

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 November 2009 (19.11.2009)

PCT

(10) International Publication Number
WO 2009/138779 A1

(51) International Patent Classification:
A61K 31/517 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/GB2009/050494

(22) International Filing Date:
11 May 2009 (11.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/052,706 13 May 2008 (13.05.2008) US
61/110,664 3 November 2008 (03.11.2008) US
61/120,583 8 December 2008 (08.12.2008) US

(71) Applicant (for all designated States except MG, US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **IACONA, Lisa, Renee, Bailey** [US/US]; AstraZeneca R&D Wilmington, 1800 Concord Pike, Wilmington, Delaware 19850 (US). **SMITH, Ian** [GB/GB]; AstraZeneca R&D Alderely, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **STUART, Mary** [IE/GB]; AstraZeneca R&D Alderely, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMBINATION COMPRISING 4- (3-CHLORO-2-FLUOROANILINO) -7-METHOXY-6- { [1- (N-METHYLCARBAMOYLMETHYL) PIPERIDIN- 4-YL] OXYQUINAZOLINE

(57) Abstract: A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable salt thereof, and an endocrine agent suitable for use in the treatment of breast cancer is described. Also described is the use of the combination in the treatment of cancer.



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COMBINATION COMPRISING

4- (3-CHLORO-2-FLUOROANILINO) -7 -METHOXY- 6- { [1 - (N-METHYLCARBAMOYLMETHYL) PIPERIDIN - 4 -YL] OXY }
QUINAZOLINE

The present invention relates to a combination comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable salt thereof, hereafter "Compound (I)",
5 and an endocrine agent suitable for use in the treatment of breast cancer.

The combination is expected to be useful for the treatment or prophylaxis of cancer. The invention also relates to a pharmaceutical composition comprising such combinations and to the use thereof in the manufacture of a medicament for use in the treatment or prophylaxis of cancer, such as breast cancer.

10 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,
15 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
20 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.*,
25 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,
30 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. 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
5 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
10 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,
15 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
20 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
25 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
30 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.

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.

5 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).

10 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.

15 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.

20 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.

25 Estrogens such as ethinyl estradiol have been used in the treatment of advanced breast cancer in patients that have become resistant to endocrine therapies such as tamoxifen and aromatase inhibitors such as anastrozole. The estrogen appears to restore sensitivity to endocrine agents in these patients.

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.

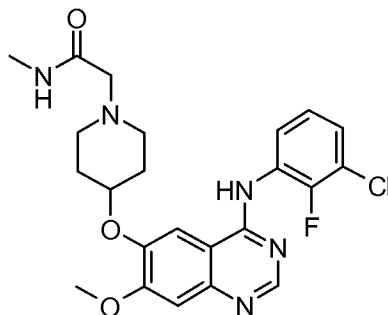
Other clinical trials of gefitinib with an aromatase inhibitor or tamoxifen have generally shown modest or no benefit. In some cases the literature suggests that in the clinical setting, adding gefitinib to standard aromatase inhibitor treatment may be
20 antagonistic to anastrozole, resulting in a reduction in objective tumour response rate than using anastomose 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 in a phase II clinical trial, that although the combination of gefitinib and anastrozole appears to give a reduction in
30 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. This novel and unexpected result suggests that combinations of an EGFR tyrosine kinase inhibitor with an endocrine agent

suitable for use in the treatment of breast cancer, such as an aromatase inhibitor, may in fact provide a significant clinical benefit in patients treated with this combination.

Compound **(I)** is disclosed in International Patent Application Publication number WO2005/028469 as Example 1 therein and is of the structure:



Compound **(I)**

In WO2005/028469 it is stated that compounds disclosed therein may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

WO2005/028469 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and many different types of chemotherapeutic agent.

Nowhere in WO2005/028469 is the specific combination of Compound **(I)** and an endocrine agent suitable for use in the treatment of breast cancer suggested.

Compound **(I)** is an erbB receptor tyrosine kinase inhibitor, in particular Compound **(I)** is a potent inhibitor of EGFR and erbB2 receptor tyrosine kinases.

There is a growing body of pre- and clinical evidence suggesting that, in addition to signalling via EGFR and erbB2 homodimers, cell signalling mediated by EGFR, erbB2 & erbB3 heterodimers may be an important oncogenic signalling pathway (Sergina et al., Nature, 2007, 445, 437; Ritter et al., Clin Cancer Res. 2007, 13, 4909; Johnston et al., JCO, 2008, 26, 1066). Since erbB3 does not have an intrinsic tyrosine kinase activity, activation of the erbB3 receptor is achieved only through the formation of heterodimeric receptor complexes with other kinase-active receptors including particularly EGFR and erbB2. EGFR and erbB2 heterodimers formed with erbB3 are thought to drive tumour growth in tumours where these receptors are expressed.

We have found in pre-clinical experiments that Compound **(I)** also inhibits erbB3 mediated signalling through the inhibition of phosphorylation of erbB3 following ligand stimulated EGFR/erbB3 and/or erbB2/erbB3 heterodimerisation. Accordingly, Compound **(I)** exhibits a unique erbB tyrosine kinase inhibitory effect compared to other erbB tyrosine kinase inhibitors such as gefitinib or erlotinib that act primarily as EGFR tyrosine kinase inhibitors. We have carried out pre-clinical studies which suggest that Compound **(I)** exhibits improved anti-tumour effects compared to EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib. Without wishing to be bound by theory, it is thought that the improved properties may result from the inhibition of the erbB3 mediated signalling by Compound **(I)**.

The novel result that the combination of an EGFR tyrosine kinase inhibitor with an aromatase inhibitor provides a beneficial anti-tumour effect in a clinical setting, together with our finding that Compound **(I)** exhibits enhanced erbB tyrosine kinase inhibitory properties compared to gefitinib, suggests that a combination of Compound **(I)** with an endocrine agent suitable for use in the treatment of breast cancer may provide beneficial anti-cancer effects.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)**, and an endocrine agent suitable for use in the treatment of breast cancer.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and an endocrine agent selected from a selective estrogen receptor modulator, an aromatase inhibitor and a selective estrogen receptor down regulator.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and an endocrine agent selected from a selective estrogen receptor modulator and an aromatase inhibitor.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and an anti-estrogen agent.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and a selective estrogen receptor modulator.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and an aromatase inhibitor.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and an estrogen receptor down-regulator.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and a progesterone receptor antagonist.

5 According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and luteinizing hormone-releasing hormone agonist.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, and a progestogen.

10 According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, an estrogen and an endocrine agent suitable for use in the treatment of breast cancer.

According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, an estrogen and an selective aromatase inhibitor.

15 According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)**, an estrogen and selective estrogen receptor modulator.

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
20 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
25 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
30 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.

5 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.

10 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.

15 References herein to “Compound (**I**)” unless stated otherwise include Compound (**I**) and pharmaceutically acceptable salts thereof. Similarly references to any of the endocrine agents described herein are intended to cover the agent and pharmaceutically acceptable salts thereof unless specified otherwise.

20 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
25 the beneficial effect of the combination.

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 pharmaceutically acceptable salt of the compound.

30 Where cancer is referred to, particularly it refers to oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewing’s tumour, neuroblastoma, Kaposi’s sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, brain cancer, renal cancer, lymphoma and

leukaemia. In one embodiment it refers to breast cancer, for example hormone receptor-positive breast cancer. In another embodiment cancer refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and / or breast cancer. In another embodiment cancer refers to SCLC. In addition, it refers to NSCLC. In addition, it refers to colorectal cancer. In addition, it refers to ovarian cancer. In addition, more particularly it refers to breast cancer. In addition, more particularly it refers to hormone receptor positive breast cancer, especially to hormone receptor positive breast cancer in post-menopausal women. In one embodiment it refers to 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 it refers to early stage non-metastatic estrogen and/or progesterone receptor positive breast cancer, especially to early stage non-metastatic estrogen and/or progesterone receptor positive breast cancer in post-menopausal women. In addition, more particularly it refers to metastatic hormone receptor positive breast cancer, especially to metastatic hormone receptor positive breast cancer in post-menopausal women. Still furthermore it refers to metastatic estrogen and/or progesterone receptor positive breast cancer, especially to metastatic estrogen and/or progesterone receptor positive breast cancer in post-menopausal women. Furthermore, it refers to bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and / or renal cancer. In addition it refers to endometrial, liver, stomach, thyroid, rectal and / or brain cancer. In another embodiment of the invention, particularly the cancer is in a non-metastatic state. In another embodiment of the invention, particularly the cancer is in a metastatic state. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces skin metastases. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces lymphatic metastases. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces brain metastases.

Where the treatment of cancer is referred to particularly this is the treatment of cancerous tumours expressing one or more of the erbB family of receptors, for example EFGR, erbB2 and/or erbB3 receptors. The anti-cancer effect of the combination 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 for example the FDA publication "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" May 2007

5 (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 regrowth of tumour on cessation of treatment or slowing of disease progression.

The combination use of Compound **(I)** and certain endocrine agents suitable for use
10 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 receptor modulators include, for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene. Fulvestrant also exhibits anti-estrogen effects and as such may be considered
15 to be a selective estrogen receptor modulator.

In one aspect the selective estrogen receptor modulator is tamoxifen.

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

20 In one aspect the aromatase inhibitor is selected from anastrozole. In one aspect the 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
25 inhibitor is selected from rogletimide. In one aspect the aromatase inhibitor is selected 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
30 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.

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

5 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 N-oxide.

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

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

20 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 -methylestra-1,3,5(10)-triene-3, 17 α -diol.

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

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

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

30 A further particular estrogen receptor down-regulator for use in the present invention is 11 β -fluoro-3-(2-tetrahydropyranoyloxy)-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-
5 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
10 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.

15 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
20 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-
25 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 LHRH agonists as well as peptides or peptide derivatives. Peptide and peptide derivatives include for example:

- i) buserelin (US Patent 4 024 248)
- 30 (pyr)Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)⁶-Leu-Arg-Pro-NHCH₂CH₃
- ii) triptorelin (US Patent 4 010 125)
- (pyr)Glu-His-Trp-Ser-Tyr-Trp-Leu-Arg-Pro-Gly-NH₂
- iii) leuprorelin (Us Patent 4 005 063)

- (pyr)Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHCH₂CH₃
- iv) goserelin (US Patent 4 100 274)
- (pyr)Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)-Leu-Arg-Pro-(Azygly)NH₂
- v) deslorelin (US Patent 4 659 695)
- 5 (pyr)Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NH-CH₂-CH₂-NH₂
- vi) histerelin (US Patent 4 244 946)
- (pyr)Glu-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NH-CH₂-CH₃
- vii) avorelin (US 5 668 254)
- (pyr)Glu-His-Trp-Ser-Tyr-D-Trp(2-Me)-Leu-Arg-Pro-NH-CH₂-CH₃
- 10 viii) nafarelin (US Patent 4 234 571)
- (pyr)Glu-His-Trp-Ser-Tyr-D-Nal(2)-Leu-Arg-Pro-NH-CH₂-CH₃;

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

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

15 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.

20 Estrogens may be used to restore hormone sensitivity to tumours which have become resistant to endocrine therapy. Accordingly, combinations comprising Compound **(I)**, an endocrine agent suitable for use in the treatment of breast cancer and an estrogen form a further aspect of the present invention. Estrogens include for example stilbestrol or ethinylestradiol.

