

METHOD FOR SELECTING PERSONALIZED TRI-THERAPY FOR CANCER TREATMENT**FIELD OF THE INVENTION**

The present invention relates to the field on oncology, especially to personalized medicine in cancer therapy. More particularly, it relates a new concept of therapeutic approach, the triple regimen therapy and method for selecting the most appropriate combinations of drugs for treating cancer in a particular subject.

BACKGROUND OF THE INVENTION

Lung cancer is the most common malignancy worldwide with a staggering 1.8 million cases diagnosed per year. Over half of NSCLC are diagnosed at the metastatic stage. Even utilizing the standard of care in the Western world, consisting mainly of chemotherapeutic agents and radiation therapy, there has been little impact on mortality, with only 30% of all patients diagnosed (regardless of stage) alive at one year, and a dismal 1 and 5 year survival rates of about 8-15% and 4%, respectively for those with metastatic disease. For patients that have failed first line therapy, the median survival is only about 7 months.

Progress brought by targeted therapies such as matching EGFR activating mutations or ALK translocation have shown substantial response rates, demonstrating the potency of molecularly-matched targeted therapy, but monotherapies such as these apply to only small subsets of patients, and virtually all patients develop resistance and succumb to their disease. This is perhaps not unexpected, as patients often harbor multiple molecular aberrations that require prosecution. The power of combination therapy has been illustrated in diseases such as Hodgkin's lymphoma where cure was effected by combinations. Further in the modern era of targeted therapy, combinations targeting the same pathway (e.g. trametanib (MEK) inhibitor together with dabrafenib (BRAF inhibitor) in BRAF-mutant melanoma, or resistance pathways (combining PIK3CA and MEK inhibitors) are already being tested and have shown efficacy, in some cases, but no cure and no significant impact on survival. Combinations of targeted therapy in NSCLC have, however, to date, been very limited in scope.

Personalized medicine today offers modest benefits in advanced metastatic disease (especially lung cancer). Mono-therapies have failed to cure advanced diseases. Most combination chemotherapies lack an underlying biologic or molecular rationale.

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

SUMMARY

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 disclosure presents a new scientific rationale to associate combination of therapies. Accordingly, in an aspect the present 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 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, 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

mRNA expression of tumor vs normal, (referred as mRNA TvN fold change);

- wholly or partially sequencing genes of Table 1 or 9, thereby identifying the presence of activating mutation in the tumor sample ;
- 5 - for each intervention point of the group or subgroup of intervention points, determining the level of miRNAs of the genes of the intervention point as disclosed in Table 11, thereby determining a fold change of miRNAs level of tumor vs normal, (referred as miRNA TvN fold change);
- 10 - optionally, for each intervention point of the group or subgroup of intervention points, determining the copy number variation of the genes of the intervention point as disclosed in Table 1 or 9, thereby determining a tumor vs normal fold change for the amplified genes;
- 15 - calculating a mean miRNAs fold change for each gene as the average of the miRNA TvN fold changes for the gene, calculating a corrected mRNA TvN fold change 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 being used to calculate the arithmetic mean of the mRNA TvN fold changes of the genes for each intervention point
- 20 - calculating a score for each pathway based on the characterization data, wherein
 - if, in the tumor sample, the presence of an activating mutation of a gene of an intervention point is detected, then a maximal score is given to the intervention point, in particular a score of 10 if the scoring is from 1 to 10;
 - 25 - a score, preferably from 1 to 10, is calculated based on the arithmetic mean of the mRNA TvN fold changes of the genes for each intervention point of the group or subgroup of intervention points, provided that the mRNA TvN fold change of a gene is taken into consideration only if its value is at least 1.3; and

- the score of each intervention point of the group or subgroup of intervention points is either

a) the sum of the score due to the presence of an activating mutation and the score calculated by the average of the mRNA TvN fold changes; or

b) the score due to the presence of an activating mutation if there is a mutation or the score calculated based on the arithmetic mean of the mRNA TvN fold changes in absence of mutation; and

- classifying the intervention points according to the calculated scores.

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 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 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 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, 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 disclosure relates to the use of a drugs combination in the preparation of a medicament for the treatment of cancer, wherein the drugs combination is 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

anti PD1L + MEK inhibitor + angiogenesis inhibitor

anti PD1L + MEK inhibitor + MET inhibitor

anti PD1L + MEK inhibitor + CDK4,6 inhibitor

anti CTLA4 + MEK inhibitor + MtorPI3K dual inhibitor

5 anti CTLA4 + MEK inhibitor + MET inhibitor

anti CTLA4 + MEK inhibitor + angiogenesis inhibitor, and

anti CTLA4 + MEK inhibitor + CDK4,6 inhibitor, wherein the drug combination is selected by the method disclosed above.

Preferably, the drugs included in the combination are selected from those disclosed in Table

10 1. More preferably, the drugs combination is selected in the group consisting of

Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + PF-384 (Pfizer)

Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + Axitinib (Pfizer) or Motesanib (Takeda)

Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + Crizotinib (Pfizer)

15 Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + Palbociclib (Pfizer)

Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + PF-384 (Pfizer)

Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + Axitinib (Pfizer) or Motesanib (Takeda)

Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + Crizotinib (Pfizer)

20 Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + Palbociclib (Pfizer)

Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + PF-384 (Pfizer)

Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + Axitinib (Pfizer) or Motesanib (Takeda)

Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + Crizotinib (Pfizer)

25 Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + Palbociclib (Pfizer)

Tremelimumab (Astra Zeneca) + Selumetinib (Astra Zeneca) + PF-384 (Pfizer)

Tremelimumab (Astra Zeneca) + Selumetinib (Astra Zeneca) + Crizotinib (Pfizer)

Tremelimumab (Astra Zeneca) + Selumetinib (Astra Zeneca) + Axitinib (Pfizer)

30 or Motesanib (Takeda), and

Tremelimumab (Astra Zeneca) + Selumetinib + Palbociclib (Pfizer).

Preferably, the cancer is a lung cancer, more preferably a NSCLC.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. The framework for cPCM. The problem is divided into 3 parts:

- A. Mapping therapeutic efficacy to cellular components;
- B. Scoring the status of specific nodes in the interventional maps defined in (A) and
- (C) predicting combination efficacy

Figure 2. Flowchart of the scoring system.

Figure 3. In Y: Mean fold change of differential gene expression between T and N in each patient. In X: number of patients NB: for each graph, the order of patients is different. This series serve as calibrator for calculation of deciles.

Figure 4. Representation 3D of the scoring system. Axis Z shows score from 1 to 10. Axis X represents an example of interventional points, axis y represents each patient

DETAILED DESCRIPTION OF THE INVENTION

General Concept

Since monotherapies fail to cure metastatic lung cancer diseases, and dual combinations reported today on other diseases do not impact significantly survival, the inventors envision applying tri-therapy, following the historical success in AIDS.

The challenge raised by the invention is choosing triple drug combinations that can benefit a patient.

- Single drugs are doing poorly; patients respond but inevitably relapse, often within a few months. Based on the molecular complexity of metastatic disease, combinations are needed. This situation may be analogous to that with AIDS, wherein single agents resulted in incremental effects, but combination of three drugs has demonstrated long-term benefit.
- Unlike viruses, which always depend on the same proteins, tumors are heterogeneous and the biology is too complex for a single tri-therapy combination to work on all tumors.
- As a result, combinatorial precision cancer medicine (cPCM) is needed.
- A limited number of pathways may be abnormal in metastatic tumors.

The proposed approach

The inventors assert that, by reasonable assumptions, a realistic framework can be established today that would allow useful drug combinations to be identified in a

personalized way (i.e. matching the combination to the patient based on the tumor properties).

The main idea is to divide and conquer – proposing 3 steps:

1. Find a set of markers that are indicative for specific interventional points of every class of drugs: 24 markers covering 183 genes
2. Find a score that summarizes the behavior of these markers in a given patient that is both comparable to other classes and is proportional to the probability that this drug would work; and
3. Figure out how to combine drugs such that the combination is common enough to allow clinical testing yet we retain the ability to match combinations to patients with sufficient precision.

Based on these assumptions, the inventors propose the SIMS (Simplified interventional points mappins system) framework for precision combinational cancer medicine (Figure 1).

- First, they propose to reduce the enormous complexity of biological pathways and pathway cross-talk by devising a simplified map that only concentrates on the genes that are most indicative of drug target status. They propose to define "intervention points", which consists of drug targets or group of targets as well as genes upstream of the targets that together reflect a specific biological activity that is actionable through therapeutic interventions. For example, pan-HER therapies define the HER group of receptors and their ligands as a single intervention point (Figure 1a).
- The second part of the work, the inventors propose a very simple approach for prioritizing intervention points for a specific patient. The basic premise behind the score is that, when the genes associated with an intervention point are more disturbed (in terms of sequence and/or expression level), the intervention point is more likely to be crucial to the tumor. From this, it stems that the more disturbed the genes of an intervention point, the more likely it is that therapeutics targeted at that points will benefit the patient. The inventors are in the process of developing a family of simple scores that combine the level of gene expression in the tumor (relative to matched normal control), the aberrations found in the intervention points' genes, CNVs and miRNAs expression levels. Rank normalization (in the example, using deciles) is used to make the scores of different intervention points comparable.

- Finally, given a reliable system for determining which drugs are more likely to benefit the patient, a method is needed for choosing combinations that are likely to benefit the patients. Here the inventors propose a statistical approach, using a panel of 123 lung cancer patients as an example. Using the methods described above, they describe the status of 24 intervention points in the 123 patients. From this, they applied a knowledge-driven approach to look for drug combinations that are likely to synergistically benefit the patient. Using a panel of experts, they identified those pathways that co-occur frequently in the patients and are mechanistically independent. To further improve the efficacy of the proposed combinations, the inventors propose augmenting the combined targeted therapies with immunomodulating therapies (i.e. anti-CD1L and anti-CTLA). The rational behind this combination is to reduce the chance of intolerable side effects while maintain the predicted efficacy of a triple therapy regimen

Table 1 summarizes the interventional points presenting genes involved and main classes of drugs

Interventional node	Components of the interventional points	Drugs acting on interventional points
HER	EGF,TGFA,AREG,EREG,HBEGF,BTC,NRG1, NRG2,NRG4,EGFR ,ERBB2 , ERBB3,ERBB4	Dacomitinib-Panher inhibitor Pfizer
CDK4, 6	CDK4, CDK6, CCND1, CCND2, CCND3, CDKN2A, CDKN2B, CCNE1, CCNE2, CCNE3, RB1	Palbociclib CDK4, 6 inhibitor Pfizer
PLK / AURK/Kine	PLK1,AURKA,BORA,ILK,KIF11	MLN8237 (Aurora A kin inhib) Takeda
ANGIOGENESIS	VEGFA,VEGFB,VEGFC,VEGFD,VEGFR1,VEGFR2, VEGFR3,PDGFA,PDGFB,PDGFRA,PDGFRB,Kit	Axitinib antiVEGFR Pfizer Motesanib anti VEGFR/PDGFR/kit Takeda
Angiopoietins	THBS1, TGFB1, ANGPT1, ANGPT2, ANGPTL1, ANGPT4, TIE1, TEK	-
Immune mod	PD1L, PDCD1LG2, PDCD1, CTLA4, LAG3	Medi-4736 (PDL1) AZ (Astra Zeneca) AMP514 (PD1) AZ Tremelimumab (CTLA4) AZ PF-05082566 (4-1 BB)
PI3K	PIK3CA,PIK3CB,PIK3CD,PIK3CG,PIK3C2B,PRKCB, PRKCA,PRKCB,PIK3R1,PIK3R2,PIK3R3	PF-384 PI3K/mTOR-inhibitor Pfizer

		AZD8186 (PI3Kb)AZ MLN1117 (PI3Kalpha inhibitor) Takeda
MET	HGF,MET,AXL,MST1R	Crizotinib Pfizer Volitinib (cMet) AZ MLN1117, MLN0128 Takeda
MEK	MAP2K1, MAP2K2, MAP2K3, MAP2K4, MAP3K1, MAP3K2, MAP3K3, MAP3K4	Selumetinib (MEK) AZ
ERK	MAPK3,MAPK1,KSR1,MAPK11	-
Anti-apoptosis	BCL2,BCLXL,BIRC5,XIAP,BAK1 ,TP53	-
FGF	FGF1 to FGF18, FGFR1, FGFR2, FGFR3, FGFR4	AZD4547 (FGFR1, 2, 3) AZ
mTOR	mTor,AKT1,AKT2,PTEN ,TSC1,TSC2,STK11,PIM1,PIM2,PIM3	PF-384 PI3K/mTOR inhibitor Pfizer AZD2014 (TOR kinase) AZ AZD5363 (AKT1, 2 ,3) AZ AZD1208 (PIM1, 2) AZ MLN0128 (TORC1/TORC2) Takeda
Ras/Raf	KRAS,NRAS ,HRAS ,RAF1 ,BRAF, CRAF	MLN2480 (Pan-RAF inhibitor) Takeda
Telomerase	TERT,TERC,TEP1,HSP90AA1,DKC1,PTGES3	-
IGF / glycolysis	IGF1,IGF2,IGF1R,IGF2R,INSR,IRS1,PKM	Medi-573 (IGF) AZ
Wnt	CDH1, CTNNA1, CTNNB1, WNT 1, FZD1, WNT5A, B, FZD5, WIF1, DKK1	-
PARP	PARP1, BRCA1, XRCC1, RAD54L, RAD54B, ATM, ATR, CHEK1, CHEK2, WEE1	Olaparib (PARP) AZ AZD1775 (Wee1) AZ AZD6738 (ATR) AZ
HDAC	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5	
JAK-STAT	JAK1,JAK2,STAT1,STAT2,STAT3,SOCS1	
Hedgehog	SHH,PTCH1,SMO,STK36,PRKACA,SUFU,GLI1	
NOTCH	NOTCH1,Adam17,PSEN1,NCSTN,JAG1,SRRT,APH1A	
DNA Repair	ERCC1,RAD52,XRCC4,RAD51,BRCA1,NEDD8,NAE1	MLN 4924 (NEDD8 AE) Takeda
Others	RET, ALK, ROS1, UB1	

Conclusion

The inventors propose a new therapeutic approach of triple regimen therapies aiming at blocking simultaneously three different biologic abnormalities and reducing the chance of

developing the secondary resistance. In addition, for defining a combination of drugs, the inventors identified specific interventional points of drugs based on the pathways specifically up-regulated in one particular patient having a cancer. They defined a simplified intervention mapping system within the hallmarks of cancer including only signaling and regulatory pathways that can be targeted with therapeutic agents. The principle of simplification is based on the activating signal that can be blocked by a class of drugs.

Indeed, the inventors reduce the enormous complexity of biological pathways and pathway cross-talk by devising a simplified map that only concentrates on the genes that are most indicative of drug target status defined as "intervention points". These intervention points consist of drug targets or group of drug targets and some genes upstream of the drug targets that together reflect a specific biological activity which is actionable through therapeutic interventions. By upstream is referred to genes encoding a protein having an extracellular activity. For instance, pan-HER therapies define the HER group of receptors and their ligands as a single intervention point.

The inventors propose a very simple approach for prioritizing intervention points for a specific patient. The basic premise is that, when the genes associated with an intervention point are more disturbed (in terms of sequence and/or expression level), the intervention point is more likely to be crucial or critical to the tumor. From this, it stems that the more disturbed the genes of an intervention point are, the more likely it is that therapeutics targeting that points will benefit the patient. Accordingly, the inventors have developed a family of simple scores that combine the level of gene expression in the tumor (relative to matched normal control), the mutations found in the intervention points' genes, CNVs and miRNAs expression levels.

Therefore, the inventors propose a method allowing the tumor characterization of one particular subject by considering its own tumor vs normal status in the most efficient way for identifying the disturbed or activated intervention points and ranking them. The inventors developed a new mathematical modelling and scoring system to give a score (e.g., of 1 to 10) based on integration of omics data, especially gene expression, sequencing, miRNA analysis and copy number variation determination.

Then, when the intervention points are ranked, it is possible to define one or several combinations of drugs targeting a combination of disturbed or activated intervention points so as to obtain the optimized therapy of cancer for this particular patient. Preferably, the

combined therapy comprises or consists of three drugs targeting the most disturbed or activated intervention points. The method may further comprise the administration of the optimized combination of drugs to said patient. Accordingly, the method leads to rational combination therapies which are scientifically reliable and clinically feasible.

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Tumour characterization

The method comprises a step of characterizing the tumor in one patient of interest. In particular, the patient suffers from a cancer for which no effective therapy is established or admitted by physicians. The reasons of this situation could be an advanced stage of cancer, for instance a stage with metastases, a relapsed cancer after one or several lines of treatment, or even a cancer for which no established and efficient treatment is associated with. In particular, the cancers or tumors more particularly considered in the present invention are lung cancer, especially NSCLC (non-small cell lung cancer), breast cancer (in particular the triple negative breast cancer), colorectal cancers, kidney cancer, melanomas, brain cancers, liver cancers, head and neck cancers, stomach cancers and ovary cancers. Therefore, the method comprises an initial step of providing samples for the patient. Two samples are necessary, namely one tumor sample and one normal sample from the same patient. Preferably, the tumour sample and the normal sample provides from the same type of tissue. More particularly, the tumor and normal samples are histologically matched tissues. Typically, the samples can be provided by biopsies. Non-exhaustively, examples of pairs of tumor with corresponding histological normal reference tissue are the followings:

1. lung cancer adenocarcinomas or derived metastases - bronchial normal mucosa
2. breast cancer tumors or derived metastases - normal epithelial breast cells
3. colon cancers adenocarcinomas or derived metastases - normal colon mucosa
4. kidney cancers or derived metastases - normal kidney cells
5. melanomas or derived metastases - synchronous naevi
6. rhabdomyosarcomas or derived metastases - normal muscle tissue
7. liver carcinomas or derived metastases - normal liver cells
8. Oral-pharyngeals tumors (ORL) - normal buccal mucosa
9. Stomach carcinomas or derived metastases - normal stomach mucosa
10. Ovary cancer – normal Fallope tube mucosa
11. pancreatic cancers – normal parenchymatous tissue from pancreas

In order to optimize the tumor characterization, the inventors selected parameters that have to be analysed in order to establish the status of the intervention points that can be targeted by a class of drugs.

- 5 The inventors defined the main intervention points of interest, namely HER (Human Epithelial Growth Factor Receptor), CDK4,6 (Cyclin-Dependent Kinase), PLK/AURK/Kinesins (Polo-Like kinase/ Aurora Kinase/Kinesins), Angiogenesis, Angiopoietins, Immune Modulators, PI3K (Phosphoinositide-3 Kinase), MET (cMET), MEK, ERK, Anti-Apoptosis, FGF (Fibroblast Growth Factor), mTOR (mammalian target of rapamycin), Ras/Raf, Telomerase,
- 10 IGF/glycolysis (Insulin-like growth factor), Wnt, PARP (poly ADP ribose polymerase), HDAC (histone deacetylase), JAK-STAT (Janus tyrosine Kinase- Signal Transducer and Activator of Transcription), Hedgehog, NOTCH, DNA Repair and Others' intervention point (namely RET, ALK, ROS1 and UB1). These intervention points have been selected because they can be associated with an activation in a cancer. The rule that guides the choice of the invention in
- 15 this selection is to select the activation signals that can be blocked.

