effective treatments for pancreatic cancer, and especially pancreatic cancer that is associated with pain, highlights an unmet medical need for more efficient treatment strategies that improve the clinical management of patients afflicted with pancreatic cancer without significantly increasing toxicity. Considering the limited life-expectancy of patients suffering from pancreatic cancer, improvements in either survival time or quality-of-life are highly meaningful goals. Moreover, a treatment capable of simultaneously improving both of these aspects would be of particular worth.

Thus, the invention aims to solve the technical problem of providing an active ingredient that improves prior art methods for the treatment of advanced adenocarcinoma pancreatic cancer.

The invention aims to solve the technical problem of providing an active ingredient that improves prior art methods for the treatment of advanced adenocarcinoma pancreatic cancer that is associated with pain or the requirement of opioid analgesics for the treatment of disease related pain.

The invention aims to solve the technical problem of providing an active ingredient that improves prior art methods for the treatment of advanced adenocarcinoma pancreatic cancer in patients harboring a specific gene or gene expression predictor factors (i.e. a genetic/transcriptomic fingerprint).

**SUMMARY** ~~OF THE INVENTION~~

The present ~~invention~~disclosure relates to a method for the treatment of cancer in a human patient, wherein said method comprises administering to a human patient in need thereof, a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, optionally combined with at least one antineoplastic agent.

In one aspect, there is provided use of a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor in the manufacture of a medicament to treat cancer in a human patient, wherein said patient is initially selected for treatment upon the predictor factor of disease related pain intensity or upon the predictor factor of gene expression.

By "antineoplastic agent", it is referred herein to a medicament for the treatment of cancers. For example, the compounds as depicted in: Actualite Pharmaceutiques n °302 (Oct 1992) on pages 38 to 39 and 41 to 43; or in the United States Food and Drug Administration (USFDA) list of approved drugs for oncology; or in the National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012 (DHHS Publication Number 2012-150); the content of which is incorporated by reference and is selected from, an alkylating agent, an antimitotic agent, an antimetabolic

Kaposi sarcoma, laryngeal cancer, mastocytosis, melanoma, myelofibrosis, myelodysplastic syndrome (MDS), multiple myeloma, non-small-cell lung carcinoma (NSCLC), lung cancer (small cell), melanoma, nasopharyngeal carcinoma, neuroendocrine tumors, neuroblastoma, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pituitary adenoma, prostate cancer, rectal cancer, renal cell (kidney) carcinoma (RCC), salivary gland cancer, skin cancer (nonmelanoma), small intestine cancer, small lymphocytic lymphoma (SSL), soft tissue sarcoma, squamous-cell carcinoma, T cell lymphoma, testicular cancer, throat cancer, thyroid cancer, triple negative breast cancer, urethral cancer, and uterine cancer.

In one embodiment, the present ~~invention~~disclosure relates to the use as defined above wherein a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is an inhibitor of kinase activity selected from the tyrosine kinases of: c-Kit, PDGFR, Lyn, Fyn, and DDR1.

In a particular embodiment, the tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is masitinib or a pharmaceutical acceptable salt thereof, in particular the mesilate salt.

By "predictor factor" or "biomarker", it is referred herein as a single characteristic or group of characteristics that is evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In relation to the present invention, the term "predictor factor" or "biomarker" refers also to the terms, predicative biomarker, prognostic biomarker, molecular marker, genetic marker, gene predictor set, genetic fingerprint, transcriptional fingerprint, genetic print, genetic signature, tumor marker, cancer marker, biological marker, biochemical marker, and biological indicator.

According to one embodiment, the present ~~invention~~disclosure relates to the use of a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor as defined above, wherein said patient is initially selected for treatment based upon the predictor factor of pain intensity.

Thus, in one embodiment, the present ~~invention~~disclosure relates to the use of a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for the manufacture of a medicament to treat cancer in a human patient, wherein said cancer is associated with pain or requires administration of opioid analgesics for treatment of disease related pain, in human patient, wherein a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, is administered to patient in need thereof, optionally combined with at least one antineoplastic agent.

In another embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said patient is afflicted by cancer that is associated with pain or that requires administration of opioid analgesics for treatment of disease related pain, and wherein 'pain' is defined as at least one reported occurrence of a non-zero pain intensity, as determined using an (appropriate) pain intensity assessment tool. It is implicit therefore, that according to the predictor factor of pain intensity, and in the absence of any other independent predictor factor, said treatment of patient afflicted by cancer that is not associated with pain or the requirement of opioid analgesics for the treatment of disease related pain is inadvisable.

In yet another embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said patients is afflicted by cancer that is associated with pain or that requires administration of opioid analgesics for treatment of disease related pain, and wherein 'pain' is defined as above according to an (appropriate) pain intensity assessment tool, including but not limited to: the Verbal Rating Scale, the Visual Analogue Scale, the Numerical Rating Scale, the Behavior Rating Scale, the Picture Scale, the Box Scale, the Descriptor Differential nScale, the European Organization for Research and Treatment of Cancer quality-of-life questionnaire for pancreatic cancer (EORTC QLQ-PAN26), the Brief Pain Inventory (BPI), or the McGill Pain Questionnaire.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said patient is afflicted by cancer that is associated with pain that requires administration of opioid analgesics for treatment of disease related pain, and wherein 'pain' is defined as at least one reported occurrence of a Visual Analogue Scale (VAS) pain intensity score of greater than 5 (e.g. VAS >5 mm as measured on a 100 mm scale, or 5%); or a VAS pain intensity score of greater than 10 (e.g. VAS >10 mm as measured on a 100 mm scale, or 10%); or even a VAS pain intensity score of greater than 20 (e.g. VAS >20 mm as measured on a 100 mm scale, or 20%).

In another embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said patient is afflicted by cancer that is associated with pain or that requires administration of opioid analgesics for treatment of disease related pain, and wherein 'pain' is defined as at least one reported occurrence of an equivalent measure of said VAS pain intensity threshold, or at least one reported occurrence of moderate to intolerable pain according to a multidimensional or categorical pain assessment tool pain intensity rating.

