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(57) Abstract: A method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer. Also described are combinations and uses thereof in the method according to the invention.



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THERAPEUTIC TREATMENT - 355

The present invention relates to a new method for the treatment or prophylaxis of breast cancer. Particularly the invention relates to a method for the treatment of hormone sensitive breast cancer in patients that have not received prior endocrine therapy, comprising administering to the patient a combination comprising an epidermal growth factor inhibitor (EGFR inhibitor) such as an EGFR tyrosine kinase inhibitor (TKI), or a pharmaceutically acceptable salt thereof and an endocrine therapy suitable for use in the treatment of breast cancer. The invention also relates to a pharmaceutical composition comprising for use in the treatment of hormone sensitive breast cancer in patients that have not received prior endocrine therapy and to the use thereof in the manufacture of a medicament for use in the treatment or prophylaxis of hormone sensitive breast cancer.

The erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells and as such the erbB family of receptors is implicated in a number of epithelial cancers (reviewed in Olayioye *et al.*, *EMBO J.*, 2000, 19, 3159), including for example breast cancer (Sainsbury *et al.*, *Brit. J. Cancer*, 1988, 58, 458; Guerin *et al.*, *Oncogene Res.*, 1988, 3, 21; Slamon *et al.*, *Science*, 1989, 244, 707; Klijn *et al.*, *Breast Cancer Res. Treat.*, 1994, 29, 73 and reviewed in Salomon *et al.*, *Crit. Rev. Oncol. Hematol.*, 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al.*, *Brit. J. Cancer*, 1986, 54, 265; Reubi *et al.*, *Int. J. Cancer*, 1990, 45, 269; Rusch *et al.*, *Cancer Research*, 1993, 53, 2379; Brabender *et al.*, *Clin. Cancer Res.*, 2001, 7, 1850) as well as other cancers of the lung (Hendler *et al.*, *Cancer Cells*, 1989, 7, 347; Ohsaki *et al.*, *Oncol. Rep.*, 2000, 7, 603), bladder cancer (Neal *et al.*, *Lancet*, 1985, 366; Chow *et al.*, *Clin. Cancer Res.*, 2001, 7, 1957, Zhau *et al.*, *Mol Carcinog.*, 3, 254), oesophageal cancer (Mukaida *et al.*, *Cancer*, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, *Oncogene Res.*, 1987, 1, 149; Kapitanovic *et al.*, *Gastroenterology*, 2000, 112, 1103; Ross *et al.*, *Cancer Invest.*, 2001, 19, 554), cancer of the prostate (Visakorpi *et al.*, *Histochem. J.*, 1992, 24, 481; Kumar *et al.*, 2000, 32, 73; Scher *et al.*, *J. Natl. Cancer Inst.*, 2000, 92, 1866), leukaemia (Konaka *et al.*, *Cell*, 1984, 37, 1035, Martin-Subero *et al.*, *Cancer Genet Cytogenet.*, 2001, 127, 174), ovarian (Hellstrom *et al.*, *Cancer Res.*, 2001, 61, 2420), head and neck (Shiga *et al.*, *Head Neck*, 2000, 22, 599) or pancreatic cancer (Ovotny *et al.*, *Neoplasma*, 2001, 48, 188).

Accordingly it has been recognised that an inhibitor of erbB receptor tyrosine kinases should be of value as a selective inhibitor of the growth of certain carcinomas. A number of erbB tyrosine kinase inhibitors have demonstrated clinical benefit and a number of erbB tyrosine kinase inhibitors have been approved for use in the treatment of cancer.

5 For example, the EGFR tyrosine kinase inhibitors gefitinib and erlotinib for the treatment of advanced non-small cell lung cancer and lapatinib, which has erbB2 tyrosine kinase inhibitory activity, for use in metastatic breast cancer. Several other EGFR and erbB2 tyrosine kinase inhibitors are currently in development.

The use of endocrine agents is well known in the treatment of certain hormone sensitive human cancers. Numerous endocrine agents are suitable for use in the treatment of breast cancer, for example, anti-estrogen agents, selective estrogen receptor modulators (SERMs), aromatase inhibitors, estrogen-receptor down-regulator (ERDs), gonadotropin releasing hormone agonists (GnRH or LHRH analogues), an estrogen (to restore sensitivity following acquired resistance to endocrine therapy), progestogens or progesterone receptor antagonists and combinations thereof.

Anti-estrogen agents include SERMs that are agents which selectively block the action of estrogen at the estrogen receptor and include for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene. Until recently, tamoxifen was the anti-hormonal treatment of choice for the treatment of hormone sensitive breast cancer. However, it has now been shown that aromatase inhibitors are more effective than tamoxifen in post-menopausal women with hormone sensitive breast cancer.

An aromatase inhibitor is an agent that inhibits the enzyme aromatase and by that means lowers the level of the estrogen estradiol. Aromatase is an enzyme of the cytochrome P-450 superfamily and the product of the *CYP19* gene, and is highly expressed in the placenta and in the granulosa cells of ovarian follicles, where its expression depends on cyclical gonadotropin stimulation.

Aromatase catalyses the conversion of testosterone (an androgen) to estradiol (an estrogen) in many tissues including the adrenal glands, ovaries, placenta, testicles, adipose tissue and brain. Estrogen is produced directly by the ovaries and is also made by the body using aromatase. Aromatase inhibitors interfere with the body's use of aromatase.

The growth of many breast cancers is promoted by estrogens. Most estrogen after menopause comes from the action of aromatase. Aromatase inhibitors may therefore be

used to treat estrogen-dependent tumours after the menopause. Aromatase inhibitors are used mostly in women who have reached menopause, when the ovaries are no longer producing estrogen. Examples of aromatase inhibitors include anastrozole, letrozole, vorazole and exemestane.

5 The only approved estrogen-receptor down-regulator (ERD) is Faslodex (chemical name: fulvestrant). Fulvestrant is an option for post-menopausal women with advanced (metastatic) breast cancer that is hormone-receptor-positive and has stopped responding to other anti-estrogen therapy.

10 Fulvestrant offers a benefit to post-menopausal women with metastatic (advanced) hormone-receptor-positive breast cancer whose cancer has progressed on either tamoxifen or aromatase inhibitors or who cannot take other hormonal medications (possibly because of other medical conditions).

15 Fulvestrant is a competitive inhibitor of estrogen action by binding to the estrogen receptor (ER) and preventing access to estrogen and as such has anti-estrogen properties. In addition, the binding of fulvestrant to the ER results in a reduction in ER protein levels leading to a rapid degradation of the ER in the target tissue resulting in insufficient ER for binding to estrogen. The net effect is that estrogen cannot exert its biological effect due to the ER being “down-regulated” and inactivated.

20 Luteinizing hormone-releasing hormone agonists (LHRH agonists) have been used in the treatment of premenopausal breast cancer to suppress ovarian function by reducing the production of estrogen-stimulating hormones from the pituitary gland. Luteinizing hormone-releasing hormone agonists such as goserelin have proven to be as effective as surgical oophorectomy in premenopausal advanced breast cancer.

25 Progestogens such as medroxyprogesterone acetate have been shown to be effective in the treatment of breast cancer in post-menopausal women.

 Progesterone receptor antagonists act to block the action of progesterone at the progesterone receptor. Such agents, for example ZK232011 are expected to be useful in the treatment of hormone sensitive breast cancer.

30 There are disclosures in the scientific literature for combining an EGFR tyrosine kinase such as gefitinib (IressaTM) with an anti-estrogen. For example, Okubo et al., BJC, 2004, 90, 236; Shou J, JNCI 2004, 96, 926; Sabnis et al., Cancer Res. 2005, 65, 3903; and Massarweh et al, Cancer Res. 2008, 68, 826; Sabnis et al., 2005 disclose pre-clinical results

of combining gefitinib with aromatase inhibitors such as anastrozole or SERMs such as tamoxifen.

Clinical trials have been carried out to investigate the effects of combination of gefitinib with anastrozole and gefitinib with tamoxifen, for example Polychronis et al.,
5 Lancet Oncology 2005, 6, 383; and Smith et al., JCO, 2007, 25, 3816. However, to date the results of these trials have been inconclusive. Osborne et al (San Antonio Breast Cancer Symposium, December 2007 [poster number 2067]) describe a phase II trial (Clinicaltrials.gov reference NCT00229697), which combined gefitinib with tamoxifen in patients with hormone receptor positive metastatic breast cancer. Patients with newly
10 diagnosed metastatic breast cancer or that had completed adjuvant tamoxifen ≥ 1 year before study entry showed some benefit in progression free survival (PFS) and clinical benefit rate (complete response + partial response + stable disease) when treated with a combination of gefitinib and tamoxifen compared to tamoxifen alone, however, this result was not statistically significant. Furthermore, in those patients that had developed
15 metastatic breast cancer during/after adjuvant aromatase inhibitor (AI) or had failed first-line AI treatment the study failed to show a PFS benefit.

Other clinical trials of gefitinib with an aromatase inhibitor or tamoxifen have generally shown modest or no benefit. In some cases the literature suggests that in the clinical setting, adding gefitinib to standard aromatase inhibitor treatment may be
20 antagonistic to anastrozole, resulting in a reduction in objective tumour response rate than using anastrozole alone. For example Smith et al (J Clin Oncol 2007; 25(25): 3816-22) report that in a phase II trial in neoadjuvant breast cancer in post menopausal women with hormone receptor positive cancer, the addition of gefitinib to anastrozole had no additional clinical or biological effect.

25 A phase III trial combining lapatinib with the aromatase inhibitor letrozole is currently underway (trial reference NCT00073528 on www.clinicaltrials.gov), however, the results of this trial are not yet available.

We have surprisingly and unexpectedly discovered through the analysis of phase II clinical trial data, that although the combination of gefitinib and anastrozole appears to
30 give a reduction in objective response rate, the combination provides a significant increase in time to progression (TTP) and/or progression free survival (PFS) in post-menopausal women with hormone receptor positive metastatic breast cancer that had not received prior

treatment with an endocrine therapy. This novel and unexpected result suggests that combinations of an EGFR inhibitor (for example an EGFR tyrosine kinase inhibitor) with an endocrine agent suitable for use in the treatment of breast cancer (for example) an aromatase inhibitor, may in fact provide a significant anti-cancer effects in patients that have not received prior endocrine therapy.

