USE OF SUBSTITUTED 2,3-DIHYDROIMIDAZO[1,2-C]QUINAZOLINES

The present invention relates to :

- use of a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or of a pharmaceutical composition containing same, as a sole active agent, or of a combination of a) said compound or a pharmaceutical composition containing said compound and b) one or more further active agents, for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, which is classified into several subtypes in the clinic, such as hormone receptor positive breast cancer, Her2 receptor positive breast cancer, triple negative breast cancer and inflammatory breast cancer, as a single agent or in combination with one or more other active agents ;

- combinations of a) said compound and b) one or more further active agents ;

- a pharmaceutical composition comprising said compound as a sole active agent for the treatment of cancer ;

- a pharmaceutical composition comprising a combination of a) said compound and b) one or more further active agents ;

- use of biomarkers involved in the modification of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN for predicting the sensitivity and/or resistance of a cancer patient to said compound and providing a rationale-based synergistic combination as defined herein to increase sensitivity and/or to overcome resistance ;

and

- a method of determining the level of a component of one or more of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN.

BACKGROUND OF THE INVENTION

In recent decades the concept of developing anti-cancer medications which target abnormally active protein kinases has led to a number of successes. In addition to the actions of protein kinases, lipid kinases also play an important role in generating critical regulatory second messengers. The PI3K family of lipid kinases generates 3'-phosphoinositides that bind to and activate a variety of cellular targets, initiating a wide range of signal transduction cascades (Vanhaesebroeck *et al.*, 2001; Toker, 2002; Pendaries *et al.*, 2003; Downes *et al.*, 2005). These cascades ultimately induce changes in multiple cellular processes, including cell proliferation, cell survival, differentiation, vesicle trafficking, migration, and chemotaxis.

PI3Ks can be divided into three distinct classes based upon differences in both structure, and substrate preference. While members of the Class II family of PI3Ks have been implicated in the regulation of tumor growth (Brown and Shepard, 2001; Traer *et al.*, 2006), the bulk of research has focused on the Class I enzymes and their role in cancer (Vivanco and Sawyers, 2002; Workman, 2004, Chen *et al.*, 2005; Hennessey *et al.*, 2005; Stauffer *et al.*, 2005; Stephens *et al.*, 2005; Cully *et al.*, 2006).

Class I PI3Ks have traditionally been divided into two distinct sub-classes based upon differences in protein subunit composition. The Class I_A PI3Ks are comprised of a catalytic p110 catalytic subunit (p110α, p110β or p110γ) heterodimerized with a member of the p85 regulatory subunit family. In contrast, the Class I_B PI3K catalytic subunit (p110γ) heterodimerizes with a distinct p101 regulatory subunit (reviewed by

Vanhaesebroeck and Waterfield, 1999; Funaki *et al.*, 2000; Katso *et al.*, 2001). The C-terminal region of these proteins contains a catalytic domain that possesses distant homology to protein kinases. The PI3Kγ structure is similar to Class I_A p110s, but lacks the N-terminal p85 binding site (Domin and Waterfield, 1997). Though similar in overall structure, the homology between catalytic p110 subunits is low to moderate. The highest homology between the PI3K isoforms is in the kinase pocket of the kinase domain.

The Class I PI3K isoforms associate with activated receptor tyrosine kinases (RTKs) (including PDGFR, EGFR, VEGFR, IGF1-R, c-KIT, CSF-R and Met), cytokine receptors, GPCRs, integrins, or with tyrosine phosphorylated adapter proteins (such as Grb2, Cbl, IRS-1 or Gab1), via their p85 regulatory subunits resulting in stimulation of the lipid kinase activity. Activation of the lipid kinase activity of the p110ß and p110γ isoforms has been shown to occur in response to binding to activated forms of the ras Oncogene (Kodaki *et al*, 1994). In fact, the oncogenic activity of these isoforms may require binding to ras (Kang *et al.*, 2006). In contrast, the p110α and p110δ isoforms exhibit oncogenic activity independent of ras binding, through constitutive activation of Akt.

Class I PI3Ks catalyze the conversion of $PI(4,5)P_2$ [PIP_2] to $PI(3,4,5)P_3$ [PIP_3]. The production of PIP_3 by PI3K affects multiple signaling processes that regulate and coordinate the biological end points of cell proliferation, cell survival, differentiation and cell migration. PIP_3 is bound by Pleckstrin-Homology (PH) domain-containing proteins, including the phosphoinositide-dependent kinase, PDK1 and the Akt proto-oncogene product, localizing these proteins in regions of active signal transduction and also contributing directly to their activation (Klippel *et al.*, 1997; Fleming *et al.*, 2000; Itoh and Takenawa, 2002; Lemmon, 2003). This co-localization of PDK1 with Akt facilitates the phosphorylation and activation of Akt. Carboxy-terminal phosphorylation

of Akt on Ser^{473} promotes phosphorylation of Thr^{308} in the Akt activation loop (Chan and Tsichlis, 2001; Hodgekinson *et al.*, 2002; Scheid *et al.*, 2002; Hresko *et al.*, 2003). Once active, Akt phosphorylates and regulates multiple regulatory kinases of pathways that directly influence cell cycle progression and cell survival.

Many of the effects of Akt activation are mediated via its negative regulation of pathways which impact cell survival and which are commonly dysregulated in cancer. Akt promotes tumor cell survival by regulating components of the apoptotic and cell cycle machinery. Akt is one of several kinases that phosphorylate and inactivate pro-apoptotic BAD proteins (del Paso *et al.*, 1997; Pastorino *et al.*, 1999). Akt may also promote cell survival through blocking cytochrome C-dependent caspase activation by phosphorylating Caspase 9 on Ser^{196} (Cardone *et al.*, 1998).

Akt impacts gene transcription on several levels. The Akt-mediated phosphorylation of the MDM2 E3 ubiquitin ligase on Ser^{166} and Ser^{186} facilitates the nuclear import of MDM2 and the formation and activation of the ubiquitin ligase complex. Nuclear MDM2 targets the p53 tumor suppressor for degradation, a process that can be blocked by LY294002 (Yap *et al.*, 2000; Ogarawa *et al.*, 2002). Downregulation of p53 by MDM2 negatively impacts the transcription of p53-regulated pro-apoptotic genes (e.g. Bax, Fas, PUMA and DR5), the cell cycle inhibitor, $p21^{Cip1}$, and the PTEN tumor suppressor (Momand *et al.*, 2000; Hupp *et al.*, 2000; Mayo *et al.*, 2002; Su *et al.*, 2003). Similarly, the Akt-mediated phosphorylation of the Forkhead transcription factors FKHR, FKHRL and AFX (Kops *et al.*, 1999; Tang *et al.*, 1999), facilitates their binding to 14-3-3 proteins and export from the cell nucleus to the cytosol (Brunet *et al.*, 1999). This functional inactivation of Forkhead activity also impacts pro-apoptotic and pro-angiogenic gene transcription including the transcription of Fas ligand (Ciechomska *et al.*, 2003) Bim, a pro-apoptotic Bcl-2 family member (Dijkers *et al.*, 2000), and the

Angiopoietin-1 (Ang-1) antagonist, Ang-2 (Daly *et al.*, 2004). Forkhead transcription factors regulate the expression of the cyclin-dependent kinase (Cdk) inhibitor $p27^{Kip1}$. Indeed, PI3K inhibitors have been demonstrated to induce $p27^{Kip1}$ expression resulting in Cdk1 inhibition, cell cycle arrest and apoptosis (Dijkers *et al.*, 2000). Akt is also reported to phosphorylate $p21^{Cip1}$on Thr^{145} and $p27^{Kip1}$ on Thr^{157} facilitating their association with 14-3-3 proteins, resulting in nuclear export and cytoplasmic retention, preventing their inhibition of nuclear Cdks (Zhou *et al.*, 2001; Motti *et al.*, 2004; Sekimoto *et al.*, 2004). In addition to these effects, Akt phosphorylates IKK (Romashkova and Makarov, 1999), leading to the phosphorylation and degradation of IκB and subsequent nuclear translocation of NFκB, resulting in the expression of survival genes such as IAP and Bcl-X_L.

The PI3K/Akt pathway is also linked to the suppression of apoptosis through the JNK and $p38^{MAPK}$ MAP Kinases that are associated with the induction of apoptosis. Akt is postulated to suppress JNK and $p38^{MAPK}$ signaling through the phosphorylation and inhibition of two JNK/p38 regulatory kinases, Apoptosis Signal-regulating Kinase 1 (ASK1) (Kim *et al.*, 2001: Liao and Hung, 2003; Yuan *et al.*, 2003), and Mixed Lineage Kinase 3 (MLK3) (Lopez-Ilasaca *et al.*, 1997; Barthwal *et al.*, 2003; Figueroa *et al.*, 2003;). The induction of $p38^{MAPK}$ activity is observed in tumors treated with cytotoxic agents and is required for those agents to induce cell death (reviewed by Olson and Hallahan, 2004). Thus, inhibitors of the PI3K pathway may promote the activities of co-administered cytotoxic drugs.