Optionally, in an alternative method, a subgroup of intervention points can be selected among the above mentioned list of intervention points (i.e., a subgroup of 10, 12, 14, 16 or 18 intervention points). For instance, in a particular embodiment, a subgroup of intervention points of interest includes the intervention points for which drugs are available. For instance,

20 such a subgroup may include or consist in the following group: Her, CDK4,6, PLK/AURK/Kinesins, Angiogenesis, Immune Modulators PD1L and CTL14, PI3K, MET, MEK, ERK, Anti-Apoptosis, FGF, mTOR, Ras/Raf, IGF/glycolysis, Wnt, PARP, and DNA Repair.

In addition, for each intervention point, the inventors carried out a selection of genes useful for characterizing this intervention point. The list of genes is disclosed in Table 1 or 9.

- 25 In order to define the status of these intervention points in the tumor, several parameters have to be defined based on the limited list of genes that need to be investigated for each patient.

In a first aspect, expression levels of the genes of Table 1 or 9 are determined in the tumor

30 and normal samples. The expression levels are determined by measuring mRNA level. The determination of the expression level variation for these mRNA is carried out by comparing the expression levels in a tumor tissue and in the corresponding normal tissue. The gene

expression analysis allows the study of independent deregulations or deregulations due to chromosomal aberrations. Indeed, the regulation of the transformational activity of genes is complex and involves many levels of regulation: trans/cis transcription factors, promoters, chromatin regulation, and the like. Generally, all deregulations (over-expression) are considered with a ratio tumour/normal of at least 1.3. For each deregulated gene (i.e., gene with a different mRNA expression when tumor and normal samples are compared), a fold change and/or intensity of signal (proportional to the mRNA expression level) is determined. Technologies that can be used comprise Northern analysis, mRNA or cDNA microarrays, RT-PCT (in particular quantitative RT-PCR) and the like. Alternatively, the level of expression can be determined with a chip comprising a set of primers or probes specific for the list of genes of Table 1 or 9 or a set specific of genes of a subgroup of 10, 12, 14, 16 or 18 intervention points as disclosed in Table 1 or 9. Expression levels obtained from cancer and normal samples may be normalized by using expression levels of proteins which are known to have stable expression such as RPLPO (acidic ribosomal phosphoprotein PO), TBP (TATA box binding protein), GAPDH (glyceraldehyde 3-phosphate dehydrogenase) or β -actin.

It is important to note that the method according to the present invention is clearly distinct from a method of global or whole analysis of gene expression. Even if some genes can be added to the list of genes of Table 1 or 9, the gene expression is determined for less than 200, 250, or 300 genes.

In a second aspect, some genes of the list of genes of Table 1 and 9 are analyzed by sequencing (partial or whole sequencing) or by hybridization for detecting the presence or absence of mutations. For instance, exons of the genes of Table 1 or 9 can be sequenced by any method available, preferably by a method of high throughput sequencing such as Illumina or Ion Torrent method or equivalent. Alternatively, only genes with known activating mutation(s) can be analyzed. Such list of genes and mutations can change depending on the considered cancer. In a particular embodiment, the genes of Table 10 can be analyzed for the presence of mutations. More preferably, the method includes the sequencing of p53, the most frequent mutated gene in solid tumors. For instance, the method may include the determination of the presence/absence of mutations in the genes p53, KRAS or NRAS (preferably KRAS), EGFR, EBBR2, PIK3CA and BRAF. Indeed, the presence of mutation leading to a functional gain or loss has an important effect on biology of the

tumour without being always connected to variations of gene expression or of gene copy number. Many mutations are known to have a direct effect on the activity of a treatment by inducing increased sensitivities or resistances. For example, the mutations in the tyrosine kinase domain of EGFR are often associated with sensitivity to the small molecules inhibiting EGFR, the mutations in KRAS gene are associated with resistance to the treatment by monoclonal antibodies targeting EGFR. The mutational status can be determined by any method known in the art, for instance by sequencing, microsequencing or hybridization. In addition, the gene mutations are listed in in www.sanger.ac.uk/genetics/CGP/cosmic/.

In a third aspect, the copy number variation of genes are defined for the tumor sample of the subject. This analysis can be carried out by CGH (Comparative Genomic Hybridization) which makes it possible to compare the tumor DNA with the normal DNA of the same individual to detect chromosomal aberrations, i.e. copy number variation such as chromosomal losses or gains. This technology is well-known by the man skilled in the art. As an illustration of this knowledge, the following reviews or reference books can be cited: Davies et al. (2005, *Chromosome Research*, 13, 237-248). This technology is useful to identify translocations. It can be easily carried out with frozen biopsies or tumor paraffin-included material. CGH results are expressed as the ratios of copy numbers in the tumor material and in normal tissue. A threshold of 0.5 is been acknowledged to describe a gain or a loss. More this ratio is high, more the amplitude of the anomaly is important. Thus, an important anomaly is likely to have a real impact at the biological level. In a preferred embodiment, a fold change of the copy number variation is determined.

In a fourth aspect, levels of miRNAs or microRNAs for the genes of Table 1 or 9 are determined in the tumor and normal samples. More preferably, the levels of 5 miRNAs for each gene is determined. In a preferred embodiment, the miRNAs of Table 11 are analyzed. The method for measuring miRNA are well-known in the art.

Then, a fold change Tumor versus Normal tissue is determined for the 5 miRNAs and a mean fold change for each gene is calculated as the average of the fold changes of the 5 miRNAs.

Then, after the characterization step, the following parameters for the tumor of each specific patient have been determined:

- A list of genes among the list of Table 1 or 9 with a deregulated expression with a defined fold-change.
- A list of mutated genes.
- Optionally, a list of genes having a Copy Number Variation and a value (fold-change) for this CNV. In a preferred embodiment, only the genes presenting an amplification are taken into consideration.
- Optionally, a list of deregulated miRNA, in particular with an averaged fold change based on the 5 miRNA fold-change.

10 In a first embodiment, the characterization method includes the gene expression analysis and the mutated genes. In a second embodiment, the characterization method includes the gene expression analysis, the mutated genes and the Copy Number Variation. In a third embodiment, the characterization method includes the gene expression analysis, the mutated genes and the miRNA analysis. In a fourth embodiment, the characterization method includes the gene expression analysis, the mutated genes, the Copy Number Variation and the miRNA analysis. The choice of the combination of criteria can be different for each intervention point.

For instance, for some intervention points, the impact of miRNA has a major influence whereas for other intervention points, miRNA has a minor influence. As shown in the example section, for patients having NSCLC, miRNAs have a major impact on the intervention points mTOR-AKT-PTEN, RAS, ERK, PI3K and Immune Modulators, whereas the impact is minor for the intervention points Her, CDK4,6, Angiogenesis, MET, MEK, FGFR, RAF, IGF-Warburg, and PARP. In addition, for patients having NSCLC, the impact of CNV has been determined as quite low.

25 From these parameters, the method comprises that determination of the disturbed or activated intervention points in the tumor of the patient and the ranking of them by calculating a score for each intervention point.

Mathematical modeling/algorithm

30 The principles of the algorithm for calculating a score for each intervention point are the followings:

- 1- The score is designed to correlate with the likelihood that an intervention point is (abnormally) activated or disturbed in the tumor, in particular in comparison to the normal matched tissue of the same patient. It ranges from 1 to 20, the highest is the score, the most activated or disturbed is the pathway. In a preferred embodiment, the score ranges from 1 to 10. However, the scale of the score has no impact on the results.
- 2- The score may combine evidence from 4 data sources:
 - Mutations ;
 - Mean fold change in gene differently expressed in the tumor vs. normal;
 - Optionally, Mean fold change in expression of miRNA of tumor vs. normal; and,
 - Optionally, Copy number variation.

Activating mutation and the score calculation

The different data sources may carry different weights in the score. Indeed, activating mutation (e.g. K-RAS in the RAS pathway) may have decisive weight.

Then, in a first approach of the method, the maximal score is given to each intervention point comprising a gene with an activating mutation. In a preferred embodiment, the mutations associated with a maximal score are listed in Table 10. It may further include the p53 mutations. For instance, if the score ranges from 0 to 10, the maximal score of 10 is given to every intervention point comprising a gene with an activating mutation. In the absence of a mutation, the score is based on an average of the mRNA mean fold changes, optionally weighted with the level of expression of miRNAs and to a lesser extent CNV abnormalities.

In a second approach, the rules of the first approach are carried out, but the score is the sum of two scores, a first one based on mutation and a second one based on the arithmetic mean of the mRNA mean fold changes. Preferably, the range/scale of the two scores is the same. For instance, the two scores each range from 0 to 10.

In a third approach, the score is the sum of two scores, a first one based on mutation and a second one based on the mRNA mean fold change. However, a different weight/score can be given to mutations. In particular, instead of giving a score of 10 as soon as an activating mutation is detected, a lower score can be given to the activating mutation, for instance a score of 3. Accordingly, one mutation in a gene of an intervention point gives a score of 3,

two mutations a score of 6, three mutations a score of 9, more mutations the maximal score of 10. In addition, depending on the impact of the activating mutations, a different weight can be given. For instance, an activating mutation of KRAS gives a score of 10, whereas a mutation with less functional impact will count for 3. Accordingly, mutations listed in Table 10 may have a higher weight, for instance may count 10.

Calculating the mean fold-change of differentially expressed genes:

The global expression pattern is used to calculate a fold-change (f_i) of the expression of a gene i in the tumor and in the matched normal tissue. This fold change can be referred as mRNA TvN fold change. It is calculated as the ratio of the expression of a gene in tumor on the expression of the gene in a normal tissue.

For calculating the mean/average fold change of intervention point k , denoted as E_k , the fold changes of differentially expressed genes with a fold change of at least 1.3 are used. In other words, for each intervention point, an average fold-change of the genes i of the intervention point k is calculated, trimming values with a threshold of ≤ 1.3 .

Formally, we calculate E_k as the following: let M_k denote the set of genes that belong to intervention point k , and m_k denote the subset of M_k that includes only differential expressed genes with an absolute fold change ≥ 1.3 . E_k is the average of the fold change of the genes m_k .

$$m_k = \{i | i \in M_k \text{ and } |F_i| > 1.3\}$$

We then calculate the mean expression level for all the genes in m_k :

$$E_k = \bar{F}_i \text{ wherein } i \in m_k$$

In other words, the fold change for a particular intervention point is the average or arithmetic mean of the fold changes of genes belonging to the intervention point as defined in Table 1 or 9 and having a fold change T vs N of 1.3 or more.

In particular, in order to compare the fold changes of different intervention points, a relative scoring, e.g., from 1 to 10, is generated based on the percentile calculation.

Combining mRNA and miRNA measurements

To adjust for possible miRNA intervention in translation, the inventors propose to penalize discordance between miRNA and its target mRNA. For each of the genes of Table 1 or 9 that belong to the intervention points or a set thereof, the inventors determined the miRNAs

most likely to be involved in their regulation using Target scan {<http://www.targetscan.org/>}, selecting the top 5 miRNAs for each gene. Table 11 provides a list of the top 5 miRNAs for the genes of Table 1 or 9.

For each gene i , a mean miRNA fold-change can be calculated, which is denoted A_i , by averaging the fold changes of the 5 miRNAs (or less if less than 5 miRNAs are identified) that are most likely to target gene i . Then, for each gene, a mean miRNA TvN fold change is determined.

Then, a corrected fold change of a gene of an intervention point 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). The corrected fold change of a gene is then used to calculate the fold change for a particular pathway by using it in the calculation of the average fold changes of the genes belonging to the pathway as defined in Table 1 or 9 and having a fold change T vs N of 1.3 or more. Based on the corrected fold change of pathways, a corrected score, e.g., a score 1 to 10 is generated based on percentiles.

Combining mRNA and CNV measurements

Only genes with amplification are taken into account. Preferably, genes with 2-fold or higher amplification are considered as amplified. Then, a corrected fold change of a gene of an intervention point is calculated by multiplying the mRNA fold change Tumor versus Normal of the gene (mRNA TvN fold change) by the CNV fold change of the gene. The corrected fold change of a gene is then used to calculate the fold change for a particular intervention point by using it in the calculation of the average fold changes of the genes belonging to the intervention point as defined in Table 1 or 9 and having a fold change T vs N of 1.3 or more. Based on the corrected fold change of pathways, a corrected score, e.g., a score 1 to 10 is generated based on percentiles.

Score calculation

To compare intervention points, a score is given to each intervention point, taking into account mRNA expression and activating mutation. Optionally, 3 or 4 variables can be considered: activating mutations, the Fold change of mRNAs in Tumor vs. Normal, the fold change of miRNAs in Tumor vs. Normal and the copy number variation (amplifications,

deletions). In a preferred embodiment, the score is given to each intervention point, taking into account activating mutations, mRNA expression, and miRNA expression. In a particular embodiment, the miRNA is considered when calculating the score at least for the following intervention points: mTOR-AKT-PTEN, RAS, ERK, PI3K and Immune Modulators.

5 To summarize, in a first aspect, the score for each pathway is calculated as follow:

- 1- If an activating mutation is detected in one gene of the intervention point, then the score of the intervention point is the maximal score, e.g. 10 when scoring from 1 to 10.
- 2- Otherwise, the score is calculated based on the average of the fold changes tumor vs normal of the genes having an absolute fold change of at least 1.3 and belonging to the list of genes of Table 1 or 9 for the considered intervention point.
- 3- Optionally, if the miRNA level of the genes of Table 1 or 9 is measured, in particular those of Table 11, a mean miRNA fold change for each gene is calculated as the arithmetic mean of the fold change of 5 miRNAs of this gene. Then a corrected mRNA fold change for the gene 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). For calculating the mean of the mRNA tumor vs normal fold changes of the genes of an intervention point, the corrected mRNA TvN fold change for the gene is used.
- 4- Optionally, if the CNV of the genes of Table 1 or 9 (or some genes thereof) is measured with 2-fold or higher amplification, then a corrected mRNA fold change for the gene is calculated by multiplying the mRNA fold change Tumor versus Normal of the gene (mRNA TvN fold change) by the CNV fold change for the gene. For calculating the mean of the mRNA tumor vs normal fold changes of the genes of an intervention point, the corrected mRNA TvN fold change for the gene is used.

Alternatively, it can also be chosen to attribute less weight to mutations, in particular when considering the sequencing of all genes of Table 1 or 9. Accordingly, in a first alternative, the score is the sum of the score due to mutational status and the score due to the mRNA differential TvN expression. In a second alternative, in order to graduate the impact of the

mutations, a score of 3 is given by activating mutation. Then, for instance, the score of a pathway is a score based on activating mutations with a maximal score of 10 added to a score based on mRNA expression is calculated above with a maximal score of 10. Accordingly, for each intervention point, the score will be comprised between 0 and 20.

- 5 Based on the scores of the intervention points, the intervention points are ranked. The pathway ranking can allow the one skilled in the art to select one or several combinations of three activated or disturbed intervention points, especially the combination of the three most activated or disturbed intervention points according to the scores.

The pathways have been selected because drugs specific to each intervention point are
10 already or soon available for treating a patient (see Table 1). Accordingly, based on the combination of selected intervention points, a combination of drugs targeting these intervention points can be selected and proposed for treating the patient.

Therefore, the present invention 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
15 disturbed intervention points are selected by the method of the present invention and a drug is selected for each activated or disturbed intervention point, thereby providing a combination of three drugs.

Prior any administration to a patient, the efficacy of the drugs combination can be tested ex vivo. For instance, the combination can be tested on a model based on a biopsy of the tumor
20 from the patient. It can be tested on an animal model on which tumor cells from the tumor has been grafted. Alternatively, it can be tested in a pre-clinical model called Metastatic Ex Vivo Assay (MEVA). It is an in vitro 3D tissue culture through an anchorage independent system.

Then, the present invention relates to a method of treatment of a patient having a cancer or
25 a method for selecting a combination of drugs for treating a patient having a cancer, comprising:

- Providing a tumor sample and an histologically matched normal tissue from the patient;
- Characterizing the tumor sample in comparison to the normal sample as detailed
30 above;
- Calculating a score for each intervention point as detailed above;

- Selecting three activated or disturbed intervention points, preferably the three most activated or disturbed intervention points;
- Selecting a combination of drugs targeting the three selected activated or disturbed intervention points;
- 5 - Optionally, administering to the patient the selected combination of drugs.

Optionally, the method of the present invention can provide several combinations of three drugs. Indeed, in order to prevent any drug resistance, the combinations can be used sequentially.

In addition, the present invention relates to a kit and the use of such a kit for classifying
10 intervention points according to their status and for selecting a combination of three drugs
chosen as targeting the most activated or disturbed intervention points, wherein the kit
comprises means for measuring the mRNA expression level of the genes of Table 1 or 9. In
particular, such means can be primers and/or probes specific for each gene of Table 1 or 9.
Optionally, the kit may further comprise means for detecting the mutations in genes of Table
15 1 or 9. These means could be suitable for the whole sequencing of the genes of Table 1 or 9.
More preferably, the kit comprises means for detecting the mutations of Table 10. Means
can be probes specific of the nucleic acid sequence encoding a fragment including the
mutation. They can also be primers allowing the amplification and sequencing of the genes.
Optionally, the kit may further comprise means for determining the level of miRNA of genes
20 of Table 1 or 9, in particular those of Table 11. Finally, the kit may further comprise means
for determining the copy number variation of the genes of Table 1 or 9.

Finally, the present invention relates to drugs combinations of interest identified by the
method of the present invention. In a particular embodiment, the present invention relates
to a drugs combination including one drug targeting PDL1 or CTLA4 and two drugs selected
25 from the group consisting of an inhibitor of RAF, an inhibitor of Angiogenesis, an inhibitor of
MEK; an inhibitor of MET and an inhibitor of CDK 4,6.

The main reason to define triple regiment therapies as a combination of an
immunomodulator (anti PD1L or anti CTLA4) and two targeted therapies is to contain toxicity
of associations. Indeed, the main problem of combining targeted therapies might be the
30 additive toxicity. Whilst containing toxicity of dual combination was already demonstrated,
adding a third drug such as anti PD1L may contribute to an effective tolerated therapy, in
particular for metastatic NSCLC.

Accordingly, the present invention relates to a drugs combination for use in the treatment of cancer, wherein the drugs combination is selected among the combinations disclosed in Table 6, Table 7, Table 8.

Preferably, the drugs combination is the combination of three drugs. Optionally, it may include additional drugs.

In a more specific embodiment, the present invention relates to a drugs combination including a drug targeting PDL1, an inhibitor of RAF and a third targeted drug such as an inhibitor of MEK6, an inhibitor of MET, an inhibitor of CDK4,6 or an inhibitor of angiogenesis. Based on analysis of frequency of occurrence of activated interventional points, and based on analysis of trends of co-activation, the most important combinations are the following:

1. anti PD1L (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + MtorPI3K inhibitor (e.g., Pfizer)
2. anti PD1L (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + angio- inhibitor (e.g., Pfizer)
3. anti PD1L (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + met inhibitor (e.g., Pfizer)
4. anti PD1L (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + CDK4,6 inhibitor (e.g., Pfizer)

these for combinations covers 51 % of patients with NSCLC as determined in the analysis of the retrospective collection of 123 patients.