Particular combinations of the present invention include:

- 25
- Compound **(I)** and tamoxifen, or a pharmaceutically acceptable salt thereof;
 - Compound **(I)** and anastrozole, or a pharmaceutically acceptable salt thereof;
 - Compound **(I)** and exemestane, or a pharmaceutically acceptable salt thereof;
 - Compound **(I)** and letrozole, or a pharmaceutically acceptable salt thereof;
 - Compound **(I)** and aminoglutethimide, or a pharmaceutically acceptable salt thereof;

30

 - Compound **(I)** and formestane, or a pharmaceutically acceptable salt thereof;
 - Compound **(I)** and fadrozole, or a pharmaceutically acceptable salt thereof;
 - Compound **(I)** and rogletimide, or a pharmaceutically acceptable salt thereof;

- Compound (I) and vorozole, or a pharmaceutically acceptable salt thereof;
- Compound (I) and fulvestrant, or a pharmaceutically acceptable salt thereof;
- Compound (I) and AZD4992, or a pharmaceutically acceptable salt thereof; and
- Compound (I) and CH-4893237, or a pharmaceutically acceptable salt thereof.
- 5 • Compound (I) 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.
- Compound (I) 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.
- 10 • Compound (I) 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.
- Compound (I) 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.
- 15 • Compound (I) 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.
- Compound (I) 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.
- 20 • Compound (I) 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.
- Compound (I) 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.
- 25 • Compound (I) 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.
- Compound (I) 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)-triene-3, 17 β -ol.
- 30 • Compound (I) and 11 β -fluoro-3-(2-tetrahydrophyranoyloxy)-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 -ol.

- Compound (**I**) 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.
- 5 • Compound (**I**) 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.
- Compound (**I**) 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.
- Compound (**I**) 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.
- 10 • Compound (**I**) 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.
- Compound (**I**) 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.
- Compound (**I**) 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.
- 15 • Compound (**I**) 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.
- Compound (**I**) 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.
- 20 • Compound (**I**) 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.
- 25 • Compound (**I**) 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.
- Compound (**I**) 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.
- 30 • Compound (**I**) and (S)-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.

- Compound **(I)** 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.
- Compound **(I)** 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.
- Compound **(I)** 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 N-oxide.
- Compound **(I)** 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.
- Compound **(I)** 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.
- Compound **(I)** and goserelin, or a pharmaceutically acceptable salt thereof.
- Compound **(I)** and leuprorelin, or a pharmaceutically acceptable salt thereof.
- Compound **(I)** and ZK232011, or a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically-acceptable salts 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 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 exist in zwitterionic form. A particular pharmaceutically acceptable salt of Compound **(I)** is a di-fumarate salt, still more particularly Compound **(I)** di-fumarate salt Form A, as described in the Examples.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an endocrine agent suitable for use in the treatment of breast cancer, for use as a medicament.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and a selective estrogen receptor modulator for use as a medicament.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an aromatase inhibitor for use as a medicament.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an estrogen receptor down-regulator for use as a
5 medicament.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and a progesterone receptor antagonist for use as a medicament.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an LHRH agonist for use as a medicament.

10 According to a further aspect of the present invention, there is provided a combination, comprising Compound **(I)** and an endocrine agent suitable for use in treatment of breast cancer, for use in the treatment of estrogen receptor positive breast cancer.

According to a further aspect of the present invention, there is provided a
15 combination, comprising Compound **(I)** and a selective estrogen receptor modulator for use in the treatment of estrogen receptor positive breast cancer.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an aromatase inhibitor for use in the treatment of estrogen receptor positive breast cancer.

20 Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an estrogen receptor down-regulator for use in the treatment of estrogen receptor positive breast cancer.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and a progesterone receptor antagonist for use in the treatment
25 of estrogen receptor positive breast cancer.

Therefore according to the present invention, there is provided a combination, comprising Compound **(I)** and an LHRH agonist for use in the treatment of estrogen receptor positive breast cancer.

30 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and an endocrine agent suitable for use in the treatment of breast cancer in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and a selective estrogen receptor modulator in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and an aromatase inhibitor in association with
5 a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and an estrogen receptor down-regulator in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and a progesterone receptor antagonist in
10 association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically
15 acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an endocrine agent suitable for use in the treatment of breast cancer in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically
20 acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a selective estrogen receptor modulator in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically
25 acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an aromatase inhibitor in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically
30 acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an estrogen receptor down-regulator in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a progesterone receptor antagonist in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an LHRH agonist in association with a pharmaceutically acceptable diluent or carrier.

Therefore according to the present invention, there is provided a method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** 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 cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** 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 cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** 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 cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** in combination with an effective amount of an aromatase inhibitor.

Therefore according to the present invention, there is provided a method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** 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 cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** in combination with an effective amount of a progesterone receptor antagonist.

5 Therefore according to the present invention, there is provided a method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound **(I)** in combination with an effective amount of an LHRH agonist.

For the avoidance of doubt, where the treatment of 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 time period before they occur, and to a patient who already has metastases to treat the metastases themselves. Furthermore the treatment of 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 cancer relates to the prevention of metastases. In another aspect of the invention the treatment of cancer relates to the treatment of metastases. In another aspect of the invention the treatment of cancer relates to treatment of an established primary tumour or tumours or developing primary tumour or tumours. In one embodiment the treatment of cancer relates to an adjuvant treatment. In another embodiment the treatment of 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. 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. 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.

In another embodiment the combination is used to treat cancer patients that have not received any prior endocrine therapy before being treated with a combination according to the present invention. Such patients may benefit further from the anti-cancer

effects of a combination according to the present invention in for example, an improved time to progression compared to treatment using an endocrine therapy such as an aromatase inhibitor alone. For example, the combination may be used to treat breast cancer patients who have not received any prior endocrine therapy. Such prior endocrine therapy may be for example, a selective estrogen receptor modulator tamoxifen or an aromatase inhibitor such as anastrozole, more particularly tamoxifen. Particularly the combination may be used to treat hormone sensitive breast cancer in a patient that has not received prior endocrine therapy. Accordingly, the combination according to the invention may be used to treat women (particularly post-menopausal women) with hormone 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). More particularly, 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 to treat women (particularly treat post-menopausal women) with hormone sensitive early stage (non-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. For example, 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 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 is not used as a neo-adjuvant treatment. As will be understood the above methods of treatment and uses 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).

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.

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

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 Compound (**I**) in combination with an effective amount of an aromatase inhibitor such as anastrozole,

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 Compound (**I**) and an aromatase inhibitor, 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 Compound (**I**) and an aromatase inhibitor, 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 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 administering to said animal an effective amount of Compound **(I)** in combination with an effective amount of an aromatase inhibitor such as anastrozole,

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 this embodiment the combination is suitably administered as an adjuvant treatment.

In another embodiment there is provided a combination comprising Compound **(I)** and an aromatase inhibitor, for use in 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 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 Compound **(I)** and an aromatase inhibitor, 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 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

(i) selecting a warm-blooded animal, such as man, that has non-metastatic estrogen and/or progesterone positive breast cancer and 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; and

(ii) administering to said animal an effective amount of Compound **(I)** in combination with an effective amount of an aromatase inhibitor such as anastrozole.

In this embodiment the combination is suitably administered as an adjuvant treatment.

In another embodiment there is provided a combination comprising Compound **(I)** and an aromatase inhibitor, for use in the treatment of a warm-blooded animal, such as man, which has been diagnosed with non-metastatic estrogen and/or progesterone positive breast cancer and 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 Compound **(I)** and an aromatase inhibitor, in the manufacture of a medicament for the treatment of a warm-blooded animal, such as man, which has been diagnosed with non-metastatic estrogen and/or progesterone positive breast cancer and 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 the above embodiments relating to the treatment of breast cancer, the method or use according to the invention is suitably provided as an adjuvant treatment of the breast cancer.

In the above embodiments for the treatment of breast cancer, the warm-blooded animal is suitably a post-menopausal woman. 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 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 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.

According to a further aspect of the present invention, there is provided a method of treating breast cancer that has become resistant to endocrine therapy, in a warm-blooded

animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination comprising an estrogen, Compound **(I)** and an endocrine agent suitable for use in the treatment of breast cancer. Endocrine agents suitable for use in the treatment of breast cancer for use in this aspect of the invention are
5 any of the endocrine agents described hereinbefore. As mentioned above the presence of the estrogen may restore endocrine sensitivity in the tumour and thereby overcome resistance to endocrine therapy.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the
10 effects of each of the components of said treatment used alone, that is, of each of Compound **(I)** 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 greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of Compound **(I)**
15 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 a synergistic effect if the effect is therapeutically superior, as measured by, for example,
20 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 Compound **(I)** or the endocrine agent alone. Further, the effect of the combination treatment is
25 synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to Compound **(I)** 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
30 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 Compound **(I)** 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.

5 According to a further aspect of the present invention there is provided a kit comprising Compound **(I)** and an endocrine agent suitable for use in the treatment of breast cancer; optionally with instructions for use.

 According to a further aspect of the present invention there is provided a kit comprising Compound **(I)** and selective estrogen receptor modulator; optionally with
10 instructions for use.

 According to a further aspect of the present invention there is provided a kit comprising Compound **(I)** and an aromatase inhibitor; optionally with instructions for use.

 According to a further aspect of the present invention there is provided a kit comprising Compound **(I)**, and an estrogen receptor down-regulator; optionally with
15 instructions for use.

 According to a further aspect of the present invention there is provided a kit comprising:

- a) Compound **(I)**, in a first unit dosage form;
- b) an endocrine agent suitable for use in the treatment of breast cancer; in a second unit
20 dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

 According to a further aspect of the present invention there is provided a kit comprising:

- 25 a) Compound **(I)**, in a first unit dosage form;
- b) a selective estrogen receptor modulator; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

 According to a further aspect of the present invention there is provided a kit
30 comprising:

- a) Compound **(I)**, in a first unit dosage form;
- b) an aromatase inhibitor; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- a) Compound **(I)**, in a first unit dosage form;
- 5 b) an estrogen receptor down-regulator; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- 10 a) Compound **(I)**, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an endocrine agent suitable for use in the treatment of breast cancer, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- 15 d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- a) Compound **(I)**, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- 20 b) a selective estrogen receptor modulator, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- 25 a) Compound **(I)**, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an aromatase inhibitor, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

30 According to a further aspect of the present invention there is provided a kit comprising:

- a) Compound **(I)**, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

- b) an estrogen receptor down-regulator, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

An example of a unit dosage form for Compound **(I)** might be a tablet for oral administration, for example that described herein below. An example of a unit dosage form for a selective estrogen receptor modulators 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, see that described herein below.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** 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 cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and a selective estrogen receptor modulator in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and an aromatase inhibitor in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and an estrogen receptor down-regulator in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and a progesterone receptor antagonist in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)** and an LHRH agonist in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, 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 breast cancer in
5 association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which
10 comprises a selective estrogen receptor modulator in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, for use in combination with a pharmaceutical composition
15 which comprises an aromatase inhibitor in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which
20 comprises an estrogen receptor down-regulator in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which
25 comprises a progesterone receptor antagonist in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound **(I)**, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which
30 comprises an LHRH agonist in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

The pharmaceutical compositions of compound **(I)** 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
5 in a conventional manner using conventional excipients.

For example Compound **(I)** is suitably formulated as a tablet using the following excipients:

Tablet Core:

Compound **(I)**;
10 lactose;
microcrystalline cellulose;
crospovidone;
polyvidone (PVP); and
magnesium stearate

15 The tablet core may be coated with a conventional film-coating such as an HPMC based film coating which optionally contains one or more colorants and/or light protective agents. Suitably Compound **(I)** is used in the tablet as the Compound **(I)** difumarate salt, more specifically the Compound **(I)** difumarate salt. If required the Compound **(I)** may be milled prior to formulation into the tablet to provide a uniform particle size distribution of
20 the Compound **(I)** in the tablet. For example Compound **(I)** difumarate may be milled to provide an average particle size of about 5µm. Suitable milling methods are well known.

The tablets may be prepared using conventional methods and as illustrated in the Examples.

In those embodiments where Compound **(I)** is used in combination with the
25 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.

30 According to a further aspect of the present invention there is provided a kit comprising Compound **(I)** and an endocrine agent suitable for use in the treatment of breast cancer; optionally with instructions for use; for use in the treatment of cancer. Suitable

endocrine agent for use in the treatment of breast cancer are any of the endocrine agents described herein.