An additional role for PI3K/Akt signaling involves the regulation of cell cycle progression through modulation of Glycogen Synthase Kinase 3 (GSK3) activity. GSK3 activity is elevated in quiescent cells, where it phosphorylates cyclin D_1 on Ser^{286}, targeting the protein for ubiquitination and degradation (Diehl *et al.*, 1998) and blocking entry

into S-phase. Akt inhibits GSK3 activity through phosphorylation on Ser^9 (Cross *et al.*, 1995). This results in the elevation of Cyclin D_1 levels which promotes cell cycle progression. Inhibition of GSK3 activity also impacts cell proliferation through activation of the wnt/beta-catenin signaling pathway (Abbosh and Nephew, 2005; Naito *et al.*, 2005; Wilker *et al.*, 2005; Kim *et al.*, 2006; Segrelles *et al.*, 2006). Akt mediated phosphorylation of GSK3 results in stabilization and nuclear localization of the beta-catenin protein, which in turn leads to increased expression of c-myc and cyclin D1, targets of the beta-catenin/Tcf pathway.

Although PI3K signaling is utilized by many of the signal transduction networks associated with both oncogenes and tumor suppressors, PI3K and its activity have been linked directly to cancer. Overexpression of both the p110α and p110ß isoforms has been observed in bladder and colon tumors and cell lines, and overexpression generally correlates with increased PI3K activity (Bénistant *et al.*, 2000). Overexpression of p110α has also been reported in ovarian and cervical tumors and tumor cell lines, as well as in squamous cell lung carcinomas. The overexpression of p110α in cervical and ovarian tumor lines is associated with increased PI3K activity (Shayesteh *et al.*, 1999; Ma *et al.*, 2000). Elevated PI3K activity has been observed in colorectal carcinomas (Phillips *et al.*, 1998) and increased expression has been observed in breast carcinomas (Gershtein *et al.*, 1999).

Over the last few years, somatic mutations in the gene encoding p110α (PIK3CA) have been identified in numerous cancers. The data collected to date suggests that PIK3CA is mutated in approximately 32% of colorectal cancers (Samuels *et al.*, 2004; Ikenoue *et al.*, 2005), 18-40% of breast cancers (Bachman *et al.*, 2004; Campbell *et al.*, 2004; Levine *et al.*, 2005; Saal *et al.*, 2005; Wu *et al.*, 2005), 27% of glioblastomas (Samuels *et al.*, 2004; Hartmann *et al.*, 2005, Gallia *et al.*, 2006), 25% of gastric cancers (Byun *et al.*, 2003; Samuels *et al.*, 2004; Li *et al.*, 2005),

36% of hepatocellular carcinomas (Lee *et al.*, 2005), 4-12% of ovarian cancers (Levine *et al.*, 2005; Wang *et al.*, 2005), 4% of lung cancers (Samuels *et al.*, 2004; Whyte and Holbeck, 2006), and up to 40% of endometrial cancers (Oda *et al.*, 2005). PIK3CA mutations have been reported in oligodendroma, astrocytoma, medulloblastoma, and thyroid tumors as well (Broderick *et al.*, 2004; Garcia-Rostan *et al.*, 2005). Based upon the observed high frequency of mutation, PIK3CA is one of the two most frequently mutated genes associated with cancer, the other being K-ras. More than 80% of the PIK3CA mutations cluster within two regions of the protein, the helical (E545K) and catalytic (H1047R) domains. Biochemical analysis and protein expression studies have demonstrated that both mutations lead to increased constitutive p110α catalytic activity and are in fact, oncogenic (Bader *et al.*, 2006; Kang *et al.*, 2005; Samuels *et al.*, 2005; Samuels and Ericson, 2006). Recently, it has been reported that PIK3CA knockout mouse embryo fibroblasts are deficient in signaling downstream from various growth factor receptors (IGF-1, Insulin, PDGF, EGF), and are resistant to transformation by a variety of oncogenic RTKs (IGFR, wild-type EGFR and somatic activating mutants of EGFR, Her2/Neu)(Zhao *et al.*, 2006).

Functional studies of PI3K *in vivo* have demonstrated that siRNA-mediated downregulation of p110ß inhibits both Akt phosphorylation and HeLa cell tumor growth in nude mice (Czauderna *et al.*, 2003). In similar experiments, siRNA-mediated downregulation of p110ß was also shown to inhibit the growth of malignant glioma cells *in vitro* and *in vivo* (Pu *et al.*, 2006). Inhibition of PI3K function by dominant-negative p85 regulatory subunits can block mitogenesis and cell transformation (Huang *et al.*, 1996; Rahimi *et al.*, 1996). Several somatic mutations in the genes encoding the p85α and p85ß regulatory subunits of PI3K that result in elevated lipid kinase activity have been identified in a number of cancer cells as well (Janssen *et al.*, 1998; Jimenez *et al.*, 1998; Philp *et al.*, 2001; Jucker *et al.*, 2002; Shekar *et al.*, 2005). Neutralizing PI3K

antibodies also block mitogenesis and can induce apoptosis *in vitro* (Roche *et al.*, 1994: Roche *et al.*, 1998; Bénistant *et al.*, 2000). *In vivo* proof-of-principle studies using the PI3K inhibitors LY294002 and wortmannin, demonstrate that inhibition of PI3K signaling slows tumor growth *in vivo* (Powis *et al.*, 1994; Shultz *et al.*, 1995; Semba *et al.*, 2002; Ihle *et al.*, 2004).

Overexpression of Class I PI3K activity, or stimulation of their lipid kinase activities, is associated with resistance to both targeted (such as imatinib and tratsuzumab) and cytotoxic chemotherapeutic approaches, as well as radiation therapy (West et al., *2002*; Gupta *et al.*, 2003; Osaki *et al.*, 2004; Nagata *et al.*, 2004; Gottschalk *et al.*, 2005; Kim *et al.*, 2005). Activation of PI3K has also been shown to lead to expression of multidrug resistant protein-1 (MRP-1) in prostate cancer cells and the subsequent induction of resistance to chemotherapy (Lee *et al.*, 2004).

The importance of PI3K signaling in tumorigenesis is further underscored by the findings that the PTEN tumor suppressor, a PI(3)P phosphatase, is among the most commonly inactivated genes in human cancers (Li *et al.*, 1997, Steck *et al.*, 1997; Ali *et al.*, 1999; Ishii *et al.*, 1999). PTEN dephosphorylates $PI(3,4,5)P_3$ to $PI(4,5)P_2$ thereby antagonizing PI3K-dependent signaling. Cells containing functionally inactive PTEN have elevated levels of PIP_3, high levels of activity of PI3K signaling (Haas-Kogan *et al.*, 1998; Myers *et al.*, 1998; Taylor *et al.*, 2000), increased proliferative potential, and decreased sensitivity to pro-apoptotic stimuli (Stambolic *et al.*, 1998). Reconstitution of a functional PTEN suppresses PI3K signaling (Taylor *et al.*, 2000), inhibits cell growth and re-sensitizes cells to pro-apoptotic stimuli (Myers *et al.*, 1998; Zhao *et al.*, 2004). Similarly, restoration of PTEN function in tumors lacking functional PTEN inhibits tumor growth *in vivo* (Stahl *et al.*, 2003; Su *et al.*, 2003; Tanaka and Grossman, 2003) and sensitizes cells to cytotoxic agents (Tanaka and Grossman, 2003).

The class I family of PI3Ks clearly plays an important role in the regulation of multiple signal transduction pathways that promote cell survival and cell proliferation, and activation of their lipid kinase activity contributes significantly to the development of human malignancies. Furthermore, inhibition of PI3K may potentially circumvent the cellular mechanisms that underlie resistance to chemotherapeutic agents. A potent inhibitor of Class I PI3K activities would therefore have the potential not only to inhibit tumor growth but to also sensitize tumor cells to pro-apoptotic stimuli *in vivo*.

Signal transduction pathways originating from chemoattractant receptors are considered to be important targets in controlling leukocyte motility in inflammatory diseases. Leukocyte trafficking is controlled by chemoattractant factors that activate heterotrimeric GPCRs and thereby trigger a variety of downstream intracellular events. Signal transduction along one of these pathways that results in mobilization of free Ca^{2+}, cytoskelatal reorganization, and directional movement depends on lipid-dervied second messengers producted by PI3K activity (Wymann *et al.*, 2000; Stein and Waterfield, 2000).

