the LVI and the histologic grade.			
BC32	Proportion of women with invasive breast cancer undergoing ALND and having 10 or more lymph nodes removed	Outcome	C	No

11. REFERENCES

1. Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: a meta-analysis. Breast Cancer Res.Treat. 2010;120:(2):441-7.
2. Wang Z, Wu LC, Chen JQ. Sentinel lymph node biopsy compared with axillary lymph node dissection in early breast cancer: a meta-analysis. Breast Cancer Res.Treat. 2011;129:(3):675-89.
3. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Jama. 2011;305:(6):569-75.
4. Barry JM, Weber WP, Sacchini V. The evolving role of axillary lymph node dissection in the modern era of breast cancer management. Surg.Oncol. 2012;21:143-5.
5. Barry M, Kell MR. Breast cancer: Can axillary lymph node dissection be avoided? Eur.J.Surg.Oncol. 2012;38:6-7.
6. Franco R. Avoiding axilla lymph node dissection for selected breast cancer: New sentinel lymph node dissection practice-changing trials. Gastric and Breast Cancer. 2011;10:187-91.
7. Gerber B, Heintze K, Stubert J, Dieterich M, Hartmann S, Stachs A, et al. Axillary lymph node dissection in early-stage invasive breast cancer: Is it still standard today? Breast Cancer Research and Treatment. 2011;128:613-24.
8. Pepels MJ, Vestjens JH, de BM, Smidt M, van Diest PJ, Borm GF, et al. Safety of avoiding routine use of axillary dissection in early stage breast cancer: a systematic review. Review. Breast Cancer Res.Treat. 2011;125:(2):301-13.
9. Petrelli F, Cabiddu M, Ghilardi M, Borgonovo K, Barni S. Is axillary dissection still useful in node-negative early breast cancer? Eur.J.Cancer. 2012;Conference: European Breast Cancer Conference 2012, EBCC8 Vienna Austria. Conference Start: 20120321 Conference End: 20120324. Conference Publication:S201.
10. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J.Surg.Oncol. 2010;102:(2):111-8.
11. Avril A, Le BG, Lorimier G, Fondrinier E, Classe JM, Tunon-de-Lara C, et al. Locoregional recurrences in a phase III randomized trial of early breast cancer treatments with or without axillary lymph node clearance in post-menopausal patients. Eur.J.Surg.Oncol. 2010;Conference: 15th Congress of the European Society of Surgical Oncology Bordeaux France. Conference Start: 20100915 Conference End: 20100917. Conference Publication:796.
12. Avril A, Le BG, Lorimier G, Classe JM, Tunon-de-Lara C, Giard S, et al. Phase III randomized equivalence trial of early breast cancer treatments with or without axillary clearance in post-menopausal patients results after 5 years of follow-up. Eur.J.Surg.Oncol. 2011;37:(7):563-70.
13. Cody HS. The sentinel node biopsy is positive: No axillary clearance? Eur.J.Cancer. 2012;Conference: European Breast Cancer Conference 2012, EBCC8 Vienna Austria. Conference Start: 20120321 Conference End: 20120324. Conference Publication:S44.
14. Dockx Y, Huizing MT, Huyghe I, Altintas S, Van Den Wyngaert T, Van GM, et al. The role of sentinel node (SLN) procedure after neo-adjuvant chemotherapy (NACT) for node positive breast cancer (NPBC). Eur.J.Cancer. 2012;Conference: European Breast Cancer Conference 2012, EBCC8 Vienna Austria. Conference Start: 20120321 Conference End: 20120324. Conference Publication:S218.
15. Galimberti V, Chifu C, Rodriguez PS, Veronesi P, Intra M, Botteri E, et al. Positive axillary sentinel lymph node: is axillary dissection always necessary?. Review. Breast. 2011;20 Suppl 3:S96-8, 2011 Oct.:S96-S8.

16. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11:(10):927-33.

17. Kuwajerwala N, Riutta J, Dekhne N, Feczko C, Pettinga J. Comparison of lymphedema in patients with Axillary Lymph Node Dissections (ALND) to those with sentinel lymph node biopsy followed by immediate and delayed ALND. Ann.Surg.Oncol. 2010;Conference: 11th Annual Meeting of the American Society of Breast Surgeons Las Vegas, NV United States. Conference Start: 20100428 Conference End: 20100502. Conference Publication:S180.

18. Siso C, Morales S, Iglesias E, Gonzalez S, Canosa C, Pon M. Could axillary dissection be avoided after neoadjuvant chemotherapy in patients with prior positive axillary sentinel lymph node by a RT-PCR method? Eur.J.Cancer. 2012;Conference: European Breast Cancer Conference 2012, EBCC8 Vienna Austria. Conference Start: 20120321 Conference End: 20120324. Conference Publication:S221.

19. Sola M, Julian FJ, Ballester B, Rojo R, Pericas I, Pinanero A, et al. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastases. Interim analysis of the Spanish multicenter clinical trial. AATRM 048/13/2000. European Journal of Cancer, Supplement. 2010;Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain. Conference Start: 20100324 Conference End: 20100327. Conference Publication:147.

20. Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J Clin Oncol. 2009;27(18):2946-53.

21. Bulte CS, van der Heiden-van der Loo M, Hennipman A. Axillary recurrence rate after tumour negative and micrometastatic positive sentinel node procedures in breast cancer patients, a population based multicenter study. Eur J Surg Oncol. 2009;35(1):25-31.

22. Calhoun KE, Hansen NM, Turner RR, Giuliano AE. Nonsentinel node metastases in breast cancer patients with isolated tumor cells in the sentinel node: implications for completion axillary node dissection. Am J Surg. 2005;190(4):588-91.

23. Cortesi L, Proietto M, Cirilli C, Tazzioli G, Andreotti A, Federico M. Prognosis and treatment of micrometastatic breast cancer sentinel lymph node: a population-based study. J Surg Oncol. 2012;106(4):399-405.

24. Fan YG, Tan YY, Wu CT, Treseler P, Lu Y, Chan CW, et al. The effect of sentinel node tumor burden on non-sentinel node status and recurrence rates in breast cancer. Annals of Surgical Oncology. 2005;12(9):705-11.

25. Giobuin SM, Kavanagh DO, Myers E, Doherty AO, Quinn CM, Crotty T, et al. The significance of immunohistochemistry positivity in sentinel nodes which are negative on haematoxylin and eosin in breast cancer. Eur J Surg Oncol. 2009;35(12):1257-60.

26. Pepels MJ, de Boer M, Bult P, van Dijck JA, van Deurzen CH, Menke-Pluymers MB, et al. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. Ann Surg. 2012;255(1):116-21.

27. Wasif N, Maggard MA, Ko CY, Giuliano AE. Underuse of axillary dissection for the management of sentinel node micrometastases in breast cancer. Arch Surg. 2010;145(2):161-6.

28. Yi M, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, et al. Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. Annals of Surgical Oncology. 2010;3:343-51.

29. Yi M, Kuerer HM, Mittendorf EA, Hwang RF, Caudle AS, Bedrosian I, et al. Impact of the american college of surgeons oncology group z0011 criteria applied to a contemporary patient population. J Am Coll Surg. 2013;216(1):105-13.

30. Christiansen P, Friis E, Balslev E, Jensen D, Moller S, Danish Breast Cancer Cooperative G. Sentinel node biopsy in breast cancer: five years experience from Denmark. Acta Oncol. 2008;47(4):561-8.

31. Cox CE, Kiluk JV, Riker AI, Cox JM, Allred N, Ramos DC, et al. Significance of sentinel lymph node micrometastases in human breast cancer. J Am Coll Surg. 2008;206(2):261-8.

32. De Boer M, Van Deurzen CH, Van Dijck JA, Borm GF, Van Diest PJ, Adang EM, et al. Micrometastases and isolated tumor cells: Relevant and robust or rubbish? (MIRROR): Preliminary results of the MIRROR study from the Dutch breast cancer trialists' group (BOOG). Cancer Res. 2009;69(2).

33. Francissen CM, Dings PJ, van Dalen T, Strobbe LJ, van Laarhoven HW, de Wilt JH. Axillary recurrence after a tumor-positive sentinel lymph node biopsy without axillary treatment: a review of the literature. Ann Surg Oncol. 2012;19(13):4140-9.