In addition to these 4 combinations, the inventors determined that replacing PD1L with CTL14 fulfils the criteria of combining an immunomodulator with two others targeted drugs.

Four additional combinations can be envisioned, increasing the coverage of patients to 72%

5. anti CTLA4 (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + MtorPI3K inhibitor (e.g., Pfizer)
6. anti CTLA4 (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + angio- inhibitor (e.g., Pfizer)
7. anti CTLA4 (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + met inhibitor (e.g., Pfizer)
8. anti CTLA4 (e.g., AZ) + Pan RAF inhibitor (e.g., Takeda)* + CDK4,6 inhibitor (e.g., Pfizer)

It is worthwhile to mention that the Pan RAF inhibitor could be replaced with a MEK inhibitor in most of the patients. This replacement generates 8 combinations:

9. anti PD1L (e.g., AZ) + MEK inhibitor + MtorPI3K dual inhibitor (e.g., Pfizer)
10. anti PD1L (e.g., AZ) + MEK inhibitor + angio-inhibitor (e.g., Pfizer or Takeda)
11. anti PD1L (e.g., AZ) + MEK inhibitor + met inhibitor (e.g., Pfizer)
12. anti PD1L (e.g., AZ) + MEK inhibitor + CDK,-6 inhibitor (e.g., Pfizer)

- 13. anti CTLA4 (e.g., AZ) + MEK inhibitor + MtorPI3K dual inhibitor (e.g., Pfizer)
- 14. anti CTLA4 (e.g., AZ) + MEK inhibitor + metinhibitor (e.g., Pfizer)
- 15. anti CTLA4 (e.g., AZ) + MEK inhibitor + angio_inhibitor (e.g., Pfizer or Takeda)
- 16. anti CTLA4 (e.g., AZ) + MEK inhibitor + CDK4,6 inhibitor (e.g., Pfizer)

5 In a preferred embodiment, the above-mentioned drugs can be selected among those disclosed in Table 1.

More preferably, the drugs combination is selected in the group consisting of

- Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + PF-384 (Pfizer)
- Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + Axitinib (Pfizer) or
- 10 Motesanib (Takeda)
- Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + Crizotinib (Pfizer)
- Medi-4736 (Astra Zeneca) + MLN2480 (Takeda) + Palbociclib (Pfizer)
- Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + PF-384 (Pfizer)
- Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + Axitinib (Pfizer) or
- 15 Motesanib (Takeda)
- Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + Crizotinib (Pfizer)
- Tremelimumab (Astra Zeneca) + MLN2480 (Takeda) + Palbociclib (Pfizer)
- Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + PF-384 (Pfizer)
- Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + Axitinib (Pfizer) or
- 20 Motesanib (Takeda)
- Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + Crizotinib (Pfizer)
- Medi-4736 (Astra Zeneca) + Selumetinib (Astra Zeneca) + Palbociclib (Pfizer)
- Tremelimumab (Astra Zeneca) + Selumetinib (Astra Zeneca) + PF-384 (Pfizer)
- Tremelimumab (Astra Zeneca) + Selumetinib (Astra Zeneca) + Crizotinib
- 25 (Pfizer)
- Tremelimumab (Astra Zeneca) + Selumetinib (Astra Zeneca) + Axitinib (Pfizer)
- or Motesanib (Takeda), and
- Tremelimumab (Astra Zeneca) + Selumetinib v + Palbociclib (Pfizer).

By a "drugs combination", it is referred to a pharmaceutical composition comprising the
 30 drugs of the combination or to a kit or product comprising the drugs of the combination as a combined preparation for simultaneous, separate or sequential use.

The present invention relates to

- a pharmaceutical composition comprising the drugs of the combination, and a pharmaceutically acceptable carrier, in particular for use in the treatment of cancer; and/or
- a product or kit containing the drugs of the combination, as a combined preparation for simultaneous, separate or sequential use, in particular in the treatment of cancer; and/or
- a combined preparation which comprises the drugs of the combination, for simultaneous, separate or sequential use, in particular in the treatment of cancer; and/or
- a pharmaceutical composition comprising the drugs of the combination for the use in the treatment of cancer in combination with radiotherapy and/or or an additional anti-tumoral agent; and/or
- the use of a pharmaceutical composition comprising the drugs of the combination for the manufacture of a medicament for the treatment of cancer; and/or
- the use of a pharmaceutical composition comprising the drugs of the combination for the manufacture of a medicament for the treatment of cancer in combination with radiotherapy, and/or or an additional anti-tumoral agent; and/or
- a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition comprising the drugs of the combination, and a pharmaceutically acceptable carrier; and/or
- a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of the drugs of the combination; and/or
- a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition comprising the drugs of the combination in combination with radiotherapy.

In a preferred embodiment, the cancer is a lung cancer, and more preferably a NSCLC.

The following chapter, describes material, methods and results presenting full investigation of possibilities of combinations, based on magnitude and frequency of occurrence of interventional points of activation as determined by the scoring system. In addition, selection of combinations takes into account the trends of co-activation

EXAMPLES

Methods

Patients and Tissue Samples

The present study was organized by the CHEMORES initiative (Chemotherapy resistance consortium), which is an EU funded (FP6) Integrated Project involving 19 academic centres, organizations for cancer research, and research-oriented biotechnology companies in 8 European countries.

Tissue samples from a cohort of 123 patients who underwent complete surgical resection at the Institut Mutualiste Montsouris (Paris, France) between 30 January 2002 and 26 June 2006 were analysed. Clinical characteristics are given in Table 4 below. The median age of patients was 63 years (range 41-85), 34 (28%) were female and 89 (72 %) were male. The histopathology of all tumors was reviewed by the same pathologist (JvdO): 50 patients had SCC, 57 AC, 13 LCC and 3 unclassified. Using the new 7th edition TNM staging 56 were stage I, 25 stage II, 28 stage III and 4 stage IV. Adjuvant platinum based chemotherapy was administered to 61 patients. Fifty-nine patients experienced a relapse. Two-year relapse-free survival was 64%, and the median time to recurrence for the cohort was 5.2 years. After a median follow up of 40 months (range 0-92) 36 patients had died and 23 patients were alive with recurrence.

This study was performed using snap-frozen tumor and adjacent normal lung tissue. Samples were handled according to the Tumor Analysis Best Practices Working Group (*Nat Rev Genet* 2004; 5:229-237). Haematoxylin and eosin stained frozen sections, taken before and after the cutting of slides for analysis, revealed a median cell content of 85% (an inter-quartile range of 65% to 95%). All tissues were banked after written informed patient consent, and the study was approved by the Ethics Committee of Institut Gustave Roussy (IGR). Genomic investigations were performed at IGR, leader of the Genomic work-package of Chemores consortium, in the genomic center core facility certified ISO9001, labelled European reference and training center for Agilent technologies. Analyses were performed at IGR and Karolinska Institute, the leader of integrated analyzes work-package.

Table 2 - Characteristics of the patients in the study population

	n=123 (100%)
Age median (range)	63 (40.9-84.6)
Males n (%)	89 (72%)
Smoking Current	64 (52%)
Former	51 (42%)
Never	7 (6%)
Histology AC	57 (46%)
SCC	50 (41%)
LCC	13 (11%)
Other	3 (3%)
Stage 1	56 (50%)
2	25 (22%)
3	28 (25%)
4	4 (4%)
Adjuvant Chemo (%)	61 (50%)

Data availability

- 5 The microarray data related to this study have been submitted to the Array Express data repository at the European Bioinformatics Institute (<http://www.ebi.ac.uk/arrayexpress/>) under the accession numbers E-MTAB-1132 (GE), E-MTAB-1133 (CGH) and E-MTAB-1134 (MIR).

10 Oligonucleotide aCGH

- DNA samples were extracted from tissues using Qiagen QIAamp DNA Mini kit (Qiagen, Hilden, Germany). In each case, the normal tissue sample was used as the reference to its corresponding tumor sample. DNA was restriction digested and controlled by Agilent Bioanalyzer on DNA 7500 chips (Agilent Technologies, Santa Clara, CA, USA). The fragmented reference and test DNA were labelled with Cy3-dUTP or Cy5-dUTP, respectively, using Agilent Genomic DNA Labelling Kit PLUS. Samples were purified using Microcon YM-30 filters (Millipore, Billerica, MA). Hybridization was carried out on Agilent 244K arrays for 24 hours at 65°C in a rotating oven (Robbins Scientific, Mountain View, CA) at 20rpm, followed by appropriate washing steps. Scanning was performed with an Agilent G2505C DNA
- 20 Microarray scanner using default parameters. Quantification of Cy5 and Cy3 signals from

scans was performed with Feature Extraction v10.5.1.1 (Agilent Technologies) using default parameters.

CGH data processing and analysis

5 Resulting raw signals and log₂ (ratio) profiles were normalized and centered according to their dye composition (Cy5/Cy3) and local GC content. These profiles were segmented with the Circular Binary Segmentation algorithm (Olshen et al. *Biostatistics* 2004 Oct;5(4):557-72) through its implementation in the DNACopy package for R v2.8.1 using default parameters. DNA copy number imbalances were detected considering a minimum of 3 consecutive
10 probes and a minimal absolute amplitude threshold that was specific for each profile, accordingly with its internal noise. This specific internal noise was computed as one-fourth of the median of the absolute log₂ (ratio) distances across consecutive probes on the genome. Of the 128 aCGH hybridizations performed, 17 were discarded: 7 due to their clinical annotations, 2 due to anomalies in their normal reference, and 8 due to the bad quality of
15 their profile, resulting in 111 usable profiles. All aCGH coordinates in this study are mapped against the human genome as defined by the UCSC build hg18.

To assess the discovery of the genomic regions with differential anomalies between the AC, LCC and SCC populations, ANOVA tests were performed on the segmented aCGH dataset. To account for multiple testing, p-values were transformed to false discovery rate (FDR)
20 (Benjamini et al. *J Royal Statist Soc B* 1995; 57:289-300).

Gene expression and microRNA microarray assay

The lysis of 40 to 50 frozen sections of 10 micron-thickness, cut from each NSCLC tissue sample was done using a Polytron homogenizer (Ultraturrax, IMLAB, Lille, France). The RNA
25 extraction was performed with TRIzol® Reagent protocol (Invitrogen, Carlsbad, CA, USA). Total RNA was quantified and qualified with Nanodrop ND-1000 spectrometer and Bioanalyzer-2100 (Agilent Technologies).

For dual color Cy3 (normal samples) and Cy5 (tumor samples) labelling, Agilent Fluorescent Low Input Linear Amplification kit adapted for small amounts of total RNA (500 ng total RNA
30 per reaction) was used, followed by purification of labelled probes by Qiagen RNeasy Mini kit and by a protocol provided by Agilent. Gene expression profiling was performed with dye-swap, using dual-color 244K Human exon array from Agilent (custom design with the content

of the 44K Human genome plus 195000 probes, one for each exon as defined in refGene list of UCSC build hg18 (<http://genome.ucsc.edu/>). Hybridization was carried out for 17 hours at 65°C at 10 rpm, followed by washing steps. Scanned microarray images were analyzed by using Feature Extraction software version 10.5.1.1 (Agilent).

- 5 For the microRNA analysis, normal and tumor samples were hybridized on separate arrays. Agilent miRNA Microarray System with miRNA complete labelling and hybridization kit was used for Cy3 labelling. Briefly, isolated total RNAs were dephosphorylated, labelled with pCp-Cy3 and hybridized to Agilent 8x15K arrays for 20h at 55°C in a rotating oven (Robbins Scientific) at 20 rpm. Slides were washed and scanned for gene expression using an Agilent
- 10 G2565C DNA microarray scanner using defaults parameters.

Gene mutations analysis

- Sequencing was performed at IGR and at the Royal Institute of Technology (Stockholm, Sweden). DNA was extracted with QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). After
- 15 PCR amplification of target exons, sequencing reactions were carried out using the BigDye® Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA). The primer sequences are available on request. Sequencing reactions were run on a 48-capillary 3730 DNA Analyzer®. Sequence analysis and alignment was performed with SeqScape® software (Applied Biosystems). All detected mutations were confirmed in at least one independent
- 20 PCR reaction. In all 123 samples, full coding sequences of exons including oncogenic mutational hotspots were analyzed corresponding to: TP53 (NM_000546.4) exons 5-8; KRAS (NM_004448.2) exons 2 and 3; EGFR (NM_005228.3) exons 18-21; PIK3CA (NM_006218.2) exons 10 and 21; BRAF (NM_004333.4) exon 15; ERBB2 (NM_004448.2) exons 18, 20-24; KDR (NM_002253.1) exons 2, 26, 27 and 30; and AKT1 (NM_005163.2) exon 4.

25

Gene-expression data processing and normalisation

- All processing methods used for gene expression analysis were performed on the median signal from Agilent Feature Extraction raw data files using functions and packages collected in the R Bioconductor project (Gentleman et al. *Genome Biology*, 5: R80) as well as custom
- 30 written routines.

For gene expression data, dye-swap arrays were first combined (by taking the average of intensities) to obtain only one array per condition. This combination has the result of

centering the M values (log2ratios) on zero. Then, flagged spots as well as control spot were removed. Normalization was then performed using the *normalizeWithinArrays* function from R package LIMMA (Smyth GK *Statistical Applications in Genetics and Molecular Biology* 2004, vol3: N°1, article3).

- 5 For miRNA data, control spots were systematically removed, and flagged spots (glsFeatNonUnifOL and glsSaturated columns from raw files) were considered as missing values ("NA"). Array normalization was performed using the least-variant-set method (Suo et al. *RNA* 2010 Dec; 16(12): 2293-303).

10 **Differential expression analyses of miRNA expression**

To assess differentially-expressed miRNA, the inventors first estimated the fold changes and standard errors between two groups of samples by fitting a linear model for each probe with the lmFit function of LIMMA package in R. Then they applied an empirical Bayes smoothing to the standard errors from the linear model previously computed with eBayes function.

15

Scoring/ ranking of activated interventional points

The algorithm

The mathematical modelling and scoring system aims to give a score (1 to 10) based on integration of omics data, sequencing, gene expression, miRNA and copy number variations
20 determined as differences between tumor and normal, individually for each patients. SPRING scoring enables identification and ranking of activated pathways, and the overall concept is that such activated pathways should be blocked with combined targeted therapies.

- 25 **The first mathematical model** was established on the basis of a retrospective dataset from 123 patients with NSCLC for whom sequencing, Copy Number Variation, and tumor vs. normal gene expression were available. Using these data, an algorithm that provides a score of activation for each of the simplified pathway for the patient and factors in all of the above-mentioned structural and functional results has been established. The principle of the
30 algorithm is disclosed in Figure 2.

Scoring is based on an intuitive algorithm that integrates 4 types of genomic investigations of Tumor and Normal biopsies

1. **Mutations:** in V.1 the inventors used a very limited set of sequencing data, including only the genes/mutations used currently in clinical care of NSCLC: EGFr, KRAS, BRAF, PI3KCA, and HER2. Additionally they sequenced p53, the most frequent mutated gene in lung (and all solid tumors).
 - a. When a mutation is detected, the algorithm assign the maximal score 10 in the corresponding simplified pathway.
2. **Gene Expression:** For each simplified pathway, mRNA steady state level in Tumor vs. Normal is used to calculate a mean fold change of the pathway.
 - a. Values of individual Fold Change are trimmed at the threshold 1.3.
 - b. Values of individual mean fold changes for each simplified pathway are ranked in the retrospective set of data of 123 NSCLC, used as a calibrator.
 - c. As shown in 3 examples below, the range of Fold Changes is different from one to other pathway. In order to compare them, the inventors generated a relative scoring from 1 to 10 based on the percentile calculation.
3. **miRNA expression:** For each gene, the inventors selected top 5 matched miRNA from TargetScan data base.
 - a. The fold changes T vs. N steady state level for each miRNA was used to generate a mean fold change.
 - b. Fold change T vs. N for each gene was divided by the mean Fc T/N of the 5 corresponding miRNAs.
 - c. They generated then a corrected mean Fold change for each simplified pathway.
 - d. They generated a corrected score 1 to 10 based on percentiles.
4. **Copy Number Variation.** When amplification is detected, the inventors multiplied the value of the mRNA expression fold change for each gene by the value of the fold change amplification. Then they generate the corrected mean fold change of pathways and the percentiles score.

