Abstract:

A combination, comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, and a Src kinase inhibitor is described.

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The present invention relates to combinations comprising 7V-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, hereafter "Compound (I)", and a Src Family Kinase (hereafter Src kinase) inhibitor.

These combinations are 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, in particular prostate cancer.

Cancer affects an estimated 10 million people worldwide. This figure includes incidence, prevalence and mortality. More than 4.4 million cancer cases are reported from Asia, including 2.5 million cases from Eastern Asia, which has the highest rate of incidence in the world. By comparison, Europe has 2.8 million cases, North America 1.4 million cases, and Africa 627,000 cases.

In the UK and US, for example, more than one in three people will develop cancer at some point in their life. Cancer mortality in the U.S. is estimated to account for about 600,000 a year, about one in every four deaths, second only to heart disease in percent of all deaths, and second to accidents as a cause of death of children 1-14 years of age. The estimated cancer incidence in the U.S. is now about 1,380,000 new cases annually, exclusive of about 900,000 cases of non-melanotic (basal and squamous cell) skin cancer.

Cancer is also a major cause of morbidity in the UK with nearly 260,000 new cases (excluding non-melanoma skin cancer) registered in 1997. Cancer is a disease that affects mainly older people, with 65% of cases occurring in those over 65. Since the average life expectancy in the UK has almost doubled since the mid nineteenth century, the population at risk of cancer has grown. Death rates from other causes of death, such as heart disease, have fallen in recent years while deaths from cancer have remained relatively stable. The result is that 1 in 3 people will be diagnosed with cancer during their lifetime and 1 in 4 people will die from cancer. In people under the age of 75, deaths from cancer outnumber deaths from diseases of the circulatory system, including ischaemic heart disease and stroke. In 2000, there were 151,200 deaths from cancer. Over one fifth (22 per cent) of
these were from lung cancer, and a quarter (26 per cent) from cancers of the large bowel, breast and prostate.

Worldwide, the incidence and mortality rates of certain types of cancer (of stomach, breast, prostate, skin, and so on) have wide geographical differences which are attributed to racial, cultural, and especially environmental influences. There are over 200 different types of cancer but the four major types, lung, breast, prostate and colorectal, account for over half of all cases diagnosed in the UK and US. Prostate cancer is the fourth most common malignancy among men worldwide, with an estimated 400,000 new cases diagnosed annually, accounting for 3.9 percent of all new cancer cases.

Current options for treating cancers include surgical resection, external beam radiation therapy and / or systemic chemotherapy. These are partially successful in some forms of cancer, but are not successful in others. There is a clear need for new therapeutic treatments.

Recently, endothelin A receptor antagonists have been identified as potentially of value in the treatment of cancer (Cancer Research, 56, 663-668, February 15th, 1996 and Nature Medicine, Volume 1, Number 9, September 1999, 944-949).

The endothelins are a family of endogenous 21 amino acid peptides comprising three isoforms, endothelin-1, endothelin-2 and endothelin-3. The endothelins are formed by cleavage of the Trp^{21}-Val^{22} bond of their corresponding proendothelins by an endothelin converting enzyme. The endothelins are among the most potent vasoconstrictors known. They exhibit a wide range of other activities including stimulation of cell proliferation and mitogenesis, inhibition of apoptosis, extravasation and chemotaxis, and also interact with a number of other vasoactive agents.

The endothelins are released from a range of tissue and cell sources including vascular endothelium, vascular smooth muscle, kidney, liver, uterus, airways, intestine and leukocytes. Release can be stimulated by hypoxia, shear stress, physical injury and a wide range of hormones and cytokines. Elevated endothelin levels have been found in a number of disease states in man including cancers.

Src is the prototype of a family of non-receptor protein tyrosine kinases and was discovered as the transforming factor arising from avian Rous sarcoma virus (hence "Src"). Src activity is frequently dysregulated and increased in human cancers, leading to aberrant signal transduction linked to disease progression.
Src Family Kinases (SFK's), that include the ubiquitously expressed family members pp60^c-Src tyrosine kinase (c-Src), c-Yes and Fyn, are non receptor protein tyrosine kinases that play important roles in modulating intracellular signal transduction pathways in cells in response to a variety of both extracellular and intracellular stimuli.

It is known that in many cancer cell types and tissues, the activity of certain Src family members, in particular c-Src, but also c-Yes and others, is often dysregulated and increased, leading to aberrant signal transduction with consequent effects on the tumour cell phenotype and cancer progression. This is in contrast to the tightly regulated and generally low activity of SFK's in normal cells. It is known that some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright et al, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao et al, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy et al, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurgnko et al, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning et al, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski et al, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener et al, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer (Lutz et al, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8).