34. Giard S, Chauvet MP, Houpeau JL, Baranzelli MC, Carpentier P, Fournier C, et al. Sentinel node biopsy without systematic axillary dissection: Study about 1000 procedures. Gynecologie Obstetrique Fertilite. 2005;33(4):213-9.

35. Giuliano AE, Morrow M, Duggal S, Julian TB. Should ACOSOG Z0011 change practice with respect to axillary lymph node dissection for a positive sentinel lymph node biopsy in breast cancer? Clin Exp Metastasis. 2012;29(7):687-92.

36. Haid A, Knauer M, Koberle-Wuhrer R, Ammann K, Koller L, Eiter H, et al. Medium-term follow-up data after sentinel node biopsy alone for breast cancer. Eur J Surg Oncol. 2006;32(10):1180-5.

37. Helms G, Kuhn T, Moser L, Remmel E, Kreienberg R. Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection--data from a prospective randomised trial. Eur J Surg Oncol. 2009;35(7):696-701.

38. Jakub JW, Diaz NM, Ebert MD, Cantor A, Reintgen DS, Dupont EL, et al. Completion axillary lymph node dissection minimizes the likelihood of false negatives for patients with invasive breast carcinoma and cytokeratin positive only sentinel lymph nodes. Am J Surg. 2002;184(4):302-6.

39. Jeruss JS, Newman LA, Ayers GD, Cristofanilli M, Broglio KR, Meric-Bernstam F, et al. Factors predicting additional disease in the axilla in patients with positive sentinel lymph nodes after neoadjuvant chemotherapy. Cancer. 2008;112(12):2646-54.

40. Joyce DP, Solon JG, Prichard RS, Power C, Hill AD. Is there a requirement for axillary lymph node dissection following identification of micro-metastasis or isolated tumour cells at sentinel node biopsy for breast cancer? SURG. 2012;10(6):326-9.

41. Liang WC, Sickle-Santanello BJ, Nims TA. Is a completion axillary dissection indicated for micrometastases in the sentinel lymph node? Am J Surg. 2001;182(4):365-8.

42. Loong Chong CY, Mirbagheri N, Harris M, Fox J. Sentinel node micrometastases in breast cancer: a survey of Australian and New Zealand breast surgeons. ANZ J Surg. 2012;82(11):766-7.

43. Martelli G, Miceli R, Daidone MG, Vetrella G, Cerrotta AM, Piromalli D, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol. 2011;18(1):125-33.

44. Naik AM, Fey J, Gemignani M, Heerdt A, Montgomery L, Petrek J, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. Ann Surg. 2004;240(3):462-8; discussion 8-71.

45. Schulze T, Mucke J, Markwardt J, Schlag PM, Bembenek A. Long-term morbidity of patients with early breast cancer after sentinel lymph node biopsy compared to axillary lymph node dissection. J Surg Oncol. 2006;93(2):109-19.

46. Sola M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, et al. Complete Axillary Lymph Node Dissection Versus Clinical Follow-up in Breast Cancer Patients with Sentinel Node Micrometastasis: Final Results from the Multicenter Clinical Trial AATRM 048/13/2000. Ann Surg Oncol. 2013;20(1):120-7.
47. Huang WW, Huang C, Liu J, Zheng HY, Lin L. Zoledronic acid as an adjuvant therapy in patients with breast cancer: A systematic review and meta-analysis. PLoS ONE. 2012;7.
48. Mauri D, Valachis A, Polyzos NP, Tsali L, Mavroudis D, Georgoulias V, et al. Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. JNCCN Journal of the National Comprehensive Cancer Network. 2010;8:279-86.
49. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane database of systematic reviews (Online). 2012;2:CD003474.
50. Aapro MS, Coleman RE. Bone health management in patients with breast cancer: Current standards and emerging strategies. Breast. 2012;21:8-19.
51. Hadji P. Managing bone health with zoledronic acid: a review of randomized clinical study results. Review. Climacteric. 2011;14:(3):321-32.
52. Liu Y, Zhao S, Chen W, Hu F, Zhu L, Zhang Q, et al. Bisphosphonate use and the risk of breast cancer: A meta-analysis of published literature. Clin.Breast Cancer. 2012;12:276-81.
53. Luis IV, Casimiro S, Ribeiro J, Costa L. Zoledronic acid: Its use in the treatment of breast cancer. Clinical Medicine Insights: Therapeutics. 2010;2:913-26.
54. Perrin C, Edeline J, Kerbrat P. The AZURE study and meta-analysis: Zoledronic acid as adjuvant therapy in localised breast cancer. Oncologie. 2012;14:411-3.
55. Tonyali O, Arslan C, Altundag K. The role of zoledronic acid in the adjuvant treatment of breast cancer: Current perpectives. Expert Opin.Pharmacother. 2010;11:2715-25.
56. Valachis A, Polyzos NP, Georgulias V, Mavroudis D, Mauri D. Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: A meta-analysis. Gynecol.Oncol. 2010;117:139-45.
57. Valachis A, Nearchou A, Polyzos NP, Mauri D, Lind PA. Adjuvant therapy with zoledronic acid in primary breast cancer: A systematic review and meta-analysis. Eur.J.Cancer. 2011;Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden. Conference Start: 20110923 Conference End: 20110927. Conference Publication:S377.
58. Yan T, Yin W, Zhou Q, Zhou L, Jiang Y, Du Y, et al. The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials. Eur.J.Cancer. 2012;48:187-95.
59. Zhou WB, Zhang PL, Liu XA, Yang T, He W. Innegligible musculoskeletal disorders caused by zoledronic acid in adjuvant breast cancer treatment: A meta-analysis. Journal of Experimental and Clinical Cancer Research. 2011;30.
60. Aft RL, Naughton M, Trinkaus K, Weilbaecher K. Effect of (Neo)adjuvant zoledronic acid on disease-free and overall survival in clinical stage II/III breast cancer. British Journal of Cancer. 2012;107(1):26.
61. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, et al. Breast-cancer adjuvant therapy with zoledronic acid. The New England journal of medicine. 2011;365:1396-405.
62. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncology. 2011;12(7):631-41.
63. Paterson AHG, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): A multicentre, placebo-controlled, randomised trial. The lancet oncology. 2012;13(7):July.

64. Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-MacGregor M, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: An open label, randomised, phase 2 trial. The lancet oncology. 2010;11(5):May.

65. Coleman R, Woodward E, Brown J, Cameron D, Bell R, Dodwell D, et al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer. Breast cancer research and treatment. 2011;127:429-38.

66. Leal T, Tevaarwerk A, Love R, Stewart J, Binkley N, Eickhoff J, et al. Randomized trial of adjuvant zoledronic acid in postmenopausal women with high-risk breast cancer. Clin. Breast Cancer. 2010;10(6):471-6.

67. Barrett-Lee PJ, Murray N, Abraham J, Casbard A, Clements H, Maughan TS, et al. Interim safety data on the ZICE trial: A randomized phase III, open-label, multicener, parallel group clinical trial to evaluate and compare the efficacy, safety profile, and tolerability of oral ibandronate versus intravenous zoledronate in the treatment of patients with breast cancer with bone metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(15 SUPPL.1):20.

68. Bell R, Goss PE, Barrios CH, Finkelstein D, Iwata H, Martin M, et al. A randomised, double-blind, placebo-controlled multicentre phase 3 study comparing denosumab with placebo as adjuvant treatment for women with early-stage breast cancer who are at high risk of disease recurrence (D-care). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;7(150):November.

69. Bell R, Marshall H, Collinson M, Cameron D, Dodwell D, Keane M, et al. The azure trial (big 01/04). European Journal of Cancer. 2011;47(pp S376):September.

70. Body JJ. New developments in the treatment of metastatic bone disease. European Journal of Cancer. 2010;8(3):March.

71. Body J, Stopeck A, Fujiwara Y, Lipton A, Steger GG, Viniegra M, et al. Denosumab is superior to zoledronic acid for delaying or preventing skeletal related events (SRES) in breast cancer patients with bone metastases (BM): Results of a phase 3 trial. Annals of Oncology. 2010;21(pp iv60):2010.

72. Body JJ, Stopeck A, Fujiwara Y, Lipton A, Steger G, Viniegra M, et al. Results of a prospective, randomized, double-blind, double-dummy, Phase 3 study comparing denosumab with zoledronic acid for the treatment of breast cancer patients with bone metastases. Bone. 2010;46(pp S36-S37):March.