PI3Kγ modulates baseline cAMP levels and controls contractility in cells. Recent research indicates that alterations in baseline cAMP levels contribute to the increased contractility in mutant mice. This research, therefore, shows that PI3Kγ inhibitors afford potential treatments for congestive heart failure, ischemia, pulmonary hypertension, renal failure, cardiac hypertrophy, atherosclerosis, thromboembolism, and diabetes.

PI3K inhibitors would be expected to block signal transduction from GPCRs and block the activation of various immune cells, leading to a broad anti-inflammatory profile with potential for the treatment of

inflammatory and immunoregulatory diseases, including asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis and Graves' disease, diabetes, cancer, myocardial contractility disorders, thromboembolism, and atherosclerosis.

Breast cancer is a world health problem, and in the United States this disease is the second most common cause of cancer death in women. About 1 in 8 women in the United States (12%) will develop invasive breast cancer over the course of her lifetime. In 2010, an estimated 207,090 new cases of invasive breast cancer were expected to be diagnosed, along with 54,010 new cases of non-invasive breast cancer. About 39,840 women were expected to die in 2010 from breast cancer. The classification and treatment options are usually based on the receptor status. The three most important in the present classification are estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Cells with or without these receptors are called ER positive (ER+), ER negative (ER-), PR positive (PR+), PR negative (PR-), HER2 positive (HER2+), and HER2 negative (HER2-). Cells with none of these receptors are called basal-like or triple negative. Recently, DNA-based classification is also used in the clinic. As specific DNA mutations or gene expression profiles are identified in the cancer cells, this classification may guide the selection of treatments, either by targeting these changes, or by predicting from the DNA profile which non-targeted therapies are most effective.

The PI3K/PTEN/AKT pathway has been found to be frequently activated and/or mutated in human breast cancer, which contributes to the development and progression of breast cancer, as well as drug resistance. As genetic alterations of *PIK3CA* and *PTEN*, as well as PI3K pathway activation are observed in almost all breast cancer subtypes,

such as HER2 positive, hormone receptor positive, or triple negative breast cancers, it is important to define the strategy for the development of PI3K pathway inhibitors in breast cancer. The present invention is thus to identify molecular markers predicting the sensitivity and/or resistance of the cancer patients toward the PI3K inhibitors described herein. Furthermore, the present invention also relates to the identification of resistance mechanisms and therefore provides a rationale-based synergistic combination to overcome the resistance.

To the Applicant's knowledge, no specific disclosure in the prior art is known that 2,3-dihydroimidazo[1,2-c]quinazoline compounds would be effective in the treatment or prophylaxis of inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

It has been found, and this is the basis of the present invention, that 2,3-dihydroimidazo[1,2-c]quinazoline compounds, as described and defined herein, show a beneficial effect in the treatment or prophylaxis of breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

Thus, in accordance with a first aspect, the present invention relates to the use of 2,3-dihydroimidazo[1,2-c]quinazoline compounds, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as a sole active agent, or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In accordance with a second aspect, the present invention relates to combinations of :

a) a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In accordance with a third aspect, the present invention relates to pharmaceutical compositions comprising a 2,3-dihydroimidazo[1,2-

c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as a sole active agent, for the treatment of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In accordance with a fourth aspect, the present invention relates to pharmaceutical compositions comprising a combination of :

a) a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014,

AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In accordance with a fifth aspect, the present invention relates to the use of combinations of :

a) a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
or of a pharmaceutical composition containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779,

Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory beast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In accordance with a sixth aspect, the present invention relates to use of biomarkers involved in the modification of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN for predicting the sensitivity and/or resistance of a patient with cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer, to a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined herein, thus providing a rationale-based synergistic combination as defined herein to overcome the resistance (patient stratification).

In accordance with a seventh aspect, the present invention relates to a method of determining the level of a component of one or more of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN, wherein :

- in said Bcl expression, said component is Bcl, for example,
- in said HER family expression and/or activation, PIK3CA signaling, said component is EGF-R, for example, and
- in said loss of PTEN, said component is PTEN, for example.

In accordance a particular embodiment of any of the above aspects of the present invention, said breast cancer is inflammatory breast cancer.

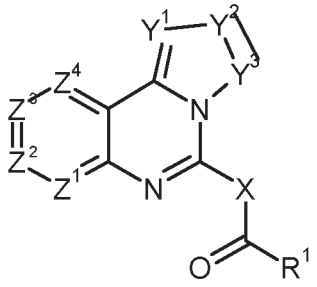
In accordance a particular embodiment of any of the above aspects of the present invention, said breast cancer is triple negative breast cancer.

In accordance a particular embodiment of any of the above aspects of the present invention, said breast cancer is Her2 receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects of the present invention, said breast cancer is hormone receptor positive breast cancer.

Detailed description of the Invention

A first aspect of the present invention relates to the use of a compound of general formula (A) :



(A)

in which :

X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

the chemical bond between Y^2------Y^3 represents a single bond or double bond,

with the proviso that when theY^2------Y^3 represents a double bond, Y^2 and Y^3 independently represent CR^4 or N, and

when Y^2------Y^3 represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4;

Z^1, Z^2, Z^3 and Z^4 independently represent CH , CR^2 or N;

R^1 represents aryl optionally having 1 to 3 substituents selected from R^{11}, C_{3-8} cycloalkyl optionally having 1 to 3 substituents selected from R^{11},
C_{1-6} alkyl optionally substituted by aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
C_{1-6} alkoxy optionally substituted by carboxy, aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
or
a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, optionally having 1 to 3 substituents selected from R^{11}, and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S,

wherein
R^{11} represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6}acyl)amino, N-(formyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkanesulfonyl) amino, N-(carboxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, N-[N,N-di(C_{1-6}alkyl)amino methylene]amino, N-[N,N-di(C_{1-6}alkyl)amino (C_{1-6}alkyl)methylene]amino, N-[N,N-di(C_{1-6}alkyl)amino C_{2-6}alkenyl]amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, C_{3-8}cycloalkyl, C_{1-6} alkylthio, C_{1-6}alkanesulfonyl, sulfamoyl, C_{1-6}alkoxycarbonyl,

N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101}, N-(aryl C_{1-6}alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101}, aryl C_{1-6}alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101},

C_{1-6}alkyl optionally substituted by mono-, di- or tri-halogen, amino, N-(C_{1-6}alkyl)amino or N,N-di(C_{1-6}alkyl)amino,

C_{1-6}alkoxy optionally substituted by mono-, di- or tri-halogen, N-(C_{1-6}alkyl)sulfonamide, or N-(aryl)sulfonamide,

or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R^{101}

wherein

R^{101} represents halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, pyridyl,

C_{1-6} alkyl optionally substituted by cyano or mono-di- or tri- halogen,

and

C_{1-6}alkoxy optionally substituted by cyano, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-

di(C_{1-6}alkyl)aminocarbonyl or mono-, di- or tri-halogen;

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{1-6} acyloxy, aminoC_{1-6} acyloxy, C_{2-6}alkenyl, aryl,

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, amino, amino C_{1-6}alkyl, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, N-(C_{1-6}alkyl)carbonylamino, phenyl, phenyl C_{1-6} alkyl, carboxy, C_{1-6}alkoxycarbonyl, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)amino, -C(O)- R^{20} wherein

R^{20} represents C_{1-6} alkyl, C_{1-6} alkoxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, oxo, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, phenyl, or benzyl,

C_{1-6} alkyl optionally substituted by R^{21},
or
C_{1-6} alkoxy optionally substituted by R^{21},
wherein

R^{21} represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (hydroxyC_{1-6} alkyl) amino, N-(halophenylC_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxyC_{1-6} alkoxy, -C(O)- R^{201}, -NHC(O)- R^{201}, C_{3-8}cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N , and optionally substituted by hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, aminoC_{1-6}alkyl, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, or benzyl,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(halophenylC_{1-6} alkyl) amino, C_{1-6}alkyl, aminoC_{1-6} alkyl, aminoC_{2-6} alkylenyl, C_{1-6} alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N, and optionally substituted by hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino or benzyl;

R^3 represents hydrogen, halogen, aminocarbonyl, or C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or mono-, di- or tri- halogen;

R^4 represents hydrogen or C_{1-6} alkyl;

R^5 represents hydrogen or C_{1-6} alkyl; and

R^6 represents halogen, hydrogen or C_{1-6} alkyl,

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a particular embodiment of the above-mentioned first aspect, the present invention relates to the use of a compound selected from the following list,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral

agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer :

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

2-(7, 8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethylenol;

N-(7, 8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

6-(acetamido)-N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-{5-[2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;

2-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)-N,N-dimethylacetamide;

2-[7-methoxy-8-(tetrahydro-2H-pyran-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

2-[8-(2-hydroxyethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetic acid;

4-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)butanoic acid;

({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetonitrile;

2-[7-methoxy-8-(2H-tetrazol-5-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

2-[7-methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-3-ol ;

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;