According to a first aspect of the present invention there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer.

Therefore according to the present invention, there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent selected from a selective estrogen receptor modulator, an aromatase inhibitor, a selective estrogen receptor down-regulator, a progesterone receptor antagonist and an LHRH agonist.

Therefore according to the present invention, there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of a selective estrogen receptor modulator.

Therefore according to the present invention, there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment, which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an aromatase inhibitor.

Therefore according to the present invention, there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment, which comprises

administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an estrogen receptor down-regulator.

Therefore according to the present invention, there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not
5 received prior endocrine therapy, in need of such treatment, which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of a progesterone receptor antagonist.

Therefore according to the present invention, there is provided a method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not
10 received prior endocrine therapy, in need of such treatment, which comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an LHRH agonist.

In one embodiment of the present invention there is provided a method of treating estrogen receptor positive breast cancer, in a post-menopausal woman that has not received
15 prior endocrine therapy, in need of such treatment which comprises administering to said woman an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer. Suitable endocrine agents and EGFR inhibitors are any of the agents described herein.

In another embodiment of the present invention there is provided a method of
20 treating estrogen receptor positive breast cancer, in a post-menopausal woman that has not received prior tamoxifen therapy, in need of such treatment which comprises administering to said woman an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer. Suitable endocrine agents and EGFR inhibitors are any of the agents described herein.

25 In another embodiment of the present invention there is provided a method of treating estrogen receptor positive breast cancer, in a post-menopausal woman that has not received a prior aromatase inhibitor therapy such as anastrozole, in need of such treatment which comprises administering to said woman an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the
30 treatment of breast cancer. Suitable endocrine agents and EGFR inhibitors are any of the agents described herein.

In one embodiment of the present invention there is provided a method of treating estrogen receptor positive metastatic breast cancer, in a post-menopausal woman that has not received prior endocrine therapy, in need of such treatment which comprises administering to said woman an effective amount of an EGFR inhibitor in combination
5 with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer. Suitable endocrine agents and EGFR inhibitors are any of the agents described herein.

In another embodiment of the present invention there is provided a method of treating estrogen receptor positive metastatic breast cancer, in a post-menopausal woman
10 that has not received prior tamoxifen therapy, in need of such treatment which comprises administering to said woman an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer. Suitable endocrine agents and EGFR inhibitors are any of the agents described herein.

In another embodiment of the present invention there is provided a method of treating estrogen receptor positive metastatic breast cancer, in a post-menopausal woman that has not received a prior aromatase inhibitor therapy such as anastrozole, in need of such treatment which comprises administering to said woman an effective amount of an
15 EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer. Suitable endocrine agents and EGFR inhibitors are
20 any of the agents described herein.

In one embodiment the EGFR inhibitor used in the method according to the invention is an EGFR TKI.

According to another feature of the invention there is provided the use of an EGFR
25 inhibitor, in combination with an endocrine agent suitable for use in the treatment of breast cancer, in the manufacture of a medicament for use in the treatment of hormone sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

According to another feature of the invention there is provided the use of an EGFR
30 inhibitor, in combination with a selective estrogen receptor modulator, in the manufacture of a medicament for use in the treatment of hormone sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

According to another feature of the invention there is provided the use of an EGFR inhibitor, in combination with an aromatase inhibitor, in the manufacture of a medicament for use in the treatment of hormone sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

5 According to another feature of the invention there is provided the use of an EGFR inhibitor, in combination with a selective estrogen receptor down-regulator, in the manufacture of a medicament for use in the treatment of hormone sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

10 According to another feature of the invention there is provided the use of an EGFR inhibitor, in combination with a progesterone receptor antagonist, in the manufacture of a medicament for use in the treatment of hormone sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

15 According to another feature of the invention there is provided the use of an EGFR inhibitor, in combination with an LHRH agonist, in the manufacture of a medicament for use in the treatment of hormone sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

20 According to another feature of the invention there is provided the use of an EGFR inhibitor, in combination with an endocrine agent suitable for use in the treatment of breast cancer, in the manufacture of a medicament for use in the treatment of estrogen receptor positive breast cancer, in a post-menopausal woman that has not received prior endocrine therapy. Suitable EGFR inhibitors and endocrine agents are as herein defined.

25 According to another feature of the invention there is provided the use of an EGFR inhibitor, in combination with an endocrine agent suitable for use in the treatment of breast cancer, in the manufacture of a medicament for use in the treatment of estrogen receptor positive metastatic breast cancer, in a post-menopausal woman that has not received prior endocrine therapy. Suitable EGFR inhibitors and endocrine agents are as herein defined.

In one embodiment the EGFR inhibitor used in the use according to the invention is an EGFR TKI.

30 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and an endocrine agent suitable for use in the treatment of breast cancer, for use in the treatment of hormone sensitive breast cancer in a warm-blooded animal such as man that has not received prior endocrine therapy.

According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and a selective estrogen receptor modulator, for use in the treatment of hormone sensitive breast cancer in a warm-blooded animal such as man that has not received prior endocrine therapy.

5 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and an aromatase inhibitor, for use in the treatment of hormone sensitive breast cancer in a warm-blooded animal such as man that has not received prior endocrine therapy.

10 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and a selective estrogen receptor down-regulator, for use in the treatment of hormone sensitive breast cancer in a warm-blooded animal such as man that has not received prior endocrine therapy.

15 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and a progesterone receptor antagonist, for use in the treatment of hormone sensitive breast cancer in a warm-blooded animal such as man that has not received prior endocrine therapy.

20 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and an LHRH agonist, for use in the treatment of hormone sensitive breast cancer in a warm-blooded animal such as man that has not received prior endocrine therapy.

25 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and an endocrine agent suitable for use in the treatment of breast cancer, for use in the treatment of estrogen positive breast cancer in a post-menopausal woman that has not received prior endocrine therapy. Suitable endocrine agents and EGFR inhibitors are as defined herein.

30 According to a further aspect of the present invention there is provided a combination comprising an EGFR inhibitor and an endocrine agent suitable for use in the treatment of breast cancer, for use in the treatment of estrogen positive metastatic breast cancer in a post-menopausal woman that has not received prior endocrine therapy. Suitable endocrine agents and EGFR inhibitors are as defined herein.

In one embodiment the EGFR inhibitor used in the combinations according to the invention is an EGFR TKI.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of an EGFR inhibitor (for example an EGFR TKI), optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment that has not received prior endocrine therapy, for use in the treatment of hormone sensitive breast cancer. Suitable endocrine agents for use in this aspect of the invention include any of the endocrine agents described herein.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an EGFR inhibitor (for example an EGFR TKI) and an endocrine agent suitable for use in the treatment of breast cancer in association with a pharmaceutically acceptable diluent or carrier, for use in the treatment of hormone sensitive breast cancer in a patient that has not received prior endocrine therapy.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an EGFR inhibitor (for example an EGFR TKI), in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an endocrine agent suitable, for use in the treatment of hormone sensitive breast cancer in a patient that has not received prior endocrine therapy.

According to a further aspect of the present invention there is provided a kit comprising an EGFR inhibitor (for example an EGFR TKI) and an endocrine agent suitable for use in the treatment of breast cancer; optionally with instructions for use; for use in the treatment of hormone sensitive breast cancer in a patient that has not received prior endocrine therapy.

Herein the term “endocrine agent suitable for use in the treatment of breast cancer” refers to any endocrine agent that exhibits anti-cancer activity against breast cancer cells or tumours. Such activity includes in-vitro and/or in-vivo activity. Such endocrine agents include for example, an endocrine agent selected from an anti-estrogen agent, a selective estrogen receptor modulator, an aromatase inhibitor, a selective estrogen receptor down regulator, an LHRH agonist, a progesterone receptor antagonist and a progestogen.

Herein where the term “anti-estrogen” means any agent that acts to block or modulate the binding of estrogen to the estrogen receptor, for example by competitively binding to the estrogen receptor, by interacting with estrogen to inhibit binding to the receptor, by inhibiting estrogen levels or by modulating the expression or function of the estrogen receptor.

The term “selective estrogen receptor modulator” refers to an agent that binds to the estrogen receptor and thereby modifies estrogen binding to the receptor, for example by acting as a receptor antagonist in breast cancer.

The term “aromatase inhibitor” is used it is to be understood that this refers to any agent, which inhibits the enzyme aromatase and by that means lowers the level of the estrogen estradiol.

An “estrogen receptor down-regulator” is an agent, which binds to the estrogen receptor leading to a reduction in ER protein levels and degradation of the estrogen receptor in the target tissue and by those means prevents estrogen from exerting its biological actions.

A “progesterone receptor antagonist” is an agent that acts at the progesterone receptor as an antagonist to inhibit binding of progesterone to the receptor.

Herein where the term “LHRH agonist” is used it is to be understood that this refers to any chemical compound, or a pharmaceutically acceptable salt thereof, including small molecules and peptides, which acts as an agonist at the LHRH receptor, whether by an interaction with the LHRH binding site or by an allosteric mechanism, i.e. acts at a position on the LHRH receptor different to the LHRH binding site.

References herein to the endocrine agents and the EGFR inhibitors unless stated otherwise include the endocrine agents and EGFR inhibitors, and pharmaceutically acceptable salts thereof.

Herein, where the term “combination” is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention “combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination. Similarly reference to the “use or administration

of an EGFR inhibitor, in combination with an endocrine agent” also refers to simultaneous, separate or sequential administration.

In one aspect, where a compound or a pharmaceutically acceptable salt thereof, is referred to this refers to the compound only. In another aspect this refers to a
5 pharmaceutically acceptable salt of the compound.

