

Therefore, there is a strong need to define, for each specific patient, the best combinations of drugs for treating cancer.

~~SUMMARY OF THE INVENTION~~

The inventors present a novel concept of therapy in cancer, in particular metastatic lung cancer, based on tri therapy associating three targeted drugs. They created a simplified interventional mapping system (SIMS) merging knowledge from drugs and hallmarks of cancer. An interventional point means a target/gene, or a group of targets/genes, activated and that can be blocked by a drug. They described 24 interventional points based on a collection of 183 genes. Method of investigation of status of activation of the interventional points is based on complete genomics investigation of dual tumor and normal biopsies matched from strictly the same points, and preferably comprise sequencing, copy number variation gene expression and miRNA expression. An algorithm was developed to create a scoring system, e.g. from 1 to 10, enabling the ranking of the activated interventional points in each patient.

Based on score and trends of co-activation of interventional points, the ~~invention-disclosure~~ presents a new scientific rationale to associate combination of therapies. Accordingly, in an aspect the present ~~invention-disclosure~~ relates to a method for determining in a patient having a cancer a classification of intervention points according to their activation status, wherein

- the intervention points comprise the group consisting of the HER, CDK4,6, PLK/AURK/Kinesins, Angiogenesis, Angiopoietins, Immune Modulators, PI3K, MET, MEK, ERK, Anti-Apoptosis, FGF, mTOR, Ras/Raf, Telomerase, IGF/glycolysis, Wnt, PARP, HDAC, JAK-STAT, Hedgehog, NOTCH pathway, DNA Repair and Others' (namely RET, ALK, ROS1 and UB1), or any subgroup thereof of at least 10 intervention points; and the genes of each intervention point are defined according to Table 1 or 9;
- the method comprises
- characterizing a tumor sample in comparison to a normal histologically matched sample from the same patient, including
- for each pathway of the group or subgroup of intervention points, determining the mRNA expression level of the genes of the intervention point as disclosed in Table 1 or 9, thereby determining a fold change of

Preferably, the genes of Table 10 are sequenced for detecting the presence of mutations as defined in Table 10 and p53 gene is sequenced.

Preferably, for each intervention point of the group or subgroup of intervention points, the method comprises determining the miRNAs level of the genes of the pathway as disclosed in Table 1 or 9, in particular the level of miRNAs of the genes of the pathway as disclosed in Table 11. More preferably, before the step of score calculation, a mean miRNAs fold change for each gene is calculated as the average of the miRNA TvN fold changes for the gene, a corrected mRNA TvN fold change is calculated by dividing the mRNA fold change Tumor versus Normal of the gene (mRNA TvN fold change) by the mean fold change for the miRNAs of the gene (mean miRNA TvN fold change), and the corrected mRNA TvN fold change of the gene is then used to calculate the arithmetic mean of the mRNA TvN fold changes of the genes for each intervention point. In a preferred embodiment, the level of miRNAs is determined and used to calculate a corrected mRNA TvN fold change for the genes of the following intervention points: mTOR-AKT-PTEN, RAS, ERK, PI3K and Immune Modulators.

Preferably, for each intervention point of the group or subgroup of intervention points, the method comprises determining the copy number variation of the genes of the pathway as disclosed in Table 1 or 9. More preferably, before the step of score calculation, a corrected mRNA TvN fold change of a gene of an intervention point is calculated by multiplying the mRNA TvN fold change of the gene by the CNV fold change of the gene, and the corrected mRNA TvN fold change of the gene is then used to calculate the arithmetic mean of the mRNA TvN fold changes of the genes for each intervention point.

Preferably, the subgroup of intervention points consists in the following group: Her, CDK4,6, PLK/AURK/Kinesins, Angiogenesis, Immune Modulators, PI3K, MET, MEK, ERK, Anti-Apoptosis, FGF, mTOR, Ras/Raf, IGF/glycolysis, Wnt, PARP, and DNA Repair.

Preferably, it further comprise selecting a group of three activated or disturbed intervention points in a patient having a cancer, wherein three intervention points are selected among the intervention points having the highest scores, preferably the three intervention points having the highest scores.

In another aspect, the present invention-disclosure also relates to a method for selecting a combination of three drugs useful for treating a patient having a cancer, wherein a group of three activated or disturbed intervention points are selected by the method of claim 9 and a drug is selected for each or disturbed intervention point, thereby providing a combination of three drugs.