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens et al, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer et al, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic


As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

Therefore according to the present invention, there is provided a combination, comprising Compound (I), and a Src kinase inhibitor. The combination of Compound (I) and Src kinase inhibitor can have a particular benefit in the treatment of cancer.

Herein where the term "Src kinase inhibitor" is used it is to be understood that this refers to any chemical compound, or a pharmaceutically acceptable salt thereof, which inhibits one or more members of the Src Family Kinases, including, but not limited to c-Src, c-Yes and Fyn.

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

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.

Where cancer is referred to, particularly it refers to rhabdomyosarcoma, 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. More particularly it refers to prostate cancer. In
addition, more particularly it refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and/or breast cancer. In addition, more particularly it refers to SCLC. In addition, more particularly it refers to NSCLC. In addition, more particularly it refers to colorectal cancer. In addition, more particularly 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. In addition, more particularly it refers to metastatic hormone receptor positive breast cancer. Furthermore, more particularly 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 aspect of the invention, the cancer is not melanoma. In another embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces metastases to the bone. 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, the cancer is in a non-metastatic state.

Where the treatment of cancer is referred to particularly this is the treatment of cancerous tumours expressing endothelin A. This treatment is in terms of one or more of the extent of the response, the response rate, the time to disease progression and the survival rate. It is further expected that the combination use of Compound (I) and particular Src kinase inhibitors will have a beneficial effect in preventing the onset of cancer in warm-blooded animals, such as man.

Particular compounds, or pharmaceutically acceptable salts thereof possessing Src kinase inhibitor activity include:

- 4-(6-chloro-2,3-methylene dioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (Compound No. 73 within Example 14 of WO 01/94341 also know as code number AZD0530) or a pharmaceutically-acceptable salt thereof;
- 4-(6-chloro-2,3-methylene dioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline di-fumarate salt (see for example WO 2006/064217);
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-
ynylo-piperazin-1-yl)propoxy]quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-[3-(4-isobutyrylpiperazin-
1-yl)propoxy]-6-methoxyquinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-6-methoxy-7-[3-[4-(2,2,2-
trifluoroethyl)piperazin-1-yl]propoxy]quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-6-methoxy-7-[2-(4-prop-2-
ynylo-piperazin-1-yl)ethoxy]quinazoline,
• 7-[2-(4-acetyl-piperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy-pyrid-4-
ylamo)-5-tetrahydropyran-4-yloxy quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-[2-(3RS,4SR)-3,4-
methylenedioxy-pyrrolidin-1-yl]ethoxy]-5-tetrahydropyran-4-yloxy quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-[2-(4-prop-2-yloxy-
pyridin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxy quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-[3-(4-prop-2-
ynylo-piperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxy quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-(2-morpholinopropoxy)-5-
tetrahydropyran-4-yloxyquinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-(3-morpholinopropoxy)-5-
tetrahydropyran-4-yloxyquinazoline,
• 7-[2-(4-acetyl-piperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy-pyrid-4-
ylamo)-5-isopropoxyquinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-5-isopropoxy-7-(2-piperazin-
1-yloxy)quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-7-{2-[4-(2-
hydroxyethyl)piperazin-1-yl]ethoxy}-5-isopropoxyquinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-5-isopropoxy-7-(2-pyrrolidin-
1-yloxy)quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-pyrid-4-ylamino)-5-isopropoxy-7-(2-
piperidinoethoxy)quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-isopropoxy-7-(3-morpholinoethoxy)quinazoline,
• 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-isopropoxy-7-[(2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline, and
• 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline or a pharmaceutically-acceptable salt thereof; in particular a mesylate, tosylate or sulphate salt thereof;
• bosutinib or a pharmaceutically-acceptable salt thereof;
• dasatinib or a pharmaceutically-acceptable salt thereof;
• KX-Ol or a pharmaceutically-acceptable salt thereof; and
• XL-228 or a pharmaceutically-acceptable salt thereof.

It is to be understood that certain Src kinase inhibitors discussed herein, may have additional kinase inhibitory activity, for example they might inhibit breakpoint cluster region/ Abelson (BCR/ABL or AbI) kinase.

