

Câncer de Mama

AC-D

Adriamicina: 60 mg/m ²	IV	D1
Ciclofosfamida: 600 mg/m ²	IV	D1 a cada 21 dias X 4 ciclos
Docetaxel: 100mg/m ²	IV	D1 após 4 ciclos de AC
a cada 21 dias X 4 ciclos		Ref. (1-3)

OU

Doxorrubicina: 60 mg/m ²	IV	D1
Ciclofosfamida: 600 mg/m ²	IV	D1 a cada 21 dias X 4 ciclos
Docetaxel: 35mg/m ²	IV	D1 após 4 ciclos de AC
semanal X 12 semanas		Ref. (2, 3)

AC-T

Doxorrubicina: 60 mg/m ²	IV	D1
Ciclofosfamida: 600 mg/m ²	IV	D1 a cada 21 dias X 4 ciclos
Paclitaxel: 175mg/m ²	IV	D1 após 4 ciclos de AC
a cada 21 dias X 4 ciclos		Ref. (2)

Doxorrubicina: 60 mg/m ²	IV	D1
Ciclofosfamida: 600 mg/m ²	IV	D1 a cada 21 dias X 4 ciclos
Paclitaxel: 80mg/m ²	IV	D1 após 4 ciclos de AC
semanal X 12 semanas		Ref. (2, 3)

TAC

Doxorrubicina: 50 mg/m ²	IV	D1
Ciclofosfamida: 500 mg/m ²	IV	D1
Docetaxel: 75 mg/m ²	IV	D1
Ciprofloxacina: 500mg	VO BID	D5-D14
Filgrastima: 300mcg	SC	D2-D14
a cada 21 dias X 6 ciclos		
Ref. (4, 5)		

AC

Doxorrubicina: 60 mg/m² IV D1
Ciclofosfamida: 600 mg/m² IV D1 a cada 21 dias X 4 ciclos
Ref. (6-8)

FAC

5-Fluorouracil: 500 mg/m² IV D1
Doxorrubicina: 50 mg/m² IV D1
Ciclofosfamida: 500 mg/m² IV D1 a cada 21 dias X 6 ciclos
Ref. (9, 10)

CMF oral

Ciclofosfamida: 100 mg/m² VO D1 a D 14
Methotrexate: 40 mg/m² IV D1
5-Fluorouracil: 600 mg/m² IV D1 a cada 28 dias X 6 ciclos
Ref. (11)

CMF

Ciclofosfamida: 600mg/m² IV D1
Methotrexate: 40 mg/m² IV D1
5-Fluorouracil: 600 mg/m² IV D1 a cada 21 dias X 6 ciclos
Ref. (12)

CMF

Ciclofosfamida: 600mg/m² IV D1 e D8
Methotrexate: 40 mg/m² IV D1 e D8
5-Fluorouracil: 600 mg/m² IV D1 e D8 a cada 28 dias X 6
ciclos

TC

Docetaxel: 75mg/m² IV D1
Ciclofosfamida: 600 mg/m² IV D1 a cada 21 dias X 4 ciclos
Ref.(13)

FEC 100

5-Fluorouracil: 500mg/m ²	IV	D1
Epirrubicina: 100 mg/m ²	IV	D1
Ciclofosfamida: 500 mg/m ²	IV	D1 a cada 21 dias X 6 ciclos
Ref. (14-16)		

FEC 100- Docetaxel

5-Fluorouracil: 500mg/m ²	IV	D1
Epirrubicina: 100 mg/m ²	IV	D1
Ciclofosfamida: 500 mg/m ²	IV	D1
Docetaxel: 100mg/ m ²	IV	D1 após FEC
a cada 21 dias X 3 ciclos		Ref. (17)

TCH

Docetaxel: 75mg/m ²	IV	D1
Carboplatina: AUC 6	IV	D1 a cada 21 dias X 6 ciclos
Trastuzumabe: 8mg/kg	IV	D1 ATAQUE
Trastuzumabe: 6mg/kg	IV	D1 a cada 21 dias por 1 ano

AC-TH

Doxorrubicina: 60mg/m ²	IV	D1
Ciclofosfamida: 600mg/m ²	IV	D1 a cada 21 dias X 4 ciclos
Paclitaxel: 80mg/m ²	IV	D1 após 4 ciclos de AC
semanal X 12 semanas		
Trastuzumabe: 4mg/kg	IV	D1 ATAQUE
Trastuzumabe: 2mg/kg	IV	D1 semanal por 1 ano
Ref.(18)		