In another embodiment the present ~~invention~~disclosure relates to the method as defined above wherein said patient is afflicted by pancreatic cancer that is associated with pain or the requires the administration of opioid analgesics for treatment of disease related pain, and wherein pain is defined as at least one reported occurrence of a Visual Analogue Scale (VAS) pain intensity score of greater than 20 (e.g. VAS >20 mm as measured on a 100 mm scale, or 20%).

According to one embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein said patient is initially selected for treatment based upon gene expression predictor factors.

According to one embodiment, said gene expression predictor factors are derived from a blood sample of a patient, preferably on a whole peripheral blood sample of said patient. Peripheral blood is blood that circulates through the heart, arteries, capillaries and veins. The terms "whole blood" are used as opposed to a fraction of blood, obtained through separation of particular components of blood. An example of fraction is peripheral blood mononuclear cells. Hence, in one particular embodiment said gene expression predictor factors are derived from peripheral blood cell samples collected prior to treatment with said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof.

Thus, in one embodiment, the present ~~invention~~disclosure relates to a method of treatment of cancer, wherein a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, optionally combined with at least one antineoplastic agent, is administered to a patient in need thereof, wherein said patient has a peripheral blood up-regulation or down-regulation of at least one of the following genes: ACOX-1 , TNFRSFS10B, RPS23, ABCC3, LYN, HIF1 ALPHA, ABCC1 , IGJ, UBE2H, or PARP-2, or homologous thereof.

The up-regulation or down-regulation of a given gene in a given patient is quantified in terms of a Delta Cycle Threshold (DCt) value, which is the gene expression level with respect to one or more reference genes. Such reference genes, or housekeeping genes, are characterized by a constant level of expression and therefore serve as an internal control. DCt values are inversely proportional to the level of gene expression; therefore, in the case of up-regulated genes a lower DCt value indicates a greater level of expression, whilst in the case of down-regulated genes a higher DCt value indicates a lower level of expression. It is understood that slight modifications to the defined Delta Cycle Threshold cut-offs are implicit,

for example in the range of ±10% or even ±25%, reflecting the fact that the optimal threshold may be located in proximity to those cut-offs tested and that the patient population studied was only a representative cohort of the general cancer population.

The term "homologous" is defined as a polynucleotide sequence having a degree of identity of at least 80%, preferably 85%, more preferably 90%, and even more preferably 99% of the gene sequence (full length). The degree of identity refers to sequence identity between two sequences. Identity can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When an equivalent position in the compared sequences is occupied by the same base, then the molecules are identical at that position. Various alignment algorithms and/or programs may be used for determining the homology of two sequences, including FASTA and BLAST.

In another embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein said patient has a concomitant up-regulation or down-regulation of at least two genes selected from: ACOX-1 , TNFRSFS10B, RPS23, ABCC3, LYN, HIF1 A, ABCC1 , IGJ, UBE2H, and PARP-2. For example, dual-gene combinations include, but are not restricted to: the concomitant up-regulation of genes ACOX-1 and TNFRSF10B; the concomitant down-regulation of gene RPS23 and up-regulation of gene ACOX-1 ; the concomitant up-regulation of genes ABCC3 and LYN; the concomitant up-regulation of genes HIF1 A and TNFRSF10B; the concomitant down-regulation of genes ABCC1 and IGJ; the concomitant down-regulation of genes UBE2H and PARP-2. Individually, these pairs of regulated genes are referred to as 'gene expression predictor factors', and collectively they are referred to as the 'genetic fingerprint' or 'transcriptional fingerprint'. Six pairs of regulated genes compose the 'genetic/transcriptional fingerprint'. Patients identified as having at least one gene expression predictor factor are considered to be harboring the 'genetic/transcriptional fingerprint'. It is implicit that in the absence of any other independent predictor factor, said treatment of any patient lacking said genetic/transcriptional fingerprint is inadvisable.

In one embodiment, the concomitant up-regulation of genes ACOX-1 and TNFRSF10B corresponds to patient Delta Cycle Threshold values of less than or equal to 3.81 for ACOX-1 and less than or equal to 7.63 for TNFRSF10B; more preferably to patient Delta Cycle Threshold values of less than or equal to 3.36 for ACOX-1 and less than or equal to 6.71 for TNFRSF10B;and even more preferably to patient Delta Cycle Threshold values of less than or equal to 3.05 for ACOX-1 and less than or equal to 6.1 for TNFRSF10B.

In one embodiment, the concomitant down-regulation of gene RPS23 and up-regulation of gene ACOX-1 corresponds to patient Delta Cycle Threshold values of greater than 0.26 for RPS23 and less than or equal to 3.81 for ACOX-1 ; more preferably to patient Delta Cycle Threshold values of greater than 0.32 for RPS23 and less than or equal to 3.36 for ACOX-1 ; and even more preferably to patient Delta Cycle Threshold values of greater than 0.35 for RPS23 and less than or equal to 3.05 for ACOX-1 .

In one embodiment, the concomitant up-regulation of genes ABCC3 and LYN corresponds to patient Delta Cycle Threshold values of less than or equal to 5.38 for ABCC3 and less than or equal to 2.06 for LYN; more preferably to patient Delta Cycle Threshold values of less than or equal to 4.73 for ABCC3 and less than or equal to 1 .82 for LYN; and even more preferably to patient Delta Cycle Threshold values of less than or equal to 4.3 for ABCC3 and less than or equal to 1 .65 for LYN.

In one embodiment, the concomitant up-regulation of genes HIF1 A and TNFRSF10B corresponds to patient Delta Cycle Threshold values of less than or equal to 4.94 for HIF1 A and less than or equal to 7.06 for TNFRSF10B; more preferably to patient Delta Cycle Threshold values of less than or equal to 4.35 for HIF1 A and less than or equal to 6.22 for TNFRSF10B; and even more preferably to patient Delta Cycle Threshold values of less than or equal to 3.95 for HIF1 A and less than or equal to 5.65 for TNFRSF10B.