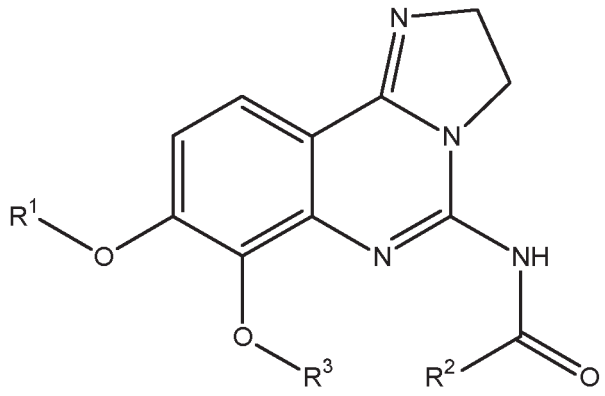
6-(acetamido)-N-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;

5-hydroxy-N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-[(4-methoxybenzyl)oxy]nicotinamide;
N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
5-hydroxy-N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{8-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-(7-bromo-8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
6-amino-N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
1-(1H-benzimidazol-5-yl)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2,4-dimethyl-1,3-thiazol-5-yl)ethylenol;
N-(9-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;
N-(7-fluoro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
6-(acetamido)-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
1-(1H-benzimidazol-5-yl)-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
N-{5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-2-yl}acetamide;
6-methyl-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
1-(1H-benzimidazol-5-yl)-2-[8-(4-methylpiperazin-1-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]ethylenol;
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
N-[7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;
N-(7,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-{5-[2-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;
N-{5-[2-(7-bromo-9-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide; and
2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethylenol;

Another embodiment of the present invention encompasses the use of a compound having the formula (I) :



(I)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, in which :

R^1 represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 represents a heteroaryl optionally substituted with 1, 2 or 3 R^6 groups ;

R^3 represents alkyl or cycloalkyl ;

R^4 represents hydrogen, hydroxy or alkoxy ; and

R^5 and $R^{5'}$ may be the same or different and represent independently, hydrogen, alkyl, cycloalkylalklyl, or alkoxyalkyl or R^5 and $R^{5'}$ may be taken together with the nitrogen atom to which they are bound to form a 3-7 membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups, or R^4 and R^5 may be taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more $R^{6'}$ groups ;

each occurrence of R^6 may be the same or different and is independently halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring, heterocyclylalkyl, alkyl-OR^7, alkyl-SR^7, alkyl-$N(R^7)(R^{7'})$, alkyl-COR^7,-CN, -$COOR^7$, -$CON(R^7)(R^{7'})$, -OR^7, -SR^7, -$N(R^7)(R^{7'})$, or -NR^7COR^7 each of which may be optionally substituted with 1 or more R^8 groups ;

each occurrence of $R^{6'}$ may be the same or different and is independently alkyl, cycloalkylalklyl, or alkyl-OR^7;

each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, or heteroarylalkyl ;

each occurrence of R^8 is independently nitro, hydroxy, cyano, formyl, acetyl, halogen, amino, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, or heteroarylalkyl ;

n is an integer from 1-4 and m is an integer from 0-4 with the proviso that when when R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing ring, $n + m \leq 4$;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^2 is a nitrogen containing heteroaryl optionally substituted with 1, 2 or 3 R^6 groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;or of pharmaceutical

compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In another preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^5 and $R^{5'}$ are independently alkyl,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In still another preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^5 and $R^{5'}$ are taken together with the nitrogen atom to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In yet another preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^4 is hydroxyl,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In another preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more R^6 groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-

)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;

- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In yet another preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^3 is methyl,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In still another preferred embodiment, the invention encompasses the use of a compound of Formula (I), wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups; more preferably pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups,

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

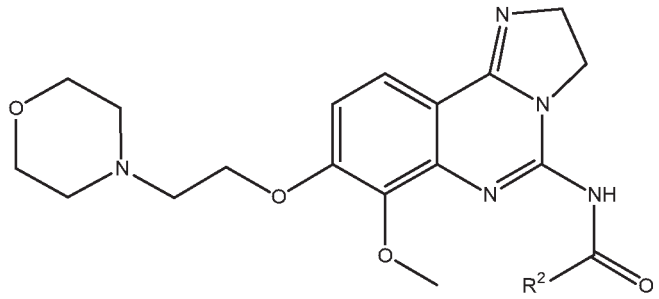
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR

kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a distinct embodiment, the invention encompasses the use of a compound of formula (Ia)



(Ia)

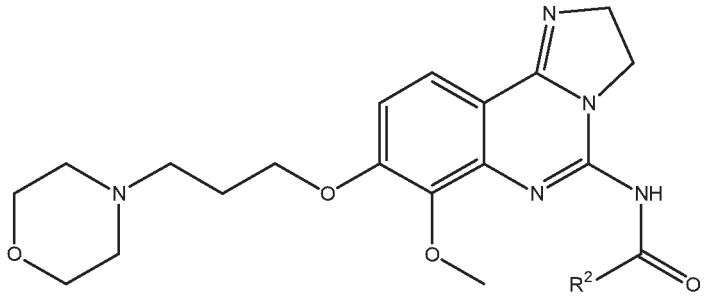
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In another distinct embodiment, the invention encompasses the use of a compound of formula (Ib) :



(Ib)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above,

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

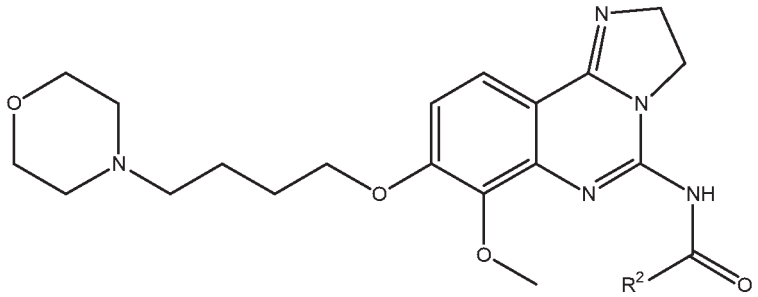
b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In still another distinct embodiment, the invention encompasses the use of a compound of formula (Ic) :



(Ic)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

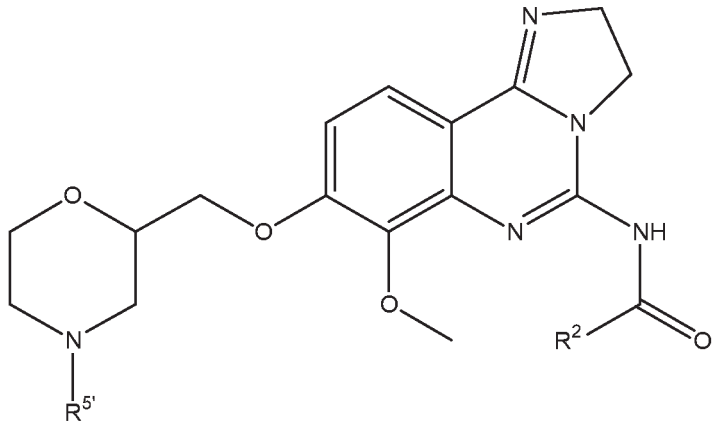
- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In yet another distinct embodiment, the invention encompasses the use of a compound of the formula (Id):



(Id)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 and R^4 are as defined above,

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

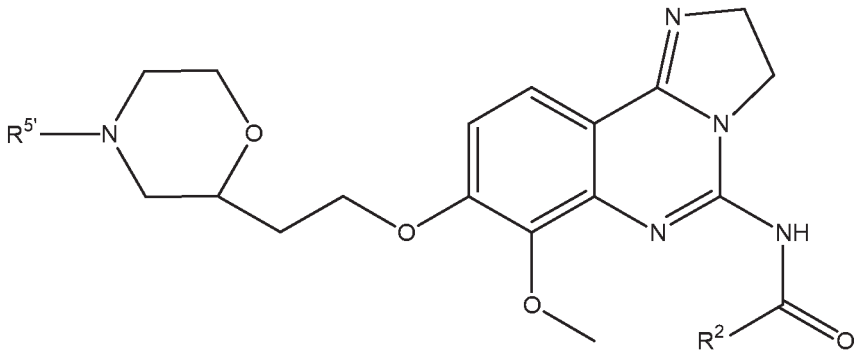
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In yet another distinct embodiment, the invention encompasses the use of a compound of the formula (Ie) :



(Ie)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 and R^4 are as defined above,

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;

- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of a compound of formula (I) - (V), wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups; more preferrably wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of combinations of :
a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In still another preferred embodiment, the invention encompasses the use of a compound having the formula :