The combinations according to the invention are used to treat hormone sensitive breast cancer. By “hormone sensitive breast cancer” is meant breast cancer that is suitable for treatment with endocrine therapies. For example estrogen and/or progesterone receptor positive breast cancer. In one embodiment the cancer is estrogen receptor positive breast
10 cancer. In another embodiment the cancer is a hormone receptor positive breast cancer, particularly to hormone receptor positive breast cancer in post-menopausal women. In one embodiment the hormone sensitive breast cancer is early stage non-metastatic hormone receptor positive breast cancer, for example early stage non-metastatic hormone receptor positive breast cancer in post-menopausal women. Still furthermore the hormone sensitive
15 breast cancer may be early stage non-metastatic estrogen and/or progesterone receptor positive breast cancer, especially early stage non-metastatic estrogen and/or progesterone (particularly estrogen) receptor positive breast cancer in post-menopausal women. In another embodiment the breast cancer is metastatic hormone receptor positive breast cancer, especially to metastatic hormone receptor positive breast cancer in post-
20 menopausal women. Still furthermore the breast cancer is metastatic estrogen and/or progesterone (particularly estrogen) receptor positive breast cancer, especially metastatic estrogen and/or progesterone (particularly estrogen) receptor positive breast cancer in post-menopausal women. In another embodiment of the invention, the breast cancer is in a non-metastatic state. In another embodiment of the invention, particularly the breast cancer is
25 in a metastatic state. In a further embodiment of the invention, particularly the breast cancer is in a metastatic state, and more particularly the cancer produces skin metastases. In a further embodiment of the invention, particularly the breast cancer is in a metastatic state, and more particularly the cancer produces lymphatic metastases. In a further embodiment of the invention, particularly the breast cancer is in a metastatic state, and
30 more particularly the cancer produces brain metastases.

The anti-cancer effect of the combination when used in the method and use according to the invention may be measured in terms of one or more of the anti-tumour

effect, the extent of the response (for example reduced tumour volume or reduced tumour burden), the response rate, the clinical benefit rate (the sum of complete response, partial response and stable disease) the time to disease progression, progression-free survival and the overall survival rate. Such clinical trial endpoints are well known and are described in
5 for example the FDA publication "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" May 2007
(www.fda.gov/CbER/gdlns/clintrialend.htm). The anti-tumour effects of the combination according to the invention may be for example one or more of inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to
10 regrowth of tumour on cessation of treatment or slowing of disease progression.

The combination use of an EGFR inhibitor and certain endocrine agents suitable for use in the treatment of breast cancer may also have a beneficial effect in preventing the onset of cancer in warm-blooded animals, such as man.

Compounds, or pharmaceutically acceptable salts thereof that are selective estrogen
15 receptor modulators include, for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene. Fulvestrant also exhibits anti-estrogen effects and as such may be considered to be a selective estrogen receptor modulator.

In one aspect the selective estrogen receptor modulators is tamoxifen.

In another embodiment the endocrine therapy suitable for use in the treatment of
20 breast cancer is not tamoxifen.

Compounds, or pharmaceutically acceptable salts thereof possessing aromatase inhibitor activity include, for example, anastrozole, exemestane, letrozole, aminoglutethimide, formestane, fadrozole, rogletimide or vorozole.

In one aspect the aromatase inhibitor is selected from anastrozole. In one aspect the
25 aromatase inhibitor is selected from exemestane. In one aspect the aromatase inhibitor is selected from letrozole. In one aspect the aromatase inhibitor is selected from aminoglutethimide. In one aspect the aromatase inhibitor is selected from formestane. In one aspect the aromatase inhibitor is selected from fadrozole. In one aspect the aromatase inhibitor is selected from rogletimide. In one aspect the aromatase inhibitor is selected
30 from vorozole.

A particular estrogen receptor down-regulator for use in the present invention is fulvestrant. A further particular estrogen receptor down-regulator for use in the present

invention is AZD4992. A further particular estrogen receptor down-regulator for use in the present invention is CH-4893237. A further particular estrogen receptor down-regulator for use in the present invention is one of the compounds from US 7,018,994, the specific examples of which are incorporated herein by reference.

5 A further particular estrogen receptor down-regulator for use in the present invention is 11β -fluoro- 7α -{5-[methyl(7,7,8,8,9,9,9-heptafluorononyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11β -fluoro- 7α -{5-[methyl(8,8,9,9,10,10,10-heptafluorodecyl)amino]pentyl}-
10 17α -methylestra-1,3,5(10)-triene-3, 17β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is (RS)- 11β -fluoro- 7α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present
15 invention is 11β -fluoro- 7α -{5-[methyl(8,8,9,9,9-pentafluorononyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11β -fluoro- 7α -{5-[methyl(9,9,10,10,10-pentafluorodecyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17β -diol N-oxide.

20 A further particular estrogen receptor down-regulator for use in the present invention is 11β -fluoro- 7α -{5-[methyl(8,8,9,9,9-pentafluorononyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11β -fluoro- 7α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17α -diol.
25

A further particular estrogen receptor down-regulator for use in the present invention is 11β -fluoro- 7α -{5-[methyl(7,7,8,8,9,9,9-heptafluorononyl)amino]pentyl}- 17α -methylestra-1,3,5(10)-triene-3, 17α -diol.

A further particular estrogen receptor down-regulator for use in the present
30 invention is 17α -ethinyl- 11β -fluoro- 7α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-estra-1,3,5(10)-triene-3, 17β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 17 α -ethinyl-11 β -fluoro-3-(2-tetrahydropyranyloxy)-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-estra-1,3,5(10)-trien-17 β -ol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-3-(2-tetrahydrofuran-2-yl)-7 α -{5-methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-trien-17 β -ol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -trifluoromethylestra-1,3,5(10)-triene-3,17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(6,6,7,7,8,8,8-heptafluorooctyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(8,8,9,9,10,10,10-heptafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(6,6,7,7,8,8,9,9,10,10,10-undecafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(5,5,6,6,7,7,8,8,8-nonafluorooctyl)aminopentyl]-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(9,9,10,10,11,11,11-heptafluoroundecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3,17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -7 α -{5-[methyl(9,9,10,10,10-pentafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3,17 β -diol.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9-heptafluorononyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3,17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-(methyl{3-[(2,3,4,5,6-pentafluorophenyl)sulfanyl]propyl}-amino)pentyl]estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]propyl}amino)-pentyl]estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]propyl}amino)-pentyl]estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is (S)-11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -mehylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is (R)-11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -mehylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5-[methyl(9,9,10,10,10-pentylfluorodecyl)amino]pentyl}estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]propyl}amino)-pentyl]estra-1,3,5(10)-trien-3-ol-17-one N-oxide.

A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]propyl}amino)-pentyl]estra-1,3,5(10)-trien-3-ol-17-one N-oxide.

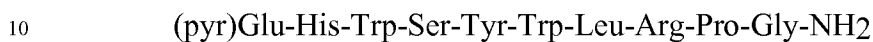
A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-7 α -{5[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5(10)-trien-3-ol-17one N-oxide.

LHRH agonists that may be used in the present invention include small molecule
 5 LHRH agonists as well as peptides or peptide derivatives. Peptide and peptide derivatives include for example:

i) buserelin (US Patent 4 024 248)



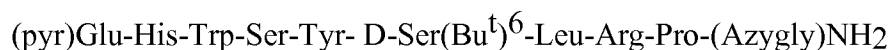
ii) triptorelin (US Patent 4 010 125)



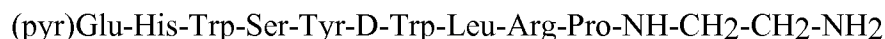
iii) leuprorelin (US Patent 4 005 063)



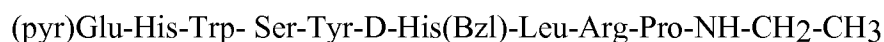
iv) goserelin (US Patent 4 100 274)



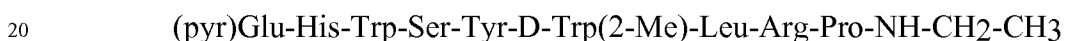
15 v) deslorelin (US Patent 4 659 695)



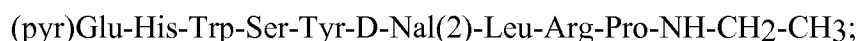
vi) histerelin (US Patent 4 244 946)



vii) avorelin (US 5 668 254)



viii) nafarelin (US Patent 4 234 571)



lutrelin, cystorelin, gonadorelin or detirelix, or a pharmaceutically acceptable salt thereof.

In one embodiment the LHRH agonist is selected from leuprorelin, buserelin,
 25 triptorelin and goserelin, or a pharmaceutically acceptable salt thereof. In another embodiment the LHRH agonist is goserelin or a pharmaceutically acceptable salt thereof.

A particular progesterone receptor antagonist is for example ZK232011 or a pharmaceutically acceptable salt thereof.

A particular progestogen is for example medroxyprogesterone acetate.

30 The EGFR inhibitor refers to an agent that acts to inhibit cell signalling mediated in part or alone by the epidermal growth factor receptor. The EGFR inhibitor may act to

inhibit EGFR tyrosine kinase. Alternatively, the agent may act to prevent ligand binding to the EGF receptor, for example an anti-EGFR antibody; or act to modify or inhibit expression of the EGF receptor; or act to prevent receptor homo- or heterodimerisation. Particularly the EGFR inhibitor is selected from a monoclonal antibody that blocks ligand binding to the extracellular domain of the EGF receptor or is an EGFR TKI. In one embodiment the EGFR inhibitor is an EGFR TKI. In another embodiment the EGFR inhibitor is a monoclonal antibody that blocks ligand binding to the extracellular domain or the EGF receptor.

Suitable EGFR TKI compounds, or a pharmaceutically acceptable salts thereof, include for example those described in EP 0566226, EP 0787722, WO 96/30347, WO 96/33980, WO 97/02266, WO 97/30034, WO 97/38983, WO 98/50038, WO 99/09016, WO 99/24037, WO 99/55683, Nature Medicine, 2000, 6, 1024-1028 and US 6,002,008 and these EGFR TKIs, particularly those of claim 1 and the named examples of these patents and applications, are incorporated herein by reference. The EGFR TKI may also inhibit other tyrosine kinases, for example the EGFR TKI may also inhibit one or more of the erbB family of receptors, for example erbB2 and/or erbB3 and or erbB4 in addition to exhibiting EGFR TKI activity.

Particular classes of EGFR TKIs are quinolines or more particularly quinazolines, or a pharmaceutically acceptable salt thereof.

