(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 November 2017 (09.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/193080 A1

(51) International Patent Classification:
G06F 19/12 (2011.01) *C12Q 1/68* (2006.01)
G06F 19/26 (2011.01)

(21) International Application Number:
PCT/US2017/031418

(22) International Filing Date:
05 May 2017 (05.05.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/332,047 05 May 2016 (05.05.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) **Title:** CHECKPOINT FAILURE AND METHODS THEREFOR

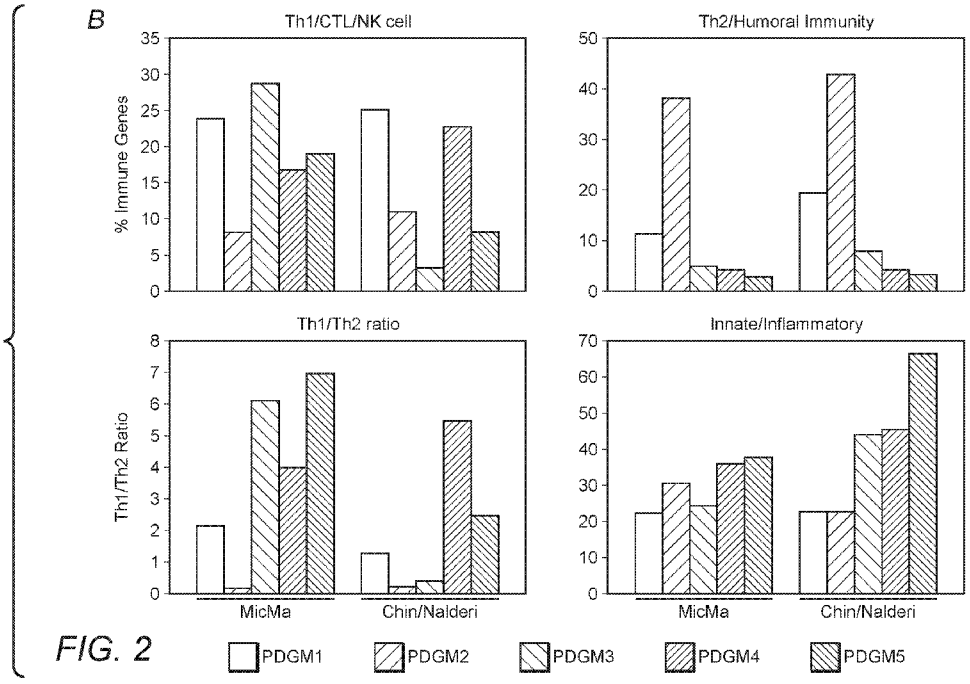

FIG. 2

(57) **Abstract:** Systems and methods for more accurate prediction of the treatment outcome for immune therapy using checkpoint inhibitors are presented in which omics data of a patient tumor sample are used. In one aspect, a pathway signature is identified as being associated with immune suppression and as being responsive to treatment with immune checkpoint inhibitors.

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Published:
— *with international search report (Art. 21(3))*

CHECKPOINT FAILURE AND METHODS THEREFOR

[0001] This application claims priority to US provisional application serial number 62/332047, filed May 5, 2016. U.S. application number 62/332,047 is incorporated herein in its entirety.

Field of the Invention

[0002] The field of the invention is computational analysis of various omics data to allow for treatment stratification for immune therapy, and especially pathway-based analysis to identify likely responders to checkpoint inhibitor treatment.

Background of the Invention

[0003] The background description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] All publications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0005] Immune therapy with genetically modified viruses has become increasingly effective and attractive route for treatment of various cancers. However, several challenges remain to be resolved. For example, the choice of suitable antigens to be expressed is non-trivial (see *e.g.*, *Nat Biotechnol.* 2012; 30(7):658-70; and *Nat Biotechnol.* 2017;35(2): 79). Moreover, even frequently or highly expressed epitopes will not guarantee a tumor-protective immune reaction in all patients. In addition, even where several neoepitopes are known and used as an immunotherapeutic composition, inhibitory factors in the tumor microenvironment may nevertheless prevent a therapeutically effective response. For example, a sufficient immune response may be blunted or even prevented by Tregs (*i.e.*, regulatory T cells) and/or MDSCs (myeloid derived suppressor cells). In addition, lack of stimulatory factors and tumor based interference with immune checkpoints, and especially PD-1 and CTLA-4, may still further prevent a therapeutic response to immune therapy.