According to another feature of the invention there is provided the use of Compound (I), 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 cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with a selective estrogen receptor modulator in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with an aromatase inhibitor in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with an estrogen receptor down-regulator in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with a progesterone receptor antagonist in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with an LHRH agonist in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with an endocrine agent suitable for use in the treatment of breast cancer, in the treatment of cancer (for example hormone sensitive breast cancer), in a warm-blooded animal, such as man. 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 present invention there is provided a combination comprising Compound (I) and an endocrine agent suitable for use in the treatment of breast cancer, for use in the treatment of cancer (for example 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 present invention there is provided a combination treatment comprising the administration of an effective amount of Compound **(I)**, 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, for use in the treatment of cancer (for example hormone sensitive breast cancer). Suitable endocrine agents for use in this aspect of the invention include any of the endocrine agents described herein.

The amount of Compound **(I)**, or a pharmaceutically acceptable salt thereof, administered would be that sufficient to provide the desired pharmaceutical effect. For instance, Compound **(I)** could be administered to a warm-blooded animal orally, at a unit dose less than 1g daily but more than 1mg. Particularly Compound **(I)** could be administered to a warm-blooded animal, at a unit dose of less than 250 mg per day. In another aspect of the invention, Compound **(I)** could be administered to a warm-blooded animal, at a unit dose of less than 160 mg per day. In a further aspect of the invention, Compound **(I)** could be administered to a warm-blooded animal, at a unit dose of less than 50 mg per day. The dose of Compound **(I)** may be administered as a single daily dose or as multiple fractions of the total daily dose. For example, the total daily dose of Compound **(I)** 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 compound **(I)** may be administered as a one or more tablets containing, for example 1, 2.5, 10, 40 or 100mg of Compound **(I)**. In a further embodiment a dose of Compound **(I)** of 40, 80, 100, 160, 200 or 240mg of Compound **(I)** is administered twice a day. In these embodiments the Compound **(I)** is suitably administered as the Compound **(I)** difumarate salt in an amount sufficient to give the required dose of the Compound **(I)** free base. For example, in a particular embodiment a dose of Compound **(I)** difumarate equivalent to 160 mg of Compound **(I)** as the free base is administered twice a day. In another particular embodiment a dose of Compound **(I)** difumarate equivalent to 200 mg of Compound **(I)** as the free base is administered twice a day. In another particular

embodiment a dose of Compound **(I)** difumarate equivalent to 240 mg of Compound **(I)** as the free base is administered twice a day.

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 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 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 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.

Compound **(I)** may be prepared as described in Example 1 of WO2005/028469. Alternatively Compound **(I)** may be prepared as described in the Examples.

When Compound **(I)** is used in the form of a di-fumarate salt, the salt may be prepared as described in the Examples.

Legends to Figures

Figure 1 shows the marked improvement in time to progression of patients treated with anastrozole plus gefitinib compared to patients 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 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 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.

Figure 5 shows an X-ray powder diffraction pattern (XRPD) for Compound (I) difumarate Form A. The x-axis shows the 2-theta value and the y-axis the counts.

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.

In the Examples unless otherwise stated :-

(i) yields are given for illustration only and are not necessarily the maximum attainable;

(ii) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$ which refers to the protonated mass ion; reference to M^+ is to the mass ion generated by loss of an electron; and reference to $M-H^+$ is to the mass ion generated by loss of a proton;

(iii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 500 MHz using perdeuterio dimethyl sulfoxide ($DMSO-d_6$) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(iv) chemical symbols have their usual meanings; SI units and symbols are used;

(v) solvent ratios are given in volume:volume (v/v) terms;

(vi) in the examples given below the number of moles and the yield stated refer to the raw materials and reagents at 100% w/w, thereby taking account of the purity of the materials used.

Example A

Preparation of 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6- $\{[1-(N$ -methylcarbamoylmethyl)piperidin-4-yl]oxy $\}$ quinazoline (Compound (I))

2-Chloro-N-methylacetamide (3.720 kg, 34.60 mol) and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride (13.70 kg, 27.25 mol), were dissolved in acetonitrile (79.2 kg). To the stirred suspension, at ambient temperature, was added triethylamine (17.40 kg, 172.11 mol). The resulting clear solution was heated to reflux and held for 3 hours. The solution was cooled to 20°C (product crystallized at 50°C). Water (54.2 kg) was added to the reactor and the suspension was stirred for a further 2 hours at 20°C. The product was filtered and washed with water (34 kg) followed by cold (0°C) acetonitrile (13.0 kg). The product was recrystallised from acetonitrile (94.6 kg), isolated by filtration and washed with cold (0°C) acetonitrile (13.2 kg). A further recrystallisation of this product was then carried out as above from acetonitrile (75.2 kg). The solid was then dried under vacuum to give the title product as a white solid (6.50 kg, 50%); 1H NMR Spectrum: ($CDCl_3$) 1.98 (m, 2H), 2.08 (m, 2H), 2.46

(-m, 2H), 2.85 (m, 2H), 2.87 (d, 3H), 3.07 (s, 2H), 4.02 (s, 3H), 4.49 (m, 1H), 7.16 (m, 4H), 7.31 (m, 2H), 8.49 (m, 1H), 8.71 (s, 1H); Mass spectrum: MH^+ 474.

The 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline used as the starting material was prepared as follows:

5 **Step 1: 6-Acetoxy-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline hydrochloride**

6-Acetoxy-7-methoxyquinazolin-4-one (International Patent Application WO 96/15118, Example 39 thereof; 21.4 kg, 89.3 mol) was suspended in toluene (150 kg). To this was added N-ethyldiisopropylamine (13.3 kg, 103 mol). The brown suspension was heated to 70°C then phosphorus oxychloride (36.0 kg, 228 mol) was charged. The reaction mixture was stirred at 70°C for 5 hours. Further toluene (84.0 kg) was added followed by 3-chloro-2-fluoroaniline (14.88 kg, 102 mol). The reaction mixture was stirred at 70°C for 2 hours during which time a solid precipitated. The suspension was cooled to 25°C and held at this temperature for 93 hours. The reaction mixture was filtered and the filter cake washed with toluene (2 x 55.5 kg). The cake was further washed with a mixture of ethanol (24.5 kg) and water (32.0 kg) twice, then ethanol (50.5 kg) twice and the solid then dried under vacuum to give the title product as a beige solid (33.4 kg, 78%); 1H NMR: 2.37 (s, 3H), 4.00 (s, 3H), 7.34 (ddd, 1H), 7.48 (s, 1H), 7.52 (ddd, 1H), 7.61 (ddd, 1H), 8.62 (s, 1H), 8.86 (s, 1H); Mass Spectrum: 362.4, 364.4.

Step 2: 4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline

20 6-Acetoxy-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline hydrochloride from step 1 (33.5 kg, 69.6mol) was suspended in methanol (198 kg). To the stirred suspension at 25°C was added water (86 kg) and sodium hydroxide (31.5 kg, 32%). The resulting solution was stirred at 60°C for 4.5 hours and then cooled to 25°C. Acetic acid (approximately 16.0 kg) was added until a pH of 5.5-6.0 was achieved at which point the product precipitates from solution. After the addition of further methanol (5.5 kg) the suspension was stirred for 90 minutes. The product was filtered then washed with 25% aqueous methanol (39.0 kg MeOH + 17.0 kg Water) and then methanol (55.5 kg). The crude solid was dried under vacuum at 40°C. The crude solid was slurried with water (145 kg) and stirred for 2 hours at 65°C. The slurry was cooled to 20°C and filtered. The filter cake was washed with methanol (2 x 21.5 kg), then dried under vacuum at 40°C to give a the title product as a light brown solid (21.85 kg, 98%); 1H NMR: 3.95 (s, 3H), 7.19 (s, 1H), 7.23 (dd, 1H), 7.42 (dd, 1H), 7.50 (dd, 1H), 7.64 (s, 1H), 8.32 (s, 1H), 9.43 (s, 1H), 9.67 (br.s, 1H); Mass Spectrum: 320.4, 322.4.

Step 3: 6-[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxy quinazoline

4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline from Step 2 (15.591 kg, 48.44mol), *tert*-Butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (prepared as in Chemical & Pharmaceutical Bulletin 2001, **49(7)**, 822-829; 16.20 kg, 57.99 mol) and potassium carbonate (7.978 kg, 57.73 mol) were dissolved in N-methylpyrrolidinone (114.2 kg), and the mixture was heated to 100°C with stirring. Heating was continued at 100°C (95°C - 105°C) for 5 hours. The mixture was then cooled to 80°C and quenched by the addition of water (216.6 kg).

The batch was stirred at 80°C for a further 60 minutes then cooled to 20°C over 2 hours, during which time the product crystallized. The product was isolated by filtration. The product was dissolved in hot (reflux) methanol (200 L). To this mixture was added water (20 L), which induced crystallization. The suspension was cooled to 0°C and filtered. Vacuum drying at 50°C afforded the title product, 18.80 kg (77%); ¹H NMR: 1.40 (s, 9H), 1.60-1.65 (m, 2H), 1.95-2.00 (m, 2H), 3.20-3.25 (m, 2H), 3.65-3.70 (m, 2H), 3.92 (s, 3H), 4.68 (m, 1H), 7.21 (s, 1H), 7.27 (dd, 1H), 7.47 (ddd, 1H), 7.51 (dd, 1H), 7.85 (s, 1H), 8.36 (s, 1H), 9.53 (s, 1H); Mass Spectrum: 503.5, 505.5.

Step 4: 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride

6-[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline from step 3 (18.80 kg, 37.38 mol) was suspended in isopropanol (139.8 kg), and heated to 40°C with stirring. Hydrochloric acid (15.40 kg, ~156.3 mol) was charged to the vessel over 50 minutes, allowing an exotherm of approximately 9°C to occur. During the charging of the acid, the suspension dissolved to give a clear solution. The solution was heated slowly to reflux over approximately 90 minutes, and then held at reflux for a further 3 hours. The product crystallised out during this reflux period. The thick suspension was cooled to 0°C and filtered. The filter cake was washed twice with cold (0°C) isopropanol (2 x 20.6 kg). The product was dried under vacuum at 50°C to give the title product, 13.60 kg (73%); ¹H NMR: 1.53-1.64 (m, 2H), 2.00-2.05 (m, 2H), 2.64-2.72 (m, 2H), 3.00-3.07 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 7.20 (s, 1H), 7.26 (ddd, 1H), 7.47 (dd, 1H), 7.50 (dd, 1H), 7.82 (s, 1H), 8.34 (s, 1H), 9.56 (s, 1H); Mass Spectrum: 403.2, 405.2.

Example B Preparation of 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (Compound (I))

2-Chloro-N-methylacetamide (24.22 g, 223.1 mmol) and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride (86.00 g, 160.9 mmol), were slurried in acetonitrile (537 ml). To the stirred suspension, at ambient temperature, was added triethylamine (101 ml, 723.9 mmol). The reaction was heated to 75°C held for 5 hours. The solution was cooled to 70°C and ethanol (268 ml) added. The reaction was cooled to 45°C and water (9.6 ml) added. Compound (I) (0.42 g) was added to establish crystallisation and then the slurry cooled to 20°C over 2 hours. After stirring for a further 12 hours the product was isolated by filtration. The filter cake was washed twice with acetonitrile (102 ml): ethanol (51 ml): water (1.8 ml) and then with water (153 ml). The product was dried *in vacuo* at 60°C to give the title compound as a white solid (45.9g, 60%); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.76 - 1.87 (m, 2 H) 2.01 - 2.11 (m, 2 H) 2.35 - 2.44 (m, 2 H) 2.64 (d, *J*=4.74 Hz, 3 H) 2.72 - 2.80 (m, 2 H) 2.95 (s, 2 H) 3.95 (s, 3 H) 4.51 - 4.63 (m, 1 H) 7.23 (s, 1 H) 7.29 (td, *J*=8.08, 1.29 Hz, 1 H) 7.46 - 7.58 (m, 2 H) 7.75 (q, *J*=4.60 Hz, 1 H) 7.83 (s, 1 H) 8.38 (s, 1 H) 9.59 (s, 1 H) Mass spectrum: MH⁺ 474.