In one embodiment, the concomitant down-regulation of genes ABCC1 and IGJ corresponds to patient Delta Cycle Threshold values of greater than 2.63 for ABCC1 and less than or equal to 5.29 for IGJ; more preferably to patient Delta Cycle Threshold values of greater than 3.15 for ABCC1 and less than or equal to 6.35 for IGJ; and even more preferably to patient Delta Cycle Threshold values of greater than 3.5 for ABCC1 and less than or equal to 7.05 for IGJ.

In one embodiment, the concomitant down-regulation of genes UBE2H and PARP-2 corresponds to patient Delta Cycle Threshold values of greater than 2.78 for UBE2H and greater than 5.33 for PARP-2; more preferably to patient Delta Cycle Threshold values of greater than 3.33 for UBE2H and greater than 6.39 for PARP-2; and even more preferably to patient Delta Cycle Threshold values of greater than 3.7 for UBE2H and greater than 7.1 for PARP-2.

In another embodiment, the present ~~invention~~disclosure relates to a method of treatment of cancer, wherein a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or

a pharmaceutically acceptable salt thereof, optionally combined with at least one antineoplastic agent, is administered to a patient in need thereof, wherein said patient has a peripheral blood up-regulation of the gene ACOX-1 , or homologous thereof.

In one embodiment, the up-regulation of gene ACOX-1 corresponds to patient Delta Cycle Threshold value of less than or equal to 3.81; more preferably of less than or equal to 3.36; and even more preferably of less than or equal to 3.05.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein masitinib is administered at a daily dose of 4.5 to 12.0 mg/kg/day, with the preferred embodiment for patients with cancer being a starting daily dose of 6.0 to 7.5 mg/kg/day.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein masitinib is dose escalated by increments of 1 .5 mg/kg/day to reach a maximum of 12.0 mg/kg/day.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, is administered orally.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, is administered twice a day.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above comprising a long term administration of an effective amount of said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, over more than 3 months.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a pharmaceutically acceptable salt thereof, is administered in combination with the at least one antineoplastic agent, as a neoadjuvant, adjuvant, concomitant, or concurrent regimen.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, especially masitinib or a

pharmaceutically acceptable salt thereof, and the at least one antineoplastic agent are administered separately, simultaneously or sequentially in time.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above, for treatment of pancreatic cancer, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered in combination with at least one antineoplastic agent selected from marketing medicaments for the treatment of cancer.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein said patient suffers from unresectable adenocarcinoma pancreatic cancer or metastatic adenocarcinoma pancreatic cancer.

In one embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein said pancreatic cancer patient is in need thereof, as defined by either the defined gene expression predictor factor or pain intensity predictor factor, and wherein said at least one antineoplastic agent is selected from: gemcitabine (Gemzar®; Lilly), erlotinib (Tarceva®; Roche), paclitaxel (Taxol®, Abraxane®; Bristol-Myers Squibb), Folfirinox, 5-fluorouracil (5-FU), capecitabine, cisplatin, oxaliplatin, irinotecan, leucovorin, and any combination of these antineoplastic agents.

In one embodiment, said at least one antineoplastic agent is gemcitabine.

In one preferred embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein a product consisting of gemcitabine and masitinib or a pharmaceutically acceptable salt or hydrate thereof is used.

In one preferred embodiment, the present ~~invention~~disclosure relates to the method as defined above, wherein masitinib is administered daily at a starting dose of 6.0 ± 1 .5 mg/kg/day with a maximum allowable dose of 9.0 mg/kg/day, and gemcitabine is administered at a weekly dose of 1000 ± 250 mg/m$^2$ of patient surface area for up to seven consecutive weeks as a start, followed by a week off-treatment, followed by cycles of weekly dose of 1000 ± 250 mg/m$^2$ for 3 weeks, every 28 days

According to another embodiment, the present ~~invention~~disclosure relates to a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for use in a method for the treatment of a cancer as defined above, optionally in combination with at least one antineoplastic agent.

According to another embodiment, the present ~~invention~~disclosure relates to a pharmaceutical composition or kit comprising a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for use in a method for the treatment of a cancer as defined above, optionally in combination with at least one antineoplastic agent.

According to another embodiment, the present ~~invention~~disclosure relates to the use of a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for the preparation of a medicament, or a pharmaceutical composition, for the treatment of a cancer as defined above, optionally in combination with at least one antineoplastic agent.

According to another ~~aspect~~embodiment, the ~~invention~~disclosure relates to a therapeutic management plan for the treatment of cancer, in particular of pancreatic cancer in a human patient, wherein said management plan comprises the identification of treatable patients based upon the defined predictor factor of gene expression.

In one embodiment, the gene expression therapeutic management plan mentioned above is applied to patients with pancreatic cancer; wherein, if a patient harbors at least one gene expression predictor factor, and is therefore classified as belonging to the defined 'genetic/ transcriptional fingerprint' subpopulation, then said patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine. If a patient does not harbor at least one gene expression predictor factor, and is therefore classified as belonging to the defined 'non genetic/ transcriptional fingerprint' subpopulation, then said patient is treated with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.

In another embodiment, the gene expression therapeutic management plan mentioned above is applied to patients with cancer other than pancreatic cancer; wherein, if a patient harbors at least one gene expression predictor factor then said patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one antineoplastic agent. If a patient does not harbor at least one gene expression predictor factor then said patient is treated with at least one antineoplastic agent.

According to another ~~aspect~~embodiment, the ~~invention~~disclosure relates to a therapeutic management plan for the treatment of cancer, in particular of pancreatic cancer in a human patient, based upon the defined predictor factor of pain intensity, wherein said management plan comprises:

a) determining if said patient is afflicted by cancer that is associated with pain or requires administration of at least one opioid analgesic for treatment of disease related pain, with pain intensity preferably defined as a reported occurrence of a Visual Analogue Scale (VAS) score higher than 5 mm on a 100 mm scale; and optionally

b) determining if said disease related pain is defined as a reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than a predetermined value for said cancer on a 100 mm scale, and in particular for pancreatic cancer a Visual Analogue Scale (VAS) pain intensity score higher than 20 mm on a 100 mm scale.