Table 3 summarises scores obtained for all patients of the 123 NSCLC, for a selection of interventional points

patient	Histo	He r	CD K 4_6	ANGI O	PI3 K	ME T	ME K	ER K	FG F	mTO R	RA S	RA F	PAR P	JAK_STA T	PDL1	CTLA 4
AGG600716	AC	1	3	5	2	4	9	3	5	5	6	3	8	6	9	9
ANO420520	AC	5	6	7	7	10	2	1	3	2	7	4	5	8	10	9
ARC270517	SCC	9	4	1	1	1	3	1	8	2	3	2	8	2	1	4
AVI260916	AC	2	2	5	7	2	8	9	9	7	10	10	5	8	9	2
AZE450213	AC	8	10	9	4	7	7	5	2	3	2	9	3	9	2	10
BAR331123	SCC	8	7	10	10	6	4	7	9	8	8	8	7	7	7	10
BAS260512	AC	10	1	3	1	3	5	2	1	4	4	5	6	5	5	3
BAS260724	AC	5	10	8	3	9	6	5	2	1	6	5	4	5	10	8
BEM291129	SCC	5	1	1	6	5	4	6	6	2	5	4	1	8	5	7
BEN480707	SCC	1	1	2	4	5	8	4	2	3	9	6	2	7	10	5
BEN410529	LCC	7	3	9	5	5	7	3	6	2	10	10	5	6	8	8
BER520430	AC	7	2	4	2	3	3	4	6	7	7	3	2	1	4	2
BIE410219	SCC	10	9	7	7	5	7	6	9	7	10	4	9	8	3	8
BOU480910	AC	9	3	6	2	5	8	2	7	5	6	4	3	6	3	6
BOU291129	SCC	2	9	1	10	9	3	2	5	7	1	1	10	3	4	1
BOU520111	AC	6	5	5	5	6	2	9	8	7	1	6	5	4	6	10
BRO521127	AC	4	8	8	2	7	9	7	1	2	2	5	6	10	6	10
BRZ470326	AC	10	9	9	8	10	10	5	6	10	2	1	8	7	10	8
CAM520101	Other SCLC	10	9	6	8	10	9	6	7	4	2	1	1	10	3	7
CAP460215	LCC	1	4	1	3	10	2	4	2	5	3	10	9	2	2	4
CHA280524	AC	8	5	2	8	9	4	10	1	3	4	5	3	5	1	4
CHA571008	LCC	8	5	5	1	6	2	6	2	1	3	2	5	3	5	6
CHA470718	LCC	4	6	10	3	9	7	10	6	10	3	7	2	5	7	9
CHE511225	AC	6	9	1	2	8	6	8	3	9	3	9	10	9	6	7
COU420201	AC	2	10	1	10	4	5	10	7	8	6	10	10	1	1	5
CRE420423	SCC	6	10	10	6	8	6	1	10	10	9	5	4	7	9	9
DAM20041	SCC	2	10	9	7	2	10	3	3	6	10	9	4	9	9	10

3																
DAV320407	SCC	1	5	10	2	7	3	5	10	4	2	7	6	2	7	7
DEL330821	AC	7	8	7	10	10	9	4	3	9	10	7	4	10	9	10
DEP351121	SCC	5	9	6	8	6	6	10	8	10	2	6	9	2	4	3
DES580418	AC	10	6	3	7	9	7	8	6	8	5	8	10	10	8	7
DEW440406	AC	5	4	6	4	7	3	4	3	3	6	6	2	2	5	5
DHE321214	Other ADE C	9	6	3	6	10	4	1	9	5	9	10	6	6	5	5
DOM590729	SCC	3	10	3	9	7	4	10	8	5	8	4	10	4	10	5
DUV330713	SCC	6	5	10	4	4	8	9	7	9	2	8	10	6	10	4
ECU520713	AC	3	10	8	1	8	2	7	9	10	8	8	3	3	5	1
EDO300812	SCC	7	5	2	9	8	7	4	3	9	7	5	9	5	4	7
ELA540809	LCC	4	8	4	1	1	3	2	10	5	9	10	4	3	5	2
ELB330728	AC	10	3	6	7	7	5	3	2	1	7	6	10	7	6	9
FER471031	AC	4	2	8	2	4	3	4	3	8	4	6	7	2	7	5
FER461230	SCC	3	5	7	6	5	7	2	6	6	5	5	1	4	3	3
FIL381013	AC	10	10	9	6	7	10	3	1	4	3	10	3	10	10	8
FLA490711	AC	5	5	8	1	2	2	5	5	8	1	1	10	1	3	2
FOR440321	AC	7	6	9	6	10	5	7	4	4	1	8	1	7	4	6
FOR410727	SCC	6	7	4	10	3	10	6	3	7	6	4	6	8	10	6
FRO440806	AC	2	2	3	5	6	9	8	1	3	6	8	2	3	5	7
GAN350811	SCC	10	8	4	10	9	6	5	6	6	1	7	8	1	1	3
GAR410813	SCC	6	7	6	9	6	1	10	5	4	4	1	10	6	8	6
GAR450819	SCC	10	7	3	8	4	4	4	2	4	2	4	10	7	8	8
GEF541216	AC	10	7	8	10	3	9	4	8	10	9	4	4	5	9	10
GEO270114	SCC	3	6	2	5	10	5	10	4	1	10	6	7	8	4	7
GID490224	AC	7	7	10	3	8	10	1	3	6	10	9	5	5	3	4
GIL230901	SCC	3	1	2	6	6	6	3	9	7	7	3	6	6	6	6
GIR220606	AC	9	1	3	4	7	4	10	4	4	8	9	2	2	1	3
GOE191205	AC	10	4	7	4	8	1	5	4	2	7	3	3	4	4	2
GOM450227	SCC	9	4	6	9	7	1	2	10	4	6	3	8	1	1	1

GRO250108	AC	10	9	7	10	6	8	8	4	8	10	10	8	10	8	9
GRY470526	AC	9	6	4	10	9	2	3	2	1	6	7	1	9	2	7
GUI390806	AC	10	7	3	7	3	6	3	10	6	10	10	1	8	2	4
GUI200304	AC	9	2	3	9	9	10	5	10	8	8	10	2	6	2	6
HAM640729	SCC	3	2	10	5	1	10	10	9	1	9	1	5	8	3	1
HAR331217	SCC	10	6	6	10	3	8	1	6	10	1	2	9	2	3	2
HOU501106	AC	8	3	10	6	8	9	10	8	10	5	9	5	10	4	6
IGL380217	AC	1	7	9	5	4	3	6	10	9	3	8	7	3	4	1
ISA300917	SCC	3	4	2	4	2	1	6	5	5	8	4	6	9	3	4
IVA360731	SCC	1	2	5	7	1	7	7	1	2	8	7	1	9	6	5
JAY440311	AC	7	1	8	4	2	1	2	1	5	9	3	1	4	8	6
JEA320618	LCC	10	1	3	10	9	8	6	8	8	6	10	5	9	10	5
KEI431016	SCC	4	4	9	8	9	8	4	7	10	6	4	2	4	9	9
KON381027	AC	9	8	10	1	1	2	2	1	9	1	4	3	1	2	1
KRA420928	AC	10	1	8	7	9	7	10	8	8	4	8	1	10	4	9
LAM380228	AC	6	7	10	5	4	5	5	4	4	9	7	5	3	3	4
LAN041130	LCC	10	8	1	4	10	9	1	8	9	5	10	10	4	8	10
LAN510426	SCC	10	9	1	9	3	8	3	9	3	9	7	7	10	10	10
LEF320516	SCC	8	5	10	3	8	1	9	8	8	1	2	5	3	5	1
LEF341111	SCC	7	9	8	1	2	3	9	10	10	1	2	9	2	2	3
LEJ501115	SCC	1	2	5	3	5	2	7	1	1	3	2	4	8	7	4
LEL450721	AC	1	10	1	2	10	2	8	5	9	1	1	6	7	2	9
LEM351012	LCC	9	8	4	6	3	2	6	1	10	1	2	10	1	1	1
LEN371015	SCC	3	3	1	3	6	1	10	10	9	6	1	7	5	1	3
LEP560531	AC	8	2	10	8	7	3	1	3	2	5	6	3	1	2	6
LER460716	SCC	2	1	10	5	3	3	2	5	3	9	7	4	6	6	8
MAC460101	AC	7	1	8	1	1	5	8	2	2	4	5	7	7	6	4
MAC381220	SCC	4	4	4	2	7	10	8	5	7	5	9	3	2	7	1
MAR240911	SCC	5	2	5	2	1	6	7	10	5	5	7	4	2	3	4
MAR491126	SCC	7	9	4	3	4	2	10	9	8	7	9	7	7	4	8
MAR430726	AC	9	4	8	6	3	5	6	5	3	2	7	7	5	6	7
MAR350507	SCC	7	6	5	10	6	6	9	7	8	1	9	8	9	6	5
MAR470322	LCC	3	5	7	2	5	8	7	5	7	5	5	10	9	9	9
MAT230414	SCC	4	10	2	10	4	5	7	7	10	5	4	1	7	4	8
MER490318	AC	10	2	6	8	8	8	2	3	3	10	6	3	4	9	4
NEG410311	AC	10	8	2	8	8	10	2	2	9	7	10	6	10	5	6
NIN270409	AC	10	8	7	3	10	9	5	4	3	4	10	2	8	7	7
PAN390607	AC	6	1	9	3	2	1	9	4	1	3	1	1	1	1	1
PAQ470203	LCC	1	9	5	7	1	10	3	1	9	2	3	7	3	1	2
PEC481113	AC	10	2	5	6	4	1	5	4	2	3	9	2	4	2	2
PER401217	Other ADE C	1	4	2	1	2	1	7	9	1	4	6	4	8	8	3
PER510713	AC	2	3	7	4	6	8	1	4	5	7	8	2	6	7	8

PIQ340906	SCC	5	1	9	1	1	7	7	2	6	4	2	4	1	5	2
RAB330621	SCC	6	8	5	10	2	4	6	9	2	8	5	8	2	2	2
RAM530325	AC	9	8	7	3	5	9	1	7	6	4	5	4	3	8	3
REC590707	LCC	4	9	6	8	3	10	9	6	10	3	3	9	1	8	5
REJ471005	SCC	10	6	4	9	5	7	9	9	6	2	2	8	10	6	10
RIT431108	AC	10	10	4	9	9	4	9	6	1	10	8	6	10	10	10
RIT490630	SCC	2	6	7	7	3	9	7	5	4	7	7	9	6	5	9
SAI380426	AC	5	8	10	9	8	4	5	10	7	8	1	1	6	8	3
SAU450710	SCC	3	5	2	2	1	5	9	10	1	8	5	7	1	1	1
SER300810	LCC	2	4	10	1	5	7	9	4	2	5	9	2	5	7	2
SIK471101	AC	8	3	8	5	10	5	8	2	4	10	6	3	5	6	7
SUT470608	SCC	4	3	9	7	4	6	2	5	7	4	3	9	5	7	5
TAI320613	AC	10	5	5	3	2	4	8	1	3	8	1	9	3	7	1
TAR290829	SCC	3	7	3	4	1	1	8	8	1	2	3	8	3	2	3
TAT400901	AC	9	6	10	5	10	3	1	7	6	10	2	5	4	3	6
THU220630	SCC	2	3	7	4	5	4	1	7	5	8	3	6	4	8	3
TIL420228	SCC	10	4	4	6	7	6	8	7	5	4	6	7	9	10	8
UST500306	SCC	1	10	1	10	1	5	4	4	6	3	1	9	4	1	9
VAL271009	SCC	5	3	6	5	2	6	6	8	6	5	9	8	8	9	5
VIL310309	SCC	6	10	9	8	8	1	4	6	9	9	2	8	7	9	10
WIS320823	SCC	2	3	1	8	2	9	3	7	3	9	3	9	10	10	8
YOT471216	AC	2	7	4	9	4	10	3	3	6	7	8	6	9	7	10
ZIT420630	AC	8	7	10	9	6	10	8	10	7	7	8	3	9	9	2

In the next step, the inventors made the selection of all activated interventional points. Scores 8, 9 and 10 were considered designating an important/high activation, whereas scores 6 and 7 were considered designating medium activation. Scores <6 were considered as designating non activated interventional points.

Table 4 shows the complexity of co-activation of interventional points. Each patient's tumors shows multiple activations, suggesting multiple possibilities of combinations. All 24 interventional points were analysed

ID	High activation score: 8, 9 and 10							Medium activation score: 6 and 7						
AGG600716	Ant iap	MEK	IGF	PDL1	CTLA 4	PARP	AURK A	RAS	JAK_STAT	DNA REP				
ANO420520	Ant iap	IGF_War	PDL1	CTLA 4	CDK 4_6	SCDK 4_6	RCDK 4_6	ANG IO	PI3K	RAS	WNT	DNAR EP	NOTC H	
COU420201	Ant iap	CDK 4_6	AURK A	PI3K	ERK	mTKP T	TELO ME	IGF_War	WNT	PARP	HDA C	HEDG EHOG	DNAR EP	NOTC H
ECU520713	Ant iap	CDK 4_6	SCDK 4_6	RCDK 4_6	ANGI O	MET	FGF	mTK PT	ModM TKT	RAS	RAF	TELOM E	IGF	HEDG EHOG
FER471031	Ant iap	ANGI O	mTKP T	RAF	TELO ME	PARP	PDL1							
FIL381013	Ant iap	Her	CDK 4_6	ANGI O	MEK	RAF	JAK_STAT	NOT CH	PDL1	CTLA 4	PLA URKi	RAS	JAK_STAT	DNA REP
GEF541216	Ant iap	Her	AURK A	ANGI O	AGPT	PI3K	MEK	FGF	mTKP T	ModM TKT	RAS	TELOM E	PDL1	CTLA 4
KON381027	Ant iap	Her	CDK 4_6	ANGI O	mTKP T	PLAU RKi	TELO ME	HDA C						

LAM 3802 28	Antiap	ANGIO	AG PT	RAS	IGF_ War	Her	CDK 4_6	SCDK 4_6	RCD K 4_6	RAF					
MER 4903 18	Antiap	Her	RA S	HDA C	PDL1	ANGI O	RAF	IGF_ War							
ZIT4 2063 0	Antiapo	Her	AN GI O	PI3K	MEK	ERK	FGF	RAF	IGF_ War	WNT	HDA C	JAK_ STAT	PDL1	CDK 4_6	
AVI2 6091 6	AGPT	MEK	ER K	FGF	RAS	RAF	JAK_ STAT	NOT CH	PDL1	PI3K	mTK PT	WNT	HDAC		
AZE 4502 13	Her	CDK 4_6	AN GI O	AGP T	RAF	TELO M	JAK_ STAT	CTLA 4	MET	MEK	WNT				
BAS 2605 12	Her	PARP	HD AC	HED GEH G											
BAS 2607 24	CDK 4_6	AURKA	AN GI O	MET	Antia p	TELO M	PDL1	CTLA 4	MEK	RAS	HDA C				
BER 5204 30	Her	FGF	mT KP T	RAS	IGF	HED GEH OG									
BOU 4809 10	Her	AGPT	ME K	WNT	ANGI O	FGF	RAS	IGF_ War	JAK_ STAT	NOTC H	CTLA 4				
BOU 5201 11	AGPT	FGF	CT LA 4	Her	AURK A	MET	Antia p	RAF	HDA C	DNA_ REP	PDL1				
BRO 5211 27	CDK 4_6	ANGIO	ME K	JAK_ STA T	CTLA 4										
BRZ 4703 26	Her	CDK 4_6	AU RK A	ANGI O	PI3K	MET	MEK	Antia p	mTKP T	PARP	DNA_ REP	PDL1	CTLA4	FGF	
CHA 2805 24	Her	PI3K	ME T	ERK	AGPT	WNT									
CHE 5112 25	CDK 4_6	AURKA	ME T	ERK	mTKP T	RAF	TELO M	IGF_ War	PARP	DNA_ REP	NOT CH	Her	MEK	Antia p	
DEL 3308 21	CDK 4_6	PI3K	ME T	MEK	Antia p	mTKP T	M_M TKPT	RAS	TELO M	WNT	JAK_ STAT	PDL1	CTLA4	Her	
DES 5804 18	Her	AGPT	ME T	ERK	mTKP T	RAF	TELO M	PARP	HDA C	JAK_ STAT	DNA_ REP	PDL1	PI3K	MEK	
DE W44 0406	ANGIO	MET	RA S	RAF	IGF_ War	PDL1	CTLA 4								
ELB 3307 28	Antiap	IGF_ War	PA RP	HDA C	DNA_ REP	CTLA 4	Her	AURK A	ANGI O	PI3K	MET	RAS	RAF	JAK_ STAT	
FLA 4907 11	ANGIO	AGPT	mT KP T	TEL OM	IGF_ War	WNT	PARP	HDA C	DNA_ REP	PLAU RKi					
FOR	ANGIO	MET	RA	Her	CDK	PI3K	ERK	WNT	JAK	DNA	CTLA				

4403 21			F		4_6				STAT	REP	4			
FRO 4408 06	MET	Antiap	RA S	DNA _RE P	CTLA 4	RAF								
GID 4902 24	ANGIO	MEK	RA S	RAF	WNT	Her	CDK 4_6	mTKP T	DNA_ REP	NOTC H				
GIR 2206 06	Her	ERK	RA S	RAF	AGPT	MET	HED GEH OG							
GOE 1912 05	Her	AGPT	AN GI O	RAS	HDA C	HED GEH OG								
GR O25 0108	Her	CDK 4_6	AU RK A	PI3K	MEK	ERK	mTKP T	RAS	RAF	PARP	HDA C	JAK_ STAT	PDL1	CTLA 4
GRY 4705 26	Her	PI3K	ME T	JAK_ STA T	CDK 4_6	RAS	RAF	TELO M	CTLA 4					
GUI 3908 06	Her	FGF	RA S	RAF	IGF_ War	WNT	JAK_ STAT	NOT CH	CDK 4_6	AGPT	PI3K	MEK	mTKPT	HDA C
GUI 2003 04	Her	PI3K	ME T	MEK	FGF	mTKP T	RAS	RAF	WNT	AGPT	HDA C	JAK_ STAT	CTLA4	
HOU 5011 06	Her	ANGIO	ME T	MEK	ERK	FGF	mTKP T	RAF	IGF_ War	HDAC	JAK_ STAT	HEDG EHO G	AGPT	
IGL3 8021 7	ANGIO	AGPT	FG F	mTK PT	RAF	IGF_ War	HED GEH OG	CDK 4_6	AURK A	ERK	Antia p	PARP	DNA_R EP	NOT CH
JAY 4403 11	ANGIO	RAS	PD L1	Her	AGPT	AGPT								
KRA 4209 28	Her	ANGIO	AG PT	MET	ERK	FGF	mTKP T	RAF	IGF_ War	JAK_ STAT	DNA_ _REP	CTLA 4	PI3K	MEK
LEL 4507 21	CDK 4_6	MET	ER K	Antia p	mTKP T	DNA_ REP	CTLA 4	AURK A	IGF_ War	WNT	PAR P			
LEP 5605 31	Her	ANGIO	AG PT	PI3K	MET	RAF	CTLA 4							
MAC 4601 01	ANGIO	ERK	IG F_ Wa r	WNT	Her	AURK A	TELO M	PARP	JAK_ STAT	DNA_ _REP	PDL1			
MAR 4307 26	Her	ANGIO	AG PT	PI3K	ERK	RAF	IGF_ War	PARP	HED GEH OG	PDL1				
NEG 4103 11	Her	CDK 4_6	AG PT	PI3K	MET	MEK	mTKP T	RAF	WNT	JAK_ STAT	NOT CH	RAS	IGF_ Wa r	PARP
NIN 2704 09	Her	CDK 4_6	ME T	MEK	RAF	JAK_ STAT	ANGI O	PDL1	CTLA 4					
PAN 3906 07	ANGIO	AGPT	ER K	HDA C	Her									