AC-TH

Doxorrubicina: 60mg/m ²	IV	D1
Ciclofosfamida: 600mg/m ²	IV	D1 a cada 21 dias X 4 ciclos
Paclitaxel: 175mg/m ²	IV	D1 após 4 ciclos de AC
a cada 21 dias X 4 ciclos		
Trastuzumabe: 4mg/kg	IV D1	ATAQUE
Trastuzumabe: 2mg/kg	IV D1	semanal por 1 ano Ref.(18)

AC-TH

Doxorrubicina: 60mg/m ²	IV	D1	
Ciclofosfamida: 600mg/m ²	IV	D1 a cada 21 dias X 4 ciclos	
Paclitaxel: 80mg/m ²	IV	D1 após 4 ciclos de AC	
semanal X 12 semanas			
Trastuzumabe: 4mg/kg	IV	D1	ATAQUE
Trastuzumabe: 2mg/kg	IV	D1	semanal por 1 ano

DH-FEC

Docetaxel: 100mg/m ²	IV	D1 a cada 21 dias X 4 ciclos	
Trastuzumabe: 4mg/kg	IV	D1	ATAQUE
Trastuzumabe: 2mg/kg	IV	D1	semanal por 9 semanas
5-Fluourouracil: 600mg/m ²	IV	D1	
Epirubicina: 60mg/m ²	IV	D1	
Ciclofosfamida: 600mg/m ²	IV	D1 após 4 ciclos de DH	
a cada 21 dias X 4 ciclos			
Ref. (19)			

VH-FEC

Vinorelbina: 25g/m ²	IV	D1 a cada 21 dias X 4 ciclos	
Trastuzumabe: 4mg/kg	IV	D1	ATAQUE
Trastuzumabe: 2mg/kg	IV	D1	semanal por 9 semanas
5-Fluourouracil: 600mg/m ²	IV		
Epirubicina: 60mg/m ²	IV		
Ciclofosfamida: 600mg/m ²	IV	D1 após 4 ciclos de DH	
a cada 21 dias X 4 ciclos			
Ref. (19)			

AD

Doxorrubicina: 50mg/m ²	IV	D1	
Docetaxel: 75mg/m ²	IV	D1	
a cada 21 dias			
Ref. (8)			

AT

Doxorrubicina: 60 mg/m² IV D1
Paclitaxel: 175 mg/m² IV D1 a cada 21 dias
Ref. (20)

Docetaxel + Capecitabina

Docetaxel: 75 mg/m² IV D1 a cada 21 dias
Capecitabina: 1250mg/m² VO BID D1 a D14
a cada 21 dias
Ref. (21)

Vinorelbina + Capecitabina

Vinorelbina: 25 mg/m² IV D1 e D8 a cada 21 dias
Capecitabina: 1000 mg/m² VO BID D1 a D 14 a cada 21 dias
Ref. (22, 23)

Gencitabina + Capecitabina

Gencitabina: 2000 mg/m² IV D1 a cada 21 dias
Capecitabina: 1250mg/m² VO BID D1 a D 14 a cada 21 dias
Ref. (24)

OU

Gencitabina: 800mg/m² IV D1 e D8 a cada 21 dias
Capecitabina 750mg/m² VO BID D1 a D14 a cada 21 dias
Ref. (25)

Vinorelbina + Gencitabina

Vinorelbina 25mg/m² IV D1
Gencitabina: 1000mg/m² IV D1 a cada 14 dias
Ref. (26)

Cisplatina + Gencitabina

Cisplatina: 30 mg/m² IV D1 e D8

Gencitabina: 750 mg/m² IV D1 e D8 a cada 21 dias

Ref. (27)

Doxorrubicina

Doxorrubicina: 60 mg/m² IV D1 a cada 21 dias

Ref. (28)

Epirrubicina

Epirrubicina: 75mg/m² IV D1 a cada 21 dias

Ref. (29)

Paclitaxel

Paclitaxel: 175mg/m² IV D1 a cada 21 dias

Ref. (28, 30)

OU

Paclitaxel: 90mg/m² IV D1 a cada 7 dias

Ref. (31)

Docetaxel

Docetaxel: 100mg/m² IV D1 a cada 21 dias

Ref. (32)