73. Body JJ. Prevention and treatment of side-effects of systemic treatment: Bone loss. Annals of Oncology. 2010;21(SUPPL.7):October.

74. Body JJ, Von MR, Stopeck A, Qian Y, Braun A, Chung K. Health resource utilization of subjects receiving denosumab and zoledronic acid in a randomized phase 3 trial of advanced breast cancer patients with bone metastases. Value in Health. 2010;13(7):November.

75. Bouganim N, Clemons MJ. Bone-targeted agents in the treatment of bone metastases: RANK outsider or new kid on the block? Future Oncology. 2011;7(3):381-3.

76. Brufsky AM, Harker WG, Beck JT, Bosserman L, Vogel C, Seidler C, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. Cancer. 2012;118(5):1192-201.

77. Coleman R, Marshall H, Gregory W, Bell R, Dodwell D, Keane M, et al. The AZURE trial (BIG 01/04). European Journal of Cancer.Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden.Conference Start: 20110923 Conference End: 20110927.Conference Publication: (var.pagings). 2011;47(pp S336):September.

78. Coleman RE. Bone metastases. Breast.Conference: 1st Consensus Conference on Advanced Breast Cancer, ABC1 Lisbon Portugal.Conference Start: 20111103 Conference End: 20111105.Conference Publication: (var.pagings). 2011;20(pp S19-S20):October.

79. Coleman RE, Giordano SH. Adjuvant treatment with zoledronic acid in stage II/III breast cancer: The AZURE trial. P and T. 2011;36(3):March.

80. de Boer R, Stopeck A, Fujiwara Y, Tonkin K, Fan M, Jiang Q, et al. Incidence of skeletal-related events (SREs) in breast cancer (BC) patients with bone metastases (BM): Denosumab versus zoledronic acid (ZA). Asia-Pacific Journal of Clinical Oncology. 2011;6(50):August.

81. Eidtmann H, De BR, Bundred N, Llombart-Cussac A, Davidson N, Neven P, et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Annals of Oncology. 2010;21(11):2188-94.

82. Fehm T. Bisphosphonates: Can they serve as anti cancer agents in the adjuvant setting? Breast Care. 2011;6(2):April.

83. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Poestlberger S, Dubsky PC, et al. Mature results from ABCSG-12: Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with endocrine-responsive early breast cancer. Journal of Clinical Oncology.Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States.Conference Start: 20100604 Conference End: 20100608.Conference Publication: (var.pagings). 2010;28(15 SUPPL.#1):20.

84. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Poestlberger S, Steger GG, et al. Adjuvant endocrine therapy, alone or in combination with zoledronic acid (ZOL), in premenopausal patients (PTS) with endocrineresponsive early breast cancer (EBC): Subgroup analyses of ABCSG-12. Annals of Oncology.Conference: 35th ESMO Congress Milan Italy.Conference Start: 20101008 Conference End: 20101012.Conference Publication: (var.pagings). 2010;21(pp viii79):October.

85. Gnant M, Mlineritsch B, Stoeger H, Luschn-Ebengreuth G, Poestlberger S, Dubsky PC, et al. Overall survival with adjuvant zoledronic acid in patients with premenopausal breast cancer with complete endocrine blockade: Long-term results from ABCSG-12. Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings). 2011;29(15 SUPPL.#1):20.

86. Gnant M. Carry-over effect of adjuvant zoledronic acid after 48 and 62 months: The ABCSG-12 trial. P and T. 2011;36(3):March.

87. Gnant M, Hortobagyi GN, Rugo H, Burris HA, Noguchi S, Pritchard KI, et al. Everolimus added to exemestane reduced bone markers and disease progression in bone in postmenopausal women with advanced breast cancer: Updated results from the bolero-2 trial. European Journal of Cancer.Conference: European Breast Cancer Conference 2012, EBCC8 Vienna Austria.Conference Start: 20120321 Conference End: 20120324.Conference Publication: (var.pagings). 2012;48(pp S2):March.

88. Goss PE, Barrios CH, Bell R, Finkelstein D, Iwata H, Martin M, et al. A randomized, double-blind, placebo-controlled multicenter phase III study comparing denosumab with placebo as adjuvant treatment for women with early-stage breast cancer who are at high risk of disease recurrence (D-CARE). Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings). 2011;29(15 SUPPL.#1):20.

89. Greenberg J, Stemmer SM, Bernstein-Molho R, Pelles-Avraham S, Stephansky I, Inbar MJ, et al. The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: 36-month follow-up. Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings). 2011;29(15 SUPPL.#1):20.

90. Hellriegel M, Mueller M, Reimer T, Baerens DT, Von Der AA, Hackmann J, et al. Effect of zoledronic acid on prevention of bone loss, during extended adjuvant therapy with letrozole in postmenopausal women with primary hormone receptor positive breast cancer compared to letrozole alone. European Journal of Cancer.Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden.Conference Start: 20110923 Conference End: 20110927.Conference Publication: (var.pagings). 2011;47(pp S390):September.

91. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Journal of Clinical Oncology. 2011;29(9):1125-32.

92. Hershman DL, McMahon DJ, Crew KD, Shao T, Cremers S, Brafman L, et al. Prevention of bone loss by zoledronic acid in premenopausal women undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment. Journal of Clinical Endocrinology and Metabolism. 2010;95(2):February.

93. Kim JE, Ahn JH, Jung KH, Kim SB, Kim HJ, Lee KS, et al. Zoledronic acid prevents bone loss in premenopausal women with early breast cancer undergoing adjuvant chemotherapy: a phase III trial of the Korean Cancer Study Group (KCSG-BR06-01). Breast Cancer Research & Treatment. 2011;125(1):99-106.

94. Lipton A, Stopeck A, Von MR, Henry D, Ke C, Dansey R. Denosumab vs zoledronic acid for the treatment of bone metastases: Skeletal-related events in a metaanalysis from 2 randomized, double-blind studies. Supportive Care in Cancer.Conference: 2010 International Multinational Association of Supportive Care in Cancer, MASCC/International Society for Oral Oncology, ISOO Symposium Vancouver, BC Canada.Conference Start: 20100624 Conference End: 20100626.Conf. 2010;18(pp S84-S85):June.

95. Lipton A. Should bisphosphonates be utilized in the adjuvant setting for breast cancer? Breast cancer research and treatment. 2010;122(3):August.

96. Markopoulos C, Tzoracoleftherakis E, Polychronis A, Venizelos B, Dafni U, Xepapadakis G, et al. Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: Results from the ARBI prospective clinical trial. Breast Cancer Research. 2010;12(2):R24.

97. McCloskey E, Paterson A, Kanis J, Tahtela R, Powles T. Effect of oral clodronate on bone mass, bone turnover and subsequent metastases in women with primary breast cancer. Eur.J.Cancer. 2010;46(3):February.

98. Morgan G, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro CN, et al. Zoledronic acid (ZOL) significantly reduces skeletal-related events (SRES) versus clodronate (CLO) in patients (PTS) with multiple myeloma (MM): Results of the medical research council (MRC) myeloma ix study. Annals of Oncology.Conference: 35th ESMO Congress Milan Italy.Conference Start: 20101008 Conference End: 20101012.Conference Publication: (var.pagings). 2010;21(pp viii350):October.

99. Morgan G, Lipton A. Antitumor effects and anticancer applications of bisphosphonates. Seminars in oncology. 2010;37(pp S30-40):Oct.

100. Neville-Webbe HL, Gnant M, Coleman RE. Potential anticancer properties of bisphosphonates. Seminars in oncology. 2010;37(SUPPL.):June.

101. Nuzzo F, Gallo C, Lastoria S, Di MM, Piccirillo MC, Gravina A, et al. Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: The randomized phase 3 hoboe study. Annals of Oncology. 2012;23(8):mdr600.

102. Perrone F, Gallo C, Lastoria S, Nuzzo F, Graina A, Landi G, et al. Bone effects of adjuant tamoxifen (T), letrozole (L), or L plus zoledronic acid (Z) in early breast cancer (EBC): The phase III HOBOE study. Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings). 2011;29(15 SUPPL.#1):20.