In one embodiment said predetermined value for said disease related pain is 20 mm on a 100 mm scale.

In one embodiment, the pain intensity therapeutic management plan mentioned above is applied to patients with pancreatic cancer; wherein, if the result of step (a) is negative, then the patient is treated with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine. If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one drug targeting epidermal growth factor receptor (EGFR), and particularly erlotinib, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one mitotic inhibitor, and particularly paclitaxel, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one combination of drugs including fluorouracil, leucovorin, irinotecan, or oxaliplatin, and particularly Folfirinox. If the result of step (a) is positive and the result of step (b) is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.

In another embodiment, the pain intensity therapeutic management plan mentioned above is applied to patients with cancer other than pancreatic cancer; wherein, if the result of step (a) is negative, then the patient is treated with at least one antineoplastic agent. If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one antineoplastic agent. If the result of step (a) is positive and the result of step (b) is

positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one antineoplastic agent.

According to another ~~aspect~~embodiment, the ~~invention~~disclosure relates to a global therapeutic management plan for the treatment of cancer, in particular of pancreatic cancer in a human patient, wherein said management plan comprises the identification of treatable patients based upon sequential application of the gene expression therapeutic management plan and pain intensity therapeutic management plan. Thus, in the pain intensity therapeutic management plan mentioned above, step (a) can be preceded by step (a') consisting in the identification of patients that harbor at least one gene expression predictor factor, as described above.

In one embodiment, the global therapeutic management plan mentioned above is applied to pancreatic cancer, wherein: if the result of step (a') is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; if the result of step (a') is negative, then step (a) of the pain intensity therapeutic management plan for pancreatic cancer is invoked. Specifically, said management plan comprises:

a) determining if said patient is afflicted by pancreatic cancer that is associated with pain or requires administration of at least one opioid analgesic for treatment of disease related pain, with pain intensity preferably defined as a reported occurrence of a Visual Analogue Scale (VAS) score higher than 5 mm on a 100 mm scale; and optionally
b) determining if said disease related pain is defined as a reported occurrence of a

Visual Analogue Scale (VAS) pain intensity score higher than 20 mm on a 100 mm scale.

If the result of step (a) is negative, then the patient is treated with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.

If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one drug targeting epidermal growth factor receptor (EGFR), and particularly erlotinib, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one mitotic inhibitor, and particularly paclitaxel, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one combination of

## CLAIMS

1. A method for the treatment of cancer in a human patient, wherein said method comprises administering to a human patient in need thereof, at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor.

2. The method of claim 1, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered in combination with at least one antineoplastic agent.

3. The method of claim 2, wherein said antineoplastic agent is selected from: an alkylating agent, an antimitotic agent, an antimetabolic agent, an anti-topoisomerase I agent, a platinum analog, an antibiotic agent, a hormonal agent, an anti-angiogenic agent, a genotoxic agent, a cytotoxic agent, a biologic agent, or an additional tyrosine kinase inhibitor. In particular: abarelix, abiraterone acetate, aldesleukin, altretamine, anastrozole, arsenic trioxide, asparaginase, axitinib, azacitidine, bendamustine hydrochloride, bevacizumab, bexarotene, bicalutamide, leomycin, bortezomib, brentuximab vedotin, busulfan, cabazitaxel, Campath, Camptosar, capecitabine, carboplatin, carfilzomib, carmustine, cetuximab, chlorambucil, cisplatin, cladribine (2CDA), clofarabine, crizotinib, cyclophosphamide, cytarabine (ARA-C), cytosine arabinoside, dacarbazine, dactinomycin, dasatinib, daunorubicin, decitibine, degarelix, denileukin, docetaxel, doxorubicin, epirubicin, eribulin mesylate, erlotinib, estramustine phosphate, etoposide, everolimus, exemestane, floxuridine, fludarabine, fluoro-5-uracile (5 fluorouracil), fluorouridine-desoxyribose, flutamide, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, ipilimumab, irinotecan, ixabepilone, lapatinib, letrozole, leucovorin, leuprolide acetate, lomustine, mechlorethamine, megestrol, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, nelarabine, nilotinib, nilutamide, Nolvadex, ofatumumab, oxaliplatin, paclitaxel, panitumumab, pazopanib, pegaspargase, peginterferon alfa-2b, pemetrexed, pentostatin, pertuzumab, plerixafor, pralatrexate, procarbazine, Proleukin, romidepsin, sapacitabine, sipuleucel-T, sorafenib, streptozocin, sunitinib, tamoxifen, temozolomide, temsirolimus, teniposide, testolactone, tezacitabine, thioguanine, thiotepa, topotecan, toremifene citrate, trastuzumab, triptorelin, troxacitabine, valrubicin, Valstar, vandetanib, vemurafenib, vinblastine, vincristine sulfate, vinorelbine, vismodegib, vorinostat, xeloda, ziv-aflibercept, zoledronic acid, FOLFOX (oxaliplatin + 5-fluorouracil + folinic acid), FOLFIRI (irinotecan + 5-fluorouracil + folinic

acid), FOLFIRINOX (oxaliplatin + irinotecan + 5 fluorouracil + folinic acid), and any combination of these antineoplastic agent.

4. The method of any one or more of claims 1 to 3, wherein said patient is in need of treatment for at least one cancer selected from: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adrenocortical carcinoma, anal cancer, B cell lymphoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brainstem glioma, brain tumor, breast cancer, cervical cancer, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colorectal cancer (CRC), endometrial cancer, esophageal cancer, eye cancer, gallbladder cancer, gastric (stomach) cancer, gastrointestinal stromal tumor (GIST), glioblastoma multiforme (GBM), hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) carcinoma (HCC), Hodgkin's lymphoma and non-Hodgkin's lymphomas, Kaposi sarcoma, laryngeal cancer, mastocytosis, melanoma, myelofibrosis, myelodysplastic syndrome (MDS), multiple myeloma, non-small-cell lung carcinoma (NSCLC), lung cancer (small cell), melanoma, nasopharyngeal carcinoma, neuroendocrine tumors, neuroblastoma, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pituitary adenoma, prostate cancer, rectal cancer, renal cell (kidney) carcinoma (RCC), salivary gland cancer, skin cancer (nonmelanoma), small intestine cancer, small lymphocytic lymphoma (SSL), soft tissue sarcoma, squamous-cell carcinoma, T cell lymphoma, testicular cancer, throat cancer, thyroid cancer, triple negative breast cancer, urethral cancer, and uterine cancer.