[0006] Therapeutic compositions are known to block or silence immune checkpoints (*e.g.*, Pembrolizumab or Nivolumab for the PD-1 system, or Ipilimumab for the CTLA-4 system). However, administration is not consistently effective to promote a durable and therapeutically useful response. Likewise, cyclophosphamide may be used to suppress Tregs, however tends to mobilize MDSCs. Thus, a clear path to intervention in patients with low immune response to immune therapy is not apparent. More recently, a predictive model was proposed that used levels of tumor MHC class I expression as a positively correlated marker with overall tumor immunogenicity (see *J Immunother* 2013, Vol. 36, No 9, p477-489). The authors also noted a pattern where certain immune activating genes were up-regulated in strongly immunogenic tumors of some of the models, but advised that additional biomarkers should be found to help predict immunotherapy response. In another approach (*Cancer Immunol Res*; 4(5) May 2016, OF1-7), post-treatment in depth sequence and distribution analysis of tumor reactive T cell receptors was used as a proxy indicator for reactive T-cell tumor infiltration. Unfortunately, such analysis fails to provide predictive insight with respect to likely treatment success for immune therapy.

[0007] In still further known approaches, change in expression level of selected genes was used as a signature predictive of increased likelihood of being responsive to immunotherapy as described in WO 2016/109546. Similarly, US 2016/0312295 and US 2016/0312297 teach gene signature biomarkers that are useful for identifying cancer patients who are most likely to benefit from treatment with a PD-1 antagonist. While such signatures tend to be at least somewhat informative, they are generally 'static' and typically fail to reflect pathway activity that could be indicative of sensitivity and/or susceptibility to treatment with one or more checkpoint inhibitors.

[0008] Thus, even though various systems and methods of immune therapy and checkpoint inhibition are known in the art, all or almost all of them suffer from several drawbacks. Therefore, there is still a need to provide improved compositions and methods to identify patients that are responsive to immune therapy and treatment with checkpoint inhibitors.

Summary of The Invention

[0009] The inventive subject matter is directed to computational analysis of omics data to predict likely treatment success to immune therapy using checkpoint inhibitors. In one particularly preferred aspect, computational pathway analysis is performed on omics data

obtained from a tumor sample (*e.g.*, breast cancer tumor sample containing tumor infiltrating lymphocytes), wherein the pathway analysis uses a cluster of features and pathways that are associated with specific subsets of immune related genes. In still further preferred aspects, the features and pathways are associated with an up-regulated FOXM1 signaling pathway, with the presence and/or inhibition of tumor infiltrating lymphocytes, with a low (as compared to healthy tissue) Th1/Th2 ratio, and with a basal-like character.

[0010] In one aspect of the inventive subject matter, the inventors contemplate a method of predicting a likely therapeutic outcome for immune therapy of a cancer with a checkpoint inhibitor (*e.g.*, CTLA-4 or a PD-1 inhibitor). Preferred methods comprise a step of obtaining omics data from a tumor of the patient, wherein the omics data comprise at least one of whole genome sequencing data and RNA sequencing data, and a further step of using pathway analysis to identify from the omics data a plurality of highly expressed genes in a plurality of immune related pathways having a plurality of respective pathway elements. In another step, the highly expressed genes are associated with a likely response of the cancer to treatment with the checkpoint inhibitor when the highly expressed genes are indicative of a Th2/humoral response and a low Th1/Th2 ratio, and in a still further step, a patient record is updated or generated record with an indication of the likely response of the cancer to treatment with the checkpoint inhibitor when the highly expressed genes are indicative of a Th2/humoral response and a low Th1/Th2 ratio.

[0011] Preferred immune related pathways include an immune cell function pathway, a pro-inflammatory signaling pathway, and an immune suppression pathway, and/or the pathway element controls activity of Th1 differentiation, Th2 differentiation, B cell differentiation, macrophage differentiation, T cell activation, and/or an immunoproteasome. For example, while some contemplated pathway elements will control activity of NFkB, and/or IFNalpha responsive gen, other pathway elements include cytokines, and especially IL12 beta, IFNgamma, IL4, IL5, and IL10. Further contemplated pathway elements include one or more chemokines, including CCL17, CCL11, and CCL26.