The 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride used as the starting material was prepared as follows:

Step 1: 6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxy quinazoline

4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (prepared as described in Step 2 of Example A; 60.00 g, 0.1828 mol), *tert*-Butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (88.04 g, 0.3107 mol) and potassium carbonate (30.31 g, 0.2193 mol) were suspended in ethanol (584 ml) and water (58 ml), and the mixture was heated to reflux with stirring. Heating was continued at reflux for 16.5 hours. The mixture was then cooled to 70°C and water (234 ml) was added over 60 minutes.

The batch was stirred at 65°C for a further 2 hours to establish crystallisation. The slurry was cooled to 20°C over 6 hours. The product was isolated by filtration. The filter cake was slurried with aqueous ethanol (ethanol 117 ml, water 58 ml) and then displacement washed with aqueous ethanol (ethanol 117 ml, water 58 ml). The filter cake was then slurried with water (175 ml) and then displacement washed with water (175 ml).

The product was dried *in vacuo* at 40°C to give the title compound (81.5 g, 84%); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.42 (s, 9 H) 1.60 - 1.70 (m, 2 H) 1.96 - 2.04 (m, 2 H) 3.23 - 3.30 (m, 2 H) 3.65 - 3.75 (m, 2 H) 3.95 (s, 3 H) 4.68 - 4.75 (m, 1 H) 7.24 (s, 1 H) 7.29 (t, *J*=8.06 Hz, 1 H) 7.49 (t, *J*=7.50 Hz, 1 H) 7.54 (t, *J*=7.19 Hz, 1 H) 7.88 (s, 1 H) 8.39 (s, 1 H) 9.57 (s, 1 H); Mass Spectrum: 503.5, 505.5.

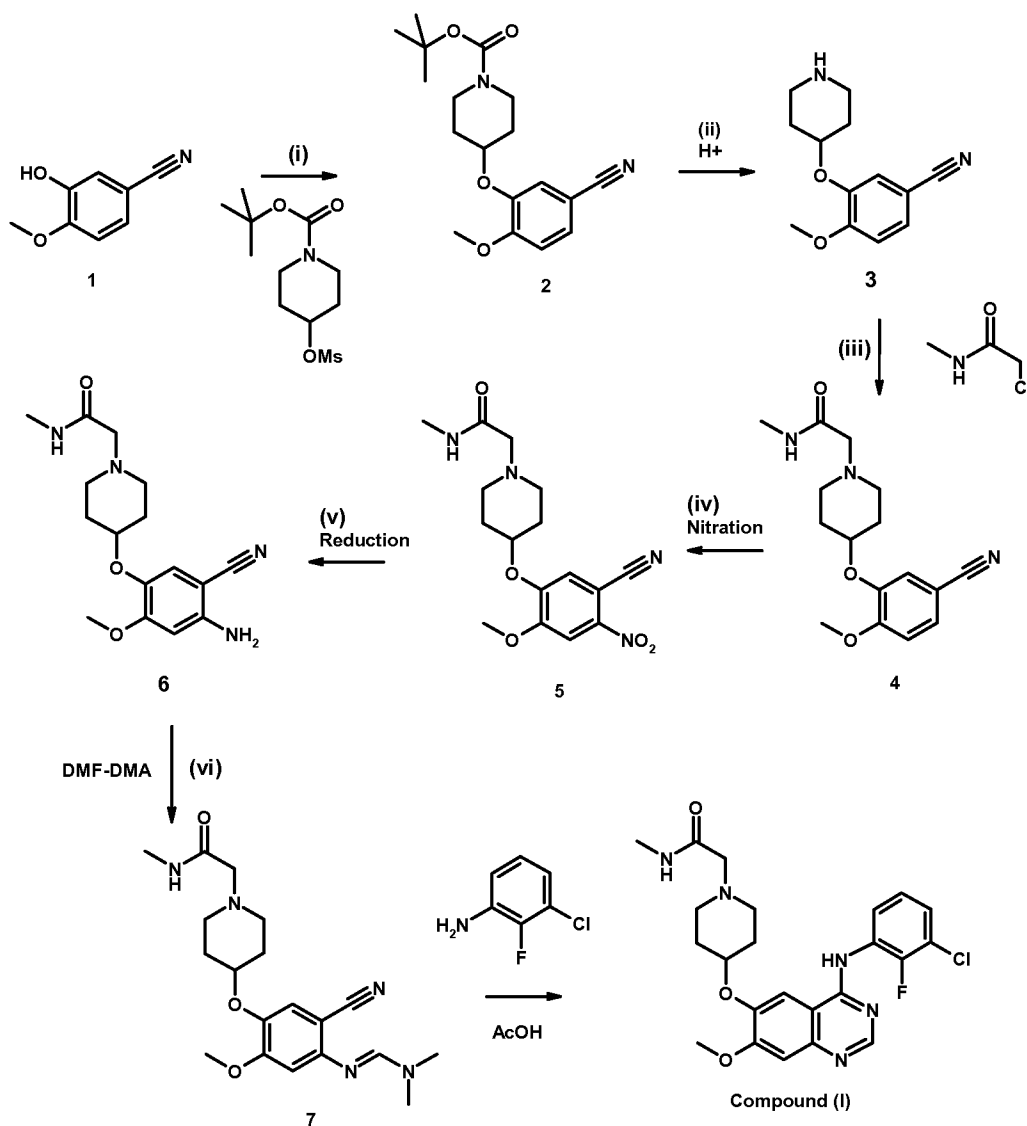
Step 2: 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride

6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (10.00 g, 0.1879 mol) was suspended in industrial methylated spirits (95 ml), and heated to 35°C with stirring. Hydrochloric acid (6.59 ml, approximately 0.7891 mol) was charged to the vessel allowing an exotherm of approximately 5.5°C to occur. During the charging of the acid, the suspension dissolved to give a clear solution. The solution was heated slowly to 70°C over approximately 90 minutes, and then held at 70°C for a further 1 hour. The reaction is then cooled to 0°C over 4 hours during which time the product crystallises. The product was isolated by filtration and then filter cake was washed twice with industrial methylated spirits (2 x 14 ml). The product was dried *in vacuo* at 50°C to give the title product (9.04 g, 88%); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.91 - 2.01 (m, 2 H) 2.27 - 2.35 (m, 2 H) 3.15 - 3.26 (m, 2 H) 3.26 - 3.35 (m, 2 H) 4.02 (s, 3 H) 5.07 - 5.15 (m, 1 H) 7.35 (td, *J*=8.08, 1.29 Hz, 1 H) 7.46 (s, 1 H) 7.52 (ddd, *J*=8.03, 5.23 Hz, 1 H) 7.63 (ddd, *J*=8.22, 6.76, 1.62 Hz, 1 H) 8.83 (s, 1 H) 8.91 (s, 1 H) 9.02 - 9.13 (m, 1 H) 9.20 - 9.31 (m, 1 H) 12.51 (br. s., 1 H)); Mass Spectrum: 403.2, 405.2.

Example C Preparation of 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (Compound (I))

Compound (I) was prepared according to the scheme shown below:

5



2-[4-(5-cyano-4-{{[(dimethylamino)methylene]amino}}-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (7, 7.00g, 17.71mmoles), was suspended in methoxybenzene (35.8g). Acetic acid (16.6g) was charged and to the resulting solution was added 3-chloro-2-fluoroaniline (2.71g, 18.07mmoles). The reaction mixture was heated at 90°C for 20 hours then cooled to 20°C. Water (37.04g) was charged to the reaction mixture, and the organic layer discarded. To the resulting aqueous mixture was charged isopropanol (39.00g), followed by aqueous ammonia (20.79g, 25%). The

10

reaction mixture was heated to 30°C and seeded with Compound (I), which induced crystallisation. The reaction was then cooled to 0°C and the product isolated by filtration. The filter cake was washed twice with a mixture of water (7.28g) and isopropanol (4.68g), then dried to afford the Compound (I) (5.65g, 55% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.79 (m, 2 H) 2.04 (m, 2 H) 2.38 (m, 2 H) 2.62 (d, *J*=4.5 Hz, 3 H) 2.74 (m, 2 H) 2.94 (s, 2 H) 3.93 (s, 3 H) 4.56 (tt, *J*=8.1, 3.8 Hz, 1 H) 7.21 (s, 1 H) 7.28 (m, 1 H) 7.50 (m, 2 H) 7.73 (q, *J*=4.5 Hz, 1 H) 7.81 (s, 1 H) 8.36 (s, 1 H) 9.56 (br.s, 1 H); Mass Spectrum: *m/z* (M + H)⁺ 474.2, 476.2.

The 2-[4-(5-cyano-4-[(dimethylamino)methylene]amino)-2-methoxyphenoxy]piperidin-1-yl]-*N*-methylacetamide (7), used as the starting material was prepared as follows:

Step 1. Preparation of tert-butyl 4-(5-cyano-2-methoxyphenoxy)piperidine-1-carboxylate (2)

3-hydroxy-4-methoxybenzonitrile (1, 6.00g, 39.62mmole), *tert*-butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (16.6g, 59.44mmoles) (Chemical & Pharmaceutical Bulletin 2001, **49**(7), 822-829); and potassium carbonate (6.71g, 47.55mmoles) were suspended in isopropanol (78.98g) and the mixture was heated at reflux with stirring. Additional *tert*-butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (2.08g, 7.43mmoles) was added to push the reaction to completion. The mixture was then cooled and quenched by the addition of water (100.47g). Seeding with *tert*-butyl 4-(5-cyano-2-methoxyphenoxy)piperidine-1-carboxylate (2) followed by cooling to 0°C resulted in a crystalline product, which was isolated by filtration. The filter cake was washed with a mixture of water (8.86g) and isopropanol (6.97g), followed by water (23.64g) and then dried to give the title compound (10.75g, 80% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.39 (s, 9 H) 1.48 (m, 2 H) 1.88 (m, 2 H) 3.13 (m, 2 H) 3.67 (m, 2 H) 3.83 (s, 3 H) 4.56 (tt, *J*=8.1, 3.8 Hz, 1 H) 7.13 (d, *J*=8.4 Hz, 1 H) 7.42 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.51 (d, *J*=1.9 Hz, 1 H); Mass Spectrum: *m/z* (M + H)⁺ 333.1.

Step 2. Preparation of 4-methoxy-3-(piperidin-4-yloxy)benzonitrile (3)

Tert-butyl 4-(5-cyano-2-methoxyphenoxy)piperidine-1-carboxylate (2, 39.31g, 118.26mmoles) was suspended in ethanol (155.53g) and heated to 40°C. To this slurry was slowly added HCl (46.61g, 573.04mmoles). The mixture was heated to 60°C and held for 3 hours. The reaction mixture was cooled to 20°C and seed was charged initiating crystallisation. The resulting solid was isolated by filtration at 0°C, washed twice with

ethanol (62.21g) and then dried to give the title compound as the hydrochloride salt (29.84g, 77% yield); ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.84 (m, 2 H) 2.09 (m, 2 H) 3.02 (ddd, $J=12.7, 8.9, 3.4$ Hz, 2 H) 3.20 (m, 2 H) 3.84 (s, 3 H) 4.63 (tt, $J=7.7, 3.6$ Hz, 1 H) 7.15 (d, $J=8.5$ Hz, 1 H) 7.45 (dd, $J=8.5, 1.9$ Hz, 1 H) 7.56 (d, $J=1.9$ Hz, 1 H) 9.16 (br. s, 2 H); Mass Spectrum: m/z (M + H) $^+$ 233.2.

