Neth.: Hycamtin; ***Norw.:*** Hycamtin; ***Pol.:*** Hycamtin; ***Port.:*** Hycamtin; ***Rus.:*** Hycamtin (Гикамтин); ***S.Afr.:*** Hycamtin; ***Singapore:*** Hycamtin; ***Spain:*** Hycamtin; ***Swed.:*** Hycamtin; ***Switz.:*** Hycamtin; ***Thai.:*** Hycamtin; Topotel; ***Turk.:*** Hycamptin; ***UK:*** Hycamtin; ***USA:*** Hycamtin; ***Venez.:*** Hycamtin†.

Toremifene Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de toremifeno; FC-1157a; Toremifen Sitrat; Torémifène, Citrate de; Toremifeni Citras. 2-{*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy}-*N*,*N*-dimethylethylamine citrate.

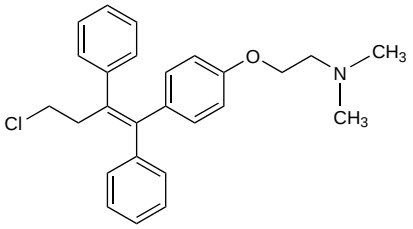
Торемифена Цитрат

$C_{26}H_{28}ClNO,C_6H_8O_7$ = 598.1.

CAS — 89778-26-7 (toremifene); 89778-27-8 (toremifene citrate).

ATC — L02BA02.

ATC Vet — QL02BA02.



(toremifene)

Adverse Effects and Precautions

As for Tamoxifen Citrate, p.772.

Use of toremifene is contra-indicated in patients with pre-existing endometrial hyperplasia, or in those with severe thromboembolic disease or severe hepatic impairment. Toremifene must be used with caution in patients with uncompensated heart failure or severe angina. Patients with bone metastases should be monitored for signs and symptoms of hypercalcaemia.

Interactions

Toremifene is metabolised by cytochrome P450 isoenzyme CYP3A4, and potent enzyme-inducing drugs such as phenytoin, phenobarbital and carbamazepine, might be expected to increase toremifene metabolism, thereby lowering the serum concentration. Conversely, azole antifungals and macrolide antibacterials may inhibit toremifene metabolism by inhibiting the isoenzyme.

Use with drugs that decrease renal calcium excretion, such as thiazide diuretics, may increase the incidence of hypercalcaemia. Use with coumarin anticoagulants should be avoided as there is a risk of increased bleeding time.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of toremifene in 9 subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Pharmacokinetics

Toremifene citrate is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations of toremifene within 3 hours. Plasma concentration declines biexponentially; the mean distribution half-life is about 4 hours and the elimination half-life is about 5 days. It is extensively bound to plasma proteins, mainly albumin. Toremifene is metabolised principally by the cytochrome P450 isoenzyme CYP3A4; the main metabolite is N-demethyltoremifene, which is reported to have anti-oestrogenic activity but with weak anti-tumour activity. It undergoes enterohepatic circulation and is eliminated mainly in the faeces as metabolites. About 10% is excreted in the urine.

◊ Reviews.

1. Taras TL, *et al.* Clinical pharmacokinetics of toremifene. *Clin Pharmacokinet* 2000; **39:** 327–34.

Uses and Administration

Toremifene is an anti-oestrogen with properties similar to those of tamoxifen (p.775). It is used in the treatment of metastatic breast cancer (p.661) in postmenopausal women with oestrogen-receptor positive tumours. It is also being investigated for the treatment of lung tumours and for the management of prostate cancer.

Toremifene is given orally as the citrate, but doses are calculated in terms of the base; 88.4 mg of toremifene citrate is equivalent to about 60 mg of toremifene. A dose of toremifene 60 mg once daily is used.

◊ References.