[0012] Therefore, and among other suitable pathway elements, especially contemplated elements are selected form the group consisting of IL12B, IFNG, PSMA3, THY1, CCL17, PRKCQ, NFATC3, NFATC2, CCL11, CCL26, IFNAR2, SQSTM1, IRAK4, NFKBIA, IL6ST, MAP3K1, IRF1, IRF9, PTGS2, IL4, IL5, IGHG3, IL4R, IL13RA2, PIGR, IL13RA1, STAT6, FCER2, IGHG1, IL10, STAT5A, PRKCE, CSF1R, ARG1, LTA, SELP, FKBP3,

LCP2, and DOK2. Where the pathway element is a complex, especially contemplated complexes are selected form the group consisting of IFN-gamma/IRF1, STAT6 (dimer)/PARP14, IL4/IL4R/JAK1, IL4R/JAK1, STAT6 (dimer)/ETS1, PI3K/BCAP/CD19, IL4/IL4R/JAK1/IL2Rgamma/JAK3/DOK2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHIP, IL4/IL4R/JAK1/IL13RA1/JAK2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHC/SHIP, IL4/IL4R/JAK1/IL2Rgamma/JAK3/FES/IRS2, IL4/IL4R/JAK1/IL2Rgamma/JAK3, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHC/SHIP/GRB2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/IRS1, IL4/IL4R/JAK1/IL2Rgamma/JAK3/FES, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHP1.

[0013] In further contemplated aspects, the omics data may further comprise siRNA data, DNA methylation status data, transcription level data, and/or proteomics data. Most preferably, the pathway analysis comprises PARADIGM analysis, and/or the omics data are normalized against the same patient (before or after treatment). Typically, the cancer is a breast cancer, and the highly expressed genes will further include FOXM1. However, contemplated highly expressed genes may further include non-immune genes encoding a protein involved in at least one of mitogenic signaling, stress signaling, apoptosis, calcium/calmodulin signaling, G-protein signaling, PI3K/AKT signaling, RTK signaling, Wnt signaling, and cAMP signaling, non-immune genes encoding a protein involved in at least one of cell cycle control, DNA damage response, and chromatin remodeling, and/or non-immune genes selected from the group consisting of MAPK1, MAPK14, NRP2, HIF1A, CALM1, CREB1, CSNK1A1, CSNK1G3, CCNH, FANCE, FANCA, TFIIH, ITGB3, RASA1, GNG2, PDGFRB, AKT1, and PIK3R1. In further contemplated methods, the likely therapeutic outcome is predicted prior to therapy with the checkpoint inhibitor, and/or the immune therapy may further comprise administration of at least one of a genetically modified virus and a genetically modified NK cell.

[0014] Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawing.

Detailed Description

[0015] The inventors have discovered systems and methods of predicting a likely treatment outcome of cancer immune therapy by computational analysis of pathway signatures found in

tumor tissue to identify the immune status of a tumor. In especially preferred aspects of the inventive subject matter, positive treatment outcome with checkpoint inhibitors is predicted in breast cancer where a tumor has attributes of an up-regulated FOXM1 signaling pathway, with presence and/or inhibition of tumor infiltrating lymphocytes, with a low (as compared to healthy tissue) Th1/Th2 ratio, and with a basal-like character.

[0016] In this context, it should be appreciated that contemplated systems and methods take advantage of differentially expressed genes (using mRNA quantity and copy number as the main contributors) in pathways versus the same genes in healthy tissue as predictor. Most typically, differentially expressed genes will be up-regulated relative to the same genes in healthy tissue, however, down-regulated genes are also contemplated (and often present in genes associated with Th1 phenotype). Moreover, it should also be recognized that pathway analysis (*e.g.*, using PARADIGM) provides a significant advantage in such analysis identifies active pathways in subsets of patients that would otherwise be indistinguishable where genes are studied at a single level. Particularly preferred methods of pathway analysis make use of techniques from probabilistic graphical models to integrate functional genomics data onto a known pathway structure. Such analysis not only provides better discrimination of patients with respect to prognosis than any of the molecular levels studied separately, but also allows for identification of immune status of a tumor based on characteristics that are reflected in specific immune related pathway activities, and particularly with FOXM1 signaling pathway activity, activity of Th1 and Th2 related pathways, pathway activity associated with innate immunity, and pathways associated with sub-type of cancer (*e.g.*, luminal, basal). Indeed, clustering of results from pathway analysis revealed distinct groups of differential pathway activity as is discussed in more detail below.

[0017] For example, and as discussed in more detail below, the inventors observed that all clusters that were associated with good outcome (increased survival time) were significantly enriched in genes associated with antitumor immunity at the expense of the Th2/humoral immune response, which is also consistent with a higher ratio of Th1/Th2 genes in these clusters. On the other hand, the cluster that was associated with poorer outcome (decreased survival time) was significantly enriched in Th2/humoral-related genes and had significantly lower Th1/Th2 ratios. Notably, the inventors discovered that the pathway activities in such cluster was also prognostic for treatment success with one or more checkpoint inhibitors.