Step 3. Preparation of 2-[4-(5-cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (4)

4-Methoxy-3-(piperidin-4-yloxy)benzonitrile hydrochloride salt (**3**, 28.36g, 95.82mmoles), 2-chloro-N-methylacetamide (12.37g, 114.98mmoles) and potassium carbonate (33.11g, 239.55mmoles) were suspended in acetonitrile (161.36g). The reaction mixture was heated at reflux for 3 hours. The reaction mixture was cooled to 20°C and water (386.26g) was charged. The reaction was heated to 75°C and the volume reduced by distillation. Upon cooling crystallisation occurred. The resulting solid was isolated by filtration, washed twice with water (77.25g and 128.75g) and then dried to give the title compound (27.95g, 94% yield); ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.68 (m, 2 H) 1.91 (m, 2 H) 2.29 (m, 2 H) 2.61 (d, $J=4.7$ Hz, 3 H) 2.67 (m, 2 H) 2.88 (s, 2 H) 3.83 (s, 3 H) 4.41 (tt, $J=8.3, 4.0$ Hz, 1 H) 7.11 (d, $J=8.4$ Hz, 1 H) 7.40 (dd, $J=8.4, 1.9$ Hz, 1 H) 7.47 (d, $J=1.9$ Hz, 1 H) 7.68 (q, $J=4.7$ Hz, 1 H); Mass Spectrum: m/z (M + H) $^+$ 304.2.

Step 4. Preparation of 2-[4-(5-cyano-2-methoxy-4-nitrophenoxy)piperidin-1-yl]-N-methylacetamide (5)

2-[4-(5-Cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (**4**, 8.78g, 26.11mmoles) was suspended in acetic acid (22.82g, 364.87mmoles) and the resulting reaction mixture cooled to 5°C. To this was added sulfuric acid (23.64g, 234.95mmoles) maintaining the reaction temperature below 30°C. To the resulting solution was added nitric acid (2.40g, 26.63mmoles). The reaction mixture was then heated to 35°C and held for 3 hours. Additional nitric acid (117 mg, 1.31 mmoles) and sulphuric acid (1.31g 13.1 mmoles) were charged and the reaction mixture was heated at 35°C for 30 minutes. The solution was cooled to 20°C and quenched with aqueous ammonia (92.45g 1.36 moles), resulting in an increase in temperature to 50°C. To the resulting slurry was added, propionitrile (61.58g 1.12 moles) and water (19g). The reaction mixture was heated to 80°C resulting in a clear solution, which upon settling gave two layers. The bottom layer was removed. The reaction mixture was cooled to 20°C resulting in a thick slurry. The solid was isolated by filtration, washed with propionitrile (6.16g 112.0 mmoles) and dried

to afford the title compound (7.44g, 82% yield); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.72 (m, 2 H) 1.97 (m, 2 H) 2.35 (m, 2 H) 2.61 (d, $J=4.7$ Hz, 3 H) 2.66 (m, 2 H) 2.90 (s, 2 H) 3.96 (s, 3 H) 4.73 (tt, $J=8.4, 4.0$ Hz, 1 H) 7.71 (q, $J=4.7$ Hz, 1 H) 7.82 (s, 1 H) 7.86 (s, 1 H). Mass Spectrum: m/z ($M + H$) $^+$ 349.2

5 **Step 5. Preparation of 2-[4-(4-amino-5-cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (6)**

2-[4-(5-Cyano-2-methoxy-4-nitrophenoxy)piperidin-1-yl]-N-methylacetamide (**5**, 7.42g, 19.38mmoles) was suspended in water (44.52g) and methanol (5.35g). To this was added sodium dithionite (11.91g, 58.15mmoles) and the resulting reaction mixture was heated to 60°C. To the reaction mixture was added hydrochloric acid (46.98g, 463.89mmoles), resulting in a solution, which was held at 60°C for 3 hours. The reaction mixture was then allowed to cool to 20°C. Aqueous sodium hydroxide (15.51g 182.2mmoles) was charged followed by 2-methyltetrahydrofuran (58.0g). The reaction mixture was heated to 60°C, which upon settling gave two layers and the lower aqueous layer was discarded. The volume of the reaction mixture was reduced by vacuum distillation and methyl tert-butyl ether (18.54g) was added to give a slurry which was cooled to 10°C. and then the solid was collected by filtration. The solid was washed with 2-methyltetrahydrofuran (5.8g) and dried to give the title compound (5.4g, 78% yield); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.62 (m, 2 H) 1.82 (m, 2 H) 2.20 (m, 2 H) 2.60 (d, $J=4.7$ Hz, 3 H) 2.65 (m, 2 H) 2.86 (s, 2 H) 3.72 (s, 3 H) 4.00 (tt, $J=8.3, 4.0$ Hz, 1 H) 5.66 (br. s, 2 H) 6.39 (s, 1 H) 6.94 (s, 1 H) 7.65 (q, $J=4.7$ Hz, 1 H) Mass Spectrum: m/z ($M + H$) $^+$ 319.2

15 **Step 6. Preparation of 2-[4-(5-cyano-4-[(dimethylamino)methylene]amino)-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (7)**

25 2-[4-(4-Amino-5-cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (**6**, 18.21g, 52.05mmoles) was suspended in 2-methyltetrahydrofuran (99.62g). To this was added acetic acid (162.79mg), and N,N-dimethylformamide dimethyl acetal (DMA) (8.63g, 70.27mmoles) and the resulting reaction mixture was heated at 76°C for 16hrs. Additional N,N-dimethylformamide dimethyl acetal (639.41mg, 5.20mmoles) was added to the reaction mixture to ensure the reaction completed. The reaction mixture was cooled to 30°C during which time crystallisation occurred. The resulting solid was isolated by filtration, washed with 2-methyltetrahydrofuran (14.23g) and dried to afford the title compound (19.53g, 97% yield); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.65 (m, 2 H) 1.86

(m, 2 H) 2.24 (m, 2 H) 2.60 (d, $J=4.7$ Hz, 3 H) 2.66 (m, 2 H) 2.87 (s, 2 H) 2.95 (s, 3 H) 3.04 (s, 3 H) 3.81 (s, 3 H) 4.19 (tt, $J=8.2, 3.8$ Hz, 1 H) 6.72 (s, 1 H) 7.15 (s, 1 H) 7.67 (q, $J=4.7$ Hz, 1 H) 7.90 (s, 1 H); Mass Spectrum: m/z (M + H)⁺ 374.2.

5 Example D

Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A

A solution of fumaric acid (2.7 g, 23.22mmol) in methanol (95 ml) was added to a
10 mixture of 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (5.62g at 89% w/w, 10.55 mmol) in isopropanol (100 ml) maintaining the temperature >65°C. The mixture was heated at reflux for one hour before clarification. The reaction mixture was cooled to 30°C over 90 minutes and held for 30 minutes to establish crystallisation. The reaction was
15 cooled to 0°C over 2 hours and held for 1 hour before isolation by filtration. The filter cake was washed twice with cold isopropanol (2 x 10 ml) and dried *in vacuo* at 50°C to give the title compound as a white solid (5.84 g, 78%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70
20 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example E

Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A

A solution of fumaric acid (1.4 kg, 12.1mol) in methanol (26.6 kg) was added to a mixture of 2-[4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (2.93 kg, 84.8% w/w, 5.24mol) in isopropanol (39 kg) maintaining the temperature >65°C. A line wash of
30 methanol (3.6 kg) was charged. The mixture was heated at reflux for one hour before clarification, followed by a line wash of methanol (7 kg). The reaction mixture was distilled at atmospheric pressure to remove 47 kg of distillates. Isopropanol (15.8 kg was added and the reaction mixture distilled to remove 15.6 kg of distillates. Crystallisation

occurred during the distillation. Isopropanol (21 kg) was added and the reaction cooled to 0°C over 8 hours and held for 1 hour before isolation by filtration. The filter cake was washed with cold 50:50 isopropanol:MeOH (4kg) followed by cold isopropanol (4kg) and dried *in vacuo* at 50°C to give the title compound as a white solid (3.64 kg, 98%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example F

Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl }oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A

2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl }oxy)piperidin-1-yl]-N-methylacetamide (Compound **(I)**) (60.19 g at 88% w/w, 111.8 mmol) was dissolved in ethyl acetate (1550 ml). The solution was clarified by filtration and the filter washed with ethyl acetate (53 ml). The solution was cooled to 40°C. A clarified solution of fumaric acid (26.60 g, 257.0mmol) in isopropanol (408 ml) was then added over 1 hour. The filter used to clarify the fumaric acid solution was then washed with isopropanol (37 ml). After holding for 1 hour at 40°C the reaction was cooled to 20°C over 1 hour. The reaction mixture was held for 13.5 hours before isolating the product by filtration. The filter cake was washed twice with ethyl acetate (82 ml) : isopropanol (24 ml) and then dried *in vacuo* at 40°C to give the title compound as a white solid (72.32 g, 90%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example G**Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A**

2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (2.75 g at assumed 100% w/w, 5.80 mmol) was dissolved in ethyl acetate (94 ml) and isopropanol (14 ml). The solution was distilled such that 25.2 ml of distillates were collected. The solution was cooled to 40°C. A clarified solution of fumaric acid (1.38 g, 11.90 mmol) in isopropanol (21 ml) was then added over 1 hour. Compound (I) difumarate Form A seed was added (3.7 mg, 5.3 µmol). The filter used to clarify the fumaric acid solution was then washed with isopropanol (2 ml). After holding for 1 hour at 40°C the reaction was cooled to 20°C over 2 hours. The reaction mixture was held for 15 hours before isolating the product by filtration. The filter cake was washed twice with ethyl acetate (4.3 ml): isopropanol (1.2 ml) and then dried *in vacuo* at 40°C to give the title compound as a white solid (72.32 g, 90%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example H**Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A**

2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (1g, 1.86mmoles) and fumaric acid (0.44g, 3.81mmoles) were suspended in water (4.4g) and heated to 85°C. The reaction mixture was cooled to 60°C at 1°C/minute and Compound (I) Form A seed was added when the temperature was 77°C. The resulting solid was isolated by filtration, washed twice with acetone (0.70g per wash) and dried in a vacuum oven at 40°C to afford the title compound (0.89g, 68% yield), ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.84 (m, 2 H) 2.08 (m, 2 H) 2.55 (m, 2 H) 2.63 (d, J=4.7 Hz, 3 H) 2.86 (m, 2 H) 3.12 (s, 2 H) 3.93 (s, 3 H)

4.59 (tt, J=7.8, 3.7 Hz, 1 H) 6.62 (s, 4 H) 7.21 (s, 1 H) 7.27 (td, J=8.1, 1.3 Hz, 1 H) 7.49 (m, 2 H) 7.86 (m, 2 H) 8.36 (s, 1 H) 9.63 (br. s., 1 H).

Compound **(I)** difumarate Form A is a free flowing powder. X-ray powder diffraction of Compound **(I)** difumarate (Figure 5) indicates that the material is crystalline. The X-Ray Powder Diffraction analysis was carried out using a Siemens D5000 powder X-ray diffractometer fitted with a scintillation detector; the X-Ray source was Cu K α , giving a wavelength of 1.54Å; data were collected over the range 2-theta 2 - 40°, in increments of 2-theta 0.02°, with 1 second per increment and was categorised into the categories identified in the table below:

% Relative Intensity*	Definition
25 – 100	vs (very strong)
10 – 25	s (strong)
3 – 10	m (medium)
1 – 3	w (weak)

* The relative intensities are derived from diffractograms measured with fixed slits.

Persons skilled in the art of X-ray powder diffraction will realise that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values (see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996, for further information)

Tablet formulation of Compound (I)

Compound **(I)** tablets may be manufactured using conventional wet granulation, compression and film coating processes as illustrated in the example below in which Compound **(I)** difumarate was used. The powdered ingredients are charged to a mixer and mixed to produce a uniform distribution of drug substance. A binder solution is prepared and added to the powders with further mixing until a suitable wet mass is formed. The wet mass is passed through a screen and the resultant granules dried to an appropriate moisture

content. The dried granules are passed through an appropriately sized screen and blended with magnesium stearate before compressing into tablet cores using conventional tableting equipment. The compressed cores are coated with an aqueous suspension of film coating components using a conventional perforated drum coater.