OU

Docetaxel: 40mg/m² IV

D1, D8, D15, D22, D29, D36 com 14 dias de folga

Ref. (33)

Capecitabina

Capecitabina: 1250mg/m² VO BID D1 a D14 a cada 21 dias

Ref. (34)

Vinorelbina

Vinorelbina: 30mg/m² IV D1 e D8 a cada 21 dias

Ref. (35)

Doxorrubicina Lipossomal

Doxo lipossomal: 40mg/m² IV D1 a cada 28 dias Ref. (36)

Gencitabina

Gencitabina: 750mg/m² IV D1, D8, D15 a cada 28 dias

Ref. (37)

Trastuzumabe

Trastuzumabe: 8mg/kg IV D1 ATAQUE

Trastuzumabe: 6mg/kg IV D1 a cada 21 dias

Ref. (38)

OU

Trastuzumabe: 4mg/kg IV D1 ATAQUE

Trastuzumabe: 2mg/kg IV D1 a cada 7 dias

Ref. (39)

Paclitaxel + Trastuzumabe

Paclitaxel: 175mg/m² IV D1 a cada 21 dias

Trastuzumabe: 4mg/kg IV D1 ATAQUE

Trastuzumabe: 2mg/kg IV D1 a cada 7 dias

subsequente Ref. (40)

OU

Paclitaxel: 90mg/m² IV D1 a cada 7 dias

Trastuzumabe: 4mg/kg IV D1 ATAQUE

Trastuzumabe: 2mg/kg IV D1 a cada 7 dias

subsequente

Ref. (41)

Docetaxel + Trastuzumabe

Docetaxel: 100mg/m ²	IV	D1 a cada 21 dias
Trastuzumabe: 4mg/kg	IV	D1 ATAQUE
Trastuzumabe: 2mg/kg	IV	D1 a cada 7 dias

subsequente
Ref. (42)

OU

Docetaxel: 35mg/m ²	IV	D1 a cada 7 dias
Trastuzumabe: 4mg/kg	IV	D1 ATAQUE
Trastuzumabe: 2mg/kg	IV	D1 a cada 7 dias

subsequente
Ref. (43)

Vinorelbina + Trastuzumabe

Vinorelbina: 25mg/m ²	IV	D1 a cada 7 dias
Trastuzumabe: 4mg/kg	IV	D1 ATAQUE
Trastuzumabe: 2mg/kg	IV	D1 a cada 7 dias

subsequente
Ref. (44)

Gencitabina + Trastuzumabe

Gencitabina: 1200mg/m ²	IV	D1 e D8
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a cada 21 dias

Trastuzumabe: 4mg/kg	IV	D1 ATAQUE
Trastuzumabe: 2mg/kg	IV	D1 a cada 7 dias

subsequente
Ref. (45)

Vinorelbina Oral

Vinorelbina: 80mg/m² D1 semanal após 3 administrações com dose de 60mg/m² semanal para testar mielossensibilidade
Ref. (71)

Gencitabina + Paclitaxel

Gencitabina: 1250mg/m² IV D1 e D8

Paclitaxel: 175mg/m² IV D1 a cada 21 dias

Ref. (46, 47)

Gencitabina + Docetaxel

Gencitabina: 1000mg/m² IV D1 e D8

Docetaxel: 75mg/m² IV D1 a cada 21 dias

Ref. (48)

Gencitabina + Vinorelbina

Gencitabina: 1200mg/m² IV D1 e D8

Vinorelbina : 30mg/m² IV D1 e D8 a cada 21 dias

Ref. (49)

Lapatinibe + Capecitabina

Lapatinibe: 1250mg VO/dia contínuo

Capecitabina : 2000mg/m² VO D1 a D14

a cada 21 dias

Ref. (50)

Lapatinibe + Trastuzumabe

Lapatinibe: 1250mg VO/dia contínuo

Trastuzumabe: 4mg/kg IV D1 ATAQUE

Trastuzumabe: 2mg/kg IV D1 a cada 7 dias

Tamoxifeno

Tamoxifeno: 20mg VO Diariamente 5 anos/indefinido

Ref. (51, 52)

Anastrozol

Anastrozol: 1mg VO Diariamente 5 anos/indefinido

Ref. (53-55)

Letrozol

Letrozol: 2,5mg VO Diariamente indefinido
Ref. (56, 57)

Exemestano

Exemestano: 25mg VO Diariamente indefinido
Ref. (58, 59)