Particular compounds, or pharmaceutically acceptable salts thereof possessing EGFR TKI activity include:

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839, also known as gefitinib and Iressa[™]);

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, or a pharmaceutically-acceptable salt thereof (linked to the code numbers CP 358774 and OSI-774 (the monomethanesulphonate salt) also known as erlotinib and Tarceva[™]);

6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (linked to the code numbers PD 183805 and CI 1033);

4-[(1*R*)-1-phenylethylamino]-6-(4-hydroxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (linked to the code numbers PKI-166, CGP 75166 and CGP 59326);

N-[4-(3-bromoanilino)quinazolin-6-yl]but-2-ynamide (linked to the code numbers CL-387785 and EKB-785); and

4-(3-chloro-4-fluoroanilino)-3-cyano-6-(4-dimethylaminobut-2(E)-enamido)-7-ethoxyquinoline (EKB-569).

In one embodiment the EGFR TKI is selected from ZD1839, CP 358774, CI 1033, PKI-166, CL-387785 and EKB-569, or a pharmaceutically acceptable salt thereof. In another embodiment the EGFR TKI is selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof. In a further embodiment the EGFR TKI is gefitinib or a pharmaceutically acceptable salt thereof. In a further embodiment the EGFR TKI is erlotinib or a pharmaceutically acceptable salt thereof. In a further embodiment the EGFR inhibitor is not gefitinib. In a further embodiment the EGFR inhibitor is an EGFR TKI other than gefitinib. In a further embodiment the EGFR inhibitor is 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable salt thereof, such as a difumarate salt. In a further embodiment the EGFR inhibitor is not 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable salt thereof.

Further particular EGFR TKIs, or pharmaceutically acceptable salts thereof, include for example an EGFR TKI selected from BE-23372M, BE-23372M derivatives Banyu, BIBX-1382, BBR-1611, naamidine A, AS-23, DAB-720, ADL-681, CGP-52411, CGP-60261, CGP-62706 series, PKI-166, CP-292597, erlotinib, PD-0158780, hbEGF-toxin, Prizm, RG-13022, RG-14620, RG-50875, AG-1478, VRCTC-310, SU-5271, lapatinib, HKI-272, BMS-599626, BIBW-2992, ARRY-334543 and PF-299804.

Antibodies that act as EGFR inhibitors include for example C225 (cetuximab or ErbituxTM), panitumumab, matuzumab (EMD7200), nimotuzumab, TP-38, DAB389-EGF, IMC-11F8 or ALT-110. In one embodiment the EGFR inhibitor is cetuximab. In another embodiment the EGFR inhibitor is panitumumab.

Therefore in one embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and an endocrine agent suitable for use in the treatment of breast cancer.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib,

or a pharmaceutically acceptable salt thereof, and an endocrine agent selected from a selective estrogen receptor modulator, an aromatase inhibitor and a selective estrogen receptor down regulator.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and an endocrine agent selected from a selective estrogen receptor modulator and an aromatase inhibitor.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and an anti-estrogen agent.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and a selective estrogen receptor modulator.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and an aromatase inhibitor.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and an estrogen receptor down-regulator.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and a progesterone receptor antagonist.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and luteinizing hormone-releasing hormone agonist.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises an EGFR TKI selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof, and a progestogen.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt

thereof, and an endocrine agent selected from a selective estrogen receptor modulator, an aromatase inhibitor and a selective estrogen receptor down regulator.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and an endocrine agent selected from a selective estrogen receptor modulator and an aromatase inhibitor.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and an anti-estrogen agent.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and a selective estrogen receptor modulator.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and an aromatase inhibitor.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and an estrogen receptor down-regulator.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and a progesterone receptor antagonist.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and luteinizing hormone-releasing hormone agonist.

In another embodiment the combination for use in the composition, method and use according to the invention, comprises gefitinib, or a pharmaceutically acceptable salt thereof, and a progestogen.

Particular combinations of for use in the combinations methods, uses and compositions according to the present invention include:

- gefitinib and tamoxifen, or a pharmaceutically acceptable salt thereof;
- gefitinib and anastrozole, or a pharmaceutically acceptable salt thereof;
- gefitinib and exemestane, or a pharmaceutically acceptable salt thereof;

- gefitinib and letrozole, or a pharmaceutically acceptable salt thereof;
- gefitinib and aminoglutethimide, or a pharmaceutically acceptable salt thereof;
- gefitinib and formestane, or a pharmaceutically acceptable salt thereof;
- gefitinib and fadrozole, or a pharmaceutically acceptable salt thereof;
- 5 • gefitinib and rogletimide, or a pharmaceutically acceptable salt thereof;
- gefitinib and vorozole, or a pharmaceutically acceptable salt thereof;
- gefitinib and fulvestrant, or a pharmaceutically acceptable salt thereof;
- gefitinib and AZD4992, or a pharmaceutically acceptable salt thereof; and
- gefitinib and CH-4893237, or a pharmaceutically acceptable salt thereof.
- 10 • gefitinib and 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,9-heptafluorononyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(8,8,9,9,10,10,10-heptafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- 15 • gefitinib and (RS)-11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]-pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(8,8,9,9,9-pentafluorononyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- 20 • gefitinib and 11 β -fluoro-7 α -{5-[methyl(9,9,10,10,10-pentafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(8,8,9,9,9-pentafluorononyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.
- 25 • gefitinib and 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 α -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,9-heptafluorononyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 α -diol.
- 30 • gefitinib and 17 α -ethinyl-11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)-amino]pentyl}-estra-1,3,5(10)-triene-3, 17 β -diol.

- gefitinib and 17 α -ethinyl-11 β -fluoro-3-(2-tetrahydropyranoyloxy)-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-estra-1,3,5(10)-trien-17 β -ol.
- gefitinib and 11 β -fluoro-3-(2-tetrahydrofuranoyloxy)-7 α -{5-methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-trien-17 β -ol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -trifluoromethylestra-1,3,5(10)-triene-3,17 β -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(6,6,7,7,8,8,8-heptafluorooctyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(8,8,9,9,10,10,10-heptafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(6,6,7,7,8,8,9,9,10,10,10-undecafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(5,5,6,6,7,7,8,8,8-nonafluorooctyl)aminopentyl]-17 α -methylestra-1,3,5(10)-triene-3, 17 β -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(9,9,10,10,11,11,11-heptafluoroundecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3,17 β -diol.
- gefitinib and 11 β -7 α -{5-[methyl(9,9,10,10,10-pentafluorodecyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3,17 β -diol.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9-heptafluorononyl)amino]pentyl}-17 α -methylestra-1,3,5(10)-triene-3,17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -{5-(methyl{3-[(2,3,4,5,6-pentafluorophenyl)sulfanyl]propyl}-amino)pentyl]estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]propyl}amino)-pentyl]estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.

- gefitinib and 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]propyl}amino)-pentyl]estra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- 5 • gefitinib and 11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5 (10)-triene-3,17 β -diol N-oxide.
- gefitinib and (S)-11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -mehylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- 10 • gefitinib and (R)-11 β -fluoro-7 α -{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}-17 α -mehylestra-1,3,5(10)-triene-3, 17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -{5-[methyl(9,9,10,10,10-pentylfluorodecyl)amino]pentyl}estra-1,3,5(10)-triene-3,17 β -diol N-oxide.
- gefitinib and 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]propyl}amino)-pentyl]estra-1,3,5(10)-trien-3-ol-17-one
- 15 N-oxide.
- gefitinib and 11 β -fluoro-7 α -[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]propyl}amino)-pentyl]estra-1,3,5(10)-trien-3-ol-17-one N-oxide.
- 20 • gefitinib and 11 β -fluoro-7 α -{5[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5(10)-trien-3-ol-17one N-oxide.
- gefitinib and goserelin, or a pharmaceutically acceptable salt thereof.
- gefitinib and leuprorelin, or a pharmaceutically acceptable salt thereof.
- gefitinib and ZK232011, or a pharmaceutically acceptable salt thereof.
- 25 • erlotinib and tamoxifen, or a pharmaceutically acceptable salt thereof.
- erlotinib and anastrozole, or a pharmaceutically acceptable salt thereof.
- erlotinib and exemestane, or a pharmaceutically acceptable salt thereof.
- erlotinib and letrozole, or a pharmaceutically acceptable salt thereof.
- erlotinib and aminoglutethimide, or a pharmaceutically acceptable salt thereof.
- 30 • erlotinib and formestane, or a pharmaceutically acceptable salt thereof.
- erlotinib and fadrozole, or a pharmaceutically acceptable salt thereof.

- erlotinib and rogletimide, or a pharmaceutically acceptable salt thereof.
- erlotinib and vorozole, or a pharmaceutically acceptable salt thereof.
- erlotinib and fulvestrant, or a pharmaceutically acceptable salt thereof.
- erlotinib and goserelin, or a pharmaceutically acceptable salt thereof.
- 5 • erlotinib and leuprorelin, or a pharmaceutically acceptable salt thereof.
- lapatinib and tamoxifen, or a pharmaceutically acceptable salt thereof.
- lapatinib and anastrozole, or a pharmaceutically acceptable salt thereof.
- lapatinib and exemestane, or a pharmaceutically acceptable salt thereof.
- lapatinib and letrozole, or a pharmaceutically acceptable salt thereof.
- 10 • lapatinib and aminoglutethimide, or a pharmaceutically acceptable salt thereof.
- lapatinib and formestane, or a pharmaceutically acceptable salt thereof.
- lapatinib and fadrozole, or a pharmaceutically acceptable salt thereof.
- lapatinib and rogletimide, or a pharmaceutically acceptable salt thereof.
- lapatinib and vorozole, or a pharmaceutically acceptable salt thereof.
- 15 • lapatinib and fulvestrant, or a pharmaceutically acceptable salt thereof.
- lapatinib and goserelin, or a pharmaceutically acceptable salt thereof.
- lapatinib and leuprorelin, or a pharmaceutically acceptable salt thereof.
- cetuximab and tamoxifen, or a pharmaceutically acceptable salt thereof.
- cetuximab and anastrozole, or a pharmaceutically acceptable salt thereof.
- 20 • cetuximab and exemestane, or a pharmaceutically acceptable salt thereof.
- cetuximab and letrozole, or a pharmaceutically acceptable salt thereof.
- cetuximab and aminoglutethimide, or a pharmaceutically acceptable salt thereof.
- cetuximab and formestane, or a pharmaceutically acceptable salt thereof.
- cetuximab and fadrozole, or a pharmaceutically acceptable salt thereof.
- 25 • cetuximab and rogletimide, or a pharmaceutically acceptable salt thereof.
- cetuximab and vorozole, or a pharmaceutically acceptable salt thereof;
- cetuximab and fulvestrant, or a pharmaceutically acceptable salt thereof.
- cetuximab and goserelin, or a pharmaceutically acceptable salt thereof.
- cetuximab and leuprorelin, or a pharmaceutically acceptable salt thereof.
- 30 • panitumumab and tamoxifen, or a pharmaceutically acceptable salt thereof.
- panitumumab and anastrozole, or a pharmaceutically acceptable salt thereof.