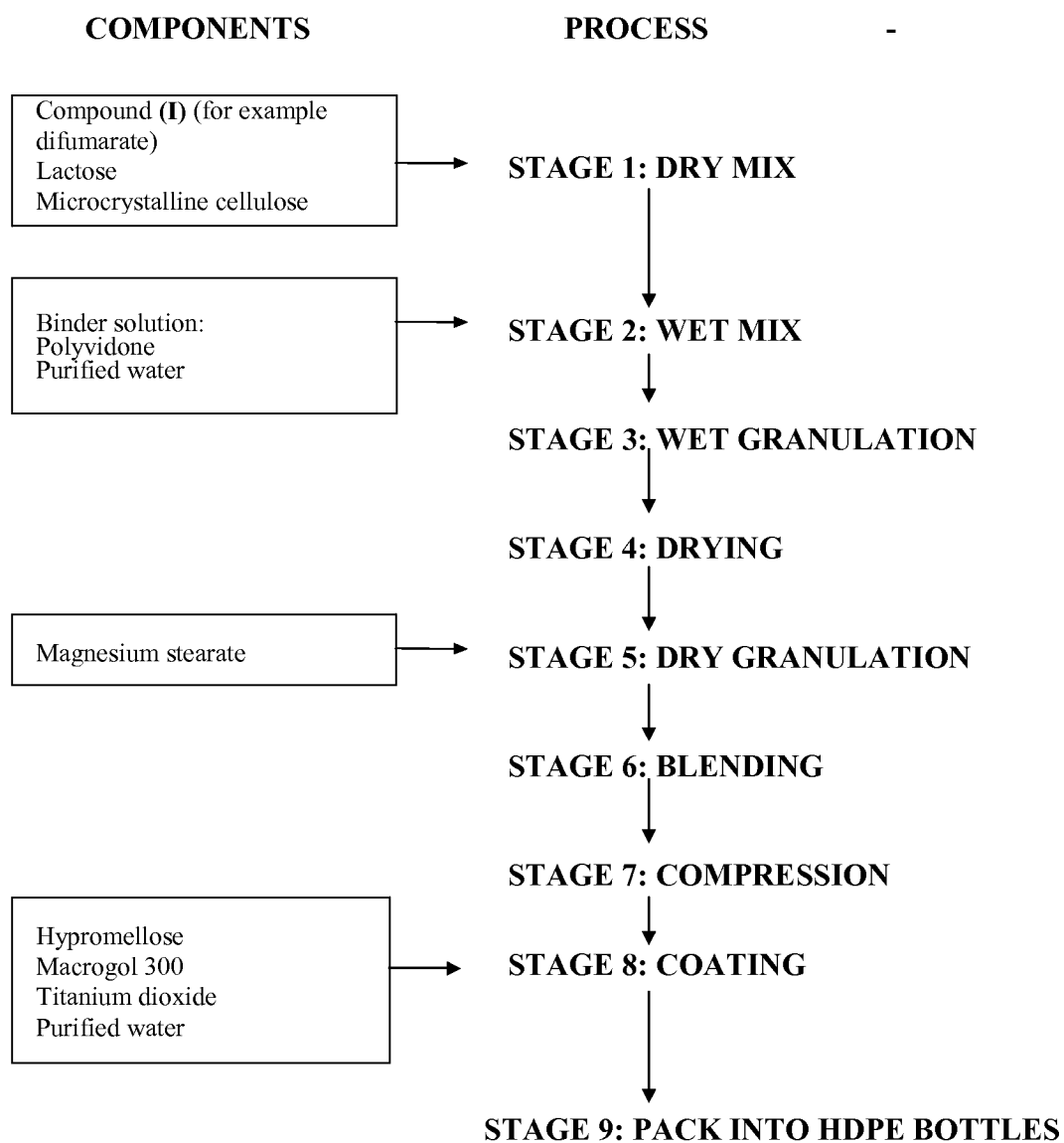
Film-coated tablets containing Compound **(I)** Difumarate Form A equivalent to 2.5, 10, 40 and 100 mg of compound **(I)** prepared as described above are illustrated in the table below:

Tablet strength ¹	2.5 mg	10 mg	40 mg	100mg
Ingredient	g/batch	g/batch	g/batch	g/batch
Tablet core				
Compound (I) Difumarate Form A ²	37.25	149.0	448.1	448.1
Lactose (450 mesh)	782.75	671.0	371.9	371.9
Microcrystalline cellulose (PH101)	100.0	100.0	100.0	100.0
Crospovidone	50.0	50.0	50.0	50.0
Polyvidone	20.0	20.0	20.0	20.0
Magnesium stearate	10.0	10.0	10.0	10.0
Core tablet weight	100 mg	100 mg	133 mg	333 mg
Tablet coating				
Opadry White (03B28460)	23.0	23.0	23.3	23.0
Hypromellose ³	15.0	15.0	15.0	15.0
Titanium dioxide ³	5.0	5.0	5.3	5.0
Macrogol 300 ³	3.0	3.0	3.0	3.0
Purified water ⁴	177.0	177.0	176.7	177.0
Nominal coated tablet weight	102.1 mg	102.1 mg	136.1 mg	140.6 mg

5

1. Tablet strengths refer to the equivalent amount of Compound **(I)** free base present in the tablet.
2. The Compound **(I)** difumarate was micronised prior to formulation to give an average particle size of less than about 5µm.
3. The hypromellose, macrogol 300 and titanium dioxide are included as Opadry White (03B28460), supplied by Colorcon.
4. Purified water is used as the solvent/carrier fluid during film-coating and is removed during the coating process.

A suitable manufacturing process is outlined below:



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.

- 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.

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:

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) and plasma estradiol levels in the laboratory specified postmenopausal range
 - bilateral oophorectomy
2. Histologically confirmed metastatic ER and/or PR positive adenocarcinoma of the breast as determined in local laboratories at each investigator site
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.
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/mm³ and platelets > 100 000/mm³
 - 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 marked progression free survival (PFS) 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.

5 **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
10 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;
15 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
20 illustrated in Figure 4.

Conclusions:

Anastrozole plus gefitinib was well tolerated and associated with a marked advantage in time to progression compared to anastrozole plus placebo in postmenopausal women with newly diagnosed hormone receptor positive metastatic breast cancer.

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

A Phase II Randomised, Double-Blind, Stratified, Multi-Centre Trial Comparing the 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:

- 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:

- 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
- 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
- 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 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, response, and safety variables
- 5 • 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
- To obtain tumour tissue for biologic studies in this patient population

10 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
15 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
 - 20 • 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,
 - 25 • 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 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 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.

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 - 8.9 months). The interaction test p-value was 0.13.

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

Preclinical Data Comparing Compound (I) and Gefitinib

The activity of Compound (I) was compared to that of gefitinib to assess their ability to:

a) inhibit the activation (phosphorylation) of EGFR, ErbB2 and ErbB3 in ligand-stimulated cells; and

b) inhibit the basal and ligand-stimulated proliferation of MCF-7 cells.

a) Comparison of Compound (I) With Gefitinib in Ligand Driven Assays**Methods:**

KB cells and MCF-7 cells were obtained from the American Type Culture Collection (ATCC) and routinely cultured in RPMI 1640 (Phenol red free) + 10% Foetal Bovine Serum + 2mM L-Glutamine.

Treatment and Lysis of Cells:

KB cells were seeded at 5000cells/well and MCF-7 cells at 4000cells/well in 96 well plates in RPMI 1640 media containing 10% FBS. Cells were incubated for 72 hours before replacing the media with serum-free RPMI 1640 media for 24 hrs. Cells were then treated with Compound (I) or gefitinib for 90 mins at concentrations ranging from 0-10 μ M. Immediately before cell lysis, MCF-7 and KB cells were incubated for 5 minutes with ligand (heregulin ("HRG") for the MCF-7 cells and epidermal growth factor ("EGF") for the KB cells) at concentrations required to increase receptor phosphorylation to 90% of max (ED₉₀) to allow inter-assay comparison.

Measurement of p-EGFR, p-ErbB2 and p-ErbB3:

The p-EGFR status of KB cells was measured using the Human phospho-EGFR Duoset ELISA kit (R&D systems, DYC1095). The p-ErbB2 and p-ErbB3 content of MCF-7 cells were measured using the Human phospho-ErbB2 Duoset ELISA kit (R&D systems, DYC1768) and Human phospho-ErbB3 Duoset ELISA kit (R&D systems, DYC1769) respectively. The kits measured whole cell tyrosine phosphorylation of EGFR, ErbB2 or ErbB3. Assays were performed according to the manufacturers instructions, with 50 μ l lysate added per well.

Results:

The results are summarised in Table 1

Table 1: Compound activity against p-EGFR (in KB cells) and p-ErbB2 and p-ErbB3 (in MCF-7 cells)

Compound	p-EGFR Geo Mean IC ₅₀ (95% CIR*)	p-ErbB2 Geo Mean IC ₅₀ (95% CIR)	p-ErbB3 Geo Mean IC ₅₀ (95% CIR)
Compound (I)	0.004 (1.377)	0.003 (1.817)	0.004 (1.89)
Gefitinib	0.011 (1.601)	0.024 (2.827)	0.095 (2.18)

* Confidence Interval Ratio

Table 1 shows that Compound (I) is a statistically significantly more potent inhibitor of phospho-EGFR, phospho-ErbB2 and phospho-ErbB3 in these cells than gefitinib.

b) Compound (I) compared to gefitinib in basal or HRG-stimulated MCF-7 cell proliferation assay

Methods:

MCF-7 cells were routinely cultured in DMEM (Phenol red free) + 10% Foetal Bovine Serum + 2mM L-Glutamine.

Cells were seeded at 4000 cells per well in 96 well plates in DMEM media containing 1% charcoal/dextran-treated FBS and 2mM glutamine and allowed to settle for 4 hours prior to treatment with Compound (I) or gefitinib at concentrations ranging from 0-3µM and 0-10µg/ml respectively. Two hours following treatment, cells were incubated with 10ng/ml HRG, a concentration required to increase MCF-7 cell proliferation to 90% of max (ED₉₀). Basal wells were unstimulated with ligand. After incubation for 4 days, cell viability was assessed using a 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay.

Prior to IC₅₀ determination of HRG-stimulated compound-treated cells, mean basal growth at 96 hours was subtracted from each of the readouts so that proliferation driven through HRG-signalling was assessed. Basal IC₅₀ values are expressed as GI₅₀ i.e. the day 0 plate cell number (baseline reading) was subtracted from the readout at 96 hours later.

Results:

The results are summarised in Tables 2 and 3.

5 **Table 2: HRG-stimulated proliferation IC₅₀ value**

Compound	Geo Mean IC ₅₀	95% CIR
Compound (I)	0.061 μM	2.421
Gefitinib	0.386 μM	5.263

Table 3 Basal proliferation GI₅₀ values

Compound	Geo Mean GI ₅₀	95% CIR
Compound (I)	1.094 μM	4.423
Gefitinib	> 3 μM	

In the KB cells, stimulation with EGF, which specifically binds to EGFR, causes phosphorylation and therefore activation of this receptor. Similarly in the MCF-7 cells HRG, which binds specifically to ErbB3 causes it to form heterodimers with ErbB2 and both receptors become phosphorylated and activated. Tables 2 and 3 show that Compound (I) is a more potent inhibitor of HRG-stimulated MCF-7 proliferation than gefitinib. These effects on proliferation are believed to be due to the activities of these compounds on ErbB2/ErbB3 heterodimers, with Compound (I) being a much more potent inhibitor of this heterodimer than the more EGFR-selective compound gefitinib.

The MCF-7 basal assays represent a situation where there no increased stimulation or activation of erbB2/erbB3 heterodimerisation. Table 3 shows that even in such conditions Compound (I) is a more potent inhibitor of MCF-7 proliferation than gefitinib.

20 **Conclusions**

We have shown that in a phase II clinical trials in post menopausal women with hormone receptor positive metastatic breast cancer, the combined use of the EGFR tyrosine kinase inhibitor gefitinib with the aromatase inhibitor anastrozole or tamoxifen provides a surprising improvement in time to progression, despite the fact that the combination appears to reduce the objective response rate compared to anastrozole alone.