[0018] Consequently, it is contemplated that prior to treatment (or after one round of cancer treatment but before a subsequent round of cancer treatment), a tumor biopsy is obtained from a patient and that omics analysis is performed on the so obtained sample. In general, it is contemplated that the omics analysis includes whole genome and/or exome sequencing, RNA sequencing and/or quantification, and/or proteomics analysis. Most typically, the omics analysis will also include obtaining information about copy number alterations, especially amplification of one or more genes. As will be readily appreciated, it is contemplated that genomic analysis can be performed by any number of analytic methods, however, especially preferred analytic methods include next generation WGS (whole genome sequencing) and exome sequencing of both a tumor and a matched normal (healthy tissue of same patient) sample. Alternatively, the matched normal sample may also be replaced in the analysis by a reference sample (typically representative of healthy tissue). Moreover, the matched normal or reference sample may be from the same tissue type as the tumor or from blood or other non-tumor tissue.

[0019] Computational analysis of the sequence data may be performed in numerous manners. In most preferred methods, however, analysis is performed *in silico* by location-guided synchronous alignment of tumor and normal samples as, for example, disclosed in US 2012/0059670 and US 2012/0066001 using BAM files and BAM servers. Of course, alternative file formats (*e.g.*, SAM, GAR, FASTA, etc.) are also expressly contemplated herein. Regardless of the manner of analysis, contemplated DNA omics data will preferably include information about copy number, patient- and tumor specific mutations, and genomic rearrangements, including translocations, inversions, amplifications, fusion with other genes, extrachromosomal arrangement (*e.g.*, double minute chromosome), etc.

[0020] Likewise, RNA sequencing and/or quantification can be performed in all manners known in the art and may use various forms of RNA. For example, preferred materials include mRNA and primary transcripts (hnRNA), and RNA sequence information may be obtained from reverse transcribed polyA$^+$-RNA, which in turn obtained from a tumor sample and a matched normal (healthy) sample of the same patient. Likewise, it should be noted that while polyA$^+$-RNA is typically preferred as a representation of the transcriptome, other forms of RNA (hn-RNA, non-polyadenylated RNA, siRNA, miRNA, etc.) are also deemed suitable for use herein. Preferred methods also include quantitative RNA (hnRNA or mRNA) analysis and/or quantitative proteomics analysis. Most typically, RNA quantification and sequencing

is performed using qPCR and/or rtPCR based methods, although other methods (*e.g.*, solid phase hybridization-based methods) are also deemed suitable. Therefore, and viewed from another perspective, transcriptomic analysis may be suitable (alone or in combination with genomic analysis) not only for quantification of transcripts, but also to identify and quantify genes that have tumor- and patient specific mutations.

[0021] Similarly, proteomics analysis can be performed in numerous manners, and all known manners or proteomics analysis are contemplated herein. However, particularly preferred proteomics methods include antibody-based methods and mass spectroscopic methods. Moreover, it should be noted that the proteomics analysis may not only provide qualitative or quantitative information about the protein *per se*, but may also include protein activity data where the protein has catalytic or other functional activity. One example of technique for conducting proteomic assays includes U.S. patent 7,473,532 to Darfler et al. titled "Liquid Tissue Preparation from Histopathologically Processed Biological Samples, Tissues, and Cells" filed on March 10, 2004. Still other proteomics analyses include mass spectroscopic assays, and especially MS analyses based on selective reaction monitoring.

[0022] The so obtained omics data are then further processed to obtain pathway activity and other pathway relevant information using various systems and methods known in the art. However, particularly preferred systems and methods include those in which the pathway data are processed using probabilistic graphical models as described in WO 2011/139345 and WO 2013/062505, or other pathway models such as those described in WO 2017/033154, all incorporated by reference herein. Thus, it should be appreciated that pathway analysis for a patient may be performed from a single patient sample and matched control (once before treatment, or repeatedly, during and/or after treatment), which will significantly improve and refine analytic data as compared to single omics analysis that is compared against an external reference standard. In addition, the same analytic methods may further be refined with patient specific history data (*e.g.*, prior omics data, current or past pharmaceutical treatment, etc.).

[0023] Once pathway activity from the omics data of the tumor sample has been calculated, differentially activated pathways and pathway elements (*e.g.*, relative to 'normal or patient-specific normal) in the output of the pathway analysis are then analyzed against a signature that is characteristic for an immune suppressed tumor. Most typically, such signature has the features and pathways that are associated with an up-regulated FOXM1 signaling pathway,

with the presence and/or inhibition of tumor infiltrating lymphocytes, with a low (as compared to healthy tissue) Th1/Th2 ratio, and with a basal-like character.