1. Wiseman LR, Goa KL. Toremifene: a review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. *Drugs* 1997; **54:** 141–60.
2. Anonymous. Toremifene and letrozole for advanced breast cancer. *Med Lett Drugs Ther* 1998; **40:** 43–5.
3. Holli K. Adjuvant trials of toremifene vs tamoxifen: the European experience. *Oncology (Huntingt)* 1998; **12** (suppl 5): 23–7.
4. Holli K, *et al.* Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 2000; **18:** 3487–94.
5. Taneja SS, *et al.* Toremifene—a promising therapy for the prevention of prostate cancer and complications of androgen deprivation therapy. *Expert Opin Invest Drugs* 2006; **15:** 293–305.
6. Smith MR, *et al.* Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. *J Urol (Baltimore)* 2008; **179:** 152–5.
7. Smith MR, *et al.* Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: interim analysis of a multicenter phase III study. *J Clin Oncol* 2008; **26:** 1824–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fareston†; ***Austral.:*** Fareston; ***Austria:*** Fareston; ***Belg.:*** Fareston; ***Cz.:*** Fareston; ***Fin.:*** Fareston; ***Fr.:*** Fareston; ***Ger.:*** Fareston; ***Gr.:*** Fareston; ***Hung.:*** Fareston; ***Irl.:*** Fareston; ***Ital.:*** Fareston; ***Mex.:*** Fareston; ***Neth.:*** Fareston; ***NZ:*** Fareston; ***Port.:*** Fareston; ***Rus.:*** Fareston (Фарестон); ***S.Afr.:*** Fareston; ***Spain:*** Fareston; ***Swed.:*** Fareston; ***Switz.:*** Fareston; ***Thai.:*** Fareston; ***Turk.:*** Fareston; ***UK:*** Fareston; ***USA:*** Fareston.

Tositumomab *(rINN)*

B-1; Tositumomabum. Immunoglobulin G2a anti-(human antigen CD 20) (mouse monoclonal clone B1R1 γ2a-chain), disulfide with mouse monoclonal clone B1R1 λ_x-chain, dimer.

Тоситумомаб

CAS — 192391-48-3.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Infusion reactions suggestive of a cytokine release syndrome, and other hypersensitivity reactions including anaphylaxis, have been reported with tositumomab. Prolonged and severe neutropenia, thrombocytopenia, and anaemia occur commonly; full blood counts should be monitored weekly for up to 12 weeks. Other adverse effects include gastrointestinal disturbances, dehydration, abdominal pain, pleural effusion, and increased susceptibility to infection. Delayed adverse effects such as the development of secondary malignancies, leukaemia, or myelodysplastic syndrome may occur. Patients receiving the radiolabelled regimen may be susceptible to hypothyroidism and pretreatment with thyroid blocking drugs is recommended (see Uses and Administration, below); levels of thyroid-stimulating hormone should be measured before treatment and annually thereafter.

Uses and Administration

Tositumomab is an anti-B1 monoclonal antibody that is directed against the CD20 antigen found on the surface of B lymphocytes. It is radiolabelled with iodine-131 (p.2054) for the treatment of patients with CD20 antigen-expressing, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma (p.656), and including those patients who have disease refractory to rituximab.

The regimen consists of a dosimetric step, followed 7 to 14 days later by a therapeutic step. The dosimetric step consists of 450 mg of tositumomab given intravenously in 50 mL sodium chloride 0.9% over 60 minutes. Tositumomab 35 mg radiolabelled with iodine-131 is then given intravenously in 30 mL sodium chloride 0.9% over 20 minutes. This is followed by whole body imaging to determine whether biodistribution is acceptable, and to allow calculation of the therapeutic dose of radiolabelled tositumomab. In the therapeutic step, tositumomab 450 mg is given again, and followed by the calculated dose of radiolabelled tositumomab.

The rate of infusion may be halved for mild to moderate infusional toxicity, and stopped if this is severe; the infusions may be restarted at half the rate once toxicity resolves. Patients are pretreated with thyroid protective agents at least 24 hours before the first radiolabelled dose of tositumomab; treatment is continued until 2 weeks after the radiolabelled therapeutic dose. Analgesics and antihistamines are also given by mouth 30 minutes before doses of tositumomab.