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide ;
N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide;
N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide;
6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[8-(2-hydroxy-3-morpholin-4-ylpropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{7-methoxy-8-[3-(3-methylmorpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8-{2-[4-(cyclobutylmethyl)morpholin-2-yl]ethoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(7-methoxy-8-{2-[4-(2-methoxyethyl)morpholin-2-yl]ethoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-{8-[(4-ethylmorpholin-2-yl)methoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-(7-methoxy-8-{[4-(2-methoxyethyl)morpholin-2-yl]methoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-{7-methoxy-8-[(4-methylmorpholin-2-yl)methoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-4-carboxamide;
rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;

rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide;
rel-6-acetamido-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-5-carboxamide;
6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylnicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methylpyrimidine-5-carboxamide;
6-amino-5-bromo-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-5-carboxamide;
N-[7-methoxy-8-(morpholin-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-{[2-(dimethylamino)ethyl]amino}-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-1,3-thiazole-5-carboxamide;
rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

2-[(2-hydroxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-methoxypropyl)amino]pyrimidine-5-carboxamide;

2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-morpholin-4-ylpropyl)amino]pyrimidine-5-carboxamide;

2-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

2-{[2-(dimethylamino)ethyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

6-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-pyrrolidin-1-ylpyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-piperazin-1-ylnicotinamide hydrochloride;

6-[(3S)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride hydrate;

6-[(3R)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride;

6-[(4-fluorobenzyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(2-furylmethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(1H-pyrrol-1-yl)nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-morpholin-4-ylnicotinamide;

N-{7-methoxy-8-[3-(methylamino)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

6-[(2,2-dimethylpropanoyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(cyclopropylcarbonyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2,2,2-trifluoroethoxy)nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(trifluoromethyl)nicotinamide;

6-(isobutyrylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{7-methoxy-8-[3-(4-methylpiperazin-1-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-{[(methylamino)carbonyl]amino}-1,3-thiazole-4-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-{[(methylamino)carbonyl]amino}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)-1,3-thiazole-4-carboxamide;
N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-6-methylnicotinamide;
6-{[(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-pyrrolidin-1-ylnicotinamide;
6-(dimethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-piperidin-1-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(2-piperidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-{[(ethylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-fluoro-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-4-carboxamide;
2-(ethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-4-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrazine-2-carboxamide;
N-[8-(2-aminoethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
N-{8-[3-(diethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(diisopropylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(diethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylthio)pyrimidine-5-carboxamide;
N-[8-(3-aminopropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide trifluoroacetate;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-2-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
2-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-3-furamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-3-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methyl-1,3-thiazole-4-carboxamide;
6-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
6-(acetylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of a compound having the formula:

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;

5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

6-{[(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

as a sole active agent,

or of combinations of :

a) such a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such compounds or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of a compound having the formula :

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

as a sole active agent,

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer,

triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014,

AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL

(Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;

- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ;

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, which is ABT-737 ;

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer,

triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents selected from the group consisting of :

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,
for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents, which is Rapamycin (Sirolimus) ;

or of pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
or of pharmaceutical compositions containing such combinations,

for the preparation of a medicament for the treatment or prophylaxis of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

Where there is a discrepancy between the chemical name and the chemical structure depicted, the chemical structure depicted takes precedence over the chemical name given.

Without being bound by theory or mechanism, the compounds of the present invention display surprising activity for the inhibition of phosphatidylinositol-3-kinase and chemical and structural stability over those compounds of the prior art. It is believed that this surprising activity is based on the chemical structure of the compounds, in particular the basicity of the compounds as a result of R^1 being amino optionally substituted with R^5 and $R^{5'}$. Further, the appropriate choice

of R^3 and R^2 provide the necessary activity against the appropriate isoforms to allow for activity in vivo.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is inflammatory breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is triple negative breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is Her2 receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is hormone receptor positive breast cancer.

Definitions

The term `alkyl` refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, such as illustratively, methyl, ethyl, n-propyl 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

The term "alkenyl " refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or

branched chain having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-I-propenyl, 1-butenyl, 2-and butenyl.

The term "alkynyl" refers to a straight or branched chain hydrocarbonyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl.

The term "alkoxy" denotes an alkyl group as defined herein attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are methoxy and ethoxy.

The term "alkoxyakyl" denotes an alkoxy group as defined herein attached via oxygen linkage to an alkyl group which is then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. Representative examples of those groups are $-CH_2OCH_3$, $--CH_2OC_2H_5$.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaptththyl, adamantyl and norbornyl groups bridged cyclic group or sprirobicyclic groups e.g sprio (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about about 3 up to 8 carbon atoms directly attached to alkyl group which is then also attached to the main structure at any carbon from the alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobuyylethyl, cyclopentylethyl.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl .

The term "arylalkyl" refers to an aryl group as defined herein directly bonded to an alkyl group as defined herein which is then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. e.g., --$CH_2C_6H_5$, --$C_2H_5C_6H_5$.

The term "heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic or heteroaryl aromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl cinnolinyl dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazil, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl pyridazinyl, oxazolyl oxazolinyl oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl,

isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, isochromanyl .

The term "heteroaryl" refers to heterocyclic ring radical as defined herein which are aromatic. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to heteroaryl ring radical as defined herein directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "heterocyclyl" refers to a heterocylic ring radical as defined herein. The heterocylyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocylic ring radical as defined herein directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "carbonyl" refers to an oxygen atom bound to a carbon atom of the molecule by a double bond.

The term "halogen" refers to radicals of fluorine, chlorine, bromine and iodine.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration, resulting in racemic mixtures in the case of a single asymmetric center, and diastereomeric mixtures in the case of multiple asymmetric centers. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention. Preferred compounds are those, which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the

compounds of examples. The term “pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al*. “Pharmaceutical Salts,” *J. Pharm. Sci*. 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chorine salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate,

picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

The synthesis of the compounds listed above is described in International Patent Application No. PCT/EP2003/010377, published as WO 2004/029055 A1, and in International Patent Application No. PCT/US2007/024985, published as WO 2008/070150, both of which are hereby incorporated herein in their entirety by reference.

In accordance with another embodiment, the present invention relates to a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined herein, in particular 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as a sole agent, for the treatment of cancer, e.g. breast cancer,

in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is inflammatory breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is triple negative breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is Her2 receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is hormone receptor positive breast cancer.

Combination therapies

As mentioned *supra*, the present invention relates to combinations of :

a) a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined *supra*, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In a preferred embodiment, the invention encompasses combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In a preferred embodiment, the invention encompasses combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or

a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In a preferred embodiment, the invention encompasses combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or

a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex.

In a preferred embodiment, the invention encompasses the use of combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents, which is ABT-737.

In a preferred embodiment, the invention encompasses combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents selected from the group consisting of :

- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In a preferred embodiment, the invention encompasses combinations of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents, which is Rapamycin (Sirolimus).

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents (or "further active agents") where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

The additional pharmaceutical agent or agents (or "further active agent") can be, but are not limited to aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexomethasone, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole,

farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, herceptin, histrelin, hycamtin, hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lapatinib, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, lenalidomide, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel, pediapred, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, RDEA 119, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, sunitinib, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene,

actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thalidomide, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof.

In accordance with an embodiment, the additional pharmaceutical agent or agents (or "further active agent") is selected from the group consisting of : 131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, BAY 80-6946, BAY 1000394, BAY 86-9766 (RDEA 119), belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium

chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, interferon alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiostane, mercaptopurine, methotrexate, methoxsalen, Methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polysaccharide-K, porfimer sodium, pralatrexate, prednimustine, procarbazine, quinagolide, raloxifene, raltitrexed, ranimustine, razoxane, regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa,

thymalfasin, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

The additional pharmaceutical agent can also be gemcitabine, paclitaxel, cisplatin, carboplatin, sodium butyrate, 5-FU, doxirubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG, U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α-glucosidase inhibitor, a biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin or a secretin derivative.

Optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is better tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

In accordance with an embodiment, the invention relates to combinations wherein said 2,3-dihydroimidazo[1,2-c]quinazoline compound is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

In accordance with an embodiment, the invention relates to combinations wherein said further active agent is rapamycin or ABT-737.

In accordance with an embodiment, the invention relates to combinations wherein said 2,3-dihydroimidazo[1,2-c]quinazoline compound is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide and said further active agent is rapamycin or ABT-737.

Pharmaceutical compositions of the compounds of the invention

As mentioned *supra*, the present invention relates to pharmaceutical compositions :

- comprising a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as a sole active agent, for the treatment of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer, and
- comprising a pharmaceutical composition which comprises a combination of :

  a) a 2,3-dihydroimidazo[1,2-c]quinazoline compound, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

  b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

  - a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;
  - a Bcl binding peptide ;

- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

In accordance with another embodiment, the present invention relates to pharmaceutical compositions which comprise a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined herein, in particular 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as a sole agent, for the treatment of cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is inflammatory breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is triple negative breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is Her2 receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is hormone receptor positive breast cancer.