[0024] In one exemplary aspect, and as is discussed in more detail below, the signature of an immune suppressed tumor is based on the most significant portion (*e.g.*, top 500 features, top 200 features, top 100 features) of pathway features from patient groups clusters identified in a machine learning environment. For example, pathway analysis was performed for breast cancer patients in which one group (MicMa) had good outcome as evidenced by overall survival while another group (Chin/Naderi) had poor outcome as evidenced by overall survival. Here, pathway analysis allowed for definition of five different clusters in which the clusters were characterized as follows: PDGM1 = high FOXM1, high Th1/Th2 ratio, basal/ERBB2; PDGM2 = high FOXM1, low Th1/Th2 ratio, basal; PDGM3 = high FOXM1, innate immune genes, macrophage dominated, luminal; PDGM4 = high ERBB4, low angiopoietin signaling, luminal; and PDGM5 = low FOXM1, low macrophage signature, luminal A.

[0025] Of course, it should be appreciated that numerous other groupings and clusters can be used to differentiate likely treatment outcomes. For example, suitable clusters may be based on specific tumor types, patient sub-populations, and may be larger or smaller. Moreover, it should be noted that contemplated systems and methods may also be based on or include specific neoepitopes and/or T cell receptors with specificity to one more tumor related epitopes (*e.g.*, neoepitopes or cancer associated epitopes). In such case, expression of a specific neoepitope (especially a HLA-matched neoepitope) may be used as a proxy marker for immunogenicity. On the other hand, expression and/or quantity of a T cell receptor that binds a specific epitope may be used as a marker for immunogenicity. Similarly, it is noted that the distribution (*e.g.*, between tumor and circulating blood) of T cell receptors specific to a neoepitope may be used as an indicator for immunogenicity. Likewise, expression of the patient's MHC-I may be ascertained and quantified to obtain a further measure of immunogenicity. In this context, it should be appreciated that this information can be readily obtained from the omics data and that omics analysis will advantageously eliminate the need for ex vivo immune staining protocols.

[0026] Regardless of the particular clustering or grouping employed, it is contemplated that the differential pathway activities of the patient are identified and compared against the signature that is indicative of an immune suppressed tumor (comprises features and pathway

activities associated with an up-regulated FOXM1 signaling pathway, with the presence and/or inhibition of tumor infiltrating lymphocytes, with a low Th1/Th2 ratio, and with a basal-like character). Such comparison may include a comparison of one or more selected features that are representative of specific pathways (*e.g.*, identification of expression level of selected genes encoding proteins that are part of a specific signaling pathway) or may include a comparison of a set of features, where a degree of similarity is identified (*e.g.*, at least 50%, 60%, 70%, or 80% of overexpressed genes in tumor are also overexpressed in feature set of the signature. Upon determination that the patient data match or are consistent with the signature that is characteristic for immune suppression, treatment with a checkpoint may be advised (*e.g.*, by generating or updating a patient record with an indication that checkpoint inhibition may be effective).

Examples

[0027] Identification of breast cancer related pathways was performed using data sets from patient populations with known history. MicMa patients with breast cancer (n = 101) in this study were part of a cohort of patients treated for localized breast cancer from 1995 to 1998. Samples from the UPPSALA cohort, collected at the Fresh Tissue Biobank, Department of Pathology, Uppsala University Hospital, were selected from a population-based cohort of 854 women diagnosed between 1986 and 2004 with one of three types of primary breast cancer lesions: (a) pure DCIS, (b) pure invasive breast cancer 15 mm or less in diameter, or (c) mixed lesions (invasive carcinoma with an in situ component). The Mammographic Density and Genetics cohort, including 120 healthy women with no malignant disease but some visible density on mammograms, referred to here as healthy women, was included in this study. Two breast biopsies and three blood samples were collected from each woman. The Chin validation set consisted of 113 tumor samples with both expression (GEO accession no. GSE6757) and CGH data (MIAMEExpress accession E-Ucon-1). The UNC validation dataset consisted of 78 tumor samples with both expression (44 K; Agilent Technologies) and SNP-CGH (109 K; Illumina).