Patients that had not received a prior endocrine therapy such as tamoxifen appear to benefit from a further improvement in median progression free survival.

The pre-clinical data described above illustrates that Compound **(I)** is a superior erbB tyrosine kinase inhibitor compared to gefitinib and would therefore be expected to
5 provide a beneficial anti-cancer effect when used in combination with an endocrine agent suitable for use in the treatment of breast cancer (for example an aromatase inhibitor such as anastrozole, letrozole or exemestane) in the treatment of cancer, particularly hormone sensitive breast cancer such as estrogen receptor positive breast cancer.

Claims

1. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable
5 salt thereof, and an endocrine agent suitable for use in the treatment of breast cancer.
2. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable
salt thereof, and a selective estrogen receptor modulator.
10
3. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable
salt thereof, and an aromatase inhibitor.
- 15 4. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable
salt thereof, and an estrogen receptor down-regulator.
5. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-
20 methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable
salt thereof, and an LHRH agonist.
6. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-
methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable
25 salt thereof, and a progesterone receptor antagonist.
7. A combination as claimed in claim 2 wherein the selective estrogen receptor
modulator is tamoxifen.
- 30 8. A combination as claimed in claim 3 wherein the aromatase inhibitor is
anastrozole.

9. A combination as claimed in claim 3 wherein the aromatase inhibitor is exemestane.
10. A combination as claimed in claim 3 wherein the aromatase inhibitor is letrozole.
- 5 11. A combination as claimed in claim 4 wherein the estrogen receptor down-regulator is fulvestrant.
12. A combination as claimed in claim 5 wherein the LHRH agonist is goserelin or a
10 pharmaceutically acceptable salt thereof.
13. A combination as claimed in any one of claims 1-12, wherein the 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl
]oxy}quinazoline, or a pharmaceutically acceptable salt thereof, is 4-(3-chloro-2-
15 fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl
]oxy}quinazoline difumarate.
14. A combination as claimed in any one of claims 1-13 for use as a medicament.
- 20 15. A pharmaceutical composition comprising a combination as claimed in any one of claims 1-12 in association with a pharmaceutically acceptable diluent or carrier.
16. A method of treating 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
25 combination as claimed in any one of claims 1-12.
17. A method as claimed in claim 16 wherein the cancer is breast cancer.
18. A method according to claim 16 wherein the cancer is estrogen receptor positive
30 breast cancer.

19. A method according as claimed in any one of claims 16, 17 or 18 wherein the warm-blooded animal has not been treated with an endocrine agent (for example tamoxifen) prior to administration of the combination.

5 20. A method as claimed in any one of claims 16 to 19 wherein the cancer is in a metastatic state.

21. A method as claimed in any one of claims 16 to 19 wherein the cancer is in a non-metastatic state.

10

22. A method of treating estrogen receptor 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 combination as claimed in any one of claims 1-12 as an adjuvant therapy.

15

23. A method according to claim 22 wherein the warm-blooded animal is post-menopausal.

20

24. A method according to claim 22 or 23 wherein the warm-blooded animal has not been treated with an endocrine agent (for example tamoxifen) prior to administering the combination.

25

25. A method for the treatment of 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 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline, or a pharmaceutically acceptable salt thereof in combination with an effective amount of an aromatase inhibitor such as anastrozole, wherein said animal has not previously been treated with an endocrine therapy.

30

26. The method according to claim 25 wherein the breast cancer is metastatic.

27. The method according to claim 26 wherein the combination is an adjuvant treatment of the breast cancer.

28. The method according to any one of claims 25 to 27 wherein the warm-blooded
5 animal has not previously been treated with an endocrine therapy selected from a selective estrogen receptor modulator such as tamoxifen, or an aromatase inhibitor such as anastrozole.

29. The method according to any one of claims 25 to 27 wherein the 4-(3-chloro-2-
10 fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl
]oxy}quinazoline, or a pharmaceutically acceptable salt thereof is 4-(3-chloro-2-
fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl
]oxy}quinazoline difumarate.

15 30. A pharmaceutical composition which comprises a combination as claimed in any one of claims 1-13 in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

31. A composition as claimed in claim 30 wherein the cancer is estrogen receptor
20 positive breast cancer.

32. A composition as claimed in either claim 30 or 31 wherein the cancer is in a metastatic state.

25 33. A composition as claimed in either claim 30 or 31 wherein the cancer is in a non-metastatic state.

34. A composition as claimed in claim 30 for use in the treatment of estrogen receptor positive breast cancer in a patient that has not received prior endocrine therapy (for
30 example tamoxifen).

35. Use of a combination as claimed in any one of claims 1-13 in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

36. The use as claimed in claim 35 wherein the cancer is estrogen receptor positive breast cancer.

5 37. The use as claimed in either claim 35 or 36 wherein the cancer is in a metastatic state.

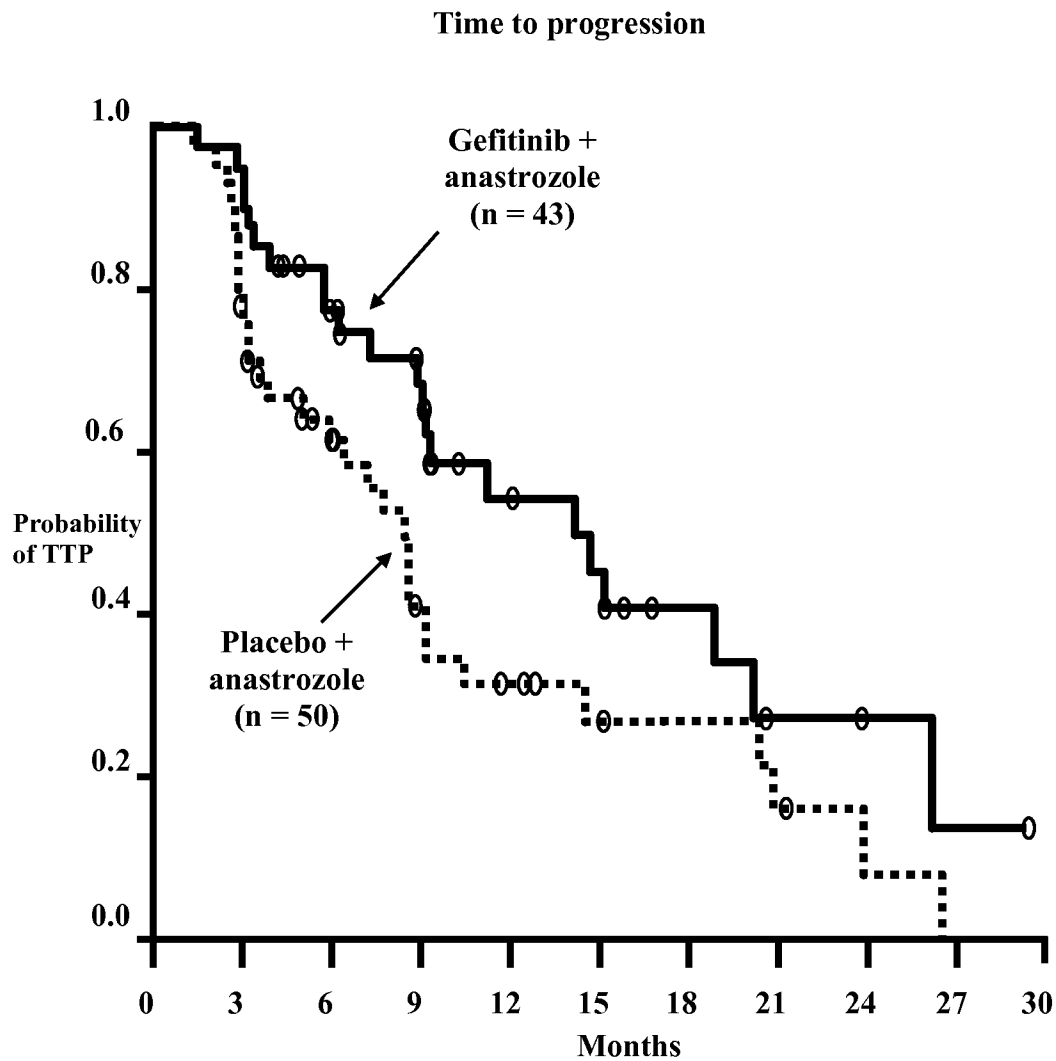
38. The use as claimed in either claim 35 or 36 wherein the cancer is in a non-metastatic state.

10

39. The use of a combination as claimed in any one of claims 1-13 in the manufacture of a medicament for use in the treatment of estrogen receptor positive breast cancer, in a warm-blooded animal, such as man that has not been received prior endocrine therapy (for example tamoxifen).

15

40. The use of a combination comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-
{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically
acceptable salt thereof and an aromatase inhibitor, in the manufacture of a medicament for
the treatment of a warm-blooded animal, such as man, which has been diagnosed with non-
20 metastatic estrogen and/or progesterone positive breast cancer and wherein said animal has
not previously been treated with an endocrine therapy.



At risk:

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

Figure 1

Fig.2.

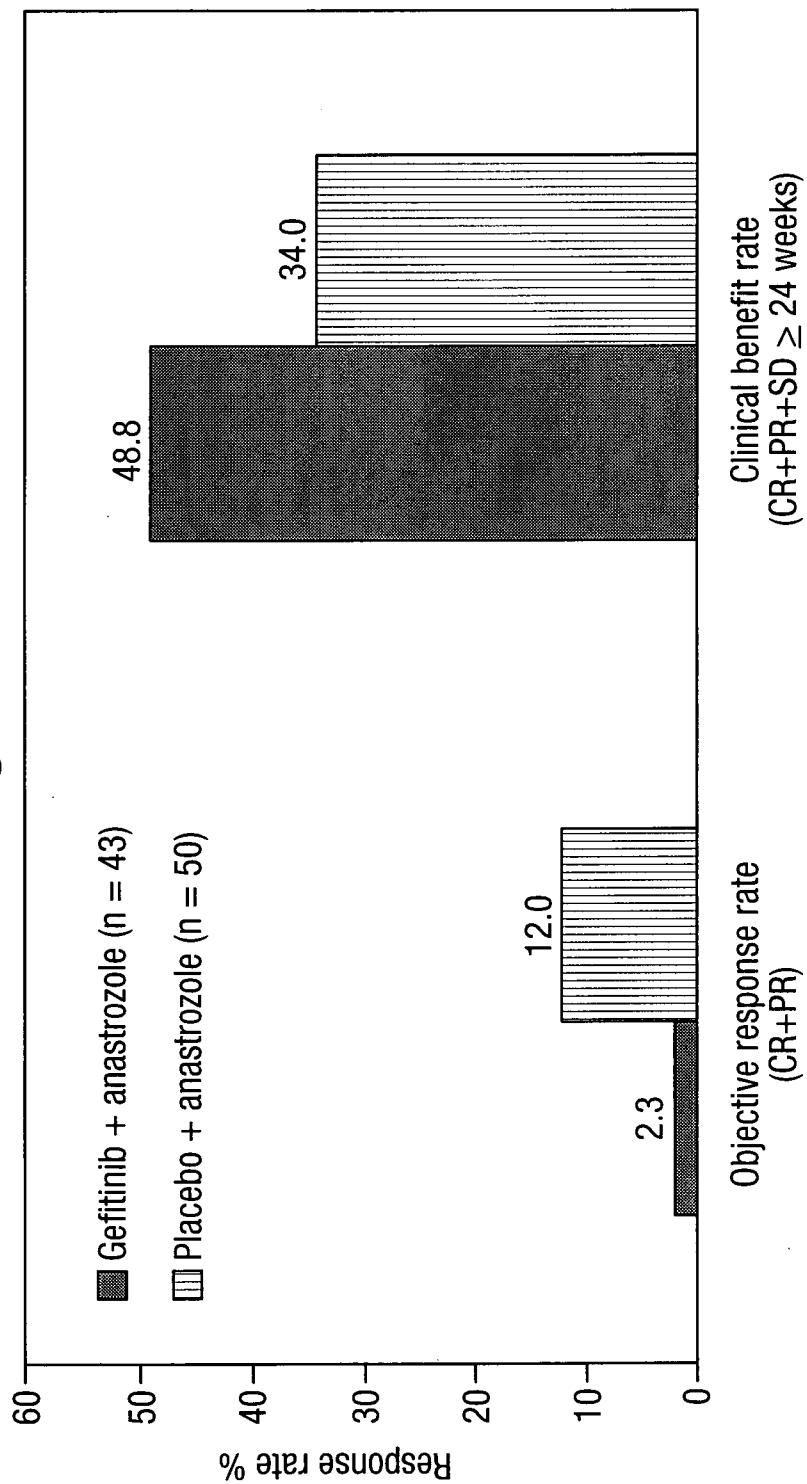


Fig.3.