Tamoxifeno + Letrozol

Tamoxifeno: 20mg VO Diariamente 5 anos
Letrozol: 2,5mg VO Diariamente 5 anos
após término Tamoxifeno
Ref. (60)

Tamoxifeno + Exemestano

Tamoxifeno: 20mg VO Diariamente 2-3 anos
Exemestano: 25mg VO Diariamente Até
completar 5 anos
Ref. (61)

Fulvestranto

Fulvestranto: 250mg IM D1 a cada 28 dias
Ref. (62)

Megestrol

Megestrol: 160 mg VO Diariamente indefinido
Ref. (63)

Toremifeno

Toremifeno: 60mg VO Diariamente indefinido
Ref. (64)

Análogo LHRH+ Tamoxifeno

LHRH: ----- IM ou SCD1 a cada 28 dias
Tamoxifeno: 20mg VO Contínuo Ref. (65)

Análogo LHRH+ Anastrozol

LHRH: ----- IM ou SCD1 a cada 28 dias
Anastrozol 1mg VO Contínuo

Dose densa AC → T

Doxorrubicina: 60 mg/m² IV no D1
Ciclofosfamida: 600 mg/m² IV no D1
Filgrastima: 300mcg SC do D2 ao D12

a cada 14 dias no total de 4 ciclos.

seguido por

Paclitaxel: 175 mg/m² IV no D1 a cada 14 dias por 4 ciclos
Filgrastima: 300mcg SC do D2 ao D12

OU

Paclitaxel: 80 mg/m² IV semanalmente por 12 semanas
Ref. (66)

ATH → TH → CMFH (NOAH trial)

Doxorrubicina: 60 mg/m² IV no D1
Paclitaxel: 175mg/m² IV D1 a cada 3 semanas X 3 ciclos

Seguido de:

Paclitaxel: 175 mg/m² IV D1 X 4 ciclos

Seguido de:

Ciclofosfamida: 600mg/m² IV D1 e D8
Methotrexate: 40mg/m² IV D1 e D8
5-Fluorouracil: 600mg/m² D1 e D8
Repetir CMF a cada 28 dias por 3 ciclos.

Trastuzumabe concomitante com toda a Quimioterapia (dose ataque 8mg/kg seguido de dose de manutenção de 6mg/kg a cada 3 semanas até completar 1 ano de terapia). Ref. (67)

Paclitaxel + Bevacizumabe (ECOG 2100)

Paclitaxel: 90 mg/m² IV no D1, D8 e D15 a cada 4 semanas, associado a

Bevacizumabe: 10mg/kg IV a cada 2 semanas.

Ref. (68)

Docetaxel + Bevacizumabe (AVADO)

Docetaxel: 100mg/m² IV no D1 a cada 3 semanas.

Bevacizumabe: 15mg/kg IV no D1 a cada 3 semanas.

Ref. (69)

Capecitabina + Bevacizumabe (RIBBON 1)

Capecitabina: 1000mg/m² VO BID por 14 dias a cada 21 dias.

Bevacizumabe: 15mg/kg IV no D1 a cada 3 semanas.

Ref. (70)

1. Bear, H.D., *et al.* The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*, 2003. 21(22): p. 4165-74.
2. Sparano, J.A., *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med*, 2008. 358(16): p. 1663-71.
3. De Laurentiis, M., *et al.* Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol*, 2008. 26(1): p. 44-53.
4. Martin, M., *et al.* Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med*, 2005. 352(22): p. 2302-13.
5. Mackey, J., *Proc.ASCO*, 2002. 21(abstract137).
6. Fisher, B., *et al.* Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National

Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol*, 1990. 8(9): p. 1483-96.

7. Fisher, B., *et al.* Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*, 1998. 16(8): p. 2672-85.
8. Nabholz, J.M., *et al.* Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. *J Clin Oncol*, 2003. 21(6): p. 968-75.
9. Martin, M., *et al.* Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. *Ann Oncol*, 2003. 14(6): p. 833-42.
10. Stewart, D.J., *et al.* Cyclophosphamide and fluorouracil combined with mitoxantrone versus doxorubicin for breast cancer: superiority of doxorubicin. *J Clin Oncol*, 1997. 15(5): p. 1897-905.
11. Bonadonna, G., *et al.* Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med*, 1976. 294(8): p. 405-10.
12. Pritchard, K.I., *et al.* Randomized trial of cyclophosphamide, methotrexate, and fluorouracil chemotherapy added to tamoxifen as adjuvant therapy in postmenopausal women with node-positive estrogen and/or progesterone receptor-positive breast cancer: a report of the National Cancer Institute of Canada Clinical Trials Group. *Breast Cancer Site Group. J Clin Oncol*, 1997. 15(6): p. 2302-11.
13. Jones, S.E., *et al.* Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol*, 2006. 24(34): p. 5381-7.
14. Coombes, R.C., *et al.* Adjuvant cyclophosphamide,

methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. The International Collaborative Cancer Group. *J Clin Oncol*, 1996. 14(1): p. 35-45.

15. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. *J Clin Oncol*, 2001. 19(3): p. 602-11.
16. Epirubicin-based chemotherapy in metastatic breast cancer patients: role of dose-intensity and duration of treatment. *J Clin Oncol*, 2000. 18(17): p. 3115-24.
17. Roche, H., *et al.* Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol*, 2006. 24(36): p. 5664-71.
18. Romond, E.H., *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*, 2005. 353(16): p. 1673-84.
19. Joensuu, H., *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*, 2006. 354(8): p. 809-20.
20. Biganzoli, L., *et al.* Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. *J Clin Oncol*, 2002. 20(14): p. 3114-21.
21. O'Shaughnessy, J., *et al.* Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*, 2002. 20(12): p. 2812-23.
22. Biganzoli, L., M. Martin, and C. Twelves, Moving forward with capecitabine: a glimpse of the future. *Oncologist*, 2002. 7 Suppl 6: p. 29-35.

- 23.** Welt, A., *et al.* Phase I/II study of capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. *Ann Oncol*, 2005. 16(1): p. 64-9.
- 24.** Andres, R., *et al.* Gemcitabine/capecitabine in patients with metastatic breast cancer pretreated with anthracyclines and taxanes. *Clin Breast Cancer*, 2005. 6(2): p. 158-62.
- 25.** Abstracts of the 27th Annual San Antonio Breast Cancer Symposium. December 8-11, 2004, San Antonio, Texas, USA. *Breast Cancer Res Treat*, 2004. 88 Suppl 1: p. S1-265.
- 26.** Stathopoulos, G.P., *et al.* Phase II trial of biweekly administration of vinorelbine and gemcitabine in pretreated advanced breast cancer. *J Clin Oncol*, 2002. 20(1): p. 37-41.
- 27.** Nagourney, R.A., *et al.* Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. *J Clin Oncol*, 2000. 18(11): p. 2245-9.
- 28.** Sledge, G.W., *et al.* Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol*, 2003. 21(4): p. 588-92.
- 29.** A prospective randomized trial comparing epirubicin monochemotherapy to two fluorouracil, cyclophosphamide, and epirubicin regimens differing in epirubicin dose in advanced breast cancer patients. The French Epirubicin Study Group. *J Clin Oncol*, 1991. 9(2): p. 305-12.
- 30.** Seidman, A.D., *et al.* Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol*, 1995. 13(10): p. 2575-81.
- 31.** Seidman, A.D., *et al.* Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol*, 1998. 16(10): p. 3353-61.
- 32.** Nabholz, J.M., *et al.* Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol*, 1999. 17(5): p. 1413-24.

33. Burstein, H.J., *et al.* Docetaxel administered on a weekly basis for metastatic breast cancer. *J Clin Oncol*, 2000. 18(6): p. 1212-9.
34. Blum, J.L., *et al.* Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol*, 1999. 17(2): p. 485-93.
35. Weber, B.L., *et al.* Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. *J Clin Oncol*, 1995. 13(11): p. 2722-30.
36. Al-Batran, S.E., *et al.* Reduced incidence of severe palmar-plantar erythrodysesthesia and mucositis in a prospective multicenter phase II trial with pegylated liposomal doxorubicin at 40 mg/m² every 4 weeks in previously treated patients with metastatic breast cancer. *Oncology*, 2006. 70(2): p. 141-6.
37. Carmichael, J., *et al.* Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol*, 1995. 13(11): p. 2731-6.
38. Baselga, J., *et al.* Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol*, 2005. 23(10): p. 2162-71.
39. Baselga, J., *et al.* Phase II study of weekly intravenous trastuzumab (Herceptin) in patients with HER2/neu-overexpressing metastatic breast cancer. *Semin Oncol*, 1999. 26(4 Suppl 12): p. 78-83.
40. Slamon, D.J., *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*, 2001. 344(11): p. 783-92.
41. Seidman, A.D., *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*, 2001. 19(10): p. 2587-95.
42. Marty, M., *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line