[0028] Data preprocessing and PARADIGM parameters were as follows: Copy number was segmented using circular binary segmentation (CBS) and then mapped to gene-level measurements by taking the median of all segments that span a RefSeq gene's coordinates in hg18. For mRNA expression, measurements were first probe-normalized by subtracting the median expression value for each probe. The manufacturer's genomic location for each probe

was converted from hg17 to hg18 using University of California, Santa Cruz liftOver tool. Per-gene measurements were then obtained by taking the median value of all probes overlapping a RefSeq gene. Methylation probes were matched to genes using the manufacturer's description. PARADIGM was run as it previously described (*Bioinformatics* 26:i237ei245), by quantile-transforming each dataset separately, but data were discretized into bins of equal size rather than at the 5% and 95% quantiles. Pathway files were from the Pathway Interaction Database (*Nucleic Acids Res* 37: D674eD679) as previously parsed.

[0029] HOPACH unsupervised clustering: Clusters were derived using the HOPACH R implementation version 2.10 (*J Stat Planning Inference* 117:275e303) running on R version 2.12. The correlation distance metric was used with all data types, except for PARADIGM IPLs, which used cosangle because of the nonnormal distribution and prevalence of zero values. For any cluster of samples that contained fewer than five samples, each sample was mapped to the same cluster as the most similar sample in a larger cluster. PARADIGM clusters in the MicMa dataset were mapped to other data types by determining each cluster's mediod (using the median function) in the MicMa dataset and then assigning each sample in another dataset to whichever cluster mediod was closest by cosangle distance. The copy number was clustered on gene-level values rather than by probe. The values that went into the clustering are from the CBS segmentation of each sample. A single value was then generated for each gene by taking the median of all segments that overlap the gene. The samples were then clustered using these gene-level copy number estimates with an uncentered correlation metric in HOPACH. For display, the genes and samples were median-centered.

[0030] Notably, unsupervised clustering in the pathway analysis lead to a sub-typing into distinct clusters with differential survivals, and the inventors unexpectedly discovered that the genes that strongly associated with each cluster defining the subtypes were largely immune-based. Notably, genes associated with good outcome as evidenced by overall survival were found to coincide with Th1 cells and Th1 signaling, cytotoxic T cells, and natural killer cells as can be seen from **Figure 1**. Moreover, genes associated with poor outcome were found to coincide with immune suppression, Th2 cells, Th2 signaling, and humoral immunity. As can be seen from panel A of Figure 1, five distinct clusters with different sizes were identified. These clusters were defined by distinct characteristics: PDGM1 had high FOXM1, high Th1/Th2 ratio, basal/ERBB2 character; PDGM2 had high FOXM1, low Th1/Th2 ratio, and basal character; PDGM3 had high FOXM1, innate immune genes, macrophage dominated

and luminal character; PDGM4 had high ERBB4, low angiopoietin signaling, and luminal character; and PDGM5 had low FOXM1, low macrophage signature, and luminal A character. Panel B of Figure 1, illustrates the corresponding Kaplan-Meier curves. As is readily evident, best survival outcome was associated with an immunogenic and Th1-biased character (PARADIGM3), while the worst survival outcome was associated with a non-immunogenic and Th2-biased character. Notably, PARADIGM2 exhibited a pathway activity signature that reflected an immune suppressed tumor. Consequently, where omics data and corresponding pathway activities are consistent with PARADIGM2 cluster, the inventors contemplate that tumors treated with checkpoint inhibitors will be responsive to such treatment and become more immunogenic.

[0031] The most significantly differentially expressed pathways and genes that comprise the PARADIGM2 cluster are summarized in the tables below. More specifically, the tables below list exemplary immune related features within the top 500 features in the cluster that was associated with high FOXM1, low Th1/Th2 ratio, and basal character, for both good and poor outcome groups. **Table 1** lists pathway entities (individual proteins or complexes) that are located in immune related pathways and that are differentially regulated relative to healthy tissue. These entities were from a subgroup of negative outcome patients.