5. The method of any one or more of claims 1 to 4, wherein said tyrosine kinase inhibitor or a mast cell inhibitor is an inhibitor of kinase activity selected from the tyrosine kinases of: c-Kit, PDGFR, Lyn, Fyn and DDR1.

6. The method of claim 5 wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is masitinib or a pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein the pharmaceutical acceptable salt of masitinib is a mesilate salt.

8. The method of any one or more of claims 1 to 7, wherein said patient is initially selected for treatment based upon the predictor factor of disease related pain intensity.

9. The method of claim 8, wherein said patient is afflicted by cancer that is associated with pain or the requirement of opioid analgesics for the treatment of disease related pain.

10. The method of claim 9, wherein said pain is defined as at least one reported occurrence of non-zero pain intensity, as determined using a pain intensity assessment tool.

11. The method of claim 9, wherein said disease related pain is defined as at least one reported occurrence of a unidimensional pain intensity assessment tool score of greater than 20%.

12. The method of claim 9, wherein said patient is diagnosed as having moderate to intolerable cancer related pain intensity according to the pain assessment tool used.

13. The method of claim 8, wherein said patient suffers from cancer that is associated with pain or requires administration of opioid analgesics for treatment of disease related pain, and wherein said disease related pain is defined as at least one reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than 5 mm on a 100 mm scale.

14. The method of claim 8, wherein said patient suffers from pancreatic cancer associated with pain or requires administration of opioid analgesics for treatment of disease related pain, and wherein said disease related pain is defined as at least one reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than 20 mm on a 100 mm scale.

15. The method of any one or more of claims 1 to 7, wherein said patient is initially selected for treatment based upon the predictor factor of gene expression.

16. The method of claim 15, wherein said gene expression predictor factors are derived from analysis of RNA expression in peripheral blood cell samples.

17. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon an up-regulation of ACOX-1, preferablycorresponding to a Delta Cycle Threshold value of less than or equal to 3.81; more preferably of less than or equal to 3.36; and even more preferably of less than or equal to 3.05.

18. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation of gene ACOX-1, preferably corresponding to a Delta Cycle Threshold value less than or equal to 3.05, and an up-regulation of gene TNFRSF10B preferably corresponding to a Delta Cycle Threshold value of less than or equal to 6.1.

19. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation of gene RPS23, preferably corresponding to a Delta Cycle Threshold value of greater than 0.35, and an up-regulation for gene ACOX-1, preferably corresponding to a Delta Cycle Threshold value of less than or equal to 3.05.

20. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene ABCC3, preferably corresponding to a Delta Cycle Threshold value less than or equal to 4.3, and an up-regulation for gene LYN, preferably corresponding to a Delta Cycle Threshold value of less than or equal to 1.65.

21. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene HIF1A, preferably, corresponding to a Delta Cycle Threshold value less than or equal to 3.95, and an up-regulation for gene TNFRSF10, preferably corresponding to a Delta Cycle Threshold value of less than or equal to 5.65.

22. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation for gene ABCC1, preferably corresponding to a Delta Cycle Threshold value greater than 3.5, and a down-regulation for gene IGJ, preferably corresponding to a Delta Cycle Threshold value of greater than 7.05.

23. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene UBE2H, preferably corresponding to a Delta Cycle Threshold value greater than 3.7, and a down-regulation for gene PARP-2, preferably corresponding to a Delta Cycle Threshold value of greater than 7.1.

24. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation of geneACOX-1, corresponding to a Delta Cycle Threshold value less than or equal to 3.36, and an up-regulation of gene TNFRSF10B corresponding to a Delta Cycle Threshold value of less than or equal to 6.71.

25. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation of gene RPS23, corresponding to a Delta Cycle Threshold value of greater than 0.32, and an up-regulation for gene ACOX-1 corresponding to a Delta Cycle Threshold value of less than or equal to 3.36.

26. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene ABCC3 corresponding to a Delta Cycle Threshold value less than or equal to 4.73, and an up-regulation for gene LYN corresponding to a Delta Cycle Threshold value of less than or equal to 1.82.

27. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene HIF1A, corresponding to a Delta Cycle Threshold value less than or equal to 4.35, and an up-regulation for gene TNFRSF10 corresponding to a Delta Cycle Threshold value of less than or equal to 6.22.

28. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation for gene ABCC1 corresponding to a Delta Cycle Threshold value greater than 3.15, and a down-regulation for gene IGJ corresponding to a Delta Cycle Threshold value of greater than 6.35.

29. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene UBE2H corresponding to a Delta Cycle Threshold value greater than 3.33, and a down-regulation for gene PARP-2 corresponding to a Delta Cycle Threshold value of greater than 6.39.

30. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation of gene ACOX-1, corresponding to a Delta Cycle Threshold value less than or equal to 3.81, and an up-regulation of gene TNFRSF10B corresponding to a Delta Cycle Threshold value of less than or equal to 7.63.

31. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation of gene RPS23, corresponding to a Delta Cycle Threshold value of greater than 0.26, and an up-regulation for gene ACOX-1 corresponding to a Delta Cycle Threshold value of less than or equal to 3.81.

32. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene ABCC3 corresponding to a Delta Cycle Threshold value less than or equal to 5.38, and an up-regulation for gene LYN corresponding to a Delta Cycle Threshold value of less than or equal to 2.06.

33. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene HIF1A, corresponding to a Delta Cycle Threshold value less than or equal to 4.94, and an up-regulation for gene TNFRSF10 corresponding to a Delta Cycle Threshold value of less than or equal to 7.06.

34. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation for gene ABCC1 corresponding to a Delta Cycle Threshold value greater than 2.63, and a down-regulation for gene IGJ corresponding to a Delta Cycle Threshold value of greater than 5.29.

35. The method of any one or more of claims 15 to 16, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene UBE2H corresponding to a Delta Cycle Threshold value greater than 2.78, and a down-regulation for gene PARP-2 corresponding to a Delta Cycle Threshold value of greater than 5.33.

36. The method of any one or more of claims 6 to 35, wherein masitinib is administered at a daily dose of 4.5 to 12.0 mg/kg/day (mg per kg bodyweight per day).

37. The method of claim 36, wherein masitinib is administered at a starting dose of 6.0 to 7.5 mg/kg/day.

38. The method of any one or more of claims 36 to 37, wherein masitinib is dose escalated by increments of 1.5 mg/kg/day to reach a maximum of 12.0 mg/kg/day.

39. The method of any one or more of the preceding claims, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered orally.

40. The method of any one or more of the preceding claims, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered twice a day.

41. The method of any one or more of the preceding claims, wherein an effective amount of said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered according to a long term administration of more than 3 months.

42. The method of any one or more of claims 2 to 41, wherein said patient is either naïve to said at least one antineoplastic agent or responding to treatment with said at least one antineoplastic agent.

43. The method of any one or more of claims 2 to 42, wherein said patient is either refractory or resistant to said at least one antineoplastic agent.

44. The method of any one or more of the claims 2 to 43, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered in combination with said at least one antineoplastic agent as a neoadjuvant, adjuvant, concomitant, or concurrent regimen.

45. The method of any one or more of claims 2 to 44, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered in combination with said at least one antineoplastic agent in a combined preparation for simultaneous, separate, or sequential use.

46. The method of any one or more of the preceding claims, for treatment of pancreatic cancer, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is administered in combination with at least one antineoplastic agent of claim 3.

47. The method of any one or more of the preceding claims, wherein said patient suffers from unresectable adenocarcinoma pancreatic cancer.

48. The method of any one or more of claims 1 to 46, wherein said patient suffers from *metastatic adenocarcinoma pancreatic cancer.*

49. The method of any one or more of claims 46 to 48, wherein said pancreatic cancer patient is in need thereof, as defined in claims 8 to 14 or 15 to 35, and wherein said at least one antineoplastic agent is selected from: gemcitabine (Gemzar®; Lilly), erlotinib (Tarceva®; Roche), paclitaxel (Taxol®, Abraxane®; Bristol-Myers Squibb), Folfirinox, 5-fluorouracil (5-FU), capecitabine, cisplatin, oxaliplatin, irinotecan, leucovorin, and any combination of these antineoplastic agents.

50. The method of claim 45, wherein, said at least one antineoplastic agent is gemcitabine.

51. The method of claim 46, wherein gemcitabine is used as antineoplastic agent and masitinib or a pharmaceutically acceptable salt or hydrate thereof is used as tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor.

52. The method of claim 51, wherein masitinib is administered daily at a starting dose of 6.0 ± 1.5 mg/kg/day with a maximum allowable dose of 9.0 mg/kg/day, and gemcitabine is administered at a weekly dose of 1000 ± 250 mg/m$^2$ of patient surface area for up to seven consecutive weeks as a start, followed by a week off-treatment, followed by cycles of weekly dose of 1000 ± 250 mg/m$^2$ for 3 weeks, every 28 days

53. A tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for use in a method for the treatment of a cancer as defined according to any one of claims 1 to 52.

54. A tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor of claim 53 in combination with at least one antineoplastic agent.

55. A pharmaceutical composition or kit comprising a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for use in a method for the treatment of a cancer as defined according to any one of claims 1 to 52.

56. A pharmaceutical composition or kit of claim 55, comprising at least one antineoplastic agent.

57. Use of a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor for the preparation of a medicament, or a pharmaceutical composition, for the treatment of a cancer as defined according to any one of claims 1 to 54.

58. Use of claim 57, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is used in combination with at least one antineoplastic agent.

59. A therapeutic management plan for the treatment of cancer, and in particular pancreatic cancer in a human patient, for identification of treatable patients based upon the predictor factor of gene expression, wherein said management plan comprises of determining if said patient is afflicted by cancer that is associated with at least one gene expression predictor factors as defined in claims 17 to 35.

60. The therapeutic management plan of claim 59, as applied to patients with pancreatic cancer, wherein:

- If the patient harbors at least one gene expression predictor factor then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.
- If the patient does not harbor at least one gene expression predictor factor then the patient is treated with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.

61. The therapeutic management plan of claim 59, as applied to patients with cancer, wherein:

- If the patient harbors at least one gene expression predictor factor then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one antineoplastic agent.

- If the patient does not harbor at least one gene expression predictor factor then the patient is treated with at least one antineoplastic agent.

62. A therapeutic management plan for the treatment of cancer, and in particular pancreatic cancer in a human patient, for identification of treatable patients based upon the predictor factor of pain intensity, wherein said management plan comprises:

    a) determining if said patient is afflicted by cancer that is associated with pain or requires administration of at least one opioid analgesic for treatment of disease related pain, with pain intensity preferably defined as a reported occurrence of a Visual Analogue Scale (VAS) score higher than 5 mm on a 100 mm scale; and optionally

    b) determining if said disease related pain is defined as a reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than a predetermined value for said cancer on a 100 mm scale, and in particular for pancreatic cancer a Visual Analogue Scale (VAS) pain intensity score higher than 20 mm on a 100 mm scale.

63. The therapeutic management plan of claim 62 as applied to patients with pancreatic cancer, wherein:

- If the result of step (a) is negative, then the patient is treated with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.
- If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one drug targeting epidermal growth factor receptor (EGFR), and particularly erlotinib, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one mitotic inhibitor, and particularly paclitaxel, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one combination of drugs including fluorouracil, leucovorin, irinotecan, or oxaliplatin, and particularly Folfirinox.
- If the result of step (a) is positive and the result of step (b) is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.