- panitumumab and exemestane, or a pharmaceutically acceptable salt thereof.
- panitumumab and letrozole, or a pharmaceutically acceptable salt thereof.
- panitumumab and aminoglutethimide, or a pharmaceutically acceptable salt thereof.
- panitumumab and formestane, or a pharmaceutically acceptable salt thereof.
- 5 • panitumumab and fadrozole, or a pharmaceutically acceptable salt thereof.
- panitumumab and rogletimide, or a pharmaceutically acceptable salt thereof.
- panitumumab and vorozole, or a pharmaceutically acceptable salt thereof.
- panitumumab and fulvestrant, or a pharmaceutically acceptable salt thereof.
- panitumumab and goserelin, or a pharmaceutically acceptable salt thereof.
- 10 • panitumumab and leuprorelin, or a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically-acceptable salts include of the EGFR inhibitor and the endocrine agent include, for example, salts with alkali metal (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with
15 methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, for those compounds which are sufficiently basic, suitable pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid. Alternatively, the compounds may
20 exist in zwitterionic form.

For the avoidance of doubt, where the treatment of breast cancer is indicated, it is to be understood that this also refers to the prevention of metastases and the treatment of metastases, i.e. cancer spread. Therefore the combination of the present invention could be used to treat a patient who has no metastases to stop them occurring, or to lengthen the
25 time period before they occur, and to a patient who already has metastases to treat the metastases themselves. Furthermore the treatment of breast cancer also refers to treatment of an established primary tumour or tumours and developing primary tumour or tumours. In one aspect of the invention the treatment of breast cancer relates to the prevention of metastases. In another aspect of the invention the treatment of breast cancer relates to the
30 treatment of metastases. In another aspect of the invention the treatment of breast cancer relates to treatment of an established primary tumour or tumours or developing primary

tumour or tumours. In one embodiment the treatment of breast cancer relates to an adjuvant treatment. In another embodiment the treatment of breast cancer refers to the neo-adjuvant treatment of cancer. Accordingly in an embodiment of the invention the combination according to the invention is used as an adjuvant treatment of hormone sensitive breast cancer, particularly as an adjuvant treatment of estrogen receptor positive breast cancer in post-menopausal women that have not received prior endocrine therapy. In another embodiment of the invention the combination according to the invention is used as a neo-adjuvant treatment of hormone sensitive breast cancer, particularly as a neo-adjuvant treatment of estrogen receptor positive breast cancer in post-menopausal women that have not received prior endocrine therapy. In another embodiment the combination is used to treat advanced (metastatic) hormone sensitive breast cancer, particularly advanced estrogen receptor positive cancer in post-menopausal women that have not received prior endocrine therapy.

As will be understood, references herein to patients not having received prior endocrine therapy, means that the patient has not received an endocrine treatment (for example, a selective estrogen receptor modulator such as tamoxifen or an aromatase inhibitor such as anastrozole) prior to being treated with the combination of the EGFR inhibitor and endocrine agent according to the present invention. Particularly the patient has not been treated with tamoxifen prior to being treated with the combination of the EGFR inhibitor and endocrine agent according to the present invention. In another embodiment the patient has not been treated with an aromatase inhibitor such as anastrozole prior to being treated with the combination of the EGFR inhibitor and endocrine agent according to the present invention.

In one embodiment the combination according to the invention may be used to treat post-menopausal women with estrogen sensitive advanced (metastatic) breast cancer who have not received prior endocrine therapy such as for example, a selective estrogen receptor modulator such as tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant.

In another embodiment the combination according to the invention may be used as an adjuvant therapy in the treatment of hormone sensitive breast cancer in patients, where such patients have not received prior endocrine therapy (such as for example, a selective

estrogen receptor modulator such as tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant).

In a further embodiment the combination according to the invention may be used as a neo-adjuvant therapy in the treatment of hormone sensitive breast cancer in patients, where such patients have not received prior endocrine therapy. In another embodiment the combination according to the invention is not used as a neo-adjuvant treatment. In one embodiment the combination is administered to post-menopausal women. In another embodiment the combination is administered to pre-menopausal women.

The term “adjuvant therapy” refers to a treatment given following removal of the primary tumour. Where the cancer is breast cancer, removal of the primary tumour may be effected by, for example, surgery (for example lumpectomy or mastectomy) and/or radiotherapy.

The term “neo-adjuvant therapy” refers to a treatment given prior to removal of the primary tumour by surgery or radiotherapy.

In a particular embodiment of the invention there is provided a method for the treatment of advanced (metastatic) estrogen and/or progesterone positive breast cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound selected from gefitinib, erlotinib and lapatinib in combination with an effective amount of an aromatase inhibitor such as anastrozole or exemestane, wherein said animal has not previously been treated with an endocrine therapy such as for example, a selective estrogen receptor modulator such as tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant.

In another embodiment there is provided a combination comprising a compound selected from gefitinib, erlotinib and lapatinib; and an aromatase inhibitor such as anastrozole or exemestane, for use in the treatment of advanced (metastatic) estrogen and/or progesterone positive breast cancer in a warm-blooded animal, such as man, wherein said animal has not previously been treated with an endocrine therapy such as for example, a selective estrogen receptor modulator such as tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant.

In another embodiment there is provided the use of a combination comprising a compound selected from gefitinib, erlotinib and lapatinib; and an aromatase inhibitor such

as anastrozole or exemestane, in the manufacture of a medicament for the treatment of advanced (metastatic) estrogen and/or progesterone positive breast cancer in a warm-blooded animal, such as man, wherein said animal has not previously been treated with an endocrine therapy such as for example, a selective estrogen receptor modulator
5 such as tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant.

In another embodiment of the invention there is provided a method for the treatment of non-metastatic estrogen and/or progesterone positive breast cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises
10 administering to said animal an effective amount of a compound selected from gefitinib, erlotinib and lapatinib in combination with an effective amount of an aromatase inhibitor such as anastrozole or exemestane,

wherein said animal has not previously been treated with an endocrine therapy such as for example, a selective estrogen receptor modulator such as tamoxifen, an aromatase
15 inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant. In this embodiment the combination is suitably administered as an adjuvant treatment.

In another embodiment there is provided a combination comprising a compound selected from gefitinib, erlotinib and lapatinib; and an aromatase inhibitor such as anastrozole or exemestane, for use in the treatment of non-metastatic estrogen and/or
20 progesterone positive breast cancer in a warm-blooded animal, such as man, wherein said animal has not previously been treated with an endocrine therapy such as for example, a selective estrogen receptor modulator such as tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant.

In another embodiment there is provided the use of a combination comprising a
25 compound selected from gefitinib, erlotinib and lapatinib and an aromatase inhibitor such as anastrozole or exemestane, in the manufacture of a medicament for the treatment of non-metastatic estrogen and/or progesterone positive breast cancer in a warm-blooded animal, such as man, wherein said animal has not previously been treated with an endocrine therapy such as for example, a selective estrogen receptor modulator such as
30 tamoxifen, an aromatase inhibitor such as anastrozole or an estrogen receptor down-regulator such as fulvestrant.

The term “post-menopausal” includes women that are naturally post-menopausal and women where the menopause has been induced, by for example, treatment with an LHRH agonist such as goserelin.

It is to be understood that where herein it is stated that a patient “has not previously
5 been treated with an endocrine therapy” or has “not received prior endocrine therapy”, it is intended that the treatment of a patient with an LHRH agonist to induce early menopause in the patient is not considered to be “prior endocrine therapy”. Accordingly, patients that have been treated with an LHRH agonist to induce early menopause are not excluded from those embodiments that are described herein as not having received “prior endocrine
10 therapy” or “not received prior endocrine therapy”. In another embodiment according to the invention the patients have not been treated with a selective estrogen receptor modulator such as tamoxifen or an aromatase inhibitor such as anastrozole or exemestane prior to being treated with the combination according to the present invention.

As will be understood in the methods of treatment and uses described herein
15 require as a step in the treatment or use the pre-selection of a patient or patients that have not received prior endocrine therapy. Following identification of such a patient or patients, the combination described herein is administered to the selected patient(s).

Herein, the treatment of cancer also refers to the prevention of cancer *per se*.

According to another aspect of the present invention the effect of a method of
20 treatment of the present invention is expected to be at least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of the EGFR inhibitor and the endocrine agent used alone.

According to another aspect of the present invention the effect of a method of
25 treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of the EGFR inhibitor and the endocrine agent used alone.

According to another aspect of the present invention the effect of a method of
treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording
30 a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination

treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with the EGFR inhibitor or the endocrine agent alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to the EGFR inhibitor or the endocrine agent alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of the EGFR inhibitor or the endocrine agent may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

An example of a unit dosage form for the EGFR inhibitor when it is an EGFR TKI might be a tablet for oral administration. An example of a unit dosage form for the EGFR inhibitor when it is an anti-body is a formulation for parenteral administration, particularly intravenous administration. An example of a unit dosage form for a selective estrogen receptor modulator might be tablet for oral administration. An example of a unit dosage form for an aromatase inhibitor might be a tablet for oral formulation, see that described herein below. An example of a unit dosage form for an estrogen receptor down-regulator might be a formulation for intramuscular administration, such as that described herein below.

The pharmaceutical compositions of the EGFR inhibitor and the endocrine agents suitable for use in the treatment of breast cancer described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

In those embodiments where the EGFR inhibitor is used in combination with the estrogen receptor down-regulator fulvestrant, the fulvestrant may be formulated as a composition suitable for intra-muscular administration, for example a composition comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol. Particular fulvestrant compositions are those described in US 6,774,122.