◊ References.

1. Kaminski MS, *et al.* Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001; **19:** 3918–28.
2. Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin Oncol* 2003; **30** (suppl): 31–8.
3. Anonymous. Iodine-131 tositumomab (Bexxar) for treatment of lymphoma. *Med Lett Drugs Ther* 2003; **45:** 86–7.
4. Friedberg JW, Fisher RI. Iodine-131 tositumomab (Bexxar): radioimmunoconjugate therapy for indolent and transformed B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2004; **4:** 18–26.
5. Davies AJ, *et al.* Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2004; **22:** 1469–79.
6. Vose JM. Bexxar : novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma. *Oncologist* 2004; **9:** 160–72.
7. Horning SJ, *et al.* Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; **23:** 712–19.
8. Kaminski MS, *et al.* I-Tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005; **352:** 441–9.
9. Fisher RI, *et al.* Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol* 2005; **23:** 7565–73.
10. Dosik AD, *et al.* Subsequent therapy can be administered after tositumomab and iodine I-131 tositumomab for non-Hodgkin lymphoma. *Cancer* 2005; **106:** 616–22.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Bexxar.

Trabectedin *(USAN, rINN)*

Ecteinascidin-743; ET-743; NSC-648766; Trabectedina; Trabectédine; Trabectedinum. (1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6′,8,-14-Trihydroxy-7′,9-dimethoxy-4,10,23-trimethyl-19-oxo-3′,4′,6,-7,12,13,14,16-octahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino-6a*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1′(2′*H*)-isoquinolin]-5-yl acetate.

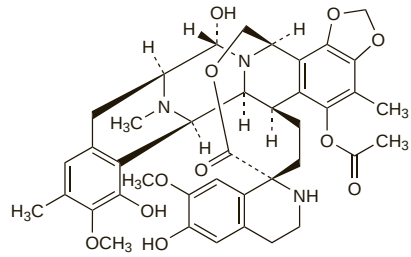
Трабектедин

$C_{39}H_{43}N_3O_{11}S$ = 761.8.

CAS — 114899-77-3.

ATC — L01CX01.

ATC Vet — QL01CX01.



Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia, thrombocytopenia, anaemia, and leucopenia are very common with trabectedin; febrile neutropenia often occurs. Full blood counts should be performed at baseline, weekly for the first 2 cycles, and then once between cycles thereafter. Dose reductions may be needed in those with haematological toxicity. Hepatobiliary disorders are also very common, and include hyperbilirubinaemia and alterations in liver function tests, which are mostly transient. Patients with liver disease should be closely monitored, and trabectedin should not be given to those with hyperbilirubinaemia.

Other very common adverse effects include gastrointestinal disturbances, anorexia, headache, and fatigue. Antiemetic prophylaxis with dexamethasone should be given to all patients. Peripheral sensory neuropathy, paraesthesia, dysgeusia, dizziness, pyrexia, and oedema are common, as are dyspnoea, cough, alopecia, myalgia, arthralgia, dehydration, hypokalaemia, hypotension, and flushing. Injection site reactions can occur, and the use of a central line is recommended.

Deaths associated with trabectedin treatment often involved a combination of adverse events including pancytopenia, febrile neutropenia, and in some cases sepsis, hepatic involvement, renal failure, and rhabdomyolysis.

Trabectedin may cause serious birth defects if given during pregnancy, although data are limited. Women and men of fertile age are advised to use effective contraception during treatment, and for 3 and 5 months, respectively, after stopping treatment. Breast

feeding is contra-indicated due to lack of data, and should be avoided for the duration of treatment and for 3 months after therapy is stopped.