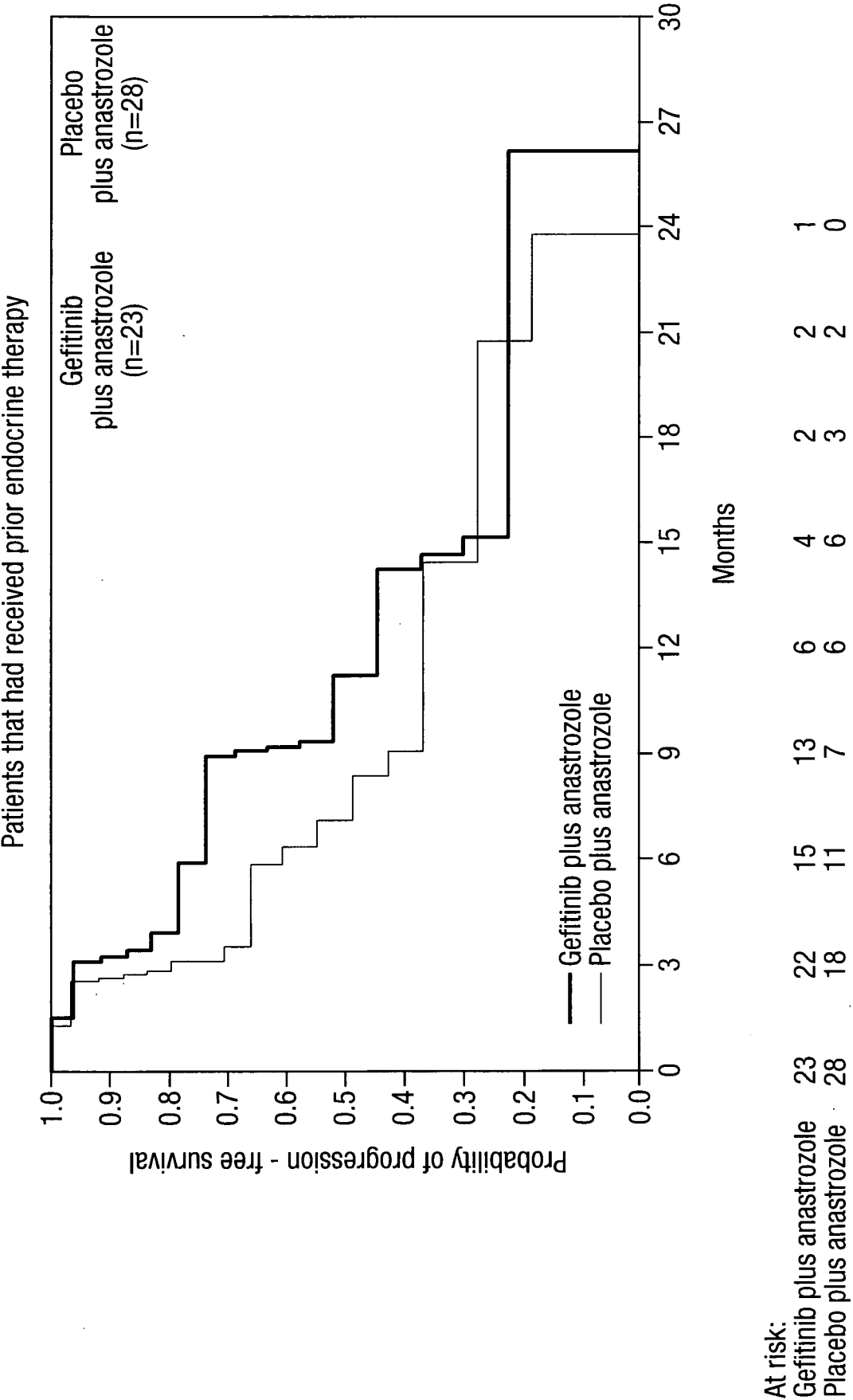
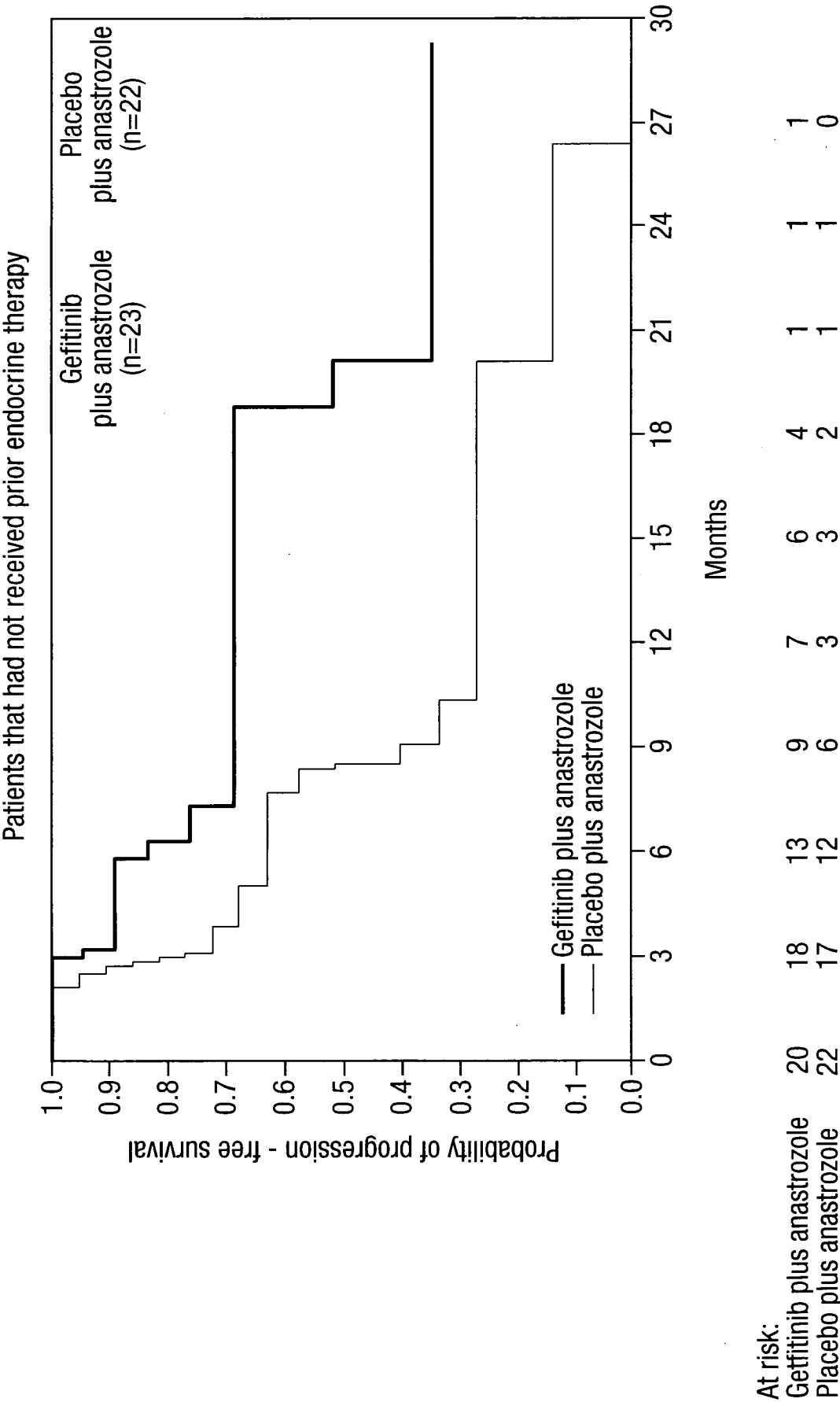
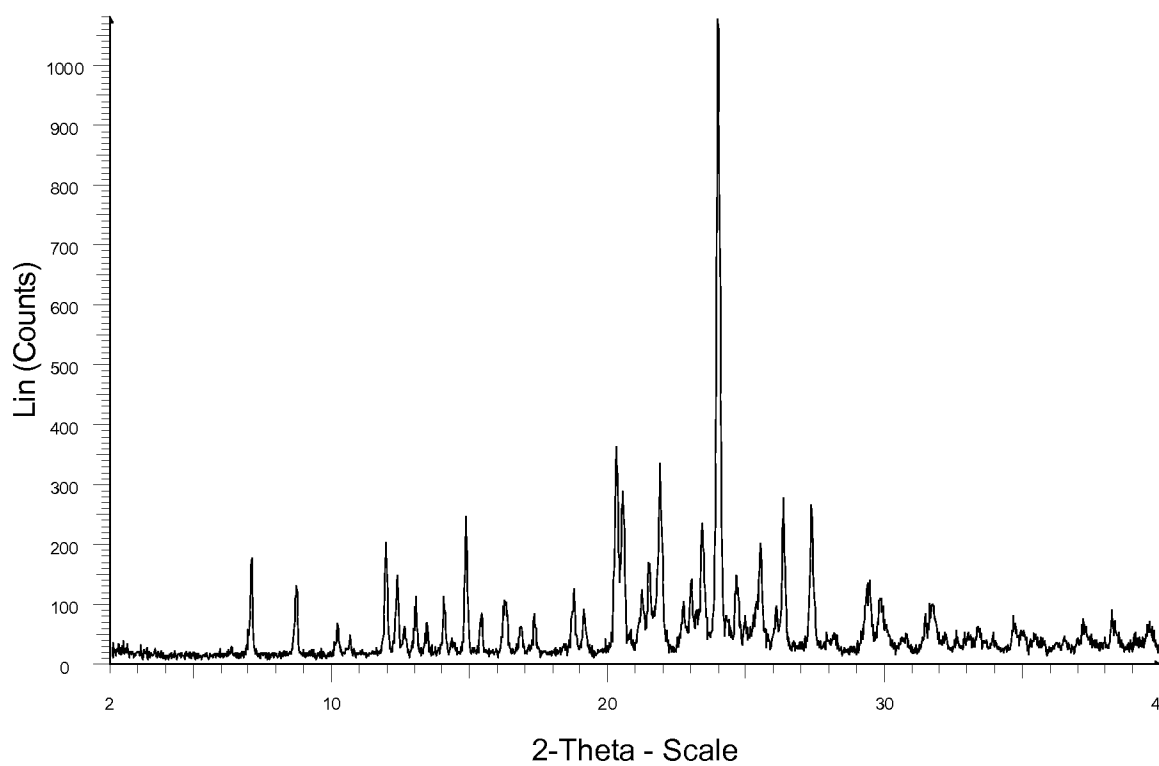


Fig.4.



Powder X-ray diffraction pattern of Compound (I) difumarate Form A

**Figure 5**

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050494

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/028469 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BRADBURY ROBERT HUGH [GB] 31 March 2005 (2005-03-31) cited in the application the whole document example 1 page 53, line 6 - page 56, line 27 page 54, line 29 - line 32 page 55, line 11 - line 17	1-40
X	WO 03/082831 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BRADBURY ROBERT HUGH [GB] 9 October 2003 (2003-10-09) the whole document example 11 page 96, line 27 - line 30 page 97, line 8 - line 14 page 98, line 23 - line 25 page 96, line 3 - line 23	1-40

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

27 August 2009

Date of mailing of the international search report

03/09/2009

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Economou, Dimitrios

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2009/050494

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