Said pharmaceutical compositions contain one or more compounds. These compositions can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active agent so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active agent. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be

prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active agent in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional

excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active agent in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a

pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active agent in solution.

Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al*, "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* 1998, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* 1999, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* 1997, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl

methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium,

methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

Lyophilized powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lypholized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 – 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention
5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active agent, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active agent in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active agent. The capsules are washed and dried. The active agent can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active agent, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active agent is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Method of treating breast cancer

The present invention also relates to a method of treating or prophylaxis of cancer, e.g. breast cancer, which is classified into several subtypes in the clinic, such as hormone receptor positive breast cancer, Her2 receptor positive breast cancer, triple negative breast cancer and inflammatory breast cancer, in a mammal, said method comprising administering a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined herein, or a pharmaceutical composition containing same, as a sole active agent, or administering a combination of a) said compound or a pharmaceutical composition containing said compound and b) one or more further active agents as defined herein.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is inflammatory breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is triple negative breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is Her2 receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is hormone receptor positive breast cancer.

The embodiments of the methods of treating or prophylaxis of cancer, e.g. breast cancer, as defined supra, are as described in the

embodiments of the use of the compounds/combinations, as described supra.

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian breast cancer. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis, in the treatment or prophylaxis of breast cancer. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound or combination of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; etc. which is effective for the treatment or prophylaxis of breast cancer.

This disorder has been well characterized in humans, but also exists with a similar etiology in other mammals, and they can be treated by administering pharmaceutical compositions of the present invention.

The term “treating” or “treatment” as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder, such as a carcinoma.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment or prophylaxis of breast cancer, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for

treatment of the indication. The amount of the active agent to be administered in the treatment of the condition can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active agent to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1,500 mg of active agent, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as

determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Biomarkers :

Biomarkers used for patient stratification are e.g. Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN for predicting the sensitivity and/or resistance of a cancer patient to said compound, thus providing rationale-based synergistic combination as defined herein to overcome the resistance.

Examples:

The invention is demonstrated in the following examples which are not meant to limit the invention in any way:

Example 1

In accordance with the invention, the compound were assessed in a cell-based assay that measures the capacity of the compounds to inhibit tumor cell proliferation following a 72-hour drug exposure. Cell viability was conducted by Invitrogen (breast Oncopanel, Invitrogen, USA), or was determined using CellTiter-Glo® Luminescent Cell Viability Assay

(Promega) as follows. Cells were plated at 300 - 5000 cells/well depending on the cell lines or microtiter plates (96- or 384-well) in 100 μL growth medium in 96-well and 20 μL growth medium in 384-well microtiterplate. For each cell line assayed, cells were plated onto a separate plate for determination of luminescence at t = 0 hour and t = 72 hour time points. Following overnight incubation at 37 °C, luminescence values for the t = 0 samples were determined. Dose plates for the t = 72 hour time points were treated with compounds diluted into growth medium. Cells were then incubated for 72 hours at 37 °C. Luminescence values for the t = 72 hour samples were determined. For data analysis, briefly, t = 0 values were subtracted from those determined for the t = 72 hour time points, for both the treated and untreated samples. Percent differences in luminescence between drug-treated and control values were used to determine the percent inhibition of growth.

Tumor cells were seeded in 384-well plates at a concentration of 1000-2500 cells/well/25 μL depending on cell lines. After overnight incubation, cells were treated with compounds (5 μL). Then, Caspase 3/7 activities were determined at 24 to 48 hours post-treatment using Caspase-Glo3/7 assay kits (Promega Cat # G8212).

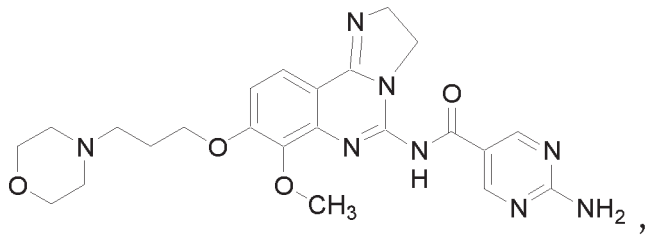
The combination effects of PI3K inhibitors and other agent were evaluated using combination index isobologram analysis (Chou et al. Pharmacology Reviews 2006). The efficacy parameters were the median effect in a 72-hour cell proliferation assay and the 24- or 48-hour Caspase 3/7 activity assay described above. Briefly, cells were plated in 384-well plate with 25 μl medium. After 24 hours, 5 μL of experimental media containing either drug 1 (D1), or drug 2 (D2), or the combination of D1 plus D2 at different ratios (0.8xD1+0.2xD2, 0.6xD1+0.4xD2, 0.4xD1+0.6xD2, 0.2xD1+0.8xD2, 0.1xD1+0.9xD2) were used to make serial three-fold dilutions to generate 7 dose curves. Experiments were

conducted in triplicate. For determination of EC_{50}s and IC_{50}s, a linear regression analysis are used to determine drug concentration which results in a 50% inhibition or efficacy. The corresponding component doses of D1 and D2 at the $E(I)C_{50}$/ $E(I)C_{90}$ were calculated and used for plotting isobolograms. The multiple drug effect was analyzed as described by Chou et al. (Pharmacology Reviews 2006) and the combination index was calculated using the formula :

Combination Index = [D1x]/ D1' + [D2x]/ D2'

where D1x and D2x refer to the Drug 1 and Drug 2 concentration at EC_{50}/IC_{50} or EC_{90}/IC_{90}, respectively, in combination; and D1' and D2' refer to the EC_{50}/IC_{50} or EC_{90}/IC_{90} values of D1 and D2, respectively, as single agents. In this analysis, values less than 1.0 indicate synergistic interactions, values greater than 1.0 indicate antagonistic interactions, and values around 1.0 indicate additive interactions.

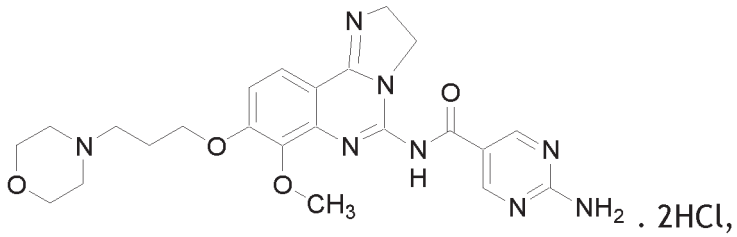
In the following, "compound of formula I" refers to 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, of structure :



(I)

or a solvate, hydrate or stereoisomer thereof.

In the following, “compound A” refers to 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride, of structure :



(A)

or a solvate, hydrate or stereoisomer thereof.

The synthesis of compound A is described in European patent application number EP 11 161 111.7, which is hereby incorporated herein in its entirety by reference.

Synthesis of compound A :

To a suspension of the compound of formula I (400 g) in water (1,1 L) at room temperature was added a 32% aqueous 32% (aqueous) hydrochloric acid solution iswith stirring dosed at room temperature to a suspension of 400 g of the compound of formula (I) in 1.1 L water until a pH of 3-4 is was reached. Additional 90 mL water (90 mL) and 32% hydrochloric acid are were added until a pH of 1.8 to 2.0 is was attained. E160 mL ethanol (160 mL) are dosed into was added to the mixture, followed by seed crystals. After stirring for 30 minutes, 1740 gadditional ethanol (2,2 L) are dosed within 5 hwas added into the mixture over 5 h, which isand the resulting mixture was subsequently stirred for 1 h. The suspension is filtered and the residue is washed first with a mixture of 130 g water and 215 g ethanol, secondly with a mixture of 80 g water and 255 g

ethanol and then with 320 g pure ethanol. The filter cake is dried at 40 °C under vacuum to yield 457 g product (99% of theory).

Characterization of compound A:

The chemical structure of compound A has been confirmed using the described methods of structural analysis.

IR and Raman spectroscopy

Apparatus and measuring conditions

FT-IR / FT-Raman-Spectrometer	Bruker IFS 66v	/	Bruker RFS 100
Spectral resolution	2 cm^{-1}	/	2 cm^{-1}
Number of interferograms	32	/	64
Wave number range	4000 - 500 cm^{-1}	/	3500 - 100 cm^{-1}
Laser power	-	/	350mW
Sample preparation	KBr pellet	/	solid in test tube

Assignment of the characteristic bands

Table: Assignment of the characteristic active vibrations to the spectrum with $\nu \equiv$ stretching vibrations; $\delta \equiv$ bending vibrations; o.o.p. $\equiv$ out of plane.