In one aspect the Src kinase inhibitor is selected from 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline di-fumarate salt.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline or a pharmaceutically-acceptable salt thereof.
In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-6-methoxy-7-\{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy\}quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-isopropoxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-(2-piperazin-1-ylethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.
In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-5-isoproxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-(2-piperidinoethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-(2-morpholinoethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-(3-morpholinepropoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isoproxy-7-{2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy} -5-isoproxyquinazoline or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from bosutinib or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from dasatinib or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from KX-O or a pharmaceutically-acceptable salt thereof.

In one aspect the Src kinase inhibitor is selected from XL-228 or a pharmaceutically-acceptable salt thereof.
Particular combinations of the present invention include:

- Compound (I) and 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline di-fumarate salt.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-acetylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.
- Compound (I) and 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.
• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 7-[2-(4-acetyl piperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-5-isopropoxyquinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-5-isopropoxy-7-(2-piperazin-1-ylethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-7-[2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy]-5-isopropoxyquinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-5-isopropoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-5-isopropoxy-7-(2-piperidinoethoxy)quinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline or a pharmaceutically-acceptable salt thereof.

• Compound (I) and 4-(5-chloro-2,3-methylenedioxy pyrid-4-ylamino)-5-isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline or a pharmaceutically-acceptable salt thereof.
Compound (I) and 4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-7-[2-[(2-dimethylaminoethyl)piperazin-1-yl]ethoxy]-5-isopropoxyquinazoline or a pharmaceutically-acceptable salt thereof.

Compound (I) and bosutinib or a pharmaceutically-acceptable salt thereof.

Compound (I) and dasatinib or a pharmaceutically-acceptable salt thereof.

Compound (I) and KX-O1 or a pharmaceutically-acceptable salt thereof.

Compound (I) and XL-228 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, fumaric acid, methanesulphonic acid and p-toluenesulphonic acid. Alternatively, the compounds may exist in zwitterionic form.

Compounds (I) exists in certain crystalline forms. In a particular aspect of the invention, Compound (I) exists in a crystalline form, referred to as Form 1 in the Cambridge crystallographic database. [N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide (ZD4054 Form 1). Acta Crystallographica, Section E: Structure Reports Online (2004), E60(10), ol817-ol819].

In another aspect the invention relates to a pharmaceutical composition as hereinabove defined in which Compound (I) is in a crystalline form.

In yet another aspect the invention relates to a pharmaceutical composition as hereinbefore defined comprising Compound (I) substantially as Form 1.

Substantially as Form 1 means that there is greater than 95% of Form 1 present. In particular there is greater than 96% Form 1. Particularly there is greater than 97% Form 1. In particular there is greater than 98% Form 1. Particularly there is greater than 99% Form 1. In particular there is greater than 99.5% Form 1. Particularly there is greater than 99.8% Form 1.

Therefore according to the present invention, there is provided a combination, comprising Compound (I) and a Src kinase inhibitor for use as a medicament.
According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I) and a Src kinase 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 acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a Src kinase inhibitor 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 a Src kinase inhibitor.

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

In addition the treatment of cancer also refers to the production of an anti-angiogenic effect in a warm blooded animal.

According to a further aspect of the present invention there is provided a kit comprising Compound (I) and a Src kinase inhibitor; optionally 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;

b) a Src kinase 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.

An example of a unit dosage form for Compound (I) might be a tablet for oral
formulation, see that described herein below. An example of a unit dosage form for a Src
kinase inhibitor might be a tablet for oral formulation.

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) a Src kinase 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 invention there is provided a pharmaceutical
composition which comprises Compound (I) and a Src kinase 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
comprises a Src kinase inhibitor in association with a pharmaceutically acceptable diluent
or carrier for use in the treatment of cancer.

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

For example Compound (I) or the Src inhibitor can be formulated as a tablet using
the following excipients:

    Compound (I);
    Lactose monohydrate or mannitol (filler);
    Croscarmellose sodium (disintegrant);
    Povidone (binder);
Magnesium stearate (lubricant);
Hypromellose (film coat component);
Polyethylene glycol 300 (film coat component); and
Titanium dioxide (film coat component).