PEC 4811 13	Her	RAF	PI3 K	NOT CH	ERK										
PER 5107 13	AGPT	MEK	RA F	CTL A4	ANGI O	MET	RAS	JAK_ STAT	PDL1						
RAM 5303 25	Her	CDK 4_6	ME K	PDL1	ANGI O	AGPT	FGF	mTKP T	IGF_ War	WNT					
RIT4 3110 8	Her	CDK 4_6	AU RK A	PI3K	MET	ERK	Antia p	RAS	RAF	HEDG EHO G	DNA_ REP	NOTC H	PDL1	CTLA 4	
SAI3 8042 6	CDK 4_6	ANGIO	AG PT	PI3K	MET	FGF	RAS	NOT CH	PDL1	AURK A	mTK PT	TELO M	IGF_ Wa r	JAK_ STAT	
SIK4 7110 1	Her	ANGIO	AG PT	MET	ERK	RAS	IGF_ War	WNT	RAF	PDL1	CTLA 4				
TAI3 2061 3	Her	ERK	RA S	WNT	PARP	HDA C	HED GEH OG	Antia p	TELO M	IGF_ War	DNA_ REP	PDL1			
TAT 4009 01	Her	AURKA	AN GI O	Antia p	RAS	CDK 4_6	FGF	mTKP T	TELO M	WNT	DNA_ REP	CTLA 4	CDK 4_6	FGF	
YOT 4712 16	AGPT	PI3K	ME K	RAF	JAK_ STAT	CTLA 4	CDK 4_6	Antia p	mTKP T	RAS	PAR P	DNA_ REP	PDL1		
ARC 2705 17	Antiap	Her	AU RK A	FGF	TELO M	IGF_ War	PARP	DNA_ REP	HDA C	HEDG E HOG					
BOU 2911 29	Antiap	CDK 4_6	AU RK A	PI3K	MET	WNT	PARP	HED GE HOG	DNA_ REP	NOTC H	mTK PT	TELO M	HDAC		
DEP 3511 21	Antiap	CDK 4_6	AU RK A	AGP T	PI3K	ERK	FGF	mTKP T	WNT	PARP	HDA C	HEDG EHO G	NOTCH	ANGI O	
DHE 3212 14	Antiap	Her	ME T	FGF	RAS	RAF	WNT	CDK 4_6	PI3K	PARP	HDA C	JAK_ STAT			
DO M59 0729	Antiap	CDK 4_6	AU RK A	PI3K	ERK	FGF	RAS	TELO M	IGF_ War	WNT	PAR P	HDAC	HEDGE HOG	DNA_ REP	
GAN 3508 11	Antiap	Her	CD K 4_ 6	AUR KA	PI3K	MET	TELO M	WNT	PARP	HEDG EHO G	DNA_ REP	NOTC H	MEK	FGF	
GEO 2701 14	Antiap	AURKA	ME T	ERK	RAS	HDA C	JAK_ STAT	HED GEH OG	DNA_ REP	NOTC H	CDK 4_6	RAF	IGF_ Wa r	WNT	
HAM 6407 29	Antiap	AURKA	AN GI O	AGP T	MEK	ERK	FGF	RAS	TELO M	IGF_ War	JAK_ STAT	HEDG EHO G	NOTCH		
JEA 3206 18	Antiap	Her	PI3 K	MET	MEK	FGF	mTKP T	RAF	TELO M	JAK_ STAT	PDL1	AURK A	ERK	RAS	
LEF 3205 16	Antiap	Her	AN GI O	MET	ERK	FGF	mTKP T	TELO M	IGF_ War	HDAC	NOT CH	AURK A	HEDGE HOG	DNA_ REP	
LEF 3411	Antiap	CDK 4_6	AU RK	ANGI O	FGF	mTKP T	PARP	HDA C	DNA_ REP	NOTC H	Her				

11			A											
LEN 3710 15	Antiap	AURKA i	ER K	FGF	mTKP T	TELO M	HED GEH OG	DNA_ REP	NOT CH	MET	RAS	WNT	PARP	
MAC 3812 20	Antiap	MEK	ER K	RAF	IGF_ War	HDA C	NOT CH	PDL1						
MAR 3505 07	Antiap	AURKA	PI3 K	ERK	mTKP T	RAF	PARP	HDA C	JAK_ STAT	DNA_ REP				
REC 5907 07	Antiap	CDK 4_6	CD K 4_ 6	AGP T	PI3K	MEK	ERK	mTKP T	TELO M	PARP	HDA C	DNA_ REP	PDL1	ANGI O
SAU 4507 10	Antiap	AGPT	ER K	FGF	RAS	TELO M	HDA C	HED GEH OG	NOT CH	PARP				
SER 3008 10	Antiap	ANGIO	ER K	RAF	IGF_ War	MEK	TELO M	NOT CH	PDL1					
VIL3 1030 9	Antiap	AURKA	AN GI O	PI3K	MET	mTKP T	RAS	HED GEH OG	PDL1	CTLA 4	Her	AGPT	FGF	WNT
BAR 3311 23	Her	AURKA	AN GI O	AGP T	PI3K	Antia p	FGF	mTKP T	RAS	RAF	TELO M	WNT	HDAC	HED GEH OG
BEM 2911 29	JAK_S TAT	PI3K	ER K	Antia p	FGF	NOT CH	CTLA 4							
BEN 4807 07	PDL1	MEK	RA S	JAK_ STA T										
BEN 4105 29	ANGIO	AGPT	Ant iap	RAS	RAF	IGF_ War	WNT	NOT CH	PDL1	CTLA 4	Her	AURK A	MEK	HDA C
BIE4 1021 9	Her	CDK 4_6	AU RK A	Antia p	FGF	RAS	JAK_ STAT	HED GEH OG	DNA REP	CTLA 4	ANGI O	MEK	ERK	mTKP T
CAM 5201 01	Her	CDK 4_6	PI3 K	MET	MEK	TELO M	IGF_ War	HDA C	JAK_ STAT	AURK A	ANGI O	AGPT	ERK	FGF
CAP 4602 15	AURKA	MET	Ant iap	PAR P	HED GEH OG	AGPT								
CHA 5710 08	Her	MET	ER K	IGF_ War	CTLA 4									
CHA 4707 18	ANGIO	AGPT	ME T	ERK	mTKP T	CTLA 4	CDK 4_6	MEK	FGF	RAF	IGF_ War	DNAR EP	PDL1	
CRE 4204 23	CDK 4_6	ANGIO	AG PT	MET	FGF	mTKP T	TELO M	IGF_ War	WNT	HEDG EHO G	NOT CH	PDL1	CTLA4	Her
DAM 2004 13	CDK 4_6	ANGIO	AG PT	RAS	RAF	JAK_ STAT	NOT CH	PDL1	CTLA 4	PI3K	mTK PT			
DAV 3204 07	AURKA	ANGIO	Ant iap	FGF	IGF_ War	WNT	HED GEH OG	DNA REP	NOT CH	MET	RAF	PARP	PDL1	CTLA 4
DUV	ANGIO	AGPT	ER	Antia	mTKP	RAF	IGF	PARP	DNA	NOTC	PDL1	Her	AURKA	FGF

330713			K	p	T		War		REP	H				
EDO300812	PI3K	mTKPT	WNT	PARP	Her	AGPT	MEK	RAS	TELOM	HDAC	NOTCH	CTLA4		
ELA540809	CDK4_6	FGF	RAS	RAF	IGF_War	WNT	HEDGEHOG	HDA	NOTCH	PDL1				
FER461230	AGPT	HEDGEHOG	ANGIO	PI3K	PI3K	MEK	FGF	mTKPT	WNT	HDAC				
FOR410727	AURKA	PI3K	WNT	JAK_STAT	HEDGEHOG	NOTCH	PDL1	Her	CDK4_6	ERK	mTKPT	RAS	TELOM	PARP
GAR410813	AURKA	PI3K	TELOM	WNT	PARP	HEDGEHOG	HEDGEHOG	DNA	NOTCH	PDL1	Her	CDK4_6	ANGIO	AGPT
GAR450819	Her	PI3K	Antiapopt	TELOM	WNT	PARP	HEDGEHOG	DNA	NOTCH	PDL1	CTLA4	CDK4_6	AGPT	HDA
GIL230901	FGF	IGF_War	HDAC	PI3K	MET	MEK	mTKPT	RAS	TELOM	PARP	JAK_STAT	HEDGEHOG	DNAREP	PDL1
GOM450227	Her	AURKA	AGPT	PI3K	Antiap	FGF	TELOM	IGF_War	PARP	HDA	HEDGEHOG	NOTCH	ANGIO	MET
HAR331217	Her	AURKA	PI3K	MEK	mTKPT	TELOM	WNT	PARP	HDA	HEDGEHOG	DNA	NOTCH	CDK4_6	ANGIO
ISA300917	ERK	Antiap	RAS	JAK_STAT	HEDGEHOG	ERK	TELOM	PARP	DNA	REP				
IVA360731	RAS	JAK_STAT	AGPT	PI3K	MEK	ERK	RAF	PDL1						
KEI431016	ANGIO	AGPT	PI3K	MET	MEK	mTKPT	PDL1	CTLA4	FGF	RAS	NOTCH			
LAN041130	Her	CDK4_6	AURKA	AGPT	MET	MEK	Antiap	FGF	mTKPT	RAF	TELOM	IGF_War	PARP	HDAC
LAN510426	Her	CDK4_6	AURKA	PI3K	MEK	Antiap	FGF	RAS	JAK_STAT	HEDGEHOG	DNA	PDL1	CTLA4	RAF
LEJ501115	JAK_STAT	AGPT	ERK	Antiap	PDL1									
LEM351012	Her	CDK4_6	AURKA	mTKPT	TELOM	IGF_War	PARP	HDA	HEDGEHOG	DNA	PI3K	ERK		
LER460716	ANGIO	RAS	CTLA4	RAF	JAK_STAT	HEDGEHOG	PDL1							
MAR240911	FGF	MEK	ERK	RAF	TELOM	IGF_War	WNT	HEDGEHOG	DNA	NOTCH				
MAR491126	CDK4_6	AURKA	AGPT	ERK	Antiap	FGF	mTKPT	WNT	HEDGEHOG	DNA	CTLA4	Her	RAS	TELOM
MAR470322	MEK	IGF_War	PARP	HDA	JAK_STAT	DNA	PDL1	CTLA4	AURKA	ANGIO	ERK	Antiapopt	mTKPT	TELOM

MAT230414	CDK4_6	AURKA	PI3K	Antip	mTKPT	TELOM	HDA C	JAK_STAT	DNA REP	PDL1	CTLA4			
PAQ470203	CDK4_6	AURKA	PI3K	MEK	Antip	mTKPT	TELOM	WNT	HDA C	DNA REP	NOTCH	PI3K	PARP	
PER401217	FGF	IGF_War	JAK_STAT	PDL1	ERK	RAF	TELOM	HEDGEHOG						
PIQ340906	ANGIO	TELOM	HDAC	NOTCH	MEK	ERK	mTKPT	IGF_War	HEDGEHOG	PDL1				
RAB330621	CDK4_6	PI3K	Antiap	FGF	RAS	TELOM	IGF_War	WNT	PARP	HDA C	HEDGEHOG	DNA REP	NOTCH	Her
REJ471005	Her	AURKA	PI3K	ERK	Antip	FGF	TELOM	PARP	HDA C	JAK_STAT	DNA REP	NOTCH	CTLA4	CDK4_6
RIT490630	MEK	WNT	PARP	NOTCH	CTLA4	CDK4_6	AURKA	ANGIO	PI3K	ERK	RAS	RAF	TELOM	IGF_War
SUT470608	ANGIO	AGPT	Antiap	WNT	PARP	HEDGEHOG	DNA REP	NOTCH	MEK	mTKPT	HDA C	PDL1		
TAR290829	ERK	Antiap	FGF	WNT	PARP	HDA C	HEDGEHOG	NOTCH	CDK4_6					
THU220630	AGPT	RAS	IGF_War	PDL1	ANGIO	FGF	TELOM	WNT	PARP	HEDGEHOG	NOTCH			
TIL420228	Her	ERK	JAK_STAT	PDL1	CTLA4	AGPT	PI3K	MET	MEK	FGF	RAF	IGF_War	PARP	HDAC
UST500306	CDK4_6	PI3K	Antiap	PARP	HDA C	HEDGEHOG	DNA REP	CTLA4	mTKPT	TELOM	WNT			
VAL271009	FGF	RAF	TELOM	WNT	PARP	JAK_STAT	PDL1	MEK	ERK	Antipopt	mTKPT	IGF_War	NOTCH	
WIS320823	AURKA	PI3K	MEK	Antipop	RAS	TELOM	WNT	PARP	HDA C	JAK_STAT	HEDGEHOG	DNA REP	NOTCH	PDL1

In a preferred embodiment, the frequency of activation of interventional points (score>5), enabling determination of the most rationale combinations is the following

5 Table 5. Trends of coactivation of interventional points

CTL A4	PD 1L	mek	mTOR	pi3k	ERK	met	AurkA	cdk4_6	HER	Angio	FGF	PARP	Ras/Raf	IGF	DNA REP	mtor/PI3K	ID	Histo
																	N° patients	
61	63	54	59	55	57	51	55	60	68	56	47	47	88	44	56	83		123
50	51	44	48	45	46	41	45	49	55	46	38	38	72	36	46	67	%	100

Table 6. Selection of most frequent combinations taking into account trends of coactivation. For each of the first and second drug number of patients (upper case) and % (lower case) are showed. For each of the third drug number of patients out of 123 and % are shown.

First drug	NB/%	Second drug	NB/%	Third drug	Nb	%
RAS/RAF	88	mTor/PI3K	60	PD1L	34	28
				CTLA4	33	27
				CDK4,6	32	26
				AURKA	29	24
				DNARepair	28	23
	72		49	ANGIO	27	22
				MET	27	22
				FGF	26	21
				PARP	24	20
				IGF	23	19
RAS/RAF	88	MET	40	CTLA4	32	26
				mTor/PI3K	27	22
				PD1L	22	18
				ANGIO	20	16
				CDK4,6	21	17
	72		33	AURKA	17	14
				FGF	17	14
				DNARepair	15	12
				IGF	13	11
				PARP	12	10
RAS/RAF	88	CDK4,6	40	mTor/PI3K	32	26
				CTLA4	27	22
				AURKA	23	19
				MET	21	17
				PD1L	20	16
	72		33	DNARepair	20	16
				ANGIO	17	14
				FGF	17	14
				PARP	17	14
				IGF	12	10
mTor/PI3K	83	RAS/RAF	60	PD1L	34	28
				CTLA4	33	27
				CDK4,6	32	26
				AURKA	29	24
				DNARepair	28	23
	67		49	MET	27	22
				ANGIO	27	22
				FGF	26	21
				PARP	24	20
				IGF	23	19
CDK4,6	63	RAS/RAF	51	mTor/PI3K	34	28
				CTLA4	27	22
				ANGIO	24	20
				IGF	23	19
				MET	22	18
	51		41	AURKA	22	18
				CDK4,6	20	16

				PD1L	20	16
				FGF	19	15
				PARP	16	13
PD1L	63	mTor/PI3K	42	RAS/RAF	34	28
				CTLA4	25	20
				DNARepair	23	19
				CDK4,6	21	17
				ANGIO	21	17
	51		34	AURKA	20	16
				IGF	19	15
				FGF	18	15
				MET	16	13
				PARP	15	12
MEK	54	RAS/RAF	42	CTLA4	29	24
				PD1L	28	23
				mTor/PI3K	28	23
				CDK4,6	19	15
				ANGIO	19	15
	44		34	IGF	19	15
				AURKA	16	13
				FGF	16	13
				DNARepair	15	12
				parp	11	9
CDK4,6	60	mTor/PI3K	48	RAS/RAF	32	26
				AURKA	32	26
				DNARepair	32	26
				CTLA4	29	24
				parp	26	21
	49		39	FGF	23	19
				MET	22	18
				PD1L	21	17
				ANGIO	20	16
				IGF	15	12
MET	51	RAS/RAF	40	CTLA4	32	26
				mTor/PI3K	27	22
				PD1L	22	18
				ANGIO	21	17
				MEK	19	15
	41		33	AURKA	17	14
				FGF	17	14
				DNARepair	15	12
				IGF	13	11
				PARP	12	10
ANGIO	56	RAS/RAF	41	mTor/PI3K	27	22
				PD1L	24	20
				MET	20	16
				MEK	19	15
				AURKA	19	15
	46		33	IGF	17	14
				CDK4,6	16	13
				FGF	15	12
				DNARepair	14	11
				PARP	7	6

Table 7 summarizes the most frequent triple combinations

First drug	NB	Second drug	NB	Third drug	Nb	%
RAS/RAF	88	mTor/PI3K	60	PD1L	34	28
RAS/RAF	88	mTor/PI3K	60	CTLA4	33	27
RAS/RAF	88	mTor/PI3K	60	CDK4,6	32	26
RAS/RAF	88	mTor/PI3K	60	AURKA	29	24
RAS/RAF	88	mTor/PI3K	60	DNARepair	28	23
RAS/RAF	88	mTor/PI3K	60	ANGIO	27	22
RAS/RAF	88	mTor/PI3K	60	MET	27	22
RAS/RAF	88	mTor/PI3K	60	FGF	26	21
RAS/RAF	88	MET	40	CTLA4	32	26
RAS/RAF	88	CDK4,6	40	CTLA4	27	22
CDK4,6	63	RAS/RAF	51	ANGIO	24	20
CDK4,6	60	mTor/PI3K	48	AURKA	32	26
CDK4,6	60	mTor/PI3K	48	DNARepair	32	26
CDK4,6	60	mTor/PI3K	48	CTLA4	29	24
CDK4,6	60	mTor/PI3K	48	PARP	26	21
MEK	54	RAS/RAF	42	CTLA4	29	24
MEK	54	RAS/RAF	42	PD1L	28	23
MEK	54	RAS/RAF	42	mTor/PI3K	28	23

Table 8. Summarizes the most frequent combinations involving and immunomodulator

First drug	NB	Second drug	NB	Third drug	Nb	%
RAS/RAF	88	mTor/PI3K	60	PD1L	34	28
RAS/RAF	88	MET	40	PD1L	22	18
RAS/RAF	88	CDK4,6	40	PD1L	20	16
PD1L	63	mTor/PI3K	42	DNARepair	23	19
PD1L	63	mTor/PI3K	42	CDK4,6	21	17
PD1L	63	mTor/PI3K	42	ANGIO	21	17
PD1L	63	mTor/PI3K	42	AURKA	20	16
PD1L	63	mTor/PI3K	42	IGF	19	15
PD1L	63	mTor/PI3K	42	FGF	18	15
PD1L	63	mTor/PI3K	42	MET	16	13
ANGIO	56	RAS/RAF	41	PD1L	24	20

First drug	NB	Second drug	NB	Third drug	Nb	%
RAS/RAF	88	mTor/PI3K	60	CTLA4	33	27
RAS/RAF	88	MET	40	CTLA4	32	26
RAS/RAF	88	CDK4,6	40	CTLA4	27	22
CDK4,6	63	RAS/RAF	51	CTLA4	27	22
PD1L	63	mTor/PI3K	42	CTLA4	25	20
MEK	54	RAS/RAF	42	CTLA4	29	24
CDK4,6	60	mTor/PI3K	48	CTLA4	29	24
MET	51	RAS/RAF	40	CTLA4	32	26

TABLE 9: Detailed List of genes

Pathway	Symbol	GeneID	Name	Refseq
HER	EGF	1950	epidermal growth factor	NM_001963
	TGFA	7039	transforming growth factor, alpha	NM_003236
	AREG	374	amphiregulin	NM_001657
	EREG	2069	epiregulin	NM_001432
	HBEGF	1839	heparin-binding EGF-like growth factor	NM_001945
	BTC	685	betacellulin	NM_001729
	NRG1	3084	neuregulin 1	AF176921; NM_004495
	NRG2	9542	neuregulin 2	ENST00000544729; NM_013982
	NRG4	145957	neuregulin 4	NM_138573
	EGFR	1956	epidermal growth factor receptor	NM_201283; NM_201282; NM_005228
	ERBB2	2064	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2	NM_001005862; AB025286
	ERBB3	2065	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3	NM_001982; NM_001005915
	ERBB4	2066	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4	NM_005235
CDK4,6	CDK4	1019	cyclin-dependent kinase 4	NM_000075
	CDK6	1021	cyclin-dependent kinase 6	NM_001259
	CCND1	595	cyclin D1	NM_053056
	CCND2	894	cyclin D2	NM_001759
	CCND3	896	cyclin D3	NM_001760
	CDKN2A,	1029	cyclin-dependent kinase inhibitor 2A	NM_058197; NM_000077
	CDKN2B	1030	cyclin-dependent kinase inhibitor 2B	NM_004936
	CCNE1	898	cyclin E1	NM_001238
	CCNE2	9134	cyclin E2	NM_057749
	RB1	5925	retinoblastoma 1	NM_000321
PLK / AURK / Kinesins	PLK1	5347	polo-like kinase 1	NM_005030
	AURKA	6790	aurora kinase A	NM_198433
	BORA	79866	bora, aurora kinase A activator	NM_024808
	ILK	3611	integrin-linked kinase	NM_001014795
	KIF11	3832	kinesin family member 11	NM_004523
ANGIOGENESIS	VEGFA	7422	vascular endothelial growth factor A	NM_001025370; NM_001025366
	VEGFB	7423	vascular endothelial growth factor B	NM_003377
	VEGFC	7424	vascular endothelial growth factor C	NM_005429
	VEGFD	2277	c-fos induced growth factor (vascular endothelial growth factor D)	NM_004469