Assigned Structure	IR Band position [cm^{-1}]	Raman Band position [cm^{-1}]
ν N-H	3336	-
ν =C-H	3176	3090
ν C-H	2942	2990 - 2963
ν NH^+	2687 - 2474	-
ν Amide I	1669	1664
ν C=C, ν C=N, δ N-H, Amide II	1618 - 1477	1619 - 1476
ν C-O	1285	1291
δ =C-H o.o.p.	812	-

$\nu \equiv$ stretching vibrations; $\delta \equiv$ bending vibrations; o.o.p. $\equiv$ out of plane

The IR spectrum is given in Figure 7.

The Raman spectrum is given in Figure 8.

UV/VIS spectroscopy

Apparatus and measuring conditions

UV/VIS spectrometer	Varian Cary 4
Cuvette	Quartz, 1 cm
Wave number range	200-800 nm
Sample preparation	4.67 mg / 500 mL water
Bands	309 nm

The UV/vis spectrum is given in Figure 9.

NMR spectroscopy

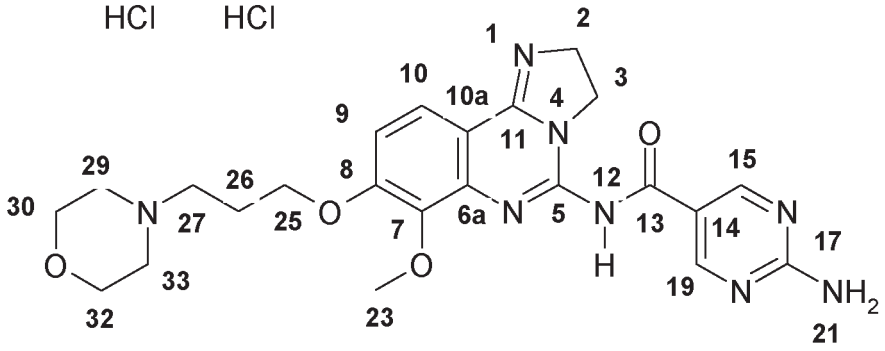
^{1}H-NMR-spectroscopy

Equipment and experimental parameters:

NMR spectrometer	Bruker, model Avance
Working frequency	500.13 MHz
Solvent	Dimethylsulfoxide (DMSO-d_6)
Internal reference compound	Tetramethylsilane (TMS)
Concentration	3.08 mg/mL solution
Diameter of sample tube	5 mm
Temperature	approx. 25°C
Technique	Fourier transform mode
Spectral width	20.65ppm

Digital resolution	0.079 Hz/Pt
Pulse length	4.5 µsec, 30° Pulse flip angle
Acquisition time	6.34sec
Relaxation time	0.5sec
No. of free induction decays	32

Structural Formula for the assignment of NMR signals



5

Chemical shift, signal multiplicity, relative number of nuclei :

H-atoms(a)	Chemical shift δ (ppm)	Multiplicity and coupling constants (b)	no. of nuclei H/molecule

H-26	2.32	M	2
H-29; H-33	3.11; 3.48	M; M	2; 2
H-30; H-32	3.83; 3.98	M; M	2; 2
H-27	3.29	M	2
$-OCH_3$	4.00	S	3
H-25	4.37	T	2
H-2; H-3	4.47; 4.19	T; T	2; 2
H-9	7.39	D	1
NH_2	7.54	S	2
H-10	8.21	D	1
H-16; H-20	8.97	S	1; 1
HCl	11.1; 12.6	bS; bS	1; 1
H-12	13.4	bS	1

a) Numbering refers to the structural formula for the assignment of NMR-signals.

b) S = Singlet bS = broad Singlet D = Doublet
T = Triplet M = Multiplet

The ^{1}H-NMR Spectrum of compound A is given in Figure 10.

^{13}C-NMR-spectroscopy

Equipment and experimental parameters

NMR spectrometer	Bruker, model Avance
Working frequency	125.76 MHz
Solvent	Dimethylsulfoxide-d_6 (DMSO)
Internal reference compound	Tetramethylsilane (TMS)
Concentration	37.2 mg/mL solution
Diameter of sample tube	5 mm
Temperature	approx. 27°C
Technique	Fourier transform mode
Spectral width	240.95 ppm
Digital resolution	0.4624 Hz/Pt
Pulse length	11.0 µsec, 90° Pulse flip angle
Acquisition time	1.08 sec
Relaxation time	4 sec
No. of free induction decays	256

Chemical shift, signal multiplicity, rel. no. of nuclei :

C-atoms(a)	Chemical shift δ (ppm)	Multiplicity and coupling constants (b)	no. of nuclei C/molecule
C-26	22.73	T	1
C-2; C-3	44.96; 45.65	T; T	1; 1
C-29; C-33	50.84	T	1; 1
C-27	53.01	T	1
OCH_3	61.24	Q	1
C-30; C-32	63.03	T	1; 1
C-25	66.81	T	1
C-10a	100.79	S	1
C-9	112.17	D	1
C-15	118.16	S	1
C-10	123.86	D	1
C-6a	132.43	S	1
C-7	133.95	S	1
C-5	148.58	S	1
C-11	156.29	S	1
C-8	156.89	S	1
C-16; C-20	160.20	D	1; 1
C-18	164.61	S	1
C=O	175.65	S	1

a) Numbering refers to the structural formula for the assignment of NMR-signals.

b) S = Single (C) D = Doublet (CH) T = Triplet (CH_2) Q = Quadruplet (CH_3)

The ^{13}C-NMR Spectra of compound A are given in Figures 11 and 12.

Mass Spectrometry

Instrumental Parameters

Mass spectrometer	Waters ZQ
Ionization mode	ESI (Electrospray-Ionization)
Solvent	CH_3CN/H_2O

Interpretation of the Spectrum

Mass value (*m/z*)	Rel. Intensity (%)	Ion Formation
481.2	46	$(M + H)^+$
354.1	5	$(C16\ H16\ N7\ O3)^+$
261.7	26	$(M + 2H + CH_3CN)^{+2}$
241.2	100	$(M + 2H)^{+2}$

The Mass Spectrum of compound A is given in Figure 13. Refer to the spectrum for relative peak intensities.

Elemental Analysis

Elemental analysis was conducted by Bayer Industry Services, Leverkusen, Germany.

Results

Element	Measured [%]	Calculated [%]	Calculated including 7.0 % water [%]	Difference
C	47.5	49.9	46.4	1.1
H	5.7	5.5	5.9	0.2
N	19.1	20.3	18.8	0.3
O	18.1	11.6	17.0	1.1
Cl	11.9	12.8	11.9	0.0
Sum	102.3	100.1	100.0	-

The elemental analysis is consistent with compound A with 7% water.

Further method of preparation of compound "A"

To a suspension of 366 g of compound of formula (I) in 1015 g water, 183 g of an aqueous hydrochloric acid solution (32%) were added while maintaining the temperature at 20 °C (+-2°) until a pH of 3 to 4 was reached. The resulting mixture was stirred at room temperature for more than 10 min. filtered and the filtercake washed with additional 82 g of water. The filtrate was adjusted to pH 1.8 to 2.0 using aqueous hydrochloric acid solution (32%). The mixture was stirred for 10 min. at room temperature, 146g of ethanol (100%) were added and stirred for another 10 min.. 1 g of seed crystals were added, followed by 1592 g ethanol within 5 h. The resulting substance was removed by filtration,

washed with a water-ethanol mixture and dried in vacuo to give 410 g (97%) of compound A of a purity >99% according to HPLC.

Molecular profiling of Compound A in 24 breast tumor cell lines indicated that tumor cells with either *PIK3CA* mutation and/or HER2 expression were extremely sensitive to Compound A with an average IC_{50} value of 17 (n=7) and 19 nM (n=8), respectively. In contrast, wild type *PIK3CA* and HER2 negative breast cancer cells (n=12) were relatively insensitive or resistant to Compound A with an average IC_{50} value of 773 nM (~40-fold higher). Using a set of breast cancer cell lines representing differential receptor expression status and genetic alterations of *PIK3CA* and *PTEN*, the anti-proliferative and apoptotic effects of Compound A were investigated. With regard to apoptosis induction, Compound A demonstrated strong activity in *PIK3CA* mutant and or HER2 positive breast tumor cells (such as BT20, BT474).

Next, the molecular features responsible for the sensitivity and/or resistance to Compound A mediated induction of apoptosis were identified. It was found that the expression of Bcl-2, but not Mcl-1 nor surviving, determined sensitivity to apoptosis. Thus, tumor cells that lack Bcl-2 expression (such as KPL-4, BT-474, and BT-20), even in the presence of high levels of EGFR and phospho-ERK in BT-20 cells, immediately underwent apoptosis after exposure to Compound A. On the other hand, cells expressing high level of Bcl-2, such as T47D ($PIK3CA^{mut}$), were resistant to apoptosis induced by Compound A, despite the potent anti-proliferative activity of Compound A (single-digit nM IC_{50}). Combining Compound A with ABT-737, an inhibitor of Bcl-2, sensitized T47D cells to apoptosis, further supporting the hypothesis that simultaneous inhibiting PI3K and Bcl-2 could synergistically enhance the tumor killing effect in Bcl-2 positive breast cancer.