64. The therapeutic management plan of claim 62 as applied to patients with cancer other than pancreatic cancer, wherein:

- If the result of step (a) is negative, then the patient is treated with at least one antineoplastic agent.
- If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one antineoplastic agent.
- If the result of step (a) is positive and the result of step (b) is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one antineoplastic agent.

65. A global therapeutic management plan for the treatment of cancer, and in particular pancreatic cancer in a human patient, for identification of treatable patients based upon sequential application of the gene expression therapeutic management plan as defined in claim 59, and the pain intensity therapeutic management plan as defined in claim 65, wherein step (a) of the pain intensity therapeutic management plan is preceded by step (a') consisting of determining if said patient is afflicted by cancer that is associated with at least one gene expression predictor factors as defined in claims 17 to 35.

66. The therapeutic management plan of claim 65, as applied to patients with pancreatic cancer wherein:

- If the result of step (a') is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.
- If the result of step (a') is negative, then step (a) of the pain intensity therapeutic management plan for pancreatic cancer is invoked (as defined in claims 62 and 63); specifically, wherein said management plan comprises:
  a) determining if said patient is afflicted by pancreatic cancer that is associated with pain or requires administration of at least one opioid analgesic for treatment of disease related pain, with pain intensity preferably defined as a reported occurrence of a Visual Analogue Scale (VAS) score higher than 5 mm on a 100 mm scale; and optionally
  b) determining if said disease related pain is defined as a reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than 20 mm on a 100 mm scale.

- If the result of step (a) is negative, then the patient is treated with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.
- If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one drug targeting epidermal growth factor receptor (EGFR), and particularly erlotinib, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one mitotic inhibitor, and particularly paclitaxel, in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine; or with at least one combination of drugs including fluorouracil, leucovorin, irinotecan, or oxaliplatin, and particularly Folfirinox.
- If the result of step (a) is positive and the result of step (b) is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one nucleoside analogue, in particular a cytidine analogue, and especially gemcitabine.

67. The therapeutic management plan of claim 65, as applied to patients with cancer other than pancreatic cancer wherein:

- If the result of step (a') is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one antineoplastic agent.
- If the result of step (a') is negative, then step (a) of the pain intensity therapeutic management plan for cancer is invoked (as defined in claims 62 and 64); specifically, wherein said management plan comprises:
  a) determining if said patient is afflicted by cancer that is associated with pain or requires administration of at least one opioid analgesic for treatment of disease related pain, with pain intensity preferably defined as a reported occurrence of a Visual Analogue Scale (VAS) score higher than 5 mm on a 100 mm scale; and optionally
  b) determining if said disease related pain is defined as a reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than a predetermined value for said cancer on a 100 mm scale.
- If the result of step (a) is negative, then the patient is treated with at least one antineoplastic agent.
- If the result of step (a) is positive and the result of step (b) is negative, then the patient is treated with at least one antineoplastic agent.

- If the result of step (a) is positive and the result of step (b) is positive, then the patient is treated with at least one tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor, and especially masitinib, optionally in combination with at least one antineoplastic agent.

## CLAIMS

1. Use of a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor in the manufacture of a medicament to treat cancer in a human patient, wherein said patient is initially selected for treatment based upon the predictor factor of disease related pain intensity or upon the predictor factor of gene expression.

2. The use according to claim **1**, wherein the tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is in combination with at least one antineoplastic agent.

3. The use according to claim **2**, wherein said antineoplastic agent is selected from: an alkylating agent, an antimitotic agent, an antimetabolic agent, an anti-topoisomerase I agent, a platinum analog, an antibiotic agent, a hormonal agent, an anti-angiogenic agent, a genotoxic agent, a cytotoxic agent, a biologic agent, or an additional tyrosine kinase inhibitor, in particular: abarelix, abiraterone acetate, aldesleukin, altretamine, anastrozole, arsenic trioxide, asparaginase, axitinib, azacitidine, bendamustine hydrochloride, bevacizumab, bexarotene, bicalutamide, leomycin, bortezomib, brentuximab vedotin, busulfan, cabazitaxel, Campath, Camptosar, capecitabine, carboplatin, carfilzomib, carmustine, cetuximab, chlorambucil, cisplatin, cladribine (2CDA), clofarabine, crizotinib, cyclophosphamide, cytarabine (ARA-C), cytosine arabinoside, dacarbazine, dactinomycin, dasatinib, daunorubicin, decitibine, degarelix, denileukin, docetaxel, doxorubicin, epirubicin, eribulin mesylate, erlotinib, estramustine phosphate, etoposide, everolimus, exemestane, floxuridine, fludarabine, fluoro-5-uracile (5 fluorouracil), fluorouridine-desoxyribose, flutamide, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, ipilimumab, irinotecan, ixabepilone, lapatinib, letrozole, leucovorin, leuprolide acetate, lomustine, mechlorethamine, megestrol, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, nelarabine, nilotinib, nilutamide, Nolvadex, ofatumumab, oxaliplatin, paclitaxel, panitumumab, pazopanib, pegaspargase, peginterferon alfa-2b, pemetrexed, pentostatin, pertuzumab, plerixafor, pralatrexate,

procarbazine, Proleukin, romidepsin, sapacitabine, sipuleucel-T, sorafenib, streptozocin, sunitinib, tamoxifen, temozolomide, temsirolimus, teniposide, testolactone, tezacitabine, thioguanine, thiotepa, topotecan, toremifene citrate, trastuzumab, triptorelin, troxacitabine, valrubicin, Valstar, vandetanib, vemurafenib, vinblastine, vincristine sulfate, vinorelbine, vismodegib, vorinostat, xeloda, ziv-aflibercept, zoledronic acid, FOLFOX (oxaliplatin + 5 fluorouracil + folinic acid), FOLFIRI (irinotecan + 5 fluorouracil + folinic acid), FOLFIRINOX (oxaliplatin + irinotecan + 5 fluorouracil + folinic acid), and any combination of these antineoplastic agent.