Interactions

Trabectedin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme (such as azole antifungals, macrolide antibacterials, or ritonavir) may increase blood concentrations of trabectedin. Equally, inducers of CYP3A4 (such as rifampicin, phenobarbital, and St John's wort) may decrease systemic exposure to trabectedin. Trabectedin is a substrate of P-glycoprotein, and use with P-glycoprotein inhibitors (such as ciclosporin and verapamil) may alter trabectedin pharmacokinetics, although the clinical significance of this interaction has not been established. Alcohol and other hepatotoxic drugs should be avoided during trabectedin treatment due to possible potentiation of hepatotoxicity. Use with live attenuated vaccines is not recommended, and use with yellow fever vaccine is specifically contra-indicated. For the effect of trabectedin on phenytoin, see p.499.

Pharmacokinetics

Trabectedin is extensively distributed in the tissues. Plasma protein binding is about 94 to 98%. It is metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4. The terminal half-life is about 180 hours. Trabectedin is excreted mainly in the faeces, with a small amount in the urine, of which less than 1% is unchanged drug.

◊ References.

1. Beumer JH, *et al.* Metabolism of trabectedin (ET-743, Yondelis) in patients with advanced cancer. *Cancer Chemother Pharmacol* 2007; **59:** 825–37.
2. Perez-Ruixo JJ, *et al.* Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet* 2007; **46:** 867–84.

Uses and Administration

Trabectedin is a novel DNA-binding agent derived from the marine tunicate, *Ecteinascidia turbinata*. It is used for the treatment of advanced soft-tissue sarcomas, after failure of anthracyclines or ifosfamide, or in patients for whom these drugs are unsuitable. The recommended dose is 1.5 mg/m^2, given as an intravenous infusion over 24 hours. The dose can be repeated at 3-week intervals as long as clinical benefit persists, provided haematological, hepatic, and renal function parameters are met. If these baseline criteria are not met, treatment must be delayed for up to 3 weeks, until the criteria are met. If haematological toxicity or hepatotoxicity occurs at any time between cycles, the dose for subsequent cycles must be reduced to 1.2 mg/m^2. Once a dose has been reduced, dose escalation for subsequent cycles is not recommended. If any toxicities recur in subsequent cycles, a further dose reduction to 1 mg/m^2 may be made; thereafter, if further toxicity occurs, treatment should be stopped. If trabectedin is given via a central venous line, which is the preferred method, the dose should be diluted in at least 500 mL of sodium chloride 0.9% or glucose 5%. If central access is unfeasible, and it is given peripherally, the dose should be diluted in at least 1 litre of diluent. Dexamethasone 20 mg is given intravenously 30 minutes before treatment with trabectedin, to reduce nausea and hepatotoxicity.

Trabectedin is also under investigation for the treatment of ovarian cancer.

◊ References.

1. van Kesteren C, *et al.* Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. *Anticancer Drugs* 2003; **14:** 487–502.
2. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Invest Drugs* 2003; **12:** 1843–53.
3. Beumer JH, *et al.* Hepatotoxicity and metabolism of trabectedin: a literature review. *Pharmacol Res* 2005; **51:** 391–8.
4. Fayette J, *et al.* ET-743: a novel agent with activity in soft tissue sarcomas. *Oncologist* 2005; **10:** 827–32.
5. Schöffski P, *et al.* Trabectedin (ET-743): evaluation of its use in advanced soft-tissue sarcoma. *Future Oncol* 2007; **3:** 381–92.
6. Carter NJ, Keam SJ. Trabectedin : a review of its use in the management of soft tissue sarcoma and ovarian cancer. *Drugs* 2007; **67:** 2257–76.
7. Schöffski P, *et al.* Clinical impact of trabectedin (ecteinascidin-743) in advanced/metastatic soft tissue sarcoma. *Expert Opin Pharmacother* 2008; **9:** 1609–18.

Administration in hepatic impairment. Licensed product information states that there are no studies of trabectedin in hepatic impairment and data are unavailable to recommend doses in these patients. However, since systemic exposure is likely to be increased in these patients, thus increasing the risk of hepatotoxicity, caution is advised and dose adjustments may be needed. Trabectedin should not be given to patients with hyperbilirubinaemia.

Administration in renal impairment. Licensed product information for trabectedin states that no dose adjustments are needed in patients with mild or moderate renal impairment, but that trabectedin should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) as no data are available for this population.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Yondelis; ***Fr.:*** Yondelis.