- treatment: the M77001 study group. *J Clin Oncol*, 2005. 23(19): p. 4265-74.
43. Esteva, F.J., *et al.* Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*, 2002. 20(7): p. 1800-8.
 44. Burstein, H.J., *et al.* Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol*, 2001. 19(10): p. 2722-30.
 45. O'Shaughnessy, J.A., *et al.* Phase II study of trastuzumab plus gemcitabine in chemotherapy-pretreated patients with metastatic breast cancer. *Clin Breast Cancer*, 2004. 5(2): p. 142-7.
 46. O'Shaughnessy, J., Gemcitabine combination chemotherapy in metastatic breast cancer: phase II experience. *Oncology (Williston Park)*, 2003. 17(12 Suppl 14): p. 15-21.
 47. Albain, K.S., *et al.* Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*, 2008. 26(24): p. 3950-7.
 48. Chan, S., *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): p. 1753-60.
 49. Martin, M., *et al.* Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. *Lancet Oncol*, 2007. 8(3): p. 219-25.
 50. Geyer, C.E., *et al.* Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*, 2006. 355(26): p. 2733-43.
 51. Fisher, B., *et al.* Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst*, 1997. 89(22): p. 1673-82.
 52. Jaiyesimi, I.A., *et al.* Use of tamoxifen for breast cancer:

- twenty-eight years later. *J Clin Oncol*, 1995. 13(2): p. 513-29.
- 53.** Howell, A., Adjuvant aromatase inhibitors for breast cancer. *Lancet*, 2005. 366(9484): p. 431-3.
- 54.** Buzdar, A.U., P.V. Plourde, and G.N. Hortobagyi, Aromatase inhibitors in metastatic breast cancer. *Semin Oncol*, 1996. 23(4 Suppl 9): p. 28-32.
- 55.** Nabholz, J.M., *et al.* Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol*, 2000. 18(22): p. 3758-67.
- 56.** Dombrowsky, P., *et al.* Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol*, 1998. 16(2): p. 453-61.
- 57.** Mouridsen, H., *et al.* Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol*, 2001. 19(10): p. 2596-606.
- 58.** Lonning, P.E., Exemestane in breast cancer: current status and future directions. *Clin Breast Cancer*, 2000. 1 Suppl 1: p. S28-33.
- 59.** Paridaens, R.J., *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. *J Clin Oncol*, 2008. 26(30): p. 4883-90.
- 60.** Goss, P.E., *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*, 2005. 97(17): p. 1262-71.
- 61.** Coombes, R.C., *et al.* A randomized trial of exemestane after

- two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*, 2004. 350(11): p. 1081-92.
- 62.** Howell, A., Future use of selective estrogen receptor modulators and aromatase inhibitors. *Clin Cancer Res*, 2001. 7(12 Suppl): p. 4402s-4410s; discussion 4411s-4412s.
- 63.** Kimmick, G.G. and H.B. Muss, Endocrine therapy in metastatic breast cancer. *Cancer Treat Res*, 1998. 94: p. 231-54.
- 64.** Hayes, D.F., *et al.* Randomized comparison of tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. *J Clin Oncol*, 1995. 13(10): p. 2556-66.
- 65.** Klijn, J.G., *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol*, 2001. 19(2): p. 343-53.
- 66.** Citron ML *et al.* Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741 *J Clin Oncol* 2003;21(8):1481.
- 67.** Gianni K, Ejeremann W, Semiglazov V, *et al.* Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; 375; 377-384.
- 68.** Miller K, Wang M, Gralow J, *et al.* A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). *Breast Cancer Res Treat.* 2005;94(suppl 1):S6. Abstract 3.

- 69.** Miles DW, Chan A, Romieu G, *et al.* Randomised, double-blind, placebo controlled, phase III study of bevacizumab (BV) with docetaxel (D) or D with placebo (PL) as 1st line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol* 2008; 26;185.
- 70.** Robert NJ, Dieras V, Glaspy J, *et al.* RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). *J Clin Oncol* 2009; 27;15s (suppl; abstr 1005).
- 71.** Freyer, T. Phase II Study of Oral Vinorelbine in First-Line Advanced Breast Cancer Chemotherapy. *JCO* Jan 1, 2003;35-40.