**4.** The use according to any one of claims **1** to **3**, wherein said patient is in need of treatment for at least one cancer selected from: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adrenocortical carcinoma, anal cancer, B cell lymphoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brainstem glioma, brain tumor, breast cancer, cervical cancer, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colorectal cancer (CRC), endometrial cancer, esophageal cancer, eye cancer, gallbladder cancer, gastric (stomach) cancer, gastrointestinal stromal tumor (GIST), glioblastoma multiforme (GBM), hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) carcinoma (HCC), Hodgkin's lymphoma and non-Hodgkin's lymphomas, Kaposi sarcoma, laryngeal cancer, mastocytosis, melanoma, myelofibrosis, myelodysplastic syndrome (MDS), multiple myeloma, non-small-cell lung carcinoma (NSCLC), lung cancer (small cell), melanoma, nasopharyngeal carcinoma, neuroendocrine tumors, neuroblastoma, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pituitary adenoma, prostate cancer, rectal cancer, renal cell (kidney) carcinoma (RCC), salivary gland cancer, skin cancer (nonmelanoma), small intestine cancer, small lymphocytic lymphoma (SSL), soft tissue sarcoma, squamous-cell carcinoma, T cell lymphoma, testicular cancer, throat cancer, thyroid cancer, triple negative breast cancer, urethral cancer, and uterine cancer.

**5.** The use according to any one of claims **1** to **4**, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is masitinib or a pharmaceutically acceptable salt thereof.

**6.** The use according to any one of claims **1** to **5**, wherein said patient is initially selected for treatment based upon the predictor factor of disease related pain intensity.

**7.** The use according to claim **6**, wherein said patient is afflicted by cancer that is associated with pain or that requires the administration of opioid analgesics for treatment of disease related pain.

**8.** The use according to claim **7**, wherein said pain is defined as at least one reported occurrence of non-zero pain intensity, as determined using a pain intensity assessment tool.

**9.** The use according to claim **7** or **8**, wherein said pain is defined as at least one reported occurrence of a unidimensional pain intensity assessment tool score of greater than 20%.

**10.** The use according to any one of claims **7** to **9**, wherein said pain is classified as being moderate to intolerable according to the pain assessment tool used.

**11.** The use according to any one of claims **7** to **10**, wherein said pain is defined as at least one reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than 5 mm on a 100 mm scale.

**12.** The use according to any one of claims **7** to **11**, wherein said pain is defined as at least one reported occurrence of a Visual Analogue Scale (VAS) pain intensity score higher than 20 mm on a 100 mm scale.

**13.** The use according to any one of claims **1** to **5**, wherein said gene expression predictor factors are derived from analysis of RNA expression in peripheral blood cell samples, and wherein said patient is initially selected for treatment based upon an up-regulation of ACOX-1 corresponding to a Delta Cycle Threshold

value of less than or equal to 3.81; more preferably of less than or equal to 3.36; and even more preferably of less than or equal to 3.05.

**14.** The use according to any one of claims **1** to **5** or **13**, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation of gene ACOX-1 corresponding to a Delta Cycle Threshold value less than or equal to 3.81 and an up-regulation of gene TNFRSF10B corresponding to a Delta Cycle Threshold value of less than or equal to 7.63.

**15.** The use according to any one of claims **1** to **5** or **13** to **14**, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation of gene RPS23 corresponding to a Delta Cycle Threshold value of greater than 0.26 and an up-regulation for gene ACOX-1 corresponding to a Delta Cycle Threshold value of less than or equal to 3.81.

**16.** The use according to any one of claims **1** to **5** or **13** to **15**, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene ABCC3 corresponding to a Delta Cycle Threshold value less than or equal to 5.38 and an up-regulation for gene LYN corresponding to a Delta Cycle Threshold value of less than or equal to 2.06.

**17.** The use according to any one of claims **1** to **5** or **13** to **16**, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant up-regulation for gene HIF1A corresponding to a Delta Cycle Threshold value less than or equal to 4.94 and an up-regulation for gene TNFRSF10 corresponding to a Delta Cycle Threshold value of less than or equal to 7.06.

**18.** The use according to any one of claims **1** to **5** or **13** to **17**, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation for gene ABCC1 corresponding to a

Delta Cycle Threshold value greater than 2.63 and a down-regulation for gene IGJ corresponding to a Delta Cycle Threshold value of greater than 5.29.

**19.** The use according to any one of claims **1** to **5** or **13** to **18**, wherein said patient is initially selected for treatment based upon a gene expression predictor factor defined as a concomitant down-regulation for gene UBE2H corresponding to a Delta Cycle Threshold value greater than 2.78, and a down-regulation for gene PARP-2 corresponding to a Delta Cycle Threshold value of greater than 5.33.

**20.** The use according to any one of claims **1** to **19**, wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is masitinib or a pharmaceutically acceptable salt thereof, and wherein masitinib is administered at a daily dose of 4.5 to 12.0 mg/kg/day (mg per kg bodyweight per day).

**21.** The use according to any one of claims **1** to **20**, in combination with at least one antineoplastic agent, wherein said patient is either naïve to said at least one antineoplastic agent or responding to treatment with said at least one antineoplastic agent.

**22.** The use according to any one of claims **1** to **20**, in combination with at least one antineoplastic agent, wherein said patient is either refractory or resistant to said at least one antineoplastic agent.

**23.** The use according to any one of claims **1** to **22**, wherein said cancer is unresectable adenocarcinoma pancreatic cancer.

**24.** The use according to any one of claims **1** to **22**, wherein said cancer is unresectable adenocarcinoma pancreatic cancer, and wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is in combination with at least one antineoplastic agent, selected from: gemcitabine (Gemzar®; Lilly), erlotinib (Tarceva®; Roche), paclitaxel (Taxol®, Abraxane®; Bristol-Myers Squibb), Folfirinox, 5-fluorouracil (5-FU), capecitabine, cisplatin, oxaliplatin, irinotecan, leucovorin, and any combination of these antineoplastic agents.