	FLT1	2321	fms-related tyrosine kinase 1	NM_001160031; NM_002019
	KDR	3791	kinase insert domain receptor (a type III receptor tyrosine kinase)	NM_002253
	FLT4	2324	fms-related tyrosine kinase 4	ENST000003768 68; NM_002020
	PDGFA	5154	platelet-derived growth factor alpha polypeptide	NM_002607; NM_033023
	PDGFB	5155	platelet-derived growth factor beta polypeptide	NM_002608
	PDGFRA	5156	platelet-derived growth factor receptor, alpha polypeptide	NM_006206
	PDGFRB	5159	platelet-derived growth factor receptor, beta polypeptide	NM_002609
	Kit	3815	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	NM_000222; NM_001093772
ANGIOPOIETINS	THBS1	7057	thrombospondin 1	NM_003246
	TGFB1	7040	transforming growth factor, beta 1	NM_000660
	ANGPT1	284	angiopoietin 1	NM_001146
	ANGPT2	285	angiopoietin 2	NM_001147
	ANGPTL1	9068	angiopoietin-like 1	NM_004673
	ANGPT4	51378	angiopoietin 4	NM_015985
	TIE1	7075	tyrosine kinase with immunoglobulin-like and EGF-like domains 1	NM_005424
	TEK	7010	TEK tyrosine kinase, endothelial	NM_000459
IMMUNO- Modulator	CD274 or PDL1	29126	CD274 molecule programmed cell death ligand 1	NM_014143
	PDCD1LG2	80380	programmed cell death 1 ligand 2	NM_025239
	PDCD1	5133	programmed cell death 1	NM_005018
	CTLA4	1493	cytotoxic T-lymphocyte-associated protein 4	NM_005214
	LAG3	3902	lymphocyte-activation gene 3	NM_002286
PI3K	PIK3CA	5290	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	NM_006218
	PIK3CB	5291	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit beta	NM_006219
	PIK3CD	5293	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic, catalytic subunit delta	NM_005026
	PIK3CG	5294	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma	NM_002649
	PIK3C2B	5287	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit type 2 beta	NM_002646; ENST000003671 84
	PRKCB	5579	protein kinase C, beta	NM_002738
	PRKCA	5578	protein kinase C, alpha	NM_002737
	PIK3R1	5295	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	NM_181523
	PIK3R2	5296	phosphoinositide-3-kinase, regulatory subunit 2 (beta)	NM_005027
	PIK3R3	8503	phosphoinositide-3-kinase, regulatory subunit 3 (gamma)	NM_003629
	HGF	3082	hepatocyte growth factor (hepapoietin A; scatter factor)	NM_001010934; NM_001010931
MET	MET	4233	met proto-oncogene	NM_000245
	AXL	558	AXL receptor tyrosine kinase	NM_021913
	MST1R	4486	macrophage stimulating 1 receptor (c-met-related tyrosine kinase)	NM_002447

MEK	MAP2K1	5604	mitogen-activated protein kinase kinase 1, E3 ubiquitin protein ligase	NM_002755
	MAP2K2	5605	mitogen-activated protein kinase kinase 2	NM_030662
	MAP2K3	5606	mitogen-activated protein kinase kinase 3	NM_145109; ENST00000534743
	MAP2K4	6416	mitogen-activated protein kinase kinase 4	NM_003010
	MAP3K1	4214	mitogen-activated protein kinase kinase kinase 1	NM_005921
	MAP3K2	10746	mitogen-activated protein kinase kinase kinase 2	NM_006609
	MAP3K3	4215	mitogen-activated protein kinase kinase kinase 3	NM_203351
	MAP3K4	4216	mitogen-activated protein kinase kinase kinase 4	NM_005922; NM_006724
ERK	MAPK3	5595	mitogen-activated protein kinase 3	NM_002746
	MAPK1	5594	mitogen-activated protein kinase 1	NM_138957
	KSR1	8844	kinase suppressor of ras 1	NM_014238
	MAPK11	5600	mitogen-activated protein kinase 11	NM_002751
ANTI- APOPTOSIS	BCL2	596	B-cell CLL/lymphoma 2	NM_000633; NM_000657
	BCL2L1	598	BCL2-like 1	NM_138578
	BIRC5	332	baculoviral IAP repeat containing 5	NM_001012271
	XIAP	331	X-linked inhibitor of apoptosis	NM_001167
	BAK1	578	BCL2-antagonist/killer 1	NM_001188
FGF	FGF1	2246	fibroblast growth factor 1 (acidic)	NM_000800; NR_026696
	FGF2	2247	fibroblast growth factor 2 (basic)	NM_002006
	FGF3	2248	fibroblast growth factor 3	NM_005247
	FGF4	2249	fibroblast growth factor 4	NM_002007
	FGF5	2250	fibroblast growth factor 5	NM_004464; NM_033143
	FGF6	2251	fibroblast growth factor 6	NM_020996
	FGF7	2252	fibroblast growth factor 7	NM_002009
	FGF8	2253	fibroblast growth factor 8 (androgen-induced)	NM_033163
	FGF9	2254	fibroblast growth factor 9	NM_002010
	FGF10	2255	fibroblast growth factor 10	NM_004465
	FGF11	2256	fibroblast growth factor 11	NM_004112
	FGF12	2257	fibroblast growth factor 12	NM_004113
	FGF13	2258	fibroblast growth factor 13	NM_004114
	FGF14	2259	fibroblast growth factor 14	NM_175929
	FGFR1	2260	fibroblast growth factor receptor 1	ENST00000496296; NM_023110; NM_001174066
	FGFR2	2263	fibroblast growth factor receptor 2	ENST00000359354; NM_022970
	FGFR3	2261	fibroblast growth factor receptor 3	NM_000142
	FGFR4	2264	fibroblast growth factor receptor 4	NM_213647
mTOR - AKT- PTEN-	mTor	2475	mechanistic target of rapamycin (serine/threonine kinase)	NM_004958
	AKT1	207	v-akt murine thymoma viral oncogene homolog 1	NM_005163
	AKT2	208	v-akt murine thymoma viral oncogene homolog 2	NM_001626
	PTEN	5728	phosphatase and tensin homolog	NM_000314

Modulators MTKPT	TSC1	7248	tuberous sclerosis 1	NM_000368; ENST00000403810
	TSC2	7249	tuberous sclerosis 2	NM_000548; NM_001077183
	STK11	6794	serine/threonine kinase 11	NM_000455
	PIM1	5292	pim-1 oncogene	NM_002648
	PIM2	11040	pim-2 oncogene	NM_006875
	PIM3	415116	pim-3 oncogene	NM_001001852
RAS	KRAS	3845	Kirsten rat sarcoma viral oncogene homolog	NM_033360; NM_004985
	NRAS	4893	neuroblastoma RAS viral (v-ras) oncogene homolog	NM_002524
	HRAS	3265	Harvey rat sarcoma viral oncogene homolog	NM_005343
RAF	RAF1	5894	v-raf-1 murine leukemia viral oncogene homolog 1	NM_002880
	BRAF	673	v-raf murine sarcoma viral oncogene homolog B	NM_004333
TELOMERASE	TERT	7015	telomerase reverse transcriptase	NM_198253
	TERC	7012	telomerase RNA component	NR_001566
	TEP1	7011	telomerase-associated protein 1	NM_007110
	HSP90AA1	3320	heat shock protein 90kDa alpha, class A member 1	NM_001017963; NM_005348
	DKC1	1736	dyskeratosis congenita 1, dyskerin	NM_001363
	PTGES3	10728	prostaglandin E synthase 3	NM_006601
IGF & Warburg	IGF1	3479	insulin-like growth factor 1 (somatomedin C)	NM_000618
	IGF2	3481	insulin-like growth factor 2 (somatomedin A)	NM_000612
	IGF1R	3480	insulin-like growth factor 1 receptor	NM_000875
	IGF2R	3482	insulin-like growth factor 2 receptor	NM_000876
	INSR	3643	insulin receptor	NM_000208
	IRS1	3667	insulin receptor substrate 1	NM_005544
	PKM	5315	pyruvate kinase, muscle	NM_001206796.1
WNT	CDH1	999	cadherin 1, type 1, E-cadherin (epithelial)	NM_004360
	CTNNA1	1495	catenin (cadherin-associated protein), alpha 1, 102 kDa	NM_001903
	CTNNB1	1499	catenin (cadherin-associated protein), beta 1, 88 kDa	NM_001904; NM_001098210
	WNT 1	7471	wingless-type MMTV integration site family, member 1	NM_005430
	FZD1	8321	frizzled class receptor 1	NM_003505
	WNT5A	7474	wingless-type MMTV integration site family, member 5A	NM_003392
	WNT5B	81029	wingless-type MMTV integration site family, member 5B	NM_030775
	FZD5	7855	frizzled class receptor 5	NM_003468
	WIF1	11197	WNT inhibitory factor 1	NM_007191
	DKK1	22943	dickkopf WNT signaling pathway inhibitor 1	NM_012242
PARP	PARP1	142	poly (ADP-ribose) polymerase 1	NM_001618; ENST00000366790
	BRCA1	672	breast cancer 1, early onset	NM_007300
	XRCC1	7515	X-ray repair complementing defective repair in Chinese hamster cells 1	NM_006297
	RAD54L	8438	RAD54-like (S. cerevisiae)	NM_003579
	RAD54B	25788	RAD54 homolog B (S. cerevisiae)	NM_012415; NM_001205262
	ATM	472	ataxia telangiectasia mutated	NM_000051;

				ENST00000389511
	ATR	545	ataxia telangiectasia and Rad3 related	NM_001184
	CHEK1	1111	checkpoint kinase 1	NM_001114121
	CHEK2	11200	checkpoint kinase 2	NM_145862; NM_001005735
	WEE1	7465	WEE1 G2 checkpoint kinase	NM_003390
HDAC	HDAC1	3065	histone deacetylase 1	NM_004964
	HDAC2	3066	histone deacetylase 2	NM_001527
	HDAC3	8841	histone deacetylase 3	NM_003883
	HDAC4	9759	histone deacetylase 4	NM_006037
	HDAC5	10014	histone deacetylase 5	NM_001015053
JAK-STAT	JAK1	3716	Janus kinase 1	NM_002227
	JAK2	3717	Janus kinase 2	NM_004972
	STAT1	6772	signal transducer and activator of transcription 1, 91 kDa	NM_139266
	STAT2	6773	signal transducer and activator of transcription 2, 113 kDa	NM_005419
	STAT3	6774	signal transducer and activator of transcription 3 (acute-phase response factor)	NM_213662
	SOCS1	8651	suppressor of cytokine signaling 1	NM_003745
HEDGEHOG	SHH	6469	sonic hedgehog	NM_000193
	PTCH1	5727	patched 1	NM_001083602; ENST00000375290
	SMO	6608	smoothened, frizzled class receptor	NM_005631
	STK36	27148	serine/threonine kinase 36	NM_015690
	PRKACA	5566	protein kinase, cAMP-dependent, catalytic, alpha	NM_002730
	SUFU	51684	suppressor of fused homolog (Drosophila)	NM_016169; NM_001178133
	GLI1	2735	GLI family zinc finger 1	NM_005269
DNA REPAIR	ERCC1	2067	excision repair cross-complementation group 1	NM_202001
	RAD52	5893	RAD52 homolog (S. cerevisiae)	NM_134424; ENST00000545967
	XRCC4	7518	X-ray repair complementing defective repair in Chinese hamster cells 4	NM_022550
	RAD51	5888	RAD51 recombinase	NM_002875
	BRCA1	672	breast cancer 1, early onset	NM_007300
	NEDD8	4738	neural precursor cell expressed, developmentally down-regulated 8	NM_006156
	NAE1	8883	NEDD8 activating enzyme E1 subunit 1	NM_001018159
NOTCH	NOTCH1	4851	notch 1	NM_017617
	Adam17	6868	ADAM metallopeptidase domain 17	NM_003183
	PSEN1	5663	presenilin 1	NM_000021; ENST00000394157
	NCSTN	23385	nicastrin	NM_015331
	JAG1	182	jagged 1	NM_000214
	SRRT	51593	serrate RNA effector molecule homolog (Arabidopsis)	NM_001128853; NM_015908; NM_001128854
	APH1A	51107	APH1A gamma secretase subunit	NM_016022; NM_001077628

Others	ROS1	6098	c-ros oncogene 1 , receptor tyrosine kinase	ENST00000403284 ; NM_002944
	ALK	238	anaplastic lymphoma receptor tyrosine kinase	NM_004304
	RET	5979	ret proto-oncogene	NM_020630; NM_020975
	UBA1	7317	ubiquitin-like modifier activating enzyme 1	NM_003334

TABLE 10 : List of genes mutations

BRAF

Nucleotide	Protein	
c.1799 T>W	p.Val600Glu	V600E
c. 1798 G>R c.1799 T>W	p.Val600Lys	V600K
c.1799 T>W c.1800G>R	p.Val600Glu	V600E
c.1780 G>R	p.Asp594Asn	D594N

5 **EGFR**

Nucleotide	Protein		Effect on EGFR inhibitors
c.2156G>C	p.Gly719Ala	G719A	Sensitivity
c.2155 G>K	p.Gly719Cys	G719C	Sensitivity
c.2117 T>Y	p.Ile706Thr	I706T	Sensitivity
c.2125 G>R	p.Glu709Lys	E709K	Sensitivity
c.2126 A>M	p.Glu709Ala	E709A	Sensitivity
c.2174 C>Y	p.Thr725Met	T725M	Sensitivity
c.2165C>M	p.Ala722Glu	A722E	Sensitivity
c.2235_2249 del	p.Glu746_Ala750del	Deletion E746-A750	Sensitivity
c.2236_2250 del	p.Glu746_Ala750del	Deletion E746-A750	Sensitivity
c.2240_2254del	p.Leu747_Thr751del	Deletion L747-T751	Sensitivity
c.2240_2257 del	p.Leu747_Pro753delinsSer	Deletion L747-P753 Insertion S	Sensitivity
c.2237_2251del	p.Glu746_Thr751delinsAla	Deletion E746-T751 Insertion A	Sensitivity
c.2239_2248delinsC	p.Leu747_Ala750delinsPro	Deletion L747-A750 Insertion P	Sensitivity
c.2239_2251delinsC	p.Leu747_Thr751delinsPro	Deletion L747-T751 Insertion P	Sensitivity
c.2237_2255 delinsT	p.Glu746_Ser752delinsVal	Deletion E746-S752 Insertion V	Sensitivity
c.2214_2231dup	p.Ile740_Lys745dup	Duplication I740-	Sensitivity

		K745	
c.2254_2277 del	p.Ser752_Ile759del	Deletion S752-I759	Sensibility
c.2219_2236dup	p.Lys745_Glu746insValProValAlaLys	K745-E746 Insertion VPVAIK	Sensibility
c.2277 C>S	p.Ile759Met	I759M	Sensibility
c.2239_2256delinsCAA	p.Leu747_Ser752delinsGln	Deletion L747-S752 Insertion Q	Sensibility
c.2369C>Y	p.Thr790Met	T790M	Resistance
c.2317_2318insACC	p.His773dup	Duplication H773	Resistance
c.2317_2318ins12	p.Pro772_His773insLeuGlyAsnPro	P772-H773 insertion LGNP	Resistance
c.2315_2326dup	p.Pro772_Cys775dup	Duplication P772-C775	Resistance
c.2300_2308 dup	p.Ala767_Val769dup	Duplication A767-V769	Resistance
c.2303_2311 dup	p.Ser768_Asp770dup	Duplication S768-D770	Resistance
c.2303_2311dup	p.Ser768_Asp770dup	Duplication S768-D770	Resistance
c.2335G>T	p.Gly779Cys	G779C	Resistance
c.2573 T>K	p.Leu858Arg	L858R	Sensibility
c.2582 T>W	p.Leu861Gln	L861Q	Sensibility

KRAS-NRAS

Nucleotide	Protein	
c.34 G>K	p.Gly12Cys	G12C
c.35 G>R	p.Gly12Asp	G12D
c.35 G>K	p.Gly12Val	G12V
c.35 G>S	p.Gly12Ala	G12A
c.34 G>R	p.Gly12Ser	G12S
c.34 G>S	p.Gly12Arg	G12R
c.38 G>R	p.Gly13Asp	G13D
c.37 G>K	p.Gly13Cys	G13C
c.182 A>W	p.Gln61Leu	Q61L
c.182 A>R	p.Gln61Arg	Q61R
c.183 A>M	p.Gln61His	Q61H
c.176 C>S	p.Ala59Gly	A59G
c.175 G>R	p.Ala59Thr	A59T
c.176 C>M	p.Ala59Glu	A59E

ERBB2

Nucleotide	Protein	
c.2313_2324dup	p.Tyr772_Ala775dup	Duplication Y772-A775
c.2318_2319insGATGGCATACGT	p.Tyr772_Ala775dup	Duplication Y772-A775
c.2326_2327insTGT	p.Gly776delinsValCys	Deletion G776 Insertion VC

c.2331_2339dup	p.Gly778_Pro780dup	Duplication G778-P780
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PIK3CA

Nucleotide	Protein	
c.1624 G>R	p.Glu542Lys	E542K
c.1633G>R	p.Glu545Lys	E545K
c.3140A>R	p.His1047Arg	H1047R
c.3140A>W	p.His1047Leu	H1047L
c.2959 G>R	p.Ala987Thr	A987T
c.3052G>A	p.Asp1018Asn	D1018N
c.3080 C>Y	p.Ala1027Val	A1027V
c.3131A>R	p.Asn1044Ser	N1044S

