monoclonal antibody trastuzumab in the treatment of cancer forms resistant to the latter is described by Hiroshi Tanaka et al. on *Clin. Cancer Res*. 17, (10) May 15 (2011).

Although the PI3K inhibitors are very effective, however the problem remains that not all the cancer forms respond effectively to a same medicament even when this is associated to other active principles.

The object of the present invention then is to provide a medicament free from such drawbacks.

Therefore, the object of the present invention is to make available new antitumour combinations providing the co-therapy with the compound of formula I and an additional antitumour agent capable of strengthening the final therapeutic effectiveness. Said object is obtained with a composition the main features thereof are specified in the first claim, whereas other features are specified in the remaining claims.

Summary

The present disclosure is based upon the finding by the present inventors that several known antitumour compounds are capable of improving the effectiveness of the compound of formula I, through a synergic effect, thus allowing to treat effectively (or at least more effectively) types of cancers resistant to the previous treatments.

In one aspect, the present disclosure refers to use of a pharmaceutical composition containing as active compound the PI3K-Class I inhibitor compound: 5-(7-methanesulfonyl-2-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrimidin-2-amine or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for an anticancer treatment in association with a second anticancer compound provided that said second compound is not the monoclonal antibody trastuzumab or the compound everolimus, and wherein said second anticancer compound is selected from the group comprising an antibody such as an anti-HER2 antibody different from trastuzumab, an EGF anti-receptor antibody, an antibody that inhibits the

vascular endothelial growth factor-A (VEGF-A), a degrader/modulator of the estrogen receptor (ER) or an epidermal growth factor receptor (EGFR) inhibitor or a protein kinase inhibitor.

In another aspect, the present disclosure refers to use of kit of parts comprising a pharmaceutical composition containing as active compound the PI3K-Class I inhibitor compound: 5-(7-methanesulfonyl-2-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrimidin-2-amine or the pharmaceutically acceptable salt thereof, and a second pharmaceutical composition containing a second anticancer compound, provided that said second compound is not the monoclonal antibody trastuzumab or the compound everolimus, and wherein said second anticancer compound is selected from the group comprising an anti-HER2 antibody different from trastuzumab, an EGF anti-receptor antibody, an antibody that inhibits the vascular endothelial growth factor-A (VEGF-A), a degrader/modulator of the estrogen receptor (ER) or an epidermal growth factor receptor (EGFR) inhibitor, or a protein kinase inhibitor, in the manufacture of a medicament for an anticancer combination treatment.

Therefore, the present disclosure relates to the following examples:

Pharmaceutical compositions containing as active compound the PI3K-Class I inhibitor compound: 5-(7-methanesulfonyl-2-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrimidin-2-amine or the pharmaceutically acceptable salt thereof, for use in an anticancer treatment in association with a second anticancer compound provided that said second compound is not the monoclonal antibody trastuzumab or the compound everolimus.

Pharmaceutical compounds wherein said second anticancer compound is selected from the group comprising an antibody such as an anti-HER2 antibody different from

trastuzumab, an EGF anti-receptor antibody, an antibody that inhibits the vascular endothelial growth factor-A (VEGF-A), or an epidermal growth factor receptor (EGFR) inhibitor, a selective degrader/modulator of the estrogen receptor (ER) or a protein kinase inhibitor.

Pharmaceutical compounds wherein said second anticancer compound is selected from the group comprising an EGF anti-receptor antibody, preferably the antibody cetuximab, an antibody that inhibits the vascular endothelial growth factor-A (VEGF-A), preferably the antibody bevacizumab, or an epidermal growth factor receptor (EGFR) inhibitor, preferably the compound gefitinib, a selective degrader/modulator of the estrogen receptor (ER), preferably the compound fulvestrant.

Pharmaceutical compositions according to the disclosure for use in an anticancer treatment of colon cancer, prostate cancer, breast cancer, lung cancer, ovarian cancer.

Pharmaceutical compositions suitable for the oral administration of the PI3k-Class I inhibitor, for use in association with a composition containing the second anticancer compound.

Pharmaceutical compositions for use in association with a pharmaceutical composition suitable for the oral or parental administration of the second anticancer compound.

The present disclosure further relates to:

Kit of parts comprising a pharmaceutical composition containing as active compound the PI3K-Class I inhibitor compound: 5-(7-methanesulfonyl-2-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrimidin-2-amine or the pharmaceutically acceptable salt thereof, and a second pharmaceutical composition containing a second anticancer compound, provided that said second compound is not the monoclonal antibody trastuzumab or the compound everolimus, for use in an anticancer

combination treatment.

Kit of parts, wherein said second anticancer compound is selected from the group comprising an antibody such as an anti-HER2 antibody different from trastuzumab, an EGF anti-receptor antibody, preferably the antibody cetuximab, an antibody that inhibits the vascular endothelial growth factor-A (VEGF-A), preferably the antibody bevacizumab, a selective degrader/modulator of the estrogen receptor (ER), preferably the compound fulvestrant, or an epidermal growth factor receptor (EGFR) inhibitor, preferably the compound gefitinib, or a protein kinase inhibitor.

Kit of parts according to any one of claims 13 to 14 wherein the anticancer combination treatment is a treatment of colon cancer, prostate cancer, breast cancer, lung cancer, ovarian cancer.

Kit of parts according to the disclosure wherein the first composition is suitable for the oral administration of the PI3k-Class I inhibitor, and the second composition is suitable for the oral or parental administration.