Trastuzumab *(BAN, rINN)*

HER-2 Monoclonal Antibody; rhuMAb HER2; Trastutsumabi; Trastuzumabum. Immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ_1-chain anti-human p185$^{c\text{-}erbB2}$ receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer.

Трастузумаб
CAS — 180288-69-1.
ATC — L01XC03.
ATC Vet — QL01XC03.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639 and p.641.

Trastuzumab has been associated with fatal hypersensitivity reactions, infusion reactions characteristic of a cytokine release syndrome, and pulmonary events including acute respiratory distress syndrome. These usually occur after the first dose of trastuzumab and are more common in patients with reduced lung function. Use of trastuzumab is contra-indicated in patients with severe dyspnoea at rest. Cardiac dysfunction and congestive heart failure may also occur and left ventricular function should be monitored before and during therapy. The risk of cardiotoxicity is increased if trastuzumab is given with anthracyclines or cyclophosphamide (see below).

There is an increase in the incidence of leucopenia, thrombocytopenia, anaemia, and febrile neutropenia when trastuzumab is given with chemotherapy, but it infrequently causes myelosuppression when used alone. Diarrhoea occurs in about 25% of patients given trastuzumab as monotherapy; the incidence increases with combination therapy. Other gastrointestinal disturbances are common, as are chills, fever, headache, arthralgia, myalgia, and rashes. Asthenia, chest pain, and renal or liver disorders have also been reported.

Effects on the heart. Cardiac events related to the use of trastuzumab include asymptomatic decreases in left ventricular ejection fraction, tachycardia, palpitations, dyspnoea, and chest pain. Congestive heart failure may develop.[1]

In a pivotal comparative trial,[2] an increased incidence of cardiac adverse events prompted a retrospective analysis. This independent review identified cardiac dysfunction in 27% of patients receiving trastuzumab, an anthracycline, and cyclophosphamide, compared with only 8% receiving an anthracycline and cyclophosphamide. In patients given trastuzumab and paclitaxel, 13% developed cardiac dysfunction compared with 1% of patients given paclitaxel alone, although all these patients had previously received an anthracycline. The incidence of severe dysfunction was highest in those patients receiving trastuzumab, an anthracycline, and cyclophosphamide.

Further analysis[3] of this and 6 other studies found that, in a total of 1219 patients, 10 heart-related deaths had been reported, and that 9 of these were patients who had received trastuzumab. However, the risk of developing cardiotoxicity was less when trastuzumab was given alone than when given with anthracyclines. Advanced age was found to be a significant risk factor, whereas giving trastuzumab and the anthracycline at different times appeared to decrease the rate of cardiotoxicity.

Licensed product information for trastuzumab warns that patients who have previously received anthracyclines may also be at increased risk of cardiotoxicity with trastuzumab treatment. Furthermore, because the half-life of trastuzumab is about 28.5 days, trastuzumab may persist in the circulation for up to 24 weeks, and patients given anthracyclines after stopping trastuzumab may still be at increased risk of cardiotoxicity. If anthracyclines are used, the patient's cardiac function should be carefully monitored. Patients with pre-existing cardiovascular disease should also be treated with caution.

However, the majority of patients who develop congestive heart failure improve with standard treatment, including the use of ACE inhibitors, beta blockers, cardiac glycosides and diuretics.[1,4,5] Cardiotoxicity may improve even in those patients who continue with trastuzumab therapy.[4,5] A small retrospective study found that cardiotoxicity appeared to be largely reversible once trastuzumab was stopped, and that therapy might even be restarted. Findings from myocardial biopsy suggested that, while the mechanism of cardiotoxicity with trastuzumab remained uncertain, it differed from that with anthracyclines.[6] A retrospective review[7] of 173 patients with metastatic breast cancer who were treated with trastuzumab-based therapy for at least 1 year found that 28% of patients experienced a cardiac event; 10.9% had grade 3 cardiotoxicity, including 1 cardiac-related death. However, cardiotoxicity, whether symptomatic or not, was generally reversible, with or without specific therapy, suggesting that maintenance or re-treatment with trastuzumab may be feasible in those patients for whom no alternative therapeutic options are available.