TABLE 11 : List of miRNA

Pathway	Symbol	GeneID	miRNAs
HER	EGF	1950	hsa-miR-4673; hsa-miR-485-5p; hsa-miR-647 ; hsa-miR-4742-5p ; hsa-miR-4797-5p
	TGFA	7039	hsa-miR-3147; hsa-miR-1178; hsa-miR-626; hsa-miR-148a; hsa-miR-1182
	AREG	374	hsa-miR-517a ; hsa-miR-34c-5p ; hsa-miR-4724-3p ; hsa-miR-556-5p ; hsa-miR-517b
	EREG	2069	hsa-miR-4713-5p ; hsa-miR-4645-5p ; hsa-miR-130a ; hsa-miR-3661 ; hsa-miR-192
	HBEGF	1839	hsa-miR-4736; hsa-miR-1207-5p; hsa-miR-4710; hsa-miR-3160-5p; hsa-miR-1271
	BTC	685	hsa-miR-4715-3p; hsa-miR-1200; hsa-miR-4661-5p; hsa-miR-934; hsa-miR-488
	NRG1	3084	hsa-miR-4632; hsa-miR-1203; hsa-miR-552; hsa-miR-4736; hsa-miR-183
	NRG2	9542	hsa-miR-3196; hsa-miR-3934; hsa-miR-4746-5p; hsa-miR-296-5p; hsa-miR-4665-5p
	NRG4	145957	hsa-miR-608; hsa-miR-1301; hsa-miR-4704-3p; hsa-miR-516b; hsa-miR-3681;
	EGFR	1956	hsa-miR-4417; hsa-miR-608; hsa-miR-885-3p; hsa-miR-4474-3p; hsa-miR-7;
	ERBB2	2064	hsa-miR-331-3p; hsa-miR-4650-5p; hsa-miR-1972; hsa-miR-4533; hsa-miR-1296;
	ERBB3	2065	hsa-miR-3199; hsa-miR-4505; hsa-miR-1287; hsa-miR-3153; hsa-miR-4290;
CDK4,6	ERBB4	2066	hsa-miR-4469; hsa-miR-193a-3p; hsa-miR-642a; hsa-miR-3907; hsa-miR-3187-3p;
	CDK4	1019	hsa-miR-4747-5p; hsa-miR-198; hsa-miR-4728-5p; hsa-miR-765; hsa-miR-4280;
	CDK6	1021	hsa-miR-3680; hsa-miR-3158-3p; hsa-miR-621; hsa-miR-644; hsa-miR-4252;
	CCND1	595	hsa-miR-4707-3p; hsa-miR-3170; hsa-miR-1193; hsa-miR-4740-3p; hsa-miR-4632;
	CCND2	894	hsa-miR-1468; hsa-miR-103b; hsa-miR-1205; hsa-miR-3065-3p; hsa-miR-4718;
	CCND3	896	hsa-miR-4701-5p; hsa-miR-4739; hsa-miR-138; hsa-miR-4749-5p; hsa-miR-3154;
	CDKN2A,	1029	hsa-miR-663b; hsa-miR-675; hsa-miR-663; hsa-miR-1291; hsa-miR-621;
	CDKN2B	1030	hsa-miR-4308; hsa-miR-718; hsa-miR-1914; hsa-miR-451; hsa-miR-346;
	CCNE1	898	hsa-miR-16; hsa-miR-874; hsa-miR-146b-3p; hsa-miR-4524; hsa-miR-3190;
	CCNE2	9134	hsa-miR-449a; hsa-miR-370; hsa-miR-4460; hsa-miR-30b; hsa-miR-485-5p;
AURK / Kine	RB1	5925	hsa-miR-4703-5p; hsa-miR-4801; hsa-miR-4432; hsa-miR-7; hsa-miR-525-5p;
	PLK1	5347	hsa-miR-296-5p; hsa-miR-4660; hsa-miR-3665; hsa-miR-3166; hsa-miR-4778-5p;
	AURKA	6790	hsa-miR-3941; hsa-miR-4655-5p; hsa-miR-4756-5p; hsa-miR-3616-3p; hsa-miR-

			4757-5p;
	BORA	79866	hsa-miR-532-3p; hsa-miR-3162-3p; hsa-miR-4713-5p; hsa-miR-4758-3p; hsa-miR-3189-5p;
	ILK	3611	hsa-miR-1908; hsa-miR-4505; hsa-miR-744; hsa-miR-4425; hsa-miR-3150a-3p;
	KIF11	3832	
ANGIOGENESIS	VEGFA	7422	hsa-miR-3668; hsa-miR-939; hsa-miR-29a; hsa-miR-339-5p; hsa-miR-16;
	VEGFB	7423	hsa-miR-2467-3p; hsa-miR-4649-3p; hsa-miR-4687-3p; hsa-miR-193a-5p; hsa-miR-1275;
	VEGFC	7424	hsa-miR-711; hsa-miR-3688-5p; hsa-miR-4687-3p; hsa-miR-128; hsa-miR-4318;
	VEGFD	2277	hsa-miR-320e; hsa-miR-135a; hsa-miR-7; hsa-miR-1184; hsa-miR-513b;
	FLT1	2321	hsa-miR-148a; hsa-miR-5095; hsa-miR-335; hsa-miR-615-3p; hsa-miR-149;
	KDR	3791	hsa-miR-4435; hsa-miR-665; hsa-miR-370; hsa-miR-136; hsa-miR-138;
	FLT4	2324	hsa-miR-4707-3p; hsa-miR-2861; hsa-miR-4728-5p; hsa-miR-2467-3p; hsa-miR-4783-5p;
	PDGFA	5154	hsa-miR-4690-5p; hsa-miR-3917; hsa-miR-4706; hsa-miR-4768-5p; hsa-miR-412;
	PDGFB	5155	hsa-miR-3202; hsa-miR-1909; hsa-miR-3689d; hsa-miR-4271; hsa-miR-625;
	PDGFRA	5156	hsa-miR-3691-3p; hsa-miR-4471; hsa-miR-34a; hsa-miR-663b; hsa-miR-3117-3p;
	PDGFRB	5159	hsa-miR-1915; hsa-miR-4292; hsa-miR-4731-5p; hsa-miR-637; hsa-miR-486-3p;
	Kit	3815	hsa-miR-4254; hsa-miR-671-5p; hsa-miR-1193; hsa-miR-222; hsa-miR-4485;
ANGIOPOIETINS	THBS1	7057	hsa-miR-3074-5p; hsa-miR-4786-3p; hsa-miR-3177-5p; hsa-miR-634; hsa-miR-4443;
	TGFB1	7040	hsa-miR-3196; hsa-miR-663; hsa-miR-296-5p; hsa-miR-3943; hsa-miR-3183;
	ANGPT1	284	hsa-miR-153; hsa-miR-4643; hsa-miR-4755-5p; hsa-miR-4789-3p; hsa-miR-3682-3p;
	ANGPT2	285	hsa-miR-135a; hsa-miR-1182; hsa-miR-513c; hsa-miR-597; hsa-miR-4251;
	ANGPTL1	9068	hsa-miR-3688-5p; hsa-miR-586; hsa-miR-4480; hsa-miR-544; hsa-miR-194;
	ANGPT4	51378	hsa-miR-296-5p; hsa-miR-4690-3p; hsa-miR-422a; hsa-miR-431; hsa-miR-665;
	TIE1	7075	hsa-miR-3151; hsa-miR-4447; hsa-miR-4723-5p; hsa-miR-486-3p; hsa-miR-4287;
	TEK	7010	hsa-miR-4713-5p; hsa-miR-300; hsa-miR-4690-3p; hsa-miR-150; hsa-miR-148a;
IMMUNO-Modulator	CD274 or PDL1	29126	hsa-miR-4443; hsa-miR-3117-3p; hsa-miR-138; hsa-miR-339-5p; hsa-miR-1273;
	PDCD1LG2	80380	hsa-miR-20a; hsa-miR-548a; hsa-miR-4661-5p; hsa-miR-3133; hsa-miR-3910;
	PDCD1	5133	hsa-miR-4290; hsa-miR-1291; hsa-miR-4763-5p; hsa-miR-2861; hsa-miR-661;
	CTLA4	1493	hsa-miR-324-5p; hsa-miR-502-5p; hsa-miR-4254; hsa-miR-3121-5p; hsa-miR-1587;
	LAG3	3902	hsa-miR-4515; hsa-miR-1269; hsa-miR-4529-3p; hsa-miR-4270; hsa-miR-628-5p;
PI3K	PIK3CA	5290	hsa-miR-4450; hsa-miR-4529-3p; hsa-miR-302d; hsa-miR-3910; hsa-miR-490-5p;
	PIK3CB	5291	
	PIK3CD	5293	hsa-miR-4537; hsa-miR-2355-5p; hsa-miR-523; hsa-miR-7; hsa-miR-484;
	PIK3CG	5294	hsa-miR-370; hsa-miR-3135b; hsa-miR-1976; hsa-miR-1276; hsa-miR-3672;
	PIK3C2B	5287	hsa-miR-361-3p; hsa-miR-4728-5p; hsa-miR-4740-3p; hsa-miR-3612; hsa-miR-4314;
	PRKCB	5579	hsa-miR-4691-5p; hsa-miR-448; hsa-miR-7; hsa-miR-668; hsa-miR-27a;
	PRKCA	5578	hsa-miR-4757-5p; hsa-miR-4685-5p; hsa-miR-4706; hsa-miR-1275; hsa-miR-4525;
	PIK3R1	5295	hsa-miR-4789-3p; hsa-miR-4789-5p; hsa-miR-4646-3p; hsa-miR-1184; hsa-miR-4660;
	PIK3R2	5296	hsa-miR-4723-5p; hsa-miR-3180; hsa-miR-4447; hsa-miR-3960; hsa-miR-3151;
	PIK3R3	8503	hsa-miR-4725-3p; hsa-miR-4435; hsa-miR-4715-5p; hsa-miR-2115; hsa-miR-4313;
MET	HGF	3082	hsa-miR-4520a-3p; hsa-miR-764; hsa-miR-4716-3p; hsa-miR-1288; hsa-miR-4710;
	MET	4233	hsa-miR-3074-5p; hsa-miR-2682; hsa-miR-34c-5p; hsa-miR-182; hsa-miR-1269b;
	AXL	558	hsa-miR-3142; hsa-miR-4728-5p; hsa-miR-924; hsa-miR-3689c; hsa-miR-432;
	MST1R	4486	hsa-miR-296-5p; hsa-miR-218; hsa-miR-1286; hsa-miR-3126-5p; hsa-miR-4284;

MEK	MAP2K1	5604	hsa-miR-4323; hsa-miR-4423-3p; hsa-miR-758; hsa-miR-34a; hsa-miR-15b;
	MAP2K2	5605	hsa-miR-1181; hsa-miR-1207-3p; hsa-miR-744; hsa-miR-663; hsa-miR-4786-5p;
	MAP2K3	5606	hsa-miR-4313; hsa-miR-3151; hsa-miR-4283; hsa-miR-4540; hsa-miR-4270;
	MAP2K4	6416	hsa-miR-4663; hsa-miR-25; hsa-miR-3065-3p; hsa-miR-4649-5p; hsa-miR-627;
	MAP3K1	4214	hsa-miR-4286; hsa-miR-1225-3p; hsa-miR-4703-3p; hsa-miR-544; hsa-miR-887;
	MAP3K2	10746	hsa-miR-519d; hsa-miR-651; hsa-miR-587; hsa-miR-34c-3p; hsa-miR-2909;
	MAP3K3	4215	hsa-miR-661; hsa-miR-1225-3p; hsa-miR-544b; hsa-miR-3922-3p; hsa-miR-4505;
	MAP3K4	4216	hsa-miR-1204; hsa-miR-3129-5p; hsa-miR-5047; hsa-miR-3691-3p; hsa-miR-3064-3p;
ERK	MAPK3	5595	hsa-miR-4270; hsa-miR-486-3p; hsa-miR-483-5p; hsa-miR-608; hsa-miR-1291;
	MAPK1	5594	hsa-miR-4667-5p; hsa-miR-4459; hsa-miR-4271; hsa-miR-4799-5p; hsa-miR-2110;
	KSR1	8844	hsa-miR-331-3p; hsa-miR-4440; hsa-miR-4291; hsa-miR-4660; hsa-miR-876-3p;
	MAPK11	5600	hsa-miR-4640-3p; hsa-miR-296-5p; hsa-miR-4292; hsa-miR-4532; hsa-miR-4685-5p;
ANTI-APOPTOSIS	BCL2	596	hsa-miR-448; hsa-miR-4691-3p; hsa-miR-3199; hsa-miR-3943; hsa-miR-342-3p;
	BCL2L1	598	hsa-miR-4447; hsa-miR-608; hsa-miR-4728-5p; hsa-miR-4649-3p; hsa-miR-4700-5p;
	BIRC5	332	hsa-miR-542-3p; hsa-miR-3940-3p; hsa-miR-4660; hsa-miR-1225-3p; hsa-miR-1273;
	XIAP	331	hsa-miR-377; hsa-miR-3150a-3p; hsa-miR-3175; hsa-miR-5095; hsa-miR-3664-5p;
	BAK1	578	hsa-miR-4419a; hsa-miR-125b; hsa-miR-4667-5p; hsa-miR-1909; hsa-miR-4739;
FGF	FGF1	2246	hsa-miR-4297; hsa-miR-3155; hsa-miR-1909; hsa-miR-566; hsa-miR-2355-5p;
	FGF2	2247	hsa-miR-195; hsa-miR-4524; hsa-miR-503; hsa-miR-646; hsa-miR-3607-5p;
	FGF3	2248	hsa-miR-3173-5p; hsa-miR-4487; hsa-miR-760; hsa-miR-4722-3p; hsa-miR-4758-3p;
	FGF4	2249	hsa-miR-4671-5p; hsa-miR-3679-3p; hsa-miR-4290; hsa-miR-361-3p; hsa-miR-767-5p;
	FGF5	2250	hsa-miR-4435; hsa-miR-4655-5p; hsa-miR-4288; hsa-miR-4463; hsa-miR-4704-3p;
	FGF6	2251	hsa-miR-4677-3p; hsa-miR-548q; hsa-miR-138; hsa-miR-639; hsa-miR-1322;
	FGF7	2252	hsa-miR-4762-5p; hsa-miR-486-5p; hsa-miR-195; hsa-miR-3920; hsa-miR-1253;
	FGF8	2253	hsa-miR-3120-3p; hsa-miR-545; hsa-miR-491-5p; hsa-miR-361-3p; hsa-miR-4720-5p;
	FGF9	2254	hsa-miR-1273c; hsa-miR-140-5p; hsa-miR-423-3p; hsa-miR-3157-5p; hsa-miR-3683;
	FGF10	2255	
	FGF11	2256	hsa-miR-4667-3p; hsa-miR-4469; hsa-miR-3192; hsa-miR-3661; hsa-miR-3649;
	FGF12	2257	hsa-miR-4747-5p; hsa-miR-3202; hsa-miR-4533; hsa-miR-4633-3p; hsa-miR-197;
	FGF13	2258	hsa-miR-1262; hsa-miR-3675-5p; hsa-miR-1185; hsa-miR-512-3p; hsa-miR-4421;
	FGF14	2259	hsa-miR-4663; hsa-miR-188-3p; hsa-miR-4299; hsa-miR-4690-5p; hsa-miR-4691-3p;
	FGFR1	2260	hsa-miR-4530; hsa-miR-4728-5p; hsa-miR-515-3p; hsa-miR-1208; hsa-miR-4667-5p;
	FGFR2	2263	hsa-miR-515-5p; hsa-miR-3177-3p; hsa-miR-423-3p; hsa-miR-4789-3p; hsa-miR-3675-5p;
	FGFR3	2261	hsa-miR-296-5p; hsa-miR-4793-3p; hsa-miR-4746-3p; hsa-miR-3918; hsa-miR-1291;
	FGFR4	2264	hsa-miR-3177-3p; hsa-miR-4726-5p; hsa-miR-1225-3p; hsa-miR-378g; hsa-miR-564;
mTOR-AKT-PTEN-	mTor	2475	hsa-miR-767-3p; hsa-miR-4762-3p; hsa-miR-496; hsa-miR-1233; hsa-miR-1229;
	AKT1	207	hsa-miR-1915; hsa-miR-4721; hsa-miR-3162-3p; hsa-miR-4738-5p; hsa-miR-4723-5p;
	AKT2	208	hsa-miR-4716-3p; hsa-miR-29b; hsa-miR-4278; hsa-miR-3943; hsa-miR-3065-3p;
	PTEN	5728	hsa-miR-642b; hsa-miR-486-5p; hsa-miR-148a; hsa-miR-3944-5p; hsa-miR-3691-5p;
Modulators MTKPT	TSC1	7248	hsa-miR-130a; hsa-miR-1537; hsa-miR-637; hsa-miR-3141; hsa-miR-3684;
	TSC2	7249	hsa-miR-4420; hsa-miR-654-3p; hsa-miR-4722-5p; hsa-miR-615-5p; hsa-miR-3922-5p;
	STK11	6794	hsa-miR-663; hsa-miR-744; hsa-miR-4723-5p; hsa-miR-3960; hsa-miR-615-5p;