The advantages offered by the disclosure can be referred to the increased effectiveness even in the treatment of forms of cancer or tumour resistant to preceding treatments and recidivisms.

Brief description of figures

Figure 1: Shows the antitumour activity of the compound MEN1611 (that is the compound of Formula I) in combination with trastuzumab on breast cancer cells JIMT-1 (HER2+, mutated on the PIK3CA gene) α) transplanted in nude mouse (immunodeficient).

Figure 2: the antitumour activity of MEN1611 is supported even by its pharmacodynamic activity, by means of the assay of immunoblotting, wherein the phosphorylation of two proteins AKT and S6, proteins downstream of PI3K, was evaluated. The treatment with the MEN1611 alone or in combination with trastuzumab (Combo), of JIMT-1, significantly inhibits the phosphorylation of the two proteins AKT

CLAIMS

1. Use of a pharmaceutical composition containing as active compound the PI3K-Class I inhibitor compound: 5-(7-methanesulfonyl-2-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrimidin-2-amine or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for an anticancer treatment in association with a second anticancer compound provided that said second compound is not the monoclonal antibody trastuzumab or the compound everolimus, and wherein said second anticancer compound is selected from the group comprising an antibody such as an anti-HER2 antibody different from trastuzumab, an EGF anti-receptor antibody, an antibody that inhibits the vascular endothelial growth factor-A (VEGF-A), a degrader/modulator of the estrogen receptor (ER) or an epidermal growth factor receptor (EGFR) inhibitor or a protein kinase inhibitor.

2. The use according to claim 1, wherein said second anticancer compound is selected from the group comprising cetuximab, bevacizumab, fulvestrant, or gefitinib.

3. The use according to any one of claims 1 or 2, wherein the cancer is colon cancer, prostate cancer, breast cancer, lung cancer, ovarian cancer.

4. The use according to claim 3, wherein the cancer is colorectal cancer with mutations of PI3KCA and *wild-type* KRAS, colorectal cancer with mutations of PI3KCA and KRAS, non-small cell lung carcinoma (NSCLC) with or without mutation on PI3KCA and EGFR, HER2-positive breast carcinoma with PI3KCA mutation, HER2-positive and ER-positive breast cancer.

5. The use according to any one of claims 1 to 4 in association with a composition containing the second anticancer compound, wherein the pharmaceutical composition is suitable for the oral administration of the PI3k-Class I inhibitor.

6. The use according to claim 5, wherein the pharmaceutical composition comprises a quantity of PI3K-Class 1 inhibitor sufficient for a unitary dosage of 1 to 10 mg/Kg body weight.

7. The use according to claim 6, wherein the unitary dosage of the PI3K-Class 1 inhibitor ranges from 5 to 7 mg/Kg body weight.

8. The use according to any one of claims 5 to 7 in association with a pharmaceutical composition suitable for the oral or parental administration of the second anticancer compound.

9. The use according to claim 8 in association with a pharmaceutical composition comprising a quantity of the second anticancer compound suitable for a unitary dosage of 10 to 80 mg/Kg body weight.

10. The use according to claim 9 in association with a pharmaceutical composition comprising a quantity of the second anticancer compound suitable for a unitary dosage of 20 to 70 mg/Kg body weight, preferably from 30 to 50 mg/Kg body weight.

11. Use of kit of parts comprising a pharmaceutical composition containing as active compound the PI3K-Class I inhibitor compound: 5-(7-methanesulfonyl-2-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrimidin-2-amine or the pharmaceutically acceptable salt thereof, and a second pharmaceutical composition containing a second anticancer compound, provided that said second compound is not the monoclonal antibody trastuzumab or the compound everolimus, and wherein said second anticancer compound is selected from the group comprising an anti-HER2 antibody different from trastuzumab, an EGF anti-receptor antibody, an antibody that inhibits the vascular endothelial growth factor-A (VEGF-A), a degrader/modulator of the estrogen receptor (ER) or an epidermal growth factor receptor (EGFR) inhibitor, or a protein kinase inhibitor, in the manufacture of a medicament for an anticancer combination

treatment.

12. The use according to claim 11, wherein said second anticancer compound is selected from the group comprising cetuximab, bevacizumab, fulvestrant, or gefitinib.

13. The use according to any one of claims 11 to 12, wherein the anticancer combination treatment is colon, prostate, breast, lung, ovarian cancer.

14. The use according to claim 13 in a combination treatment of colorectal carcinoma with mutations of PI3KCA and *wild-type* KRAS, of colorectal carcinoma with mutations of PI3KCA and KRAS, of non-small cell lung carcinoma (NSCLC) with or without mutation on PI3KCA and EGFR, HER2-positive breast cancer with PI3KCA mutation, HER2-positive and ER-positive breast cancer.

15. The use according to any one of claims 11 to 14 wherein the first pharmaceutical composition comprises a quantity of PI3K-Class 1 inhibitor sufficient for a unitary dosage of 1 to 10 mg/Kg body weight, preferably from 5 to 7 mg/Kg body weight.

16. The use according to claim 15 wherein the second composition comprises a quantity of the second anticancer compound suitable for a unitary dosage of 10 to 80 mg/Kg body weight, preferably from 20 to 70 mg/Kg or from 30 to 50 mg/Kg body weight.

17. The use according to any one of claims 11 to 16 wherein the first composition is suitable for the oral administration of the PI3k-Class I inhibitor, and the second composition is suitable for the oral or parental administration.