Compound (I) can also be formulated as a tablet using the following excipients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablet core</strong></td>
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</tr>
<tr>
<td>Compound (I)</td>
<td>10.000</td>
</tr>
<tr>
<td>Mannitol</td>
<td>110.750</td>
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<tr>
<td>Microcrystalline cellulose</td>
<td>18.750</td>
</tr>
<tr>
<td>Croscarmellose Na</td>
<td>4.500</td>
</tr>
<tr>
<td>Povidone K29/32</td>
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<tr>
<td>Magnesium stearate</td>
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<tr>
<td>Core tablet weight</td>
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</tr>
<tr>
<td><strong>Tablet coating</strong></td>
<td></td>
</tr>
<tr>
<td>Hypromellose 2910</td>
<td>3.281</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>1.563</td>
</tr>
<tr>
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<td>Iron oxide red</td>
<td>0.014</td>
</tr>
<tr>
<td>Iron oxide black</td>
<td>0.004</td>
</tr>
</tbody>
</table>

According to a further aspect of the present invention there is provided a kit
comprising Compound (I) and a Src kinase inhibitor; optionally with instructions for use;
for use in the treatment of cancer.

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) a Src kinase 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;
for use in the treatment of cancer.
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) a Src kinase 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;

for use in the treatment of cancer.

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

According to a further aspect of the present invention there is provided a combination comprising Compound (I) and a Src kinase inhibitor for the treatment of cancer.

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 a Src kinase inhibitor 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.

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 2.5mg. 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 130 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. Particularly Compound (I) could be administered to a warm-blooded animal, at a unit dose of 10 mg per day. In another aspect of the invention, particularly Compound (I) could be administered to a warm-blooded animal, at a unit dose of 15 mg per day.
Src kinase 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 50 mg to about 200 mg, particularly 50mg to 125 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. In one aspect of the invention the Src kinase inhibitor is administered to a warm-blooded animal, at a unit dose of 175 mg per day.

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

**Legends to Figures**

Figure 1 - Effects of Compound (I) and 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline di-fumarate salt (AZD0530), alone, and in combination with each other on invasion of A673 rhabdomyosarcoma cells.

In all the figures significance levels are indicated by "p=", where p<0.05 was considered as significant.

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.

**Experimental**

The following study was carried out to demonstrate the effect of endothelin-1 (ET-1), Compound (I) and AZD0530 on invasion of rhabdomyosarcoma cells through a 3-dimensional (3-D) matrix gel in vitro.
Methodology

The human rhabdomyosarcoma cell line (Giard DJ et al J Nat Cancer Inst 1973;51:1417 and McKune BK Am J Pathol 1993;142:49) has been used for all in vitro experiments. The A673 rhabdomyosarcoma cell line was routinely cultured in Dulbecco's minimal essential medium (DMEM) (phenol red free) + 10% Foetal Calf Serum (FCS) + 1% glutamine. Cell culture media and FCS were obtained from Sigma. A673 cells were kept in a humidified atmosphere of 37°C at 5% CO₂.

For invasion assays, 3-D matrix gels were prepared in the upper chamber of a transwell insert as follows: BD Matrigel® (BD Biosciences Cat# 356237 Lot# 55996 - 11.2mg/ml) was thawed on ice in 4°C fridge overnight. Matrigel solution (80µl) was added to the upper chamber of each transwell above an 8µm pore-size polycarbonate filter (Costar 24-well insert, Corning Inc.) and incubated in a humidified atmosphere 37°C and 5% CO₂ for 90 min prior to cell attachment.

Using cell dissociation solution (Sigma), A673 cells were resuspended at a cell concentration of 2x10⁵ cells per ml in serum-free DMEM media + 1% glutamine and 100µl (2x10⁴ cells/ml) was added on top of the solidified Matrigel® plug set in the upper chamber of transwell insert. In the lower chamber of transwells; 750µl of serum-free DMEM media + 1% glutamine (basal control) or serum-free media supplemented with 100nM endothelin 1 (Sigma; Cat. No. #E7764) were added. For assessment of agents in test cells, an appropriate amount of cell suspension was aliquoted into sterile eppendorf tubes to which treatment compounds were added at the following concentrations; Compound (I) at a concentration of 1µM and AZD0530 at concentrations of 0.01, 0.1, 1; and 10µM. For assessment of combinations, Compound (I) with AZD0530, were added simultaneously at the following concentrations: Compound (I) at 1µM in combination with AZD0530 at 0.01, 0.1, 1, and 10µM. Final concentration of dimethylsulphoxide (DMSO) = 0.2%. Untreated control samples were supplemented with 0.2% DMSO.

Cells were then incubated for 72 hours in a humidified atmosphere at 37°C of 5% CO₂. After incubation, cell invasion was visualized by staining the cell nuclei directly with 1µM Hoechst 33342 (Molecular Probes Europe) prepared in serum-free DMEM and incubated with cells for 30 minutes at 37°C followed by confocal microscopic analysis.
using a Bio-Rad Radiance 2000 multiphoton confocal illumination unit attached to a Nikon
Eclipse inverted microscope.