Table 1

Chin Immune-related PathwayEntity	Function	Rank
	Anti-tumor Immunity (NK cell, CTL, M1 macrophage function)	
51_T-helper 1 cell differentiation	anti-tumor immunity	39
9_IL12B	important for Th1 differentiation	125
10_IL12B	important for Th1 differentiation	138
86_IL12B	important for Th1 differentiation	170
86_IL27RA	synergizes strongly with IL12 to trigger IFNg production of naive CD4 T cells	352
110_T-helper 1 cell lineage commitment	anti-tumor immunity	388
17_STAT1	anti-tumor immunity	392
86_IL27RA/JAK1	synergizes strongly with IL12 to trigger IFNg production of naive CD4 T cells	431
86_STAT4 (dimer)	regulates IL12 responses (impt for Th1 diff) and mediating Th differentiation	471
	Pan T Cell Function	
51_CCL17	chemotactic for T cells	23
51_THY1	T cell surface antigen	43
51_T cell proliferation	T cell proliferation	55
57_alpha4/beta7 Integrin	Lymphocyte Peyer patch adhesion molecule - T cell homing	121
11_alpha4/beta7 Integrin	Lymphocyte Peyer patch adhesion molecule - T cell homing	122
124_alpha4/beta7 Integrin	Lymphocyte Peyer patch adhesion molecule - T cell homing	123
84_LCK	T cell specific kinase	317
57_alpha4/beta7 Integrin/Paxillin	Lymphocyte Peyer patch adhesion molecule - T cell homing	333
	Pro-inflammatory signaling/Innate Immunity	
51_mast cell activation	mast cell activation	2

41_RIP2/NOD2	pro-inflammatory	29
51_CCL26	chemotactic for eosinphils and basophils	35
51_CCL11	chemotactic for eosinophils	42
41_NEMO/A20/RIP2	pro-inflammatory	44
41_RIPK2	pro-inflammatory	45
117_RIPK2	pro-inflammatory	46
10_RIPK2	pro-inflammatory	47
4_CHUK	NFkB signaling	137
80_IL1 alpha/IL1R1/IL1RAP/MYD88/IRAK4	pro-inflammatory	308
80_IL1 alpha/IL1R1/IL1RAP/MYD88	pro-inflammatory	348
80_IL1 alpha/IL1R1/IL1RAP	pro-inflammatory	357
108_mol:NO	nitric oxide; pro-inflammatory	359
80_MYD88	pro-inflammatory	394
80_IRAK3	pro-inflammatory	439
80_IL1 alpha/IL1R1/IL1RAP/MYD88/IRAK4/TOLLIP	pro-inflammatory	463
80_IL1A	pro-inflammatory	498
	B cell/Humoral Immunity	
51_IL4	humoral immunity/B cell differentiation	1
51_IL13RA1	produced by activated Th2 cells; humoral immunity	3
32_EDN2	B cell/humoral immunity	4
51_IL4/IL4R/JAK1/IL13RA1/JAK2	produced by activated Th2 cells; humoral immunity	19
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/IRS1	produced by activated Th2 cells; humoral immunity	20
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHIP	produced by activated Th2 cells; humoral immunity	21
51_T-helper 2 cell differentiation	Th2 response	22
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHC/SHIP	produced by activated Th2 cells; humoral immunity	24
51_PIGR	polymeric immunoglobulin receptor	31
51_IL13RA2	produced by activated Th2 cells; humoral immunity	34
51_IL4R	humoral immunity/B cell differentiation	36
51_IL5	differentiation factor for B cells and eosinophils	38
51_IGHG3	IgG3 heavy chain	40
51_STAT6 (dimer)/ETS1	activated by IL4; Th2 differentiation	50
51_STAT6 (dimer)	activated by IL4; Th2 differentiation	51
51_STAT6	activated by IL4; Th2 differentiation	53
51_IL4R/JAK1	humoral immunity/B cell differentiation	57
51_STAT6 (dimer)/PARP14	activated by IL4; Th2 differentiation	58
51_IL4/IL4R/JAK1/IL2R gamma/JAK3	humoral immunity/B cell differentiation	62
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/FES/IRS2	humoral immunity/B cell differentiation	63
51_IL4/IL4R/JAK1	humoral immunity/B cell differentiation	64
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/DOK2	humoral immunity/B cell differentiation	68
51_IGHG1	IgG1 heavy chain	74
51_STAT6 (cleaved dimer)	activated by IL4; Th2 differentiation	75
51_FCER2	Fc fragment of IgE receptor	79
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHC/SHIP/GRB2	humoral immunity/B cell differentiation	101
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/FES	humoral immunity/B cell differentiation	124
22_B-cell antigen/BCR complex/LYN	B cell signaling	209
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHP1	humoral immunity/B cell differentiation	285
65_BLK	B cell tyrosine kinase	307
22_CD72/SHP1	B cell marker	347
43_Fc epsilon R1/FcgammaRIIB/SHIP/RasGAP/p62DOK	B cell signaling	376
51_IL13RA1/JAK2	produced by activated Th2 cells; humoral immunity	436
51_IGHE	heavy chain of IgE	71
51_BCL6	regulates IL4 signaling in B cells	494