In addition, in another aspect, the present ~~invention~~-disclosure relates to the use of a kit for classifying pathways according to their activation status, wherein the kit comprises means for measuring the mRNA expression level of the genes of Table 1 or 9 for intervention points comprising the group consisting of the HER, CDK4,6, PLK/AURK/Kinesins, Angiogenesis, Angiopoietins, Immune Modulators, PI3K, MET, MEK, ERK, Anti-Apoptosis, FGF, mTOR, Ras/Raf, Telomerase, IGF/glycolysis, Wnt, PARP, HDAC, JAK-STAT, Hedgehog, NOTCH pathway, DNA Repair and Others' (namely RET, ALK, ROS1 and UB1), or any subgroup thereof of at least 10 intervention points. Preferably, the kit further comprises means for detecting the mutations of Table 10. More preferably, the kit further comprises means for measuring the miRNA level of miRNA of Table 11 for intervention points comprising the group consisting of the HER, CDK4,6, PLK/AURK/Kinesins, Angiogenesis, Angiopoietins, Immune Modulators, PI3K, MET, MEK, ERK, Anti-Apoptosis, FGF, mTOR, Ras/Raf, Telomerase, IGF/glycolysis, Wnt, PARP, HDAC, JAK-STAT, Hedgehog, NOTCH, DNA Repair and Others' (namely RET, ALK, ROS1 and UB1), or any subgroup thereof of at least 10 intervention points. Optionally, the kit further comprises means for determining the copy number variation of the genes of Table 1 or 9 for pathways comprising the group consisting of the HER, CDK4,6, PLK/AURK/Kinesins, Angiogenesis, Angiopoietins, Immune Modulators, PI3K, MET, MEK, ERK, Anti-Apoptosis, FGF, mTOR, Ras/Raf, Telomerase, IGF/glycolysis, Wnt, PARP, HDAC, JAK-STAT, Hedgehog, NOTCH, DNA Repair and Others' (namely RET, ALK, ROS1 and UB1), or any subgroup thereof of at least 10 intervention points.

Finally, in a further aspect, the present ~~invention~~-disclosure relates to the use of a drugs combination in the preparation of a medicament for use in the treatment of cancer, wherein the drugs combination is selected among the combinations disclosed in Table 6, Table 7, Table 8 or selected in the group consisting of

- anti PD1L + Pan RAF inhibitor + MtorPI3K inhibitor
- anti PD1L + Pan RAF inhibitor + angiogenesis inhibitor
- anti PD1L + Pan RAF inhibitor + MET inhibitor
- anti PD1L + Pan RAF inhibitor + CDK4,6 inhibitor
- anti CTLA4 + Pan RAF inhibitor + MtorPI3K inhibitor
- anti CTLA4 + Pan RAF inhibitor + angiogenesis inhibitor
- anti CTLA4 + Pan RAF inhibitor + MET inhibitor
- anti CTLA4 + Pan RAF inhibitor + CDK4,6 inhibitor
- anti PD1L + MEK inhibitor + MtorPI3K dual inhibitor

15- Use of aA drugs combination in the preparation of a medicament for use in the
treatment of cancer, wherein the drugs combination is selected among the
combinations disclosed in Table 6, Table 7, Table 8 or selected in the group consisting
of

- 5 anti PD1L + Pan RAF inhibitor + MtorPI3K inhibitor
- anti PD1L + Pan RAF inhibitor + angiogenesis inhibitor
- anti PD1L + Pan RAF inhibitor + MET inhibitor
- anti PD1L + Pan RAF inhibitor + CDK4,6 inhibitor
- anti CTLA4 + Pan RAF inhibitor + MtorPI3K inhibitor
- 10 anti CTLA4 + Pan RAF inhibitor + angiogenesis inhibitor
- anti CTLA4 + Pan RAF inhibitor + MET inhibitor
- anti CTLA4 + Pan RAF inhibitor + CDK4,6 inhibitor
- anti PD1L + MEK inhibitor + MtorPI3K dual inhibitor
- anti PD1L + MEK inhibitor + angiogenesis inhibitor
- 15 anti PD1L + MEK inhibitor + MET inhibitor
- anti PD1L + MEK inhibitor + CDK,-6 inhibitor
- anti CTLA4 + MEK inhibitor + MtorPI3K dual inhibitor
- anti CTLA4 + MEK inhibitor + MET inhibitor
- anti CTLA4 + MEK inhibitor + angiogenesis inhibitor, and
- 20 anti CTLA4 + MEK inhibitor + CDK4,6 inhibitor.

16- ~~A drugs combination for~~ The use according to claim 15, wherein the drugs
combination is selected in the group consisting of

- Medi-4736 + MLN2480 + PF-384
- Medi-4736 + MLN2480 + Axitinib or Motesanib
- 25 Medi-4736 + MLN2480 + Crizotinib
- Medi-4736 + MLN2480 + Palbociclib
- Tremelimumab + MLN2480 + PF-384
- Tremelimumab + MLN2480 + Axitinib or Motesanib
- Tremelimumab + MLN2480 + Crizotinib
- 30 Tremelimumab + MLN2480 + Palbociclib
- Medi-4736 + Selumetinib + PF-384
- Medi-4736 + Selumetinib + Axitinib or Motesanib