The amount of the EGFR inhibitor, or a pharmaceutically acceptable salt thereof, administered would be that sufficient to provide the desired pharmaceutical effect. For instance, the EGFR inhibitor could be administered to a warm-blooded animal orally, at a unit dose less than 1g daily but more than 1mg. Particularly when the EGFR inhibitor is an EGFR TKI such as gefitinib or erlotinib the compound could be administered to a warm-blooded animal, at a unit dose of less than 500 mg per day, for example 250 mg per day for gefitinib and 100 or 150mg per day for erlotinib. The dose of the EGFR inhibitor may be administered as a single daily dose or as multiple fractions of the total daily dose.

For example, the total daily dose of the EGFR inhibitor may be administered as two doses, which may be the same or different. Suitably however, each fraction of the total daily dose would be approximately equal. By way of example when the EGFR inhibitor is an EGFR TKI, it may be administered as a one or more tablets containing, for example 1, 2.5, 10, 40 or 100, 150, 200, 250 or 500mg of the EGFR TKI. when the EGFR inhibitor is gefitinib, suitable tablet formulations are, for example, those described in WO03/072139.

Antibodies such as cetuximab are typically administered as an intravenous infusion at a dose of for example 400mg/m² as the initial dose followed by a weekly dose of 250mg/m².

Selective estrogen receptor modulators and aromatase inhibitors would normally be administered to a warm-blooded animal at a unit dose, of an amount known to the skilled practitioner as a therapeutically effective dose. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1mg to 40mg, particularly about 1 mg to about 20 mg, more particularly 1mg to 5 mg of each active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The estrogen receptor down-regulator will normally be administered to a warm-blooded animal at a unit dose, of an amount known to the skilled practitioner as a therapeutically effective dose. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of excipients which may vary
5 from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 20-500 mg, particularly 250 mg, of each active ingredient.

However the dose of each component of the combination will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the
10 practitioner who is treating any particular patient.

The dosage of each of the drugs and their proportions have to be composed so that the best possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

Legends to Figures

Figure 1 shows the improvement in time to progression of patients treated with anastrozole plus gefitinib compared to patient treated with anastrozole plus placebo in a phase II clinical trial on postmenopausal women with hormone receptor positive metastatic breast cancer.

Figure 2 illustrates the objective response rate and the clinical benefit rate of the anastrozole plus gefitinib treated patients compared to the patients treated with anastrozole plus placebo in the same clinical trial. In Figure 2 CR refers to complete response; PR refers to partial response; SD refers to stable disease; and TTP refers to time to
20 progression.

Figure 3 shows the probability of progression free survival over time in postmenopausal ER/PR positive metastatic breast cancer patients that had received endocrine therapy before being administered either gefitinib + anastrozole or gefitinib + placebo.

Figure 4 shows the probability of progression free survival over time in postmenopausal ER/PR positive metastatic breast cancer patients that had not received
30 endocrine therapy before being administered either gefitinib + anastrozole or gefitinib + placebo. In figures 4 and 5 the x-axis shows time in months and the y-axis the probability

of progression-free survival. In each of figures 3 and 4 the reference to “at risk” shows the number of patients over time in each of the treatment arms of the trial.

Examples

The invention is further illustrated by way of the following examples, which are intended to elaborate several embodiments of the invention. These examples are not intended to, nor are they to be construed to, limit the scope of the invention. It will be clear that the invention may be practiced otherwise than as particularly described herein. Numerous modifications and variations of the present invention are possible in view of the teachings herein and, therefore, are within the scope of the invention.

Example 1

Phase II multicenter, double-blind, randomized trial to compare anastrozole plus gefitinib (ZD1839) with anastrozole plus placebo in postmenopausal women with hormone receptor positive (HR+) metastatic breast cancer (MBC) (Clinicaltrials.gov identifier NCT00077025)

Study objectives

The target patient population for this trial was female postmenopausal patients aged 18 years or older with newly diagnosed metastatic ER and/or PgR positive breast cancer. Patients with recurrent disease during or after adjuvant tamoxifen or patients who are hormone therapy naïve are eligible for this trial.

Primary objective

The primary objective of this study was to compare the time to progression (TTP) between the two treatment arms (anastrozole/placebo and anastrozole/ZD1839) in postmenopausal patients with newly diagnosed metastatic breast cancer.

Secondary objectives

The efficacy objectives of this study were:

- To compare objective response rate (ORR) (complete response (CR) and partial response (PR) as defined by Response Evaluation Criteria (RECIST)) between the 2 treatment arms.
- To compare the clinical benefit rate (CBR) (defined as CR+PR[as per RECIST]+Stable Disease $\geq$ 24 weeks) between the 2 treatment arms.
- To compare overall survival (OS) between the 2 treatment arms.

Study Design

The trial was a phase II, multicenter, double-blind, randomized, placebo-controlled trial. Eligible patients were randomized to one of two trial arms listed below, on a 1:1 basis.

- 5 • Anastrozole given by mouth at 1 mg per day and placebo given by mouth at 1 tablet per day.
- Anastrozole given by mouth at 1 mg per day and ZD1839 given by mouth at 250 mg per day.

10 A total of 174 postmenopausal patients were planned for enrolment. Patient follow-up for survival will continue to a 75% mortality rate of all randomized patients in order to adequately characterize long-term survival.

Selection of study population**Inclusion criteria**

For inclusion in the study, patients had to fulfil all of the following criteria:

- 15 1. Post-menopausal females aged 18 years or older. Postmenopausal status is defined as:natural menopause with last menses > 1 year ago
 - radiation induced oophorectomy with last menses > 1 year ago
 - chemotherapy induced menopause with 1 year interval since last menses
 - serum follicle stimulating hormone (FSH) and luteinizing hormone (LH)
 - 20 and plasma estradiol levels in the laboratory specified postmenopausal range
 - bilateral oophorectomy
- 2. Histologically confirmed metastatic ER and/or PgR positive adenocarcinoma of the breast as determined in local laboratories at each investigator site
- 25 3. Patients who have EITHER non-measurable or measurable disease (as per RECIST) outside any previously irradiated site.
- 4. Postmenopausal patients with metastatic breast cancer who are candidates for hormonal treatment and have not received any prior hormonal treatment are eligible.
- 30 5. Patients who have developed metastatic disease while on adjuvant tamoxifen or after completion of such treatment are eligible.

6. WHO performance status of 0, 1 or 2.
7. Required laboratory values are as follows (to be obtained within 7 days of registration):
 - Adequate bone marrow function: granulocytes $> 1500/\text{mm}^3$ and platelets $> 100\,000/\text{mm}^3$
 - Bilirubin ≤ 1.5 times upper limit of normal ULN, alanine amino transferase (ALT) or aspartate amino transferase (AST) ≤ 2.5 times the ULN if no demonstrable liver metastasis, or < 5 times the ULN in the presence of liver metastasis
8. Patients must have a life expectancy > 3 months.
9. All patients must give signed written informed consent.

Method Used in Actual Trial:

A total of 94 women with newly diagnosed hormone receptor positive metastatic breast cancer were randomized (1:1) (one woman died prior to treatment) to receive anastrozole 1 mg/day and either gefitinib 250 mg/day or placebo (50 to anastrozole + placebo; 43 to anastrozole + gefitinib).

Enrollment into the trial was stopped early due to slow recruitment and hence limited statistical analyses were performed.

Results:

A time to progression advantage was seen for anastrozole + gefitinib over anastrozole + placebo (hazard ratio [A+G:A+P] 0.55, 95% CI 0.32-0.94, median 14.5 months vs. 8.2 months) and is clearly illustrated in Figure 1. A numerical advantage in clinical benefit rate (CBR) was seen for anastrozole + gefitinib vs. anastrozole + placebo (See Table A below and Figure 2). Safety and tolerability profiles showed no unexpected findings. Treatment-related adverse events (AE) were seen in 79% of patients in the anastrozole + gefitinib arm vs. 38% in the anastrozole + placebo arm and were mostly mild. Two patients in the anastrozole + gefitinib arm and 1 patient in the anastrozole + placebo arm experienced an AE with outcome of death; none were considered treatment related.

Table A. Clinical benefit rate

	Anastrozole plus gefitinib (n = 43)	Anastrozole plus placebo (n = 50)
Complete response (CR), n (%)	1 (2)	1 (2)
Partial response (PR), n (%)	0 (0)	5 (10)
Stable disease $\geq$ 24 weeks (SD), n (%)	20 (47)	11 (22)
Clinical benefit rate (CR+PR+SD), n (%)	21 (49)	17 (34)
95% CI for clinical benefit rate	33-65	21-49

Figure 2 shows that the objective response rate for the anastrozole plus gefitinib arm was lower than that observed in the anastrozole plus placebo arm. Despite this apparently negative effect on objective response, the combination of anastrozole + gefitinib showed a marked increase in time to progression.

Progression free survival in patients that had received no prior tamoxifen treatment

A post-hoc analysis of progression-free survival (PFS) was performed in two patient subgroups from the above clinical trial; those previously treated with endocrine therapy (ET) and those that were endocrine naïve (EN). The PFS, hazard ratio and associated 95% confidence interval (CI) and p-value for gefitinib relative to placebo were estimated using the Cox proportional hazards model along with interaction test for treatment by subset.

Results

In the subgroup of patients that had previously been treated with endocrine therapy, 31 PFS events were reobserved in 51 patients (hazard ratio [HR] 0.65, 95% CI 0.32, 1.33; median PFS: gefitinib +anastrozole - 11.2 months; PFS anastrozole + placebo - 7.1 months). This result is illustrated in Figure 3.

In the endocrine therapy naïve subgroup, 23 PFS events were reobserved in 42 pts (HR 0.39, 95% CI 0.16, 0.97; median PFS: gefitinib +anastrozole - 20.2 months,

anastrozole + placebo - 8.4 months). The interaction test p-value was 0.28. This result is illustrated in Figure 4.