103. Pfeiler G, Konigsberg R, Mlineritsch B, Stoger H, Singer CF, Poestlberger S, et al. Effect of change of body mass index (BMI) during therapy on the efficacy of endocrine therapy in premenopausal patients with breast cancer: An analysis of the ABCSG-12 trial. Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings). 2011;29(15 SUPPL.#1):20.

104. Pivot X, Lortholary A, Abadie-Lacourtoisie S, Mefti-Lacheraf F, Pujade-Lauraine E, Lefeuvre C, et al. Renal safety of ibandronate 6 mg infused over 15 min versus 60 min in breast cancer patients with bone metastases: a randomized open-label equivalence trial. Breast. 2011;20(6):510-4.

105. Poznak C, Hannon RA, Mackey JR, Campone M, Apffelstaedt JP, Clack G, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28:967-75.

106. Rhee Y, Song K, Lim SK, Park BW. Efficacy of a combined alendronate and calcitriol agent in Korean postmenopausal women with early breast cancer receiving aromatase inhibitor: A double-blind, randomized, placebo-controlled study. Osteoporosis International.Conference: IOF Regionals: 1st Asia-Pacific Osteoporosis Meeting Singapore Singapore.Conference Start: 20101210 Conference End: 20101213.Conference Publication: (var.pagings). 2010;21(pp S760-S761):December.

107. Safra T, Bernstein-Molho R, Greenberg J, Pelles-Avraham S, Stephansky I, Sarid D, et al. The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: a prospective, randomized, phase II trial. Oncology. 2011;81(5-6):298-305.

108. Shapiro CL, Halabi S, Hars V, Archer L, Weckstein D, Kirshner J, et al. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. Eur.J.Cancer. 2011;47:683-9.

109. Solomayer EF, Gebauer G, Hirnle P, Janni W, Luck HJ, Becker S, et al. Influence of zoledronic acid on disseminated tumor cells in primary breast cancer patients. Annals of Oncology. 2012;23(9):mdr612.

110. Takahashi S, Iwase T, Kohno N, Ishikawa T, Taguchi T, Takahashi M, et al. Zoledronic acid inhibits adjuvant letrozole-associated bone loss in postmenopausal Japanese women with early breast cancer. Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings). 2011;29(15 SUPPL.#1):20.

111. Takahashi S, Iwase T, Kohno N, Ishikawa T, Taguchi T, Takahashi M, et al. Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 12-month results. Breast cancer research and treatment. 2012;133(2):June.

112. Theriault RL. Bisphosphonates: ready for use as adjuvant therapy of breast cancer? Current opinion in obstetrics & gynecology. 2010;22(1):Feb.

113. Van Londen GJ, Perera S, Vujevich KT, Sereika SM, Bhattacharya R, Greenspan SL. The effect of risedronate on hip structural geometry in chemotherapy-induced postmenopausal women with or without use of aromatase inhibitors: a 2-year trial. Bone. 2010;46(3):655-9.

114. Von Minckwitz G, Zahm MD, Eidtmann H, Tesch H, du Bois A, Schwedler K, et al. Zoledronic acid (ZOL) as add-on therapy in patients with tumour residuals after neoadjuvant chemotherapy for primary breast cancer -first interim safety analysis of the NATAN study (GBG 36). European Journal of Cancer, Supplement.Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain.Conference Start: 20100324 Conference End: 20100327.Conference Publication: (var.pagings). 2010;8(3):March.

115. Xu L, Hao X, Zhang M, Zhang J. Clinical trial on the efficacy of zoledronic acid in preventing bone loss induced by aromatase inhibitor in breast cancer. Chinese. Chinese Journal of Clinical Oncology. 2010;37(7):15.

116. An MM, Zou Z, Shen H, Liu P, Chen ML, Cao YB, et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur.J.Clin.Pharmacol. 2010;66:(8):813-21.

117. Mackey JR, Kerbel RS, Gelmon KA, McLeod DM, Chia SK, Rayson D, et al. Controlling angiogenesis in breast cancer: a systematic review of anti-angiogenic trials. Review. Cancer Treat.Rev. 2012;38:(6):673-88.

118. Ranpura V, Pulipati B, Chu D, Zhu X, Wu S. Increased risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. Review 52 refs. Am.J.Hypertens. 2010;23:(5):460-8.

119. Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials. Review. Breast Cancer Res.Treat. 2010;122:(1):1-7.

120. Wagner AD, Thomssen C, Haerting J, Unverzagt S. Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database Syst Rev. 2012;7:CD008941.

121. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis (Structured abstract). JAMA. 2011;305:487-94.

122. Alvarez RH, Valero V, Hortobagyi GN. Emerging targeted therapies for breast cancer. J.Clin.Oncol. 2010;28:3366-79.

123. Bhinder A, Carothers S, Ramaswamy B. Antiangiogenesis therapy in breast cancer. Current Breast Cancer Reports. 2010;2:4-15.

124. Blank PR, Dedes KJ, Szucs TD. Cost effectiveness of cytotoxic and targeted therapy for metastatic breast cancer: A critical and systematic review. PharmacoEconomics. 2010;28:629-47.

125. Brufsky A. First-line treatment of metastatic breast cancer: Current strategies and emerging systemic therapies. Community Oncology. 2010;7:115-23.

126. Chan A, Miles DW, Pivot X. Bevacizumab in combination with taxanes for the first-line treatment of metastatic breast cancer. Ann.Oncol. 2010;21:2305-15.

127. Choueiri TK, Mayer EL, Je Y, Rosenberg JE, Nguyen PL, Azzi GR, et al. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. J.Clin.Oncol. 2011;29:(6):632-8.

128. Cortes J, Calvo V, Ramirez-Merino N, O'Shaughnessy J, Brufsky A, Robert N, et al. Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. Review. Ann.Oncol. 2012;23:(5):1130-7.

129. Croom KF, Dhillon S. Bevacizumab: A review of its use in combination with paclitaxel or capecitabine as first-line therapy for HER2-negative metastatic breast cancer. Drugs. 2011;71:2213-29.

130. Cuppone F, Bria E, Vaccaro V, Puglisi F, Fabi A, Sperduti I, et al. Magnitude of risks and benefits of the addition of bevacizumab to chemotherapy for advanced breast cancer patients: Meta-regression analysis of randomized trials. J.Exp.Clin.Cancer Res. 2011;30:54, 2011.:54, 2011.

131. Dienstmann R, Ades F, Saini KS, Metzger-Filho O. Benefit-risk assessment of bevacizumab in the treatment of breast cancer. Review. Drug Saf. 2012;35:(1):15-25.

132. Dirix LY, Van Dam PA, Prove AM, Vermeulen PB. Bevacizumab in the treatment of patients with advanced breast cancer: Where have we landed? Therapeutic Advances in Medical Oncology. 2010;2:331-42.

133. Garcia PA. Therapeutic approaches in young women with advanced or metastatic breast cancer. Breast Cancer Research and Treatment. 2010;123:49-52.

134. Hamilton EP, Blackwell KL. Safety of bevacizumab in patients with metastatic breast cancer. Oncology. 2011;80:314-25.

135. Kumler I, Nielsen DL. Trials of bevacizumab in breast cancer a safety review. Expert Opinion on Drug Safety. 2012;11:S37-S48.

136. Lee JB, Woo OH, Park KH, Woo SU, Yang DS, Kim AR, et al. Bevacizumab for salvage treatment of metastatic breast cancer: a systemic review and meta-analysis of randomized controlled trials. Review. Invest New Drugs. 2011;29(1):182-8.

137. Miles D, Zielinski C, Martin M, Vrdoljak E, Robert N. Combining capecitabine and bevacizumab in metastatic breast cancer: A comprehensive review. Eur.J.Cancer. 2012;48:482-91.

138. Petrelli F, Barni S. Bevacizumab in advanced breast cancer: an opportunity as second-line therapy? Med.Oncol. 2012;29:(1):1-4.

139. Rodgers M, Soares M, Epstein D, Yang H, Fox D, Eastwood A. Bevacizumab in combination with a taxane for the first-line treatment of HER2-negative metastatic breast cancer. Review. Health Technol.Assess. 2011;15 Suppl 1(Winchester, 2011 Mayyy.):1-12.

140. Brufsky AM, Hurvitz S, Perez E, Swamy R, Valero V, O'Neill V, et al. RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J.Clin.Oncol. 2011;29(32):10.