On the other hand, $PTEN^{null}$, $EGFR^{high}$ and Bcl-2 negative MDA-MB-468 tumor cells, are not only insensitive to inhibition of proliferation, but also resistant to induction of apoptosis by Compound A. Inhibition of mTORC1 by rapamycin and/or inhibition of mTORC2 by the knockdown of Rictor, sensitizes MDA-MB468 cells to Compound A with the respect to inhibition of proliferation and induction of apoptosis.

In conclusion, Compound A was extremely effective at inducing apoptosis in breast cancer cells expressing HER2 and/or *PIK3CA* mutation in the absence of Bcl-2. Compound A in combination with anti-Bcl agents or mTOR inhibitors might be the promising approach to achieve tumor responses in Bcl-2 positive tumors or EGFR expressing/$PTEN^{null}$ breast tumors, respectively. These findings provide a retionale for developing personalized therapies for the treatment of molecular subtypes of breast cancer.

Figure 1 shows the correlation of IC_{50}s of Compound A in proliferation assays and genetic status of breast cancer cell lines.

Figure 2 shows kinetics of cell growth inhibition by Compound A. The Xcelligence technique (Roche, Germany) was used to monitor effects on tumor cell growth after treatment by Compound A. Cell index (CI), which correlates with the number of cells attached to the bottom of the plate (Giordano C, Masi A, Pizzini A, Sansone A, Consalvi V, Chiaraluce R, Lucente G. Synthesis and activity of fibrillogenesis peptide inhibitors related to the 17-21 beta-amyloid sequence. Eur J Med Chem. 2009;44:179-189), was detected every 15 minutes for 80 hours treatment period. CI was normalized to the time point of treatment (at 24h CI =1).

Figure 3 shows induction of PARP cleavage by Compound A in BT-20, BT-474, ZR-75-1, T47D and MDA-MB468 cells investigated at the indicated

timepoint by western blot analysis using GAPDH as an internal protein control.

Figure 4 shows pro-survival molecules of the Bcl family investigated in untreated cells (A). Cells were lysed and western blot analysis was performed to detect Bcl-2, Mcl-1, and survivin. GAPDH was used as an internal protein control.

Figure 5 shows quantitative analysis of the combination effect of compound A and ABT-737 on Caspase 3 and 7 induction in T47D cells (C). Apoptosis induction by compound A and ABT-737 as a single agent and in combination was investigated by Caspase-Glo ® 3/7 (Promega, USA) and analyzed by software Analyze 5 (Bayer HealthCare, Germany). The combination effects are depicted by isobologram and combination index based on the formula described by Chou (Chou et al., 2006). Combination index < 1, =1, and > 1 indicate synergistic, additive, and antagonistic effects, respectively.

Figure 6 shows MDA-MB-468 cells transfected with Lentivirus expressing shRNA against Rictor. The cellular expression of the mTORC2 component Rictor was assessed by western blot analysis (A). Induction of PARP cleavage by compound A treatment in combination with inhibition of mTORC1 or mTORC2 (B). shControl and shRictor MDA-MB468 cells were treated with indicated agents for 48 hours, and cleavage of PARP was analyzed. GAPDH was used as an internal protein control.

CONTROL SUBSTANCES

Rapamicin obtained from Sigma (St Louis, MO, USA) was used as a reference inhibitor. ABT-737 was obtained from Selleck Chemicals (Houston, TX, USA)

In conclusion, Compound A was extremely effective at inducing apoptosis in breast cancer cells expressing HER2 and/or a *PIK3CA* mutation in the absence of Bcl-2. Compound A in combination with anti-Bcl agents or mTOR inhibitors should provide a promising approach to achieve tumor responses in Bcl-2 positive tumors or EGFR expressing/PTEN^{null} breast tumors, respectively. These findings provide a retionale to develop personalized therapies for the treatment of molecular subtypes of breast cancer.

Hence, as mentioned *supra*, the present invention relates to the use of biomarkers involved in the modification of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN for predicting the sensitivity and/or resistance of a patient with cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer, to a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined herein, thus providing retionale-based synergistic combination as defined herein to overcome the resistance.

In accordance with an embodiment, the present invention relates to the use of biomarkers involved in the modification of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN for predicting the sensitivity and/or resistance of a patient with cancer, e.g. breast cancer, in particular inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer, to a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined herein, thus providing a retionale-based synergistic combination as defined herein to overcome the resistance (patient stratification).

In accordance with an embodiment, the present invention relates to a method of determining the level of a component of one or more of Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN, wherein :

- in said Bcl expression, said component is Bcl, for example,
- in said HER family expression and/or activation, PIK3CA signaling, said component is EGF-R, for example, and
- in said loss of PTEN, said component is PTEN, for example.

Further, as mentioned *supra*, the present invention thus relates to combinations of :

a) a 2,3-dihydroimidazo[1,2-c]quinazoline compound as defined *supra*, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; or pharmaceutical compositions containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

and

b) one or more further active agents, in particular an active agent selected from an anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agent, more particularly one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, such as ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;

- a Bcl binding peptide ;
- a Bcl siRNA, such as PNT-2258 ;
- an antisense therapy oligonucleotide, such as BclKlex ; and
- an inhibitor of the mTOR pathway, such as rapamycin or a rapamycin analogue, such as Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235,

as defined *supra*.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is inflammatory breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is triple negative breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is Her2 receptor positive breast cancer.

In accordance a particular embodiment of any of the above aspects, or embodiments thereof, of the present invention, said breast cancer is hormone receptor positive breast cancer.

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CLAIMS

1. Use of 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide,or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
as a sole active agent,
or of a pharmaceutical composition containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,
for the preparation of a medicament for the treatment or prophylaxis of inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, or hormone receptor positive breast cancer.

2. A combination of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof; or a pharmaceutical composition containing such a compound or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, selected from ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL

(Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;

- a Bcl binding peptide ;
- a Bcl siRNA, which is PNT-2258 ;
- an antisense therapy oligonucleotide, which is BclKlex ; and
- an inhibitor of the mTOR pathway, selected from Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, selected from WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

3. The combination according to claim 2, wherein said further active agent is rapamycin.

4. The combination according to claim 2, wherein said further active agent is ABT-737.

5. A pharmaceutical composition which comprises a combination of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, selected fromABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-

)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;

- a Bcl binding peptide ;
- a Bcl siRNA, which is PNT-2258 ;
- an antisense therapy oligonucleotide, which is BclKlex ; and
- an inhibitor of the mTOR pathway, selected from Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, selected from WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235.

6. Use of a combination of :

a) 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
or of a pharmaceutical composition containing said 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

and

b) one or more further active agents selected from the group consisting of :

- a Bcl inhibitor, selected from ABT-737, ABT-263 (Navitoclax), EM20-25, YC137, GX-015-070 (Obatoclax), Tetrocarcin A, UCB-1350883, AT-101 ((-

)-Gossypol), SPC-2004 (Beclanorsen), IG-105, WL-276, BI-97C1, I-VRL (Immunovivorelbine), DATS (Allitridin), CNDO-103 (Apogossypol), D-G-3139 (Genasense), Evotec, PIB-1402, EU-517 ;

- a Bcl binding peptide ;
- a Bcl siRNA, which is PNT-2258 ;
- an antisense therapy oligonucleotide, which is BclKlex ; and
- an inhibitor of the mTOR pathway, selected from Rapamycin (Sirolimus), Everolimus (RAD-001, Afinitor), Zotarolimus (ABT-578, Endeavor), Temisirolimus (CCI-779, Torisel), Ridaforolimus (AP-23576, MK-8669), TAFA-93, or an inhibitor of mTOR kinase, such as WYE-132, OSI-027, INK-128, OSI-027, AZD-2014, AZD-8055, CC-223, ABI-009, EXEL-3885, EXEL-4451, NV-128, OXA-01, PKI-402, SB-2015, WYE-354, KU-0063794, X-387, BEZ-235 ;

or a pharmaceutical composition containing such a combination,

for the preparation of a medicament for the treatment or prophylaxis of inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer, hormone receptor positive breast cancer.

7. Use of a biomarker which is Bcl expression, HER family expression and/or activation, PIK3CA signaling and / or loss of PTEN for predicting the sensitivity and/or resistance of a patient with inflammatory breast cancer, triple negative breast cancer, Her2 receptor positive breast cancer or hormone receptor positive breast cancer, to the compound according to claim 1, thus providing rationale-based synergistic combination according to claim 2 or 3 to overcome the resistance (patient stratification).