Conclusion:

Anastrozole plus gefitinib was well tolerated and associated with a marked
5 advantage in time to progression compared to anastrozole plus placebo in postmenopausal women with newly diagnosed hormone receptor positive metastatic breast cancer, despite the fact that the combination appears to reduce the objective response rate compared to anastrozole alone.

The endocrine therapy naive patient subgroup of this trial received clinical benefit
10 when gefitinib was combined with anastrozole. These patients showed an unexpected improvement in progression free survival.

Example 2

A Phase II Randomised, Double-Blind, Stratified, Multi-Centre Trial Comparing the
15 **Nolvadex (tamoxifen) 20 Mg And Placebo Combination To The Nolvadex 20 Mg and**
ZD1839 (IRESSA™, gefitinib) 250 MG Combination In Patients With Metastatic
Breast Cancer And Estrogen Receptor (ER) and/or Progesterone (PR) Positive
Tumours (Clinicaltrials.gov identifier NCT00229697)

Primary Outcome Measures:

- 20
- Strata 1: To compare the time to progression between 2 treatment arms (ZD1839/Nolvadex vs placebo/Nolvadex).
 - Strata 2: To compare the clinical benefit rate between 2 treatment arms (ZD1839/Nolvadex vs placebo/Nolvadex).

Secondary Outcome Measures:

- 25
- To compare the clinical benefit rate between 2 treatment arms (ZD1839/Nolvadex vs placebo/Nolvadex) in Strata 1 and overall.
 - To compare time to progression between 2 treatment arms (ZD1839/Nolvadex vs placebo/Nolvadex) in Strata 2 and overall.

- To compare the objective response rate between ZD1839/Nolvadex and placebo/Nolvadex in each strata and overall
- To estimate duration of response for the ZD1839/Nolvadex and placebo/Nolvadex treatments in each strata and overall
- 5 • To compare overall survival between the ZD1839/Nolvadex and placebo/Nolvadex in each strata.
- To assess whether patients with high tumour levels of HER-2 and/or AIB1 demonstrate de novo resistance to Nolvadex therapy or have shorter TTP or response duration when compared with Nolvadex/ZD1839 treatment.
- 10 • To compare the objective response rate between the ZD1839/Nolvadex and placebo/Nolvadex treatment arms in the subset of all patients with ER+ tumours staining 2+/3+ for Her2neu by IHC.
- To compare the safety and tolerability of ZD1839/Nolvadex to placebo/Nolvadex. To determine steady-state plasma trough concentrations of tamoxifen
15 in all patients and to compare between the ZD1839/Nolvadex and placebo/Nolvadex treatment arms.
- To determine steady-state plasma trough concentrations of ZD1839 and relate values to historical data.
- To relate steady-state plasma trough concentrations of ZD1839 to demographic,
20 response, and safety variables.
- To assess the quality of life (QOL) and symptom relief based on the Functional Assessment of Cancer Therapy - Breast (FACT-B) on both treatment arms.
- To investigate subject hospital resource use and health status.
- Characterization of specific adverse events.
- 25 • To obtain tumour tissue for biologic studies in this patient population.

Eligibility

Ages Eligible for Study: 18 Years and older

Genders Eligible for Study: Female

Accepts Healthy Volunteers: No

Criteria**Inclusion Criteria:**

- Histologically confirmed metastatic adenocarcinoma of the breast (seeTNM staging Appendix I) that is ER and/or PR positive as determined in local laboratories at each investigator site (central verification of ER status will be performed after the patient starts treatment
- A tissue block from either the metastatic or primary tumor site is required.
- WHO performance status (PS) 0-2
- Patients must not be pregnant or breast-feeding. A negative pregnancy test is required within 7 days prior to randomization if pre- or peri-menopausal. Postmenopausal patients are defined as:
 - natural menopause with last menses > 1 year ago,
 - radiation induced oophorectomy with last menses > 1 year ago,
 - chemotherapy induced menopause with 1 year interval since last menses, or
 - serum FSH and LH and plasma estradiol levels in the postmenopausal range for the institution.
 - bilateral oophorectomy

Exclusion Criteria:

- Patients cannot be on hormone replacement therapy or received prior chemotherapy for metastatic disease.
- Patients previously treated with a Tyrosine Kinase inhibitor or have evidence of an active interstitial lung disease are not eligible.

- Treatment with LH-RH analog.
- Laboratory values as follow Bilirubin >1.5 times upper limit of normal ULN, alanine amino transferase (ALT) or aspartate amino transferase (AST) >2.5 times the ULN if no demonstrable liver metastases, or >5 times the ULN in the presence of liver
5 metastases
- Bone marrow function: WBC <1500 mm³

Details of the trial and the results obtained were published by Osborne et al (San Antonio Breast Cancer Symposium, December 2007 [poster number 2067]).

A post-hoc analysis of progression-free survival (PFS) was performed in two
10 patient subgroups from the above clinical trial; those previously treated with endocrine therapy (ET) and those that were endocrine naïve (EN). The PFS, hazard ratio and associated 95% confidence interval (CI) and p-value for gefitinib relative to placebo were estimated using the Cox proportional hazards model along with interaction test for treatment by subset.

15 In the subgroup of patients that had previously been treated with endocrine therapy, 95 PFS events were reobserved in 131 pts (HR 1.22, 95% CI 0.81, 1.86; median PFS: gefitinib + tamoxifen - 9.4 months, tamoxifen + placebo - 10.9 months). In the endocrine therapy naïve patient subgroup, 106 PFS events were reobserved in 158 patients (HR 0.78, 95% CI 0.52, 1.15; median PFS: gefitinib + tamoxifen - 12.1 months, tamoxifen + placebo
20 - 8.9 months). The interaction test p-value was 0.13.

Conclusion: The endocrine therapy naïve patient subgroup of this trial received clinical benefit when gefitinib was combined with tamoxifen.

CLAIMS

1. A method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment which
5 comprises administering to said animal an effective amount of an EGFR inhibitor in combination with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer.

2. A method of treating hormone sensitive breast cancer, in a warm-blooded animal, such as man, that has not received prior endocrine therapy, in need of such treatment which
10 comprises:

(i) selecting a warm-blooded animal with hormone sensitive breast cancer, which animal has not been treated with an endocrine therapy; and

(ii) administering to said animal an effective amount of an EGFR inhibitor in combination
15 with an effective amount of an endocrine agent suitable for use in the treatment of breast cancer.

3. The use of an EGFR inhibitor, in combination with a selective estrogen receptor modulator, in the manufacture of a medicament for use in the treatment of hormone
20 sensitive breast cancer, in a warm-blooded animal, such as man that has not received prior endocrine therapy.

4. A combination comprising an EGFR inhibitor and an endocrine agent suitable for use in the treatment of breast cancer, for use in the treatment of hormone sensitive breast
25 cancer in a warm-blooded animal such as man that has not received prior endocrine therapy

5. The method or use or combination according to any one of claims 1 to 4 wherein the endocrine agent is a selective estrogen receptor modulator.

6. The method or use or combination according to any one of claims 1 to 4 wherein the endocrine agent is an aromatase inhibitor.

7. The method or use or combination according to any one of claims 1 to 4 wherein the endocrine agent is an estrogen receptor down-regulator.

5 8. The method or use or combination according to any one of claims 1 to 4 wherein the endocrine agent is and an LHRH agonist.

9. The method or use or combination according to any one of claims 1 to 4 wherein the endocrine agent is a progesterone receptor antagonist.

10

10. The method or use or combination according to claim 5 wherein the selective estrogen receptor modulator is tamoxifen.

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11. The method or use or combination according to claim 6 wherein the aromatase inhibitor is anastrozole.

12. The method or use or combination according to claim 6 wherein the aromatase inhibitor is exemestane.

20

13. The method or use or combination according to claim 6 wherein the aromatase inhibitor is letrozole.

14. The method or use or combination according to claim 7 wherein the estrogen receptor down-regulator is fulvestrant.

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15. The method or use or combination according to claim 8 wherein the LHRH agonist is goserelin or a pharmaceutically acceptable salt thereof.

30

16. The method, use or combination according to any one of claims 1 to 15 wherein the EGFR inhibitor is an EGFR TKI.

17. The method, use or combination according to any one of claims 1 to 15 wherein the EGFR inhibitor is selected from gefitinib and erlotinib, or a pharmaceutically acceptable salt thereof.

5 18. The method, use or combination according to any one of claims 1 to 15 wherein the EGFR inhibitor is gefitinib, or a pharmaceutically acceptable salt thereof.

19. The method, use or combination according to any one of claims 1 to 15 wherein the EGFR inhibitor is lapatinib, or a pharmaceutically acceptable salt thereof.

10

20. The method, use or combination according to any one of claims 1 to 15 wherein the EGFR inhibitor is a monoclonal antibody.

15

21. The method, use or combination according to claim 20 wherein the monoclonal antibody is selected from cetuxmab and panitumumab.

22. The method, use or combination according to any one of claims 1 to 4 wherein the EGFR inhibitor is gefitinib and the endocrine agent is an aromatase inhibitor.

20

23. The method, use or combination according to any one of claims 1 to 4 wherein the EGFR inhibitor is gefitinib and the endocrine agent is anastrozole.

24. The method, use or combination according to any one of claims 1 to 4 wherein the EGFR inhibitor is lapatinib and the endocrine agent is exemestane.

25

25. The method, use or combination according to any one of claims 1 to 24 wherein the hormone sensitive breast cancer is estrogen receptor positive breast cancer.