141. Martin M, Roche H, Pinter T, Crown J, Kennedy MJ, Provencher L, et al. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: A phase 2, randomised, double-blind, placebo-controlled study. The Lancet Oncology. 2011;12:369-76.

142. Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28:3239-47.

143. Pivot X, Schneeweiss A, Verma S, Thomssen C, Passos-Coelho JL, Benedetti G, et al. Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: Results from AVADO. Eur.J.Cancer. 2011;47:2387-95.

144. Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J.Clin.Oncol. 2011;29:1252-60.

145. Bear HD, Tang G, Rastogi P, Geyer CE, Robidoux A, Atkins JN, et al. The effect on pCR of bevacizumab and/or antimetabolites added to standard neoadjuvant chemotherapy: NSABP protocol B-40. J.Clin.Oncol. 2011;Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607.

146. Bear HD, Tang G, Rastogi P, Geyer, Jr., C.E, Robidoux A, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. New England Journal of Medicine. 2012;366:310-20.

147. Bidard FC, Mathiot C, Degeorges A, Etienne-Grimaldi MC, Delva R, Pivot X, et al. Clinical value of circulating endothelial cells and circulating tumor cells in metastatic breast cancer patients treated first line with bevacizumab and chemotherapy. Ann.Oncol. 2010;21(9):1765-71.

148. Biganzoli L, Di VE, Jiang Z, Lichinitser M, Shen Z, Delva R, et al. First-line bevacizumab-containing therapy for breast cancer: results in patients aged>=70 years treated in the ATHENA study. Ann.Oncol. 2012;23(1):111-8.

149. Bondarenko I, Glaspy J, Brufsky A, Lipatov O, Perez EA, Chan S, et al. PFS by patient subgroup for standard chemotherapies in combination with bevacizumab (BV) in the first-line treatment of HER2-negative locally recurrent (LR) or metastatic breast cancer (mBC): Results from RIBBON-1. European Journal of Cancer. 2010;Supplement:198.

150. Brufsky A, Rivera RR, Hurvitz SA, Bondarenko IN, Smirnov V, Valero V, et al. Progression-free survival (PFS) in patient subgroups in RIBBON-2, a phase III trial of chemotherapy (chemo) plus or minus bevacizumab (BV) for second-line treatment of HER2-negative, locally recurrent or metastatic breast cancer (MBC). J.Clin.Oncol. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

151. Brufsky A, Bondarenko IN, Smirnov V. RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. In: 32nd Annual San Antonio Breast Cancer Symposium. San Antonio, TX United States; 2010. p. 17.

152. Brufsky A, Ponomarova O, Tjulandin S. Influence of disease free interval on the efficacy of capecitabine-bevacizumab for HER2-negative metastatic breast cancer (MBC) in the RIBBON-1 trial. European Journal of Cancer. 2010;Supplement 201.

153. Brufsky A. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer: Robert NJ, Dieras V, Glaspy J, et al (Virginia Cancer Specialists, Fairfax; Univ of California, Los Angeles; Genentech, South San Francisco, CA; Et al). Breast Diseases. 2011;22:412-3.

154. Brufsky A, Valero V, Tiangco B, Dakhil S, Brize A, Rugo HS, et al. Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Breast Cancer Res.Treat. 2012;133(3):1067-75.

155. Cella D, Wang M, Wagner L, Miller K. Survival-adjusted health-related quality of life (HRQL) among patients with metastatic breast cancer receiving paclitaxel plus bevacizumab versus paclitaxel alone: results from Eastern Cooperative Oncology Group Study 2100 (E2100). Breast Cancer Res.Treat. 2011;130(3):855-61.

156. Cortes J, Caralt M, Delaloge S, Cortes-Funes H, Pierga JY, Pritchard KI, et al. Safety of bevacizumab in metastatic breast cancer patients undergoing surgery. Eur.J.Cancer. 2012;48(4):475-81.

157. Dieras V, Semiglazov V, Tjulandin S. Efficacy of first-line capecitabine plus bevacizumab in patients with ER/PgR-positive metastatic breast cancer (MBC) and those previously treated with hormone therapy. European Journal of Cancer, Supplement. 2010;Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain. Conference Start: 20100324 Conference End: 20100327. Conference Publication:202.

158. Dieras V, Jassem J, Dirix LY, Guastalla JP, Bono P, Hurvitz SA, et al. A randomized, placebo-controlled phase II study of AMG 386 plus bevacizumab (Bev) and paclitaxel (P) or AMG 386 plus P as first-line therapy in patients (pts) with HER2-negative, locally recurrent or metastatic breast cancer (LR/MBC). J.Clin.Oncol. 2011;Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607.

159. Forster F, Schneeweiss A, Geberth M, Tesch H, Klare P, Kummel S, et al. Updated results from a large, multicentre study of 1st-line bevacizumab (BEV) combined with paclitaxel (PAC) for HER2-negative metastatic breast cancer (MBC) in routine oncology practice. Ann.Oncol. 2010;Conference: 35th ESMO Congress Milan Italy. Conference Start: 20101008 Conference End: 20101012. Conference Publication:viii104-viii5.

160. Glaspy J, Dieras V, Brufsky A, Miles DW, Phan SC, Shaughnessy JO. Bevacizumab (BV) in combination with chemotherapy in the treatment of HER2-negative metastatic breast cancer (mBC): PFS subgroup results from two phase III studies. European Journal of Cancer, Supplement. 2010;Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain. Conference Start: 20100324 Conference End: 20100327. Conference Publication:202.

161. Hardy-Bessard AC, Delva R, Pivot X, Espie M, Dalenc F, Coulon Sfairi MA, et al. Safety and efficacy of bevacizumab combined with taxanes in the first-line treatment of metastatic breast cancer: ATHENA study-France. Bulletin du Cancer. 2012;99(6):609-18.

162. Hegewisch-Becker S, Lerchenmuller CA, Welt A, Decker T, Just M, Steffens C, et al. Capecitabine (Cap) combined with bevacizumab (Bev) with or without vinorelbine (Vin) in first-line metastatic breast cancer (MBC): First safety results from the randomized CARIN trial. J.Clin.Oncol. 2011;Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607.

163. Lang I, Inbar M, Greil R, Kahan Z, Beslija S, Steger GG, et al. Safety subgroup analyses from the CECOG PHASE III TURANDOT TRIAL: First-line bevacizumab (BEV) in combination with capecitabine (X) or paclitaxel (P) for HER2-negative locally recurrent or metastatic breast cancer (LR/MBC). Ann.Oncol. 2010;Conference: 35th ESMO Congress Milan Italy. Conference Start: 20101008 Conference End: 20101012. Conference Publication:viii98.

164. Lang I, Inbar MJ, Greil R, Steger GG, Beslija S, Kahan Z, et al. Bevacizumab (Bev) combined with either capecitabine (X) or weekly paclitaxel (Pac) as first-line chemotherapy (CT) for HER2-negative, locally recurrent or metastatic breast cancer (LR/MBC): Preliminary safety data from the CECOG phase III TURANDOT trial. J.Clin.Oncol. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

165. Lindman H, Lipatov O, Bondarenko I, Panasci L, Coleman R. RIBBON-1: Efficacy of capecitabine-bevacizumab in patients with triple-negative metastatic breast cancer (MBC). European Journal of Cancer, Supplement. 2010;Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain. Conference Start: 20100324 Conference End: 20100327. Conference Publication:204.

166. Masuda N, Aogi K, Ohno S, Iwata H, Kashiwaba M, Fujiwara Y, et al. Phase II study of bevacizumab (Bev) combined with weekly paclitaxel (wPac) as first-line therapy for Japanese patients (pts) with HER2-negative metastatic breast cancer (MBC). J.Clin.Oncol. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

167. Mayer EL, Ligibel JA, Burstein HJ, Miller K, Carey LA, Rugo HS, et al. TBCRC 012: ABCDE, a phase II randomized study of adjuvant bevacizumab, metronomic chemotherapy (CM), diet and exercise after preoperative chemotherapy for breast cancer. J.Clin.Oncol. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

168. Mayer EL, Dhakil S, Patel T, Sundaram S, Fabian C, Kozloff M, et al. SABRE-B: An evaluation of paclitaxel and bevacizumab with or without sunitinib as first-line treatment of metastatic breast cancer. Ann.Oncol. 2010;21:2370-6.