Cell invasion was quantified as follows: Using a 20 x objective, optical sections were
scanned at 10µm intervals from the top of the Matrigel® plug down to 100µm depth.

Within each of the 10µm sections the number of nuclei stained positive with Hoeschst
stain were quantified by applying Image-Pro analysis software (Media Cybernetics) which
identifies the number of positive pixels based on assessment of the nuclear staining above a
pre-set threshold. The accumulated sum of positive nuclei present in optical sections
between 30-100µm below the top of Matrigel® was expressed as a percentage of the total
number of positive nuclei on top and within the Matrigel. This value therefore represents
the proportion of total cells within each sample invading beyond 30µm through to 100µm
in distance. Invasion data presented in IA-D represents the mean percentage of total cells
from triplicate samples invading beyond 30-100µm ± standard deviation of means.

Results
See Figures attached

Conclusion

We have shown that in vitro, in the human rhabdomyosarcoma cells, combinations
of Compound (I) with 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-
yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline di-fumarate salt (AZD0530) produce an
increased anti-invasive effect compared with single agent treatments.
Claims

1. A combination, comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, and a Src kinase inhibitor.

2. A combination as claimed in claim 1 wherein the Src kinase inhibitor is 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline or a pharmaceutically-acceptable salt thereof.

3. A combination as claimed in claim 1 wherein the Src kinase inhibitor is selected from:
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-[3-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)propoxy]quinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline,
   - 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxy]pyrrolidine-1-yloxy]-5-tetrahydropyran-4-yloxy quinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxy quinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxy quinazoline,
   - 4-(5-chloro-2,3-methylenedioxy-4-ylamino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline,
7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxyquinazoline, Brian please give structure
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-(2-piperazin-1-ylethoxy)quinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-7-{2-[4-(2-hydroxyethyl)piperazin-1-yl)ethoxy]-5-isopropoxyquinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-(2-piperidinoethoxy)quinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-(2-propargylpiperazin-1-yl)ethoxy]quinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-[2-(4-prop-2-ynyl)piperazin-1-yl)ethoxy]quinazoline,
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-5-isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline, and
4-(5-chloro-2,3-methylenedioxy)pyrid-4-ylamino)-7- {2-[4-(2-dimethylaminoacetyl)piperazin-1-yl)ethoxy]-5-isopropoxyquinazoline;
or a pharmaceutically-acceptable salt thereof.

4. A combination as claimed in claim 1 wherein the Src kinase inhibitor is bosutinib or a pharmaceutically-acceptable salt thereof.

5. A combination as claimed in claim 1 wherein the Src kinase inhibitor is dasatinib or a pharmaceutically-acceptable salt thereof.

6. A combination as claimed in any one of claims 1-5 for use as a medicament.
7. A pharmaceutical composition as claimed in any one of claims 1-5 in association with a pharmaceutically acceptable diluent or carrier.

8. 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 combination as claimed in any one of claims 1-5.

9. A method as claimed in claim 8 wherein the cancer is rhabdomyosarcoma, 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 or leukaemia.

10. A method as claimed in either claim 8 or 9 wherein the cancer is in a metastatic state.

11. A pharmaceutical composition which comprises a combination as claimed in any one of claims 1-5 in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

12. A composition as claimed in claim 11 wherein the cancer is rhabdomyosarcoma, 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 or leukaemia.

13. A composition as claimed in either claim 11 or 12 wherein the cancer is in a metastatic state.
14. The use of a combination as claimed in any one of claims 1-5 for the manufacture of a medicament for the treatment of cancer, in a warm-blooded animal, such as man.

15. The use as claimed in claim 14 wherein the cancer is rhabdomyosarcoma, 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 or leukaemia.

16. The use as claimed in either claim 14 or 15 wherein the cancer is in a metastatic state.

17. A combination as claimed in any one of claims 1-5 for the treatment of cancer.

18. The combination as claimed in claim 17 wherein the cancer is rhabdomyosarcoma, 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 or leukaemia.

19. The combination as claimed in either claim 17 or 18 wherein the cancer is in a metastatic state.
1A Compound (I) + AZD0530 0.01 μM

1B Compound (I) + AZD0530 0.1 μM

1C Compound (I) + AZD0530 1 μM

1D Compound (I) + AZD0530 10 μM

FIGURE 1