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

The present 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 masitinib or a pharmaceutically acceptable salt thereof~~a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor~~ in combination with at least one antimetabolite 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

CLAIMS

1. Use of masitinib or a pharmaceutically acceptable salt thereof~~a tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor~~ in combination with at least one antimetabolite 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.~~2. 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.~~3. The use according to claim 2~~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.~~4. The use according to claim 3~~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.~~5. The use according to claim ~~7~~ 3 or ~~8~~4, wherein said pain is defined as at least one reported occurrence of a unidimensional pain intensity assessment tool score of greater than 20%.

~~10.~~6. The use according to any one of claims ~~7~~ 3 to ~~9~~5, wherein said pain is classified as being moderate to intolerable according to the pain assessment tool used.

~~11.~~7. The use according to any one of claims ~~7~~ 3 to ~~10~~6, 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.~~8. The use according to any one of claims ~~7~~ 3 to ~~11~~7, 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.~~9. 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, with respect to references genes B2M and GAPDH, 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.~~10. The use according to any one of claims **1** ~~to 5~~ or ~~9~~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, with respect to references genes B2M and GAPDH, 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.~~11. The use according to any one of claims **1** ~~to 5~~ or ~~9~~13 to **1**0~~4~~, 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, with respect to references genes B2M and GAPDH, 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.~~12. The use according to any one of claims **1** ~~to 5~~ or ~~9~~13 to **1**1~~5~~, 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, with respect to references genes B2M and GAPDH, 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.~~13. The use according to any one of claims **1** ~~to 5~~ or ~~9~~13 to **1**2~~6~~, 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, with respect to references genes B2M and GAPDH, 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.~~14. The use according to any one of claims **1** ~~to 5~~ or ~~9~~13 to **1**3~~7~~, 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, with respect to references genes B2M and GAPDH, greater than 2.63 and a down-regulation for gene IGJ corresponding to a Delta Cycle Threshold value of greater than 5.29.

~~19.~~15. The use according to any one of claims **1** ~~to 5~~ or ~~9~~13 to **1**~~4~~8, 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, with respect to references genes B2M and GAPDH, 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.~~16. The use according to any one of claims **1** to **15**~~9~~, ~~wherein said tyrosine kinase inhibitor, mast cell inhibitor or c-Kit inhibitor is masitinib or a pharmaceutically acceptable salt thereof, and~~ wherein masitinib or a pharmaceutically acceptable salt thereof is administered at a daily dose of 4.5 to 12.0 mg/kg/day (mg per kg bodyweight per day).

~~21.~~17. The use according to any one of claims **1** to **16**~~20~~, ~~in combination with at least one antineoplastic agent,~~ wherein said patient is either naïve to said at least one ~~antineoplastic agent~~antimetabolite or responding to treatment with said at least one ~~antineoplastic agent~~antimetabolite.

~~22.~~18. The use according to any one of claims **1** to **16**~~20~~, ~~in combination with at least one antineoplastic agent,~~ wherein said patient is either refractory or resistant to said at least one ~~antineoplastic agent~~antimetabolite.

~~23.~~19 The use according to any one of claims **1** to **18**~~22~~, wherein said cancer is unresectable adenocarcinoma pancreatic cancer.

20. The use according to any one of claims **1** to **19**, wherein said at least one antimetabolite is a nucleoside analog.

21. The use according to any one of claims **1** to **20**, wherein said at least one antimetabolite is gemcitabine.

~~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.~~