169. Miles DW, Dieras V, Glaspy J, Brufsky A, Koralewski P, Phan SC, et al. Incidence of selected adverse events (AEs) in phase III studies of bevacizumab (BV) in combination with chemotherapy for the treatment of HER2-negative metastatic breast cancer (mBC). European Journal of Cancer, Supplement. 2010;Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain. Conference Start: 20100324 Conference End: 20100327. Conference Publication:196.

170. Miles DW, De Haas SL, Romieu G, Chan A, Dirix L, Cortes J, et al. Polymorphism analysis in the avado randomised phase III trial of first-line bevacizumab (BEV) combined with docetaxel in HER2-negative metastatic breast cancer (MBC). Eur.J.Cancer. 2011;Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden. Conference Start: 20110923 Conference End: 20110927. Conference Publication:S176.

171. Miller KD, O'Neill A, Perez EA, Seidman AD, Sledge GW. A phase II pilot trial incorporating bevacizumab into dose-dense doxorubicin and cyclophosphamide followed by paclitaxel in patients with lymph node positive breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group. Ann.Oncol. 2012;23(2):331-7.

172. Robert NJ, Saleh MN, Paul D, Generali D, Gressot L, Copur MS, et al. Sunitinib plus paclitaxel versus bevacizumab plus paclitaxel for first-line treatment of patients with advanced breast cancer: a phase III, randomized, open-label trial. Erratum appears in Clin Breast Cancer. 2011 Aug;11(4):273. Clinical Breast Cancer. 2011;11(2):82-92.

173. Rugo HS, Campone M, Amadori D, Wardley AM, Aldrighetti D, Conte PF, et al. Randomized phase II study of weekly versus every 3 week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bev (pac/bev) as first-line therapy for metastatic breast cancer (MBC): Final results. J.Clin.Oncol. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

174. Shaughnessy JO, Dieras V, Chan S. Consistent progression-free survival benefit of capecitabine-bevacizumab in all prespecified subgroups of the RIBBON-1 study in patients with metastatic breast cancer (MBC). European Journal of Cancer, Supplement. 2010;Conference: European Breast Cancer Conference, EBCC7 Barcelona Spain. Conference Start: 20100324 Conference End: 20100327. Conference Publication:198.

175. Smith I, Pierga JY, Biganzoli L, Cortes-Funes H, Thomssen C, Saracchini S, et al. Final overall survival results and effect of prolonged (>= 1 year) first-line bevacizumab-containing therapy for metastatic breast cancer in the ATHENA trial. Breast Cancer Res.Treat. 2011;130(1):133-43.

176. Smith IE, Pierga JY, Biganzoli L, Cortes-Funes H, Thomssen C, Pivot X, et al. First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: Safety and efficacy in an open-label study in 2251 patients. Ann.Oncol. 2011;22:595-602.

177. Thomssen C, Pierga JY, Pritchard KI, Biganzoli L, Cortes-Funes H, Petrakova K, et al. First-line bevacizumab-containing therapy for triple-negative breast cancer: analysis of 585 patients treated in the ATHENA study. Oncology. 2012;82(4):218-27.

178. Von Minckwitz G, Eidtmann H, Rezai M, Fasching PA, Tesch H, Eggemann H, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. New England Journal of Medicine. 2012;366:299-309.

179. Wachter K. Bevacizumab falls short in first neoadjuvant HER2-negative trial. Oncology Report. 2011:15-6.

180. Xu BH, Jiang ZF, Shen ZZ, Guan ZZ, Chen ZD, Cheng Y, et al. Safety and efficacy of first-line bevacizumab combined with taxane therapy in Chinese patients with HER2-negative locally recurrent or metastatic breast cancer: findings from the ATHENA study. Chinese Medical Journal. 2012;125(5):764-9.

181. Bayoudh L, Afrit M, Daldoul O, Zarrad M, Boussen H. Trastuzumab (herceptin) for the medical treatment of breast cancer . Review French. Tunis Med. 2012;90:(1):6-12.

182. Chang HR. Trastuzumab-based neoadjuvant therapy in patients with HER2-positive breast cancer. Cancer. 2010;116:2856-67.

183. Chen T, Xu T, Li Y, Liang C, Chen J, Lu Y, et al. Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis (Structured abstract). Cancer Treatment Reviews. 2011;37:312-20.

184. Costa RB, Kurra G, Greenberg L, Geyer CE. Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer. Ann.Oncol. 2010;21:2153-60.

185. Garnock-Jones KP, Keating GM, Scott LJ. Trastuzumab: A review of its use as adjuvant treatment in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. Drugs. 2010;70:215-39.

186. Gines J, Sabater E, Martorell C, Grau M, Monroy M, Casado MA. Efficacy of taxanes as adjuvant treatment of breast cancer: a review and meta-analysis of randomised clinical trials (Provisional abstract). Database of Abstracts of Reviews of Effects. 2011:485-98.

187. Grude F, Campone M, Lortholary A, Delva R, Soulie P, Kerbrat P, et al. Cardiac toxicity of trastuzumab in adjuvant and neoadjuvant breast cancer analysis. Phase IV pharmacovigilance study led by the "Observatoire des Medicaments et Innovations Therapeutiques" (OMIT B PL). Oncologie. 2010;12:362-8.

188. Hysing J, Wist E. Cardiotoxic effects of trastuzumab. Review. Tidsskr.Nor Laegeforen. 2011;131:(22):2239-41.

189. Mateu MM, Farre XG. Why we must treat HER2-positive patients with trastuzumab in first-line treatment. Cancer and Chemotherapy Reviews. 2011;6:149-55.

190. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Review. Cochrane Database Syst.Rev. 2012;4:CD006243, 2012.:CD006243, 2012.

191. Mukohara T. Role of HER2-targeted agents in adjuvant treatment for breast cancer. Chemotherapy Research and Practice. 2011;2011 , 2011. Article Number: 730360. Date of Publication: 2011.

192. Patani N, Mokbel K. Herceptin and breast cancer: an overview for surgeons. Review 101 refs. Surg.Oncol. 2010;19:(1):e11-e21.

193. Pienkowski T, Zielinski CC. Trastuzumab treatment in patients with breast cancer and metastatic CNS disease. Ann.Oncol. 2010;21:917-24.

194. Tagliabue E, Balsari A, Campiglio M, Pupa SM. HER2 as a target for breast cancer therapy. Expert Opin.Biol.Ther. 2010;10:711-24.

195. Valachis A, Mauri D, Polyzos NP, Chlouverakis G, Mavroudis D, Georgoulias V. Trastuzumab combined to neoadjuvant chemotherapy in patients with HER2-positive breast cancer: A systematic review and meta-analysis. Breast. 2011;20:485-90.

196. Valachis A, Nearchou A, Lind P, Mauri D. Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence. Breast Cancer Res.Treat. 2012;135:(3):655-62.

197. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials. PLoS ONE. 2011;6.

198. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.

199. Buzdar A, Suman V, Meric-Bernstam F, Boughey JC, Leitch AM, Unzeitig GW, et al. Preliminary safety data of a randomized phase III trial comparing a preoperative regimen of FEC-75 alone followed by paclitaxel plus trastuzumab with a regimen of paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab in patients with HER2-positive operable breast cancer (ACOSOG Z1041). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

200. Cameron DA, Marreaud S, Zaman K, Bodmer A, Pierga J, Brain E, et al. EORTC 10054 trial. Journal of Clinical Oncology. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

201. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomised controlled trial. The Lancet Oncology. 2011;12:236-44.

202. Guarneri V, Frassoldati A, Bottini A, Generali DG, Cagossi K, Artioli F, et al. Final results of a phase II randomized trial of neoadjuvant anthracycline-taxane chemotherapy plus lapatinib, trastuzumab, or both in HER2-positive breast cancer (CHER-LOB trial). Journal of Clinical Oncology. 2011;Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607.

203. Guarneri V, Frassoldati A, Bottini A, Cagossi K, Bisagni G, Sarti S, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. Journal of Clinical Oncology. 2012;30(16):1989-95.

204. Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B, Kim SB, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): A phase 3, open-label, multicentre, randomised trial. The Lancet Oncology. 2012;13:869-78.

205. Jinno H, Sato T, Takahashi M, Hayashida T, Sakata M, Hirose S, et al. A phase II neoadjuvant trial of concurrent trastuzumab and paclitaxel without anthracycline in women with HER2-positive operable breast cancer. Journal of Clinical Oncology. 2011;Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607.