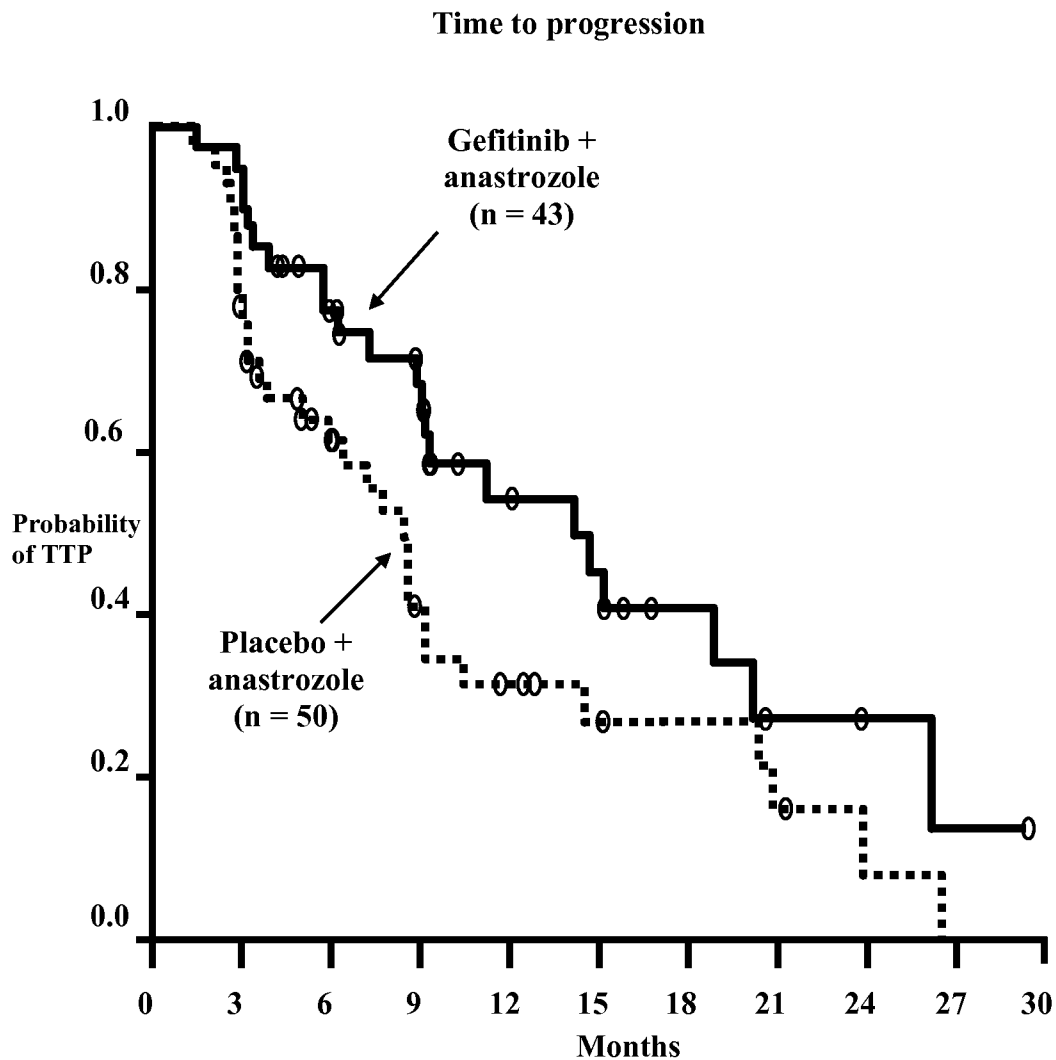
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26. The method, use or combination according to any one of claims 1 to 24 wherein the hormone sensitive breast cancer is metastatic.

27. The method, use or combination according to any one of claims 1 to 24 wherein the hormone sensitive breast cancer is non-metastatic.

28. The method, use or combination according to any one of claims 1 to 27 wherein the
5 warm-blooded animal is a post-menopausal woman.

29. The method, use or combination according to any one of claims 1 to 28 wherein the warm-blooded animal has not been treated with an endocrine therapy selected from a selective estrogen receptor modulator such as tamoxifen or an aromatase inhibitor such as
10 anastrozole prior to administration of the combination of the EGFR inhibitor and the endocrine agent.



At risk:

Gefitinib	35	23	13	9	6	5	3	1	
Placebo	40	28	22	13	10	6	3	2	1

Figure 1

Objective response rate and clinical benefit rate (RECIST)

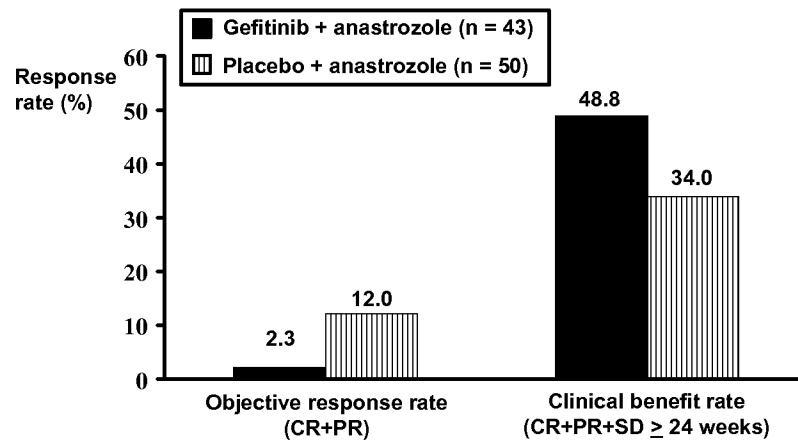
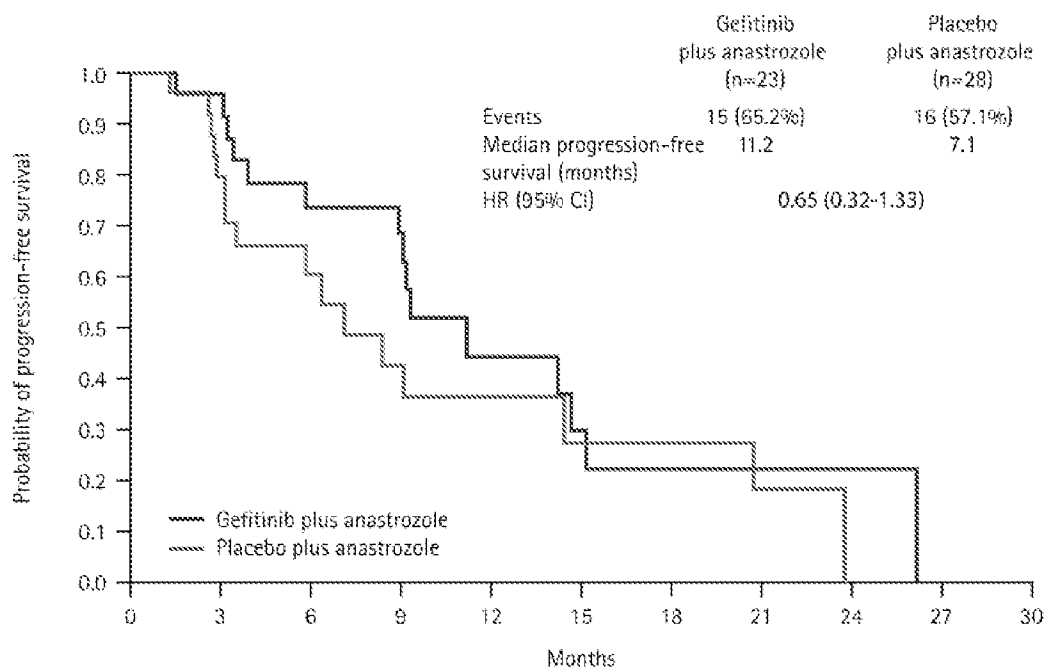


Figure 2

Progression-free survival of the gefitinib plus anastrozole vs anastrozole plus placebo study (trial 713) in patients that had received prior endocrine therapy



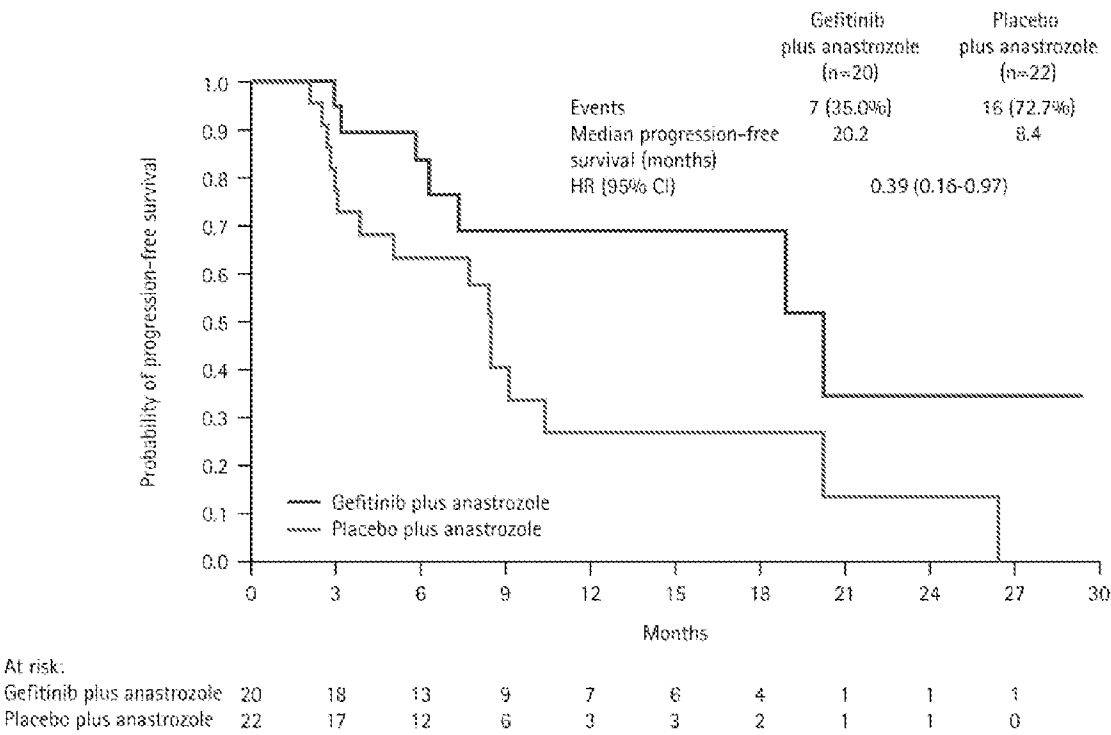
At risk:

Gefitinib plus anastrozole	23	22	15	13	6	4	2	2	1
Placebo plus anastrozole	28	18	11	7	6	6	3	2	0

HR, hazard ratio; CI, confidence interval

Figure 3

Progression-free survival of the gefitinib plus anastrozole vs anastrozole plus placebo study (trial 713) in patients that had not received prior endocrine therapy



HR, hazard ratio; CI, confidence interval

Figure 4