	Immunosuppression	
51_IL10	immunosuppressive cytokine	30
	Macrophage Function	
110_CSF2	Macrophage differentiation	355
39_CSF2	Macrophage differentiation	469
	Pan Immune Cell Function	
51_LTA	cytokine produced by lymphocytes	16
51_SELP	role in platelet activation	33
22_DAPP1	adaptor protein that functions within the immune system	131
50_LEF1	lympoid enhancer	327
112_MEF2C/TIF2	myocyte enhancer	328
25_Syndecan-1/RANTES	chemotactic for macrophages and T cells	386
22_PTPN6	protein tyrosine phosphatase expressed within the hematopoeitic lineage	395
116_INPP5D	SHIP; hematopoetic specific (negatively regulates immune function)	434
20_VAV3	GEF expressed in lymphoid cells	454
86_STAT5A (dimer)	induced by many cytokines; pro-tumorigenic properties	472

[0032] Table 2 lists pathway entities (individual proteins or complexes) that are located in non-immune related pathways and that are differentially regulated relative to healthy tissue these entities are from a subgroup of positive outcome patients. These entities were from a subgroup of negative outcome patients.

Table 2

Chin non-immune		Rank
	Cytoskeletal (actin/microtulule)	
29_KIF13B	kinesin - microtubule dynamics	398
73_SNTA1	found in muscle fibers - microtubule dynamics	497
37_ROCK2	regulates actin cytoskeleton	168
100_ROCK2	regulates actin cytoskeleton	273
108_PXN	regulates actin cytoskeleton	274
103_nectin-3/I-afadin	regulates actin cytoskeleton	275
103_nectin-3(dimer)/I-afadin/I-afadin	regulates actin cytoskeleton	276
124_PXN	regulates actin cytoskeleton	430
	14-3-3 signaling	
4_BAD/YWHAZ	14-3-3 signaling	220
4_YWHAZ	14-3-3 zeta	10
95_YWHAZ	14-3-3 zeta	11
33_YWHAZ	14-3-3 zeta	12
46_YWHAZ	14-3-3 zeta	13
92_YWHAZ	14-3-3 zeta	14
	Mitogenic response	
28_MAP2K2	activates the ERK pathway	277
22_MAP2K1	activates the ERK pathway	380
28_MAPK1	AKA: ERK1	401
7_MAPK8	AKA: ERK2	231
51_MAPKKK cascade	MAPK signaling	135
108_MAPKKK cascade	MAPK signaling	346
4_MAPKKK cascade	MAPK signaling	452
22_RAF1	MAPK signaling	126

	stress response	
108_mol:Phosphatidic acid	p38 MAPK family member	133
95_MAP3K8	activates ERK and JNK pathways	219
96_MAP3K8	activates ERK and JNK pathways	225
42_MAP3K8	activates ERK and JNK pathways	228
53_MAP3K8	activates ERK and JNK pathways	229
93_MAP2K4	activates JNK signaling	349
62_MAP2K4	activates JNK signaling	409
27_MAP2K4	activates JNK signaling	470
106_MAP2K4	activates JNK signaling	490
7_JNK cascade	stress response	269
4_JNK cascade	stress response	341
106_MAPK8	AKA: JNK1	423
108_MAPK8	AKA: JNK1	483
51_MAPK14	MAPK: role in stress response and cell cycle	105
78_MAPK8	JNK signaling	204
51_FRAP1	AKA: JNK1	100
36_ADCY3	**cAMP signaling**	397
51_BCL2L1	adenylate cyclase	41
51_SOCS1	regulates PKA signaling	15
74_mol:cAMP	cAMP signaling	448
	apoptosis	
77_BIRC5	Bcl2 - apoptosis	473
26_BIRC5	anti-apoptotic	118
114_BIRC5	anti-apoptotic	267
108_negative regulation of caspase activity	anti-apoptotic	404
4_BAD/BCL-XL/YWHAZ	anti-apoptotic	172
129_neuron apoptosis	apoptosis	306
70_apoptosis	apoptosis	493
51_ALOX15	apoptosis	6
28_CRADD	pro-apoptotic	466
4_CASP9	initiatiator caspase - apoptosis	54
130_TRAIL/TRAILR1/DAP3/GTP	death receptor	272
130_TRAIL/TRAILR1	death receptor	56
22_MAPK3	AKA: anti-apoptotic Bcl2 family member	406
	angiogenesis	
108_NOS3	eNOS: angiogenesis	447
108_Tie2/Ang1/GRB14	angiogenesis	302
108_Tie2/Ang1/ABIN2	angiogenesis	303
108_Tie