206. Masuda N, Toi M, Ueno T, Aogi K, Iwata H, Ohno S, et al. A multicenter, randomized phase II study of neoadjuvant chemotherapy including trastuzumab with cyclophosphamide with docetaxel in patients with operable HER2-positive breast cancer (JBCRG-10 study). Journal of Clinical Oncology. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608.

207. Moran MS. Radiotherapy and adjuvant trastuzumab in operable breast cancer: Tolerability and adverse event data from the NCCTG Phase III Trial N9831. Breast Diseases. 2010;21:277-8.

208. Nakamura S, Ando M, Masuda N, Aogi K, Ino H, Iwata H, et al. Randomized phase II study of primary systemic chemotherapy and trastuzumab for operable HER2 positive breast cancer. Clinical Breast Cancer. 2012;12(1):49-56.

209. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29:3366-73.

210. Perez EA, Jenkins RB, Dueck AC, Wiktor AE, Bedroske PP, Anderson SK, et al. C-MYC alterations and association with patient outcome in early-stage HER2-positive breast cancer from the north central cancer treatment group N9831 adjuvant trastuzumab trial. Journal of Clinical Oncology. 2011;29(6):651-9.

211. Procter M, Suter TM, de AE, Dafni U, Van DV, Muehlbauer S, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. Journal of Clinical Oncology. 2010;28:3422-8.

212. Rayson D, Suter T, van dV, Lluch A, van den Bosch J, Lopez-Vivanco G, et al. Cardiac safety analysis. Journal of Clinical Oncology. 2010;Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608. Conference Publication:.

213. Rayson D, Suter TM, Jackisch C, van dV, Bermejo B, van den Bosch J, et al. Cardiac safety of adjuvant pegylated liposomal doxorubicin with concurrent trastuzumab: A randomized phase II trial. Ann.Oncol. 2012;23:1780-8.

214. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer, Jr., C.E, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. Journal of Clinical Oncology. 2012;30:3792-9.

215. Sanchez-Munoz A, Duenas-Garcia R, Jaen-Morago A, Carrasco E, Chacon I, Garcia-Tapiador AM, et al. trastuzumab in stage II and III breast cancer patients. American Journal of Clinical Oncology. 2010;33:432-7.

216. Sawaki M, Tokudome N, Mizuno T, Nakayama T, Taira N, Bando H, et al. Evaluation of trastuzumab without chemotherapy as a post-operative adjuvant therapy in HER2-positive elderly breast cancer patients: randomized controlled trial RESPECT (N-SAS BC07). Japanese Journal of Clinical Oncology. 2011;41(5):709-12.

217. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28:2024-31.

218. Valero V, Slamon DJ, Eiermann W, Robert NJ, Pienkowski T, Martin M, et al. Efficacy results of node-negative HER2-amplified breast cancer subset from BCIRG 006 study: A phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin, and trastuzumab (TCH). Journal of Clinical Oncology. 2011;Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607. Conference Publication:.

219. Peters NH, Borel Rinkes IH, Zuithoff NP, Mali WP, Moons KG, PH. P. Meta-analysis of MR imaging in the diagnosis of breast lesions. Radiology. 2008;246(1):116-24.

220. Medical Advisory Secretariat of Ontario Ministry of Health and Long-Term Care. Scintimammography as an Adjunctive Breast Imaging Technology - Integrated Health Technology Literature Review. Toronto: 2007.

221. National Institute for Health and Clinical Excellence. Advanced breast cancer - Diagnosis and treatment. London: NICE; 2009. NICE Clinical guideline 81

222. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technology Assessment. 2007;11(44):iii-iv, xi-267.

223. Agency for Healthcare Research and Quality. Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities. Rockville: AHRQ; 2006.

224. Bourguet P, Hitzel A, Houvenaeghel G, Vinatier D, Bosquet L, Bonichon F, et al. [Synthesis bulletin of 2005 surveillance. Clinical practice recommendations: the use of PET-FDG in cancers of the breast, ovary and uterus]. Bulletin du Cancer. 2006;93(4):385-90.

225. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. Journal of Clinical Oncology. 2007;25(33).

226. Dhesy-Thind B, Pritchard K, Messersmith H, O'Malley F, Elavathil L, Trudeau M, et al. The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer: A Clinical Practice Guideline. Toronto: 2006. Evidence-based Series #1-17: Section 1

227. National Institute for Health and Clinical Excellence. Early and locally advanced breast cancer: diagnosis and treatment London: NICE; 2009. NICE clinical guideline 80

228. Myers R, Minuk T, Johnston M, the Diagnostic Imaging Guidelines Panel. Diagnostic Imaging in Breast Cancer - Recommendations Report. Toronto: Program in Evidence-Based Care's (PEBC) Diagnostic Imaging Guidelines Panel; 2006.

229. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008;29(16):3248-57.

230. Sloka JS, Hollett PD, Mathews M. A quantitative review of the use of FDG-PET in the axillary staging of breast cancer. Medical Science Monitor. 2007;13(3):RA37-46.

231. Ueda S, Tsuda H, Asakawa H, Omata J, Fukatsu K, Kondo N, et al. Utility of 18F-fluoro-deoxyglucose emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in combination with ultrasonography for axillary staging in primary breast cancer. BMC Cancer. 2008;8:165.

232. Veronesi U, De Cicco C, Galimberti VE, Fernandez JR, Rotmensz N, Viale G, et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. Annals of Oncology. 2007;18(3):473-8.

233. Gil-Rendo A, Zornoza G, Garcia-Velloso MJ, Regueira FM, Beorlegui C, Cervera M. Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. British Journal of Surgery. 2006;93(6):707-12.

234. Kumar R, Zhuang H, Schnall M, Conant E, Damia S, Weinstein S, et al. FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. Nuclear Medicine Communications. 2006;27(3):231-6.

235. Chow LW-C, Yip AY-S, Loo WT-Y, Lam C-K, Toi M. Celecoxib anti-aromatase neoadjuvant (CAAN) trial for locally advanced breast cancer. Journal of Steroid Biochemistry & Molecular Biology. 2008;111(1-2):13-7.

236. Lee C, Sunu C, Pignone M. Patient-Reported Outcomes of Breast Reconstruction after Mastectomy: A Systematic Review. J Am Coll Surg. 2009:123-33.

237. Yang SH, Yang KH, Li YP, Zhang YC, He XD, Song AL, et al. Breast conservation therapy for stage I or stage II breast cancer: a meta-analysis of randomized controlled trials. Annals of Oncology. 2008;19:1039-44.

238. Blichert-Toft M, Nielsen M, During M, Moller S, Rank F, Overgaard M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. Acta Oncologica. 2008;47(4):672-81.

239. Petit JY, Gentilini O, Rotmensz N, Rey P, Rietjens M, Garusi C, et al. Oncological results of immediate breast reconstruction: long term follow-up of a large series at a single institution. Breast Cancer Res Treat. 2008;112(3):545-9.

240. Langer I, Guller U, Berclaz G, Koechli OR, Moch H, Schaer G, et al. Accuracy of frozen section of sentinel lymph nodes: a prospective analysis of 659 breast cancer patients of the Swiss multicenter study. Breast Cancer Research & Treatment. 2009;113:129-36.

241. Canavese G, Catturich A, Vecchio C, Tomei D, Gipponi M, Villa G, et al. Sentinel node biopsy compared with complete axillary dissection for staging early breast cancer with clinically negative lymph nodes: results of randomized trial. Annals of Oncology. 2009;20(6):1001-7.

242. Motomura K, Nagumo S, Komoike Y, Koyama H, Inaji H. Accuracy of imprint cytology for intraoperative diagnosis of sentinel node metastases in breast cancer. Ann Surg. 2008;247(5):839-42.

243. James ML, Lehman M, Hider PN, Jeffery M, Francis DP, Hickey BE. Fraction size in radiation treatment for breast conservation in early breast cancer. Cochrane Database of Systematic Reviews. 2008(3).

244. Holli K, Hietanen P, Saaristo R, Huhtala H, Hakama M, Joensuu H. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow-up results of a randomized trial. J Clin Oncol. 2009;27(6):927-32.