The pathogenesis of the cardiotoxicity associated with trastuzumab is under investigation. A small study[8] showed specific uptake of a pretreatment tracer dose of radiolabelled trastuzumab into the myocardium of patients who subsequently developed cardiac adverse events. The human epidermal growth factor receptor 2 (HER2) gene appears essential for normal cardiac development; studies in *animals* suggest that trastuzumab may interfere with HER2 signalling and function in cardiomyocytes, and that loss of HER2 increases sensitivity to anthracycline toxicity.[4,5]

Analysis of symptomatic heart failure with trastuzumab suggests a lower incidence than that previously reported with retrospective data; however, this may be due to over-reported events in pivotal trials and the more recent exclusion of patients at risk of cardiotoxicity.[4] More recent analysis from a large study of patients given adjuvant chemotherapy with or without trastuzumab found a cumulative incidence of cardiac events (defined as confirmed New York Heart Association class III or IV cardiac dysfunction, or cardiac death) with trastuzumab of 4.1% at 3 years. The difference in cumulative incidence was 3.3% when compared with the control group.[9] Some have commented[10] that follow-up was relatively short and that long-term data on cardiac risks with trastuzumab are lacking. Reviews[11,12] have concluded that trastuzumab-induced cardiotoxicity is not dose-related and is generally reversible once the drug is stopped. However, others[13] have challenged the concept that cardiotoxicity is reversible, and the need for longer-term follow-up data, especially with respect to asymptomatic left ventricular dysfunction, has been emphasised.[11,13]

1. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002; **95:** 1592–1600.
2. Slamon DJ, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
3. Seidman A, *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20:** 1215–21.
4. Suter TM, *et al.* Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 2004; **13:** 173–83.
5. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004; **22:** 322–9.
6. Ewer MS, *et al.* Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; **23:** 7820–6.
7. Guarneri V, *et al.* Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol* 2006; **24:** 4107–15.
8. Behr TM, *et al.* Trastuzumab and breast cancer. *N Engl J Med* 2001; **345:** 995–6.
9. Tan-Chiu E, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23:** 7811–19.
10. Levine MN. Trastuzumab cardiac side effects: only time will tell. *J Clin Oncol* 2005; **23:** 7775–6.
11. Sengupta PP, *et al.* Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. *Mayo Clin Proc* 2008; **83:** 197–203.
12. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. *Drug Safety* 2008; **31:** 459–67.
13. Telli ML, *et al.* Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007; **25:** 3525–33.

Metastatic disease. There is some suggestion that patients treated with trastuzumab for metastatic breast cancer have a higher incidence of cerebral metastases. This may reflect increased survival of patients given trastuzumab, and the lack of CNS penetration by the drug,[1,2] or tumours overexpressing human epidermal growth receptor 2 (HER2) may be more likely to metastasise to the CNS.[2] A comparison[1] of trastuzumab-treated patients with a control group found that, although trastuzumab reduced the incidence of bone metastases, the development of brain metastases was similar in both groups. However, trastuzumab improved overall survival in all patients developing metastases, including those with brain metastases. A retrospective review[2] found an association between the development of cerebral metastases and both hormone-receptor negative status and the presence of visceral disease.

1. Lower EE, *et al.* Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival. *Clin Breast Cancer* 2003; **4:** 114–19.
2. Clayton AJ, *et al.* Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004; **91:** 639–43.

Peripheral vascular toxicity. A woman developed a painless prominence of the veins in her left arm and hand 3 days after receiving trastuzumab via a left hand vein. The veins were thickened and rope-like on palpation but there was no tenderness, oedema, or skin changes; there was no evidence of thrombus. She had previously received intravenous chemotherapy into left hand veins without sequelae. Biopsy suggested venous wall injury. Cardiac function was preserved, suggesting the mechanism