	PIM1	5292	hsa-miR-4749-3p; hsa-miR-761; hsa-miR-3689a-3p; hsa-miR-331-3p; hsa-miR-4436b-3p;
	PIM2	11040	hsa-miR-361-3p; hsa-miR-4532; hsa-miR-3654; hsa-miR-4645-5p; hsa-miR-4768-3p;
	PIM3	415116	hsa-miR-3195; hsa-miR-4697-5p; hsa-miR-654-5p; hsa-miR-4467; hsa-miR-637;
RAS	KRAS	3845	hsa-miR-3923; hsa-miR-4323; hsa-miR-4447; hsa-miR-513a-5p; hsa-miR-548ag;
	NRAS	4893	hsa-miR-502-5p; hsa-miR-1296; hsa-miR-1324; hsa-miR-3120-3p; hsa-miR-4271;
	HRAS	3265	hsa-miR-3667-3p; hsa-miR-4728-5p; hsa-miR-4292; hsa-miR-4532; hsa-miR-663;
RAF	RAF1	5894	hsa-miR-1291; hsa-miR-7; hsa-miR-3126-5p; hsa-miR-296-5p; hsa-miR-764;
	BRAF	673	hsa-miR-617; hsa-miR-2110; hsa-miR-3977; hsa-miR-1182; hsa-miR-1289;
TELOMERASE	TERT	7015	hsa-miR-4650-5p; hsa-miR-491-5p; hsa-miR-4651; hsa-miR-3687; hsa-miR-4292;
	TERC	7012	
	TEP1	7011	hsa-miR-1911; hsa-miR-3132; hsa-miR-136; hsa-miR-2861; hsa-miR-31;
	HSP90AA1	3320	hsa-miR-4753-5p; hsa-miR-632; hsa-miR-519e; hsa-miR-3679-3p; hsa-miR-134;
	DKC1	1736	hsa-miR-3194-3p; hsa-miR-621; hsa-miR-3620; hsa-miR-646; hsa-miR-4279;
	PTGES3	10728	hsa-miR-3189-5p; hsa-miR-3135; hsa-miR-4266; hsa-miR-3678-3p; hsa-miR-4286;
IGF & Warburg	IGF1	3479	hsa-miR-483-3p; hsa-miR-1275; hsa-miR-4435; hsa-miR-488; hsa-miR-625;
	IGF2	3481	hsa-miR-4447; hsa-miR-491-5p; hsa-miR-210; hsa-miR-3191; hsa-miR-3144-5p;
	IGF1R	3480	hsa-miR-4746-3p; hsa-miR-4784; hsa-miR-4763-3p; hsa-miR-4327; hsa-miR-3157-5p;
	IGF2R	3482	hsa-miR-4667-3p; hsa-miR-653; hsa-miR-4707-3p; hsa-miR-4736; hsa-miR-548an;
	INSR	3643	hsa-miR-2467-5p; hsa-miR-3975; hsa-miR-3188; hsa-miR-4707-3p; hsa-miR-4290;
	IRS1	3667	hsa-miR-660; hsa-miR-541; hsa-miR-4462; hsa-miR-544b; hsa-miR-183;
	PKM2	5315	hsa-miR-762; hsa-miR-625; hsa-miR-612; hsa-miR-4675; hsa-miR-4665-5p;
WNT	CDH1	999	hsa-miR-4640-3p; hsa-miR-4711-5p; hsa-miR-3689c; hsa-miR-2355-5p; hsa-miR-1296;
	CTNNA1	1495	hsa-miR-1288; hsa-miR-4440; hsa-miR-4515; hsa-miR-4705; hsa-miR-9;
	CTNNB1	1499	hsa-miR-3688-5p; hsa-miR-3162-3p; hsa-miR-4776-5p; hsa-miR-4496; hsa-miR-3619-3p;
	WNT 1	7471	hsa-miR-4488; hsa-miR-4784; hsa-miR-4695-5p; hsa-miR-4644; hsa-miR-4689;
	FZD1	8321	hsa-miR-4269; hsa-miR-4769-5p; hsa-miR-1275; hsa-miR-1324; hsa-miR-4279;
	WNT5A	7474	hsa-miR-2110; hsa-miR-4691-5p; hsa-miR-876-5p; hsa-miR-3127-3p; hsa-miR-4656;
	WNT5B	81029	hsa-miR-4316; hsa-miR-4258; hsa-miR-2909; hsa-miR-1296; hsa-miR-486-3p;
	FZD5	7855	hsa-miR-296-5p; hsa-miR-3943; hsa-miR-188-3p; hsa-miR-3661; hsa-miR-3672;
	WIF1	11197	hsa-miR-1972; hsa-miR-3938; hsa-miR-548v; hsa-miR-140-3p; hsa-miR-3977;
	DKK1	22943	hsa-miR-493; hsa-miR-4639-3p; hsa-miR-4727-5p; hsa-miR-4678; hsa-miR-934;
PARP	PARP1	142	hsa-miR-891b; hsa-miR-4536; hsa-miR-4451; hsa-miR-555; hsa-miR-7;
	BRCA1	672	hsa-miR-615-5p; hsa-miR-3667-3p; hsa-miR-4446-3p; hsa-miR-760; hsa-miR-4656;
	XRCC1	7515	hsa-miR-589; hsa-miR-4477a;
	RAD54L	8438	hsa-miR-4713-5p; hsa-miR-1225-3p; hsa-miR-3918; hsa-miR-3667-3p; hsa-miR-1291;
	RAD54B	25788	hsa-miR-587; hsa-miR-4268; hsa-miR-548s; hsa-miR-3926; hsa-miR-1;
	ATM	472	hsa-miR-892b; hsa-miR-193a-3p; hsa-miR-4735-3p; hsa-miR-4736; hsa-miR-4262;
	ATR	545	hsa-miR-3613-5p; hsa-miR-383; hsa-miR-4760-5p; hsa-miR-140-3p; hsa-miR-586;
	CHEK1	1111	hsa-miR-2355-5p; hsa-miR-541; hsa-miR-1286; hsa-miR-4733-3p; hsa-miR-16;
	CHEK2	11200	hsa-miR-3118; hsa-miR-759; hsa-miR-4276; hsa-miR-3938; hsa-miR-943;
	WEE1	7465	hsa-miR-4716-3p; hsa-miR-4723-5p; hsa-miR-424; hsa-miR-3120-3p; hsa-miR-4278;
HDAC	HDAC1	3065	hsa-miR-4284; hsa-miR-4292; hsa-miR-4271; hsa-miR-3126-5p; hsa-miR-584;

	HDAC2	3066	hsa-miR-362-5p; hsa-miR-3977; hsa-miR-3194-3p; hsa-miR-4662a-5p; hsa-miR-4720-5p;
	HDAC3	8841	hsa-miR-3189-3p; hsa-miR-1261; hsa-miR-326; hsa-miR-1302; hsa-miR-4308;
	HDAC4	9759	hsa-miR-4292; hsa-miR-4313; hsa-miR-4728-5p; hsa-miR-1225-3p; hsa-miR-4316;
	HDAC5	10014	hsa-miR-331-3p; hsa-miR-671-5p; hsa-miR-4498; hsa-miR-296-5p; hsa-miR-4505;
JAK-STAT	JAK1	3716	hsa-miR-4252; hsa-miR-4437; hsa-miR-4520a-3p; hsa-miR-323b-5p; hsa-miR-4674;
	JAK2	3717	hsa-miR-4720-5p; hsa-miR-4468; hsa-miR-3120-3p; hsa-miR-4777-3p; hsa-miR-568;
	STAT1	6772	hsa-miR-4682; hsa-miR-1252; hsa-miR-3119; hsa-miR-4697-3p; hsa-miR-2682;
	STAT2	6773	hsa-miR-665; hsa-miR-3202; hsa-miR-4292; hsa-miR-4313; hsa-miR-1289;
	STAT3	6774	hsa-miR-1299; hsa-miR-4753-5p; hsa-miR-1184; hsa-miR-874; hsa-miR-5047;
	SOCS1	8651	hsa-miR-4645-5p; hsa-miR-556-3p; hsa-miR-331-3p; hsa-miR-4716-3p; hsa-miR-324-5p;
HEDGEHOG	SHH	6469	hsa-miR-1471; hsa-miR-4749-3p; hsa-miR-4313;
	PTCH1	5727	hsa-miR-4757-5p; hsa-miR-564; hsa-miR-1262; hsa-miR-767-3p; hsa-miR-125a-3p;
	SMO	6608	hsa-miR-370; hsa-miR-4690-3p; hsa-miR-4758-3p; hsa-miR-423-3p; hsa-miR-1915;
	STK36	27148	hsa-miR-571; hsa-miR-3192; hsa-miR-581; hsa-miR-920; hsa-miR-4715-5p;
	PRKACA	5566	hsa-miR-4723-5p; hsa-miR-4665-5p; hsa-miR-608; hsa-miR-423-5p; hsa-miR-625;
	SUFU	51684	hsa-miR-3184; hsa-miR-4487; hsa-miR-4688; hsa-miR-4728-5p; hsa-miR-4741;
	GLI1	2735	hsa-miR-3943; hsa-miR-4279; hsa-miR-4292; hsa-miR-361-3p; hsa-miR-4533;
DNA REPAIR	ERCC1	2067	hsa-miR-661; hsa-miR-1913; hsa-miR-323-5p; hsa-miR-1972; hsa-miR-1268;
	RAD52	5893	hsa-miR-3922-3p; hsa-miR-4725-3p; hsa-miR-342-3p; hsa-miR-542-3p; hsa-miR-4303;
	XRCC4	7518	hsa-miR-361-5p; hsa-miR-380; hsa-miR-4520a-3p; hsa-miR-3121-5p; hsa-miR-2355-3p;
	RAD51	5888	hsa-miR-198; hsa-miR-532-3p; hsa-miR-606; hsa-miR-4430; hsa-miR-4432;
	BRCA1	672	hsa-miR-615-5p; hsa-miR-3667-3p; hsa-miR-4446-3p; hsa-miR-760; hsa-miR-4656;
	NEDD8	4738	hsa-miR-4713-3p; hsa-miR-4726-5p; hsa-miR-665; hsa-miR-1285; hsa-miR-1322;
	NAE1	8883	hsa-miR-4524; hsa-miR-646; hsa-miR-4660; hsa-miR-582-5p; hsa-miR-603;
NOTCH	NOTCH1	4851	hsa-miR-4313; hsa-miR-4268; hsa-miR-449a; hsa-miR-139-5p; hsa-miR-4727-5p;
	Adam17	6868	hsa-miR-507; hsa-miR-3918; hsa-miR-4687-5p; hsa-miR-3651; hsa-miR-1827;
	PSEN1	5663	hsa-miR-3065-3p; hsa-miR-4697-3p; hsa-miR-3120-5p; hsa-miR-4303; hsa-miR-488;
	NCSTN	23385	hsa-miR-339-5p; hsa-miR-4654; hsa-miR-1321; hsa-miR-4648; hsa-miR-3657;
	JAG1	182	hsa-miR-4692; hsa-miR-1273g; hsa-miR-920; hsa-miR-4661-5p; hsa-miR-4283;
	SRRT	51593	hsa-miR-4700-3p; hsa-miR-3190; hsa-miR-487b; hsa-miR-520f; hsa-miR-3929;
	APH1A	51107	hsa-miR-3679-3p; hsa-miR-198; hsa-miR-3173-3p; hsa-miR-4685-5p; hsa-miR-3131;
Others	ROS1	6098	hsa-miR-4693-3p; hsa-miR-4653-3p; hsa-miR-33a; hsa-miR-606; hsa-miR-3659;
	ALK	238	hsa-miR-642a; hsa-miR-646; hsa-miR-4764-3p; hsa-miR-1271; hsa-miR-4713-3p;
	RET	5979	hsa-miR-544; hsa-miR-4652-5p; hsa-miR-510; hsa-miR-31; hsa-miR-3622b-5p;
	UBA1	7317	hsa-miR-4716-3p; hsa-miR-762; hsa-miR-4640-5p; hsa-miR-3202; hsa-miR-31;

Table 12: Mutational status

	KRAS	EFGR	PIK3CA	BRAF	ERBB2	P53
1	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	80_SNP_A>G_R-Arg_exon6, 102_deletion_C_exon8
2	c.35G>K p.Gly12Val (G12V)	WT	WT	WT	WT	39_G>A_Met>Ile_exon7, 75_G>C_exon7
3	WT	WT	WT	WT	WT	47_G>T_Ser>Ile_exon7, 51_C>A_Ser>Ser_exon7
7	WT	WT	WT	WT	c.2883T>G p.Ile961Met (I961M) AGVGD:Class C0_exon 24	WT
8	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
12	c.35G>R p.Gly12Asp (G12D)	WT	WT	WT	WT	WT
15	WT	WT	WT	WT	WT	63_C>T_Gly>Gly_exon7
20	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
23	c.35G>K p.Gly12Val (G12V)	WT	WT	WT	WT	WT
25	WT	WT	c.3075C>T p.= rs17849079	WT	WT	139_A>G_Glu>Gly_exon5
29	c.35G>K p.Gly12Val (G12V)	WT	WT	WT	WT	WT
30	WT	WT	WT	WT	WT	17_G>T_exon10
32	c.35G>R p.Gly12Asp (G12D)	WT	WT	WT	WT	WT
33	WT	WT	WT	WT	WT	177_G>T_Asp>Tyr_exon5
34	WT	WT	WT	WT	WT	96_G>C_Val>Leu_exon5
36		WT	WT	nd	WT	62_G>A_Gly>Asp_exon7, and 88_insertion_G_exon7
39	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
40	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	94_G>A_Arg>His_exon5
42	WT	WT	WT	WT	WT	55_G>C_Gly>Ala_exon8
46	c.35G>K p.Gly12Val (G12V)	WT	WT	WT	WT	WT
47	WT	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	57_A>T_Arg>Stop_exon8
49	WT	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	WT
50	WT	WT	WT	WT	WT	58_insertion_G, 75_SNP_G>A_Arg>Arg_exon7
51	WT	WT	WT	WT	WT	42_A>G_Lys>Glu_exon5

57	WT	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	WT
58	WT	WT	c.2937-96A>C Non Codant	WT	WT	WT
59	WT	WT	WT	c.1799T>W p.Val600Glu (V600E)	wt	WT
61	WT	WT	WT	WT	WT	58_G>A_Gly>Ser_exon6, 65_T>A_Met>Lys_exon7, 70_G>A?_Gly?>Arg?_exon7, 129_C>T_exon7
62	WT	c.2184+19G>A Non Codant rs17337107	WT	WT	WT	WT
68	WT	WT	wt	wt	wt	47_G>T_Ser>Ile_exon7, 51_C>A_Ser>Ser_exon7, 83_C>A?_Pro?>His?_exon7
70	WT	WT	WT	WT	WT	119_G>T_Lys>Asn_exon5
71	WT	c.2320_2321ins3bp (CAC) p.Val774delinsAlaLeu exon 20	WT	WT	WT	WT
72	c.35G>S p.Gly12Ala (G12A)	WT	WT	WT	WT	152_insertion_T_exon5
74	WT	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	WT
75	WT	WT	WT	WT	WT	83_T>C_exon7
76	WT	WT	WT	WT	WT	55_A>G_Tyr>Cys_exon6
78	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
80	WT	WT	WT	WT	WT	163_A>T_His>Leu_exon5
83	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
84	WT	WT	WT	WT	WT	96_G>T_Val>Phe_exon5
88	WT	WT	WT	WT	WT	158_C>G_exon7
91	c.34G>K p.Gly12Cys (G12C)	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	80_SNP_A>G_R-Arg_exon6, 101_A>G_Glu>Gly_exon7, 106_T>A_Ser>Thr_exon7, 142_C>G_exon7
92	WT	c.2215_2229del15bp p.Lys739_Ala743de exon 20	WT	WT	WT	WT
93	WT	c.2156G>C p.Gly719Ala (G719A) VAR_026086 exon 18 c.2303G>T p.Ser768Ile (S768I) AGVGD:Class C65 exon 20	WT	WT	WT	WT
94	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
96	c.34G>K p.Gly12Cys (G12C)	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	WT
102	WT	WT	WT	WT	WT	54_T>C_Tyr>His_exon6
103	WT	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	WT
104	c.35G>K p.Gly12Val (G12V)	WT	WT	WT	WT	WT
107	WT	WT	WT	WT	WT	70_C>T_Arg>Trp_exon7,

108	WT	WT	WT	WT	WT	71_SNP_G>A_exon7 26deletion_T_exon9
111	WT	c.2313_2314ins9bp (CCCCAGGCG) p.Pro772_His773insGlnAlaPro_expn 20	WT	WT	WT	WT
113	c.34G>K p.Gly12Cys (G12C)	WT	WT	WT	WT	WT
114	WT	WT	WT	WT	WT	WT
115	WT	c.2184+19G>R Non Codant rs17337107	WT	WT	WT	WT
118	WT	WT	WT	WT	WT	99_C>G_Arg>Gly_exon5
121	c.183A>W p.Gln61His (Q61H) rs17851045 exon 3	WT	WT	WT	WT	92_C>T_exon5, 104_C<T_exon5, 128_C>G_Ser>Arg_exon8,

Table 13: Calculated scores

Wherein P means Patient, (1) refers to a score calculated based on mRNA expression, (2) refers to a score calculated based on mutation and mRNA expression, (3) refers to a score calculated based on mutation, mRNA expression, and miRNA expression, and (4) refers to a score calculated based on mutation, mRNA expression, miRNA expression and Copy Number Variation.

	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
P	Her				CDK 4-6				PLK_AURKA_Kinesins				ANGIOGENESIS				ANGIOPOIETINS			
1	2	2	1	1	4	4	3	3	7	7	7	7	5	5	6	5	2	2	2	2
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121	3	3	3	7	7	7	10	10	10	10	5	5	9	9	1	1	2	2

CLAIMS

1- A method for determining in a patient having a cancer a classification of intervention points according to their activation status, wherein

- 5 - the intervention points comprise the group consisting of 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, RET, ALK, ROS1 and UB1, or any subgroup thereof of at least 10
- 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
 - 15 - 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 mRNA expression of tumor vs normal, (referred as mRNA TvN fold change);
 - 20 - wholly or partially sequencing genes of Table 1 or 9, thereby identifying the presence of activating mutation in the tumor sample ;
 - for each intervention point of the group or subgroup of intervention points, determining the level of miRNAs of the genes of the intervention point as disclosed in Table 11, thereby determining a fold change of miRNAs level of tumor vs normal, (referred as miRNA TvN fold change);
 - 25 - optionally, for each intervention point of the group or subgroup of intervention points, determining the copy number variation of the genes of the intervention point as disclosed in
 - 30 Table 1 or 9, thereby determining a tumor vs normal fold change for the amplified genes;

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 - calculating a mean miRNAs fold change for each gene as the average of the miRNA TvN fold changes for the gene, calculating a corrected mRNA TvN fold change 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 being used to calculate the arithmetic mean of the mRNA TvN fold changes of the genes for each intervention point,
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 - calculating a score for each pathway based on the characterization data, wherein
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 - if, in the tumor sample, the presence of an activating mutation of a gene of an intervention point is detected, then a maximal score is given to the intervention point, in particular a score of 10 if the scoring is from 1 to 10;
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 - a score, preferably from 1 to 10, is calculated based on the arithmetic mean of the mRNA TvN fold changes of the genes for each intervention point of the group or subgroup of intervention points, provided that the mRNA TvN fold change of a gene is taken into consideration only if its value is at least 1.3; and
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 - the score of each intervention point of the group or subgroup of intervention points is either
 - a. the sum of the score due to the presence of an activating mutation and the score calculated by the average of the mRNA TvN fold changes; or
 - b. the score due to the presence of an activating mutation if there is a mutation or the score calculated based on the arithmetic mean of the mRNA TvN fold changes in absence of mutation; and
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 - classifying the intervention points according to the calculated scores.

- 2- The method according to claim 1, wherein the genes of Table 10 are sequenced for detecting the presence of mutations as defined in Table 10 and p53 gene is sequenced.

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- 3- The method according to claim 1, wherein 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.
- 5 4- The method according to any one of claims 1-3, wherein 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.
- 10 5- The method according to claim 4, wherein, 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
- 15 intervention point.
- 6- The method according to any one of claims 1-5, wherein 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.
- 20 7- The method according to any one of claims 1-6, wherein 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.

8- 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 7 and a drug is selected for each or disturbed intervention point, thereby providing a combination of three drugs.

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9- 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 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, RET, ALK, ROS1 and UB1, or any subgroup thereof of at least 10 intervention points;

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means for detecting the mutations of Table 10; 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, RET, ALK, ROS1 and UB1, or any subgroup thereof of at least 10 intervention points.

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10- The use of claim 9, wherein 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, RET, ALK, ROS1 and UB1, or any subgroup thereof of at least 10 intervention points.

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11- Use of a drugs combination in the preparation of a medicament for the treatment of cancer, wherein the drugs combination is selected in the group consisting of

anti PD1L + Pan RAF inhibitor + MtorPI3K inhibitor

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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
 5 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
 anti PD1L + MEK inhibitor + MET inhibitor
 10 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
 anti CTLA4 + MEK inhibitor + CDK4,6 inhibitor; and wherein the drug
 15 combination is selected by the method according to claim 8.

12- The use according to claim 11, wherein the drugs combination is selected in the group consisting of

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

 Medi-4736 + Selumetinib + Crizotinib
 30 Medi-4736 + Selumetinib + Palbociclib
 Tremelimumab + Selumetinib + PF-384

Tremelimumab + Selumetinib + Crizotinib

Tremelimumab + Selumetinib + Axitinib or Motesanib, and

Tremelimumab + Selumetinib + Palbociclib.