245. Trudeau M, Eisen A, Messersmith H, Pritchard K, and the Breast Cancer Disease Site Group. Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline. Cancer Care Ontario; 2006. Evidence-based Series #1-7: Section 1

246. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. Lancet. 2008;371:29-40.

247. Albain KS, Barlow WE, Ravdin PM, Farrar WB, Burton GV, Ketchel SJ, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. Lancet. 2009;374(9707):2055-63.

248. Amadori D, Nanni O, Volpi A, Casadei Giunchi D, Marangolo M, Livi L, et al. Phase III randomized multicenter study on the effects of adjuvant CMF in patients with node-negative, rapidly proliferating breast cancer: twelve-year results and retrospective subgroup analysis. Breast Cancer Res Treat. 2008;108(2):259-64.

249. de Azambuja E, Cardoso F, Meirsman L, Straehle C, Dolci S, Vantongelen K, et al. The new generation of breast cancer clinical trials: the right drug for the right target. Bull Cancer. 2008;95(3):352-7.

250. Ejlertsen B, Mouridsen HT, Jensen M-B, Andersen J, Cold S, Edlund P, et al. Improved outcome from substituting methotrexate with epirubicin: results from a randomised comparison of CMF versus CEF in patients with primary breast cancer. Eur J Cancer. 2007;43(5):877-84.

251. Ellis P, Barrett-Lee P, Johnson L, Cameron D, Wardley A, O'Reilly S, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial.[see comment]. Lancet. 2009;373(9676):1681-92.

252. Francis P, Crown J, Di Leo A, Buyse M, Balil A, Andersson M, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial.[see comment][erratum appears in J Natl Cancer Inst. 2008 Nov 19;100(22):1655]. J Natl Cancer Inst. 2008;100(2):121-33.

253. Gianni L, Baselga J, Eiermann W, Porta VG, Semiglazov V, Lluch A, et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol. 2009;27(15):2474-81.

254. Goldstein LJ, O'Neill A, Sparano JA, Perez EA, Shulman LN, Martino S, et al. Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E 2197. J Clin Oncol. 2008;26(25):4092-9.

255. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735.[see comment]. J Clin Oncol. 2009;27(8):1177-83.

256. Lee KS, Ro J, Nam B-H, Lee ES, Kwon Y, Kwon HS, et al. A randomized phase-III trial of docetaxel/capecitabine versus doxorubicin/cyclophosphamide as primary chemotherapy for patients with stage II/III breast cancer. Breast Cancer Res Treat. 2008;109(3):481-9.

257. Martin M, Rodriguez-Lescure A, Ruiz A, Alba E, Calvo L, Ruiz-Borrego M, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer.[see comment]. J Natl Cancer Inst. 2008;100(11):805-14.

258. Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med. 2009;360(20):2055-65.

259. Taucher S, Steger GG, Jakesz R, Tausch C, Wette V, Schippinger W, et al. The potential risk of neoadjuvant chemotherapy in breast cancer patients--results from a prospective randomized trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-07). Breast Cancer Res Treat. 2008;112(2):309-16.

260. Tokuda Y, Tajima T, Narabayashi M, Takeyama K, Watanabe T, Fukutomi T, et al. Phase III study to evaluate the use of high-dose chemotherapy as consolidation of treatment for high-risk postoperative breast cancer: Japan Clinical Oncology Group study, JCOG 9208. Cancer Sci. 2008;99(1):145-51.

261. Watanabe T, Sano M, Takashima S, Kitaya T, Tokuda Y, Yoshimoto M, et al. Oral uracil and tegafur compared with classic cyclophosphamide, methotrexate, fluorouracil as postoperative chemotherapy in patients with node-negative, high-risk breast cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. J Clin Oncol. 2009;27(9):1368-74.

262. Zander AR, Schmoor C, Kroger N, Kruger W, Mobus V, Frickhofen N, et al. Randomized trial of high-dose adjuvant chemotherapy with autologous hematopoietic stem-cell support versus standard-dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: overall survival after 6 years of follow-up. Ann Oncol. 2008;19(6):1082-9.

263. Hackshaw A, Baum M, Fornander T, Nordenskjold B, Nicolucci A, Monson K, et al. Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. Journal of the National Cancer Institute. 2009;101(5):341-9.

264. Rossi E, Morabito A, De Maio E, Di Rella F, Esposito G, Gravina A, et al. Endocrine effects of adjuvant letrozole + triptorelin compared with tamoxifen + triptorelin in premenopausal patients with early breast cancer. Journal of Clinical Oncology. 2008;26(2):264-70.

265. Eisen A, Trudeau M, Shelley W, Sinclair S, and the Breast Cancer Disease Site Group. The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations. Toronto: Cancer Care Ontario; 2008. Evidence-based Series #1-18: Section 1

266. The BIG 1-98 Collaborative Group. Letrozole Therapy Alone or in Sequence with Tamoxifen in Women with Breast Cancer. N Engl J Med. 2009;361:766-76.

267. Hadji P, Ziller M, Kieback DG, Dornoff W, Tessen HW, Menschik T, et al. Effects of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial: results of a German, 12-month, prospective, randomised substudy. Annals of Oncology. 2009;20(7):1203-9.

268. Trudeau M, Madarnas Y, McCready D, Pritchard K, Messersmith H, and the Breast Cancer Disease Site Group. The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer: A Clinical Practice Guideline. Toronto: Cancer Care Ontario; 2006. Evidence-based Series #1-24: Section 1

269. Dahabreh I, Linardou H, Siannis F, Fountzilas G, Murray S. Trastuzumab in the Adjuvant Treatment of Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The Oncologist. 2008;13:620-30.

270. Untch M, Gelber RD, Jackisch C, Procter M, Baselga J, Bell R, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol. 2008;19(6):1090-6.

271. Beslija S, Bonneterre J, Burstein H, Cocquyt V, Gnant M, Goodwin P, et al. Second consensus on medical treatment of metastatic breast cancer. Annals of Oncology. 2007;18(2):215-25.

272. Campos SM, Guastalla JP, Subar M, Abreu P, Winer EP, Cameron DA. A comparative study of exemestane versus anastrozole in patients with postmenopausal breast cancer with visceral metastases. Clinical Breast Cancer. 2009;9(1):39-44.

273. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. Journal of Clinical Oncology. 2008;26(30):4883-90.

274. Dirix LY, Ignacio J, Nag S, Bapsy P, Gomez H, Raghunadharao D, et al. Treatment of advanced hormone-sensitive breast cancer in postmenopausal women with exemestane alone or in combination with celecoxib. J Clin Oncol. 2008;26(8):1253-9.

275. Johnston SR, Semiglazov VF, Manikhas GM, Spaeth D, Romieu G, Dodwell DJ, et al. A phase II, randomized, blinded study of the farnesyltransferase inhibitor tipifarnib combined with letrozole in the treatment of advanced breast cancer after antiestrogen therapy. Breast Cancer Res Treat. 2008;110(2):327-35.

276. Flemming J, Madarnas Y, Franek JA. Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations. Toronto: Cancer Care Ontario; 2008. Evidence-based Series #1-13: Section 1

277. Dent S, Messersmith H, Trudeau M, and the Breast Cancer Disease Site Group. The Role of Gemcitabine in the Management of Metastatic Breast Cancer: A Clinical Practice Guideline. Toronto: Cancer Care Ontario; 2007. Evidence-based Series #1-12: Section 1

278. Carrick S, Parker S, Thornton CE, Ghersi D, Simes J, Wilcken N. Single agent versus combination chemotherapy for metastatic breast cancer (Review). 2009. Cochrane Database of Systematic Reviews Issue 2. Art. No.: CD003372. DOI: 10.1002/14651858.CD003372.pub3.

279. Chan S, Romieu G, Huober J, et al. Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. J Clin Oncol. 2009;27(11):1753-60.

280. von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study.[see comment]. Journal of Clinical Oncology. 2009;27(12):1999-2006.

281. Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst. 2008;100(7):475-82.

282. Andersen BL, Yang H-C, Farrar WB, Golden-Kreutz DM, Emery CF, Thornton LM, et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. Cancer. 2008;113(12):3450-8.

283. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. Journal of Clinical Oncology. 2006;24(31):5091-7.

284. Beaver K, Tysver-Robinson D, Campbell M, Twomey M, Williamson S, Hindley A, et al. Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. BMJ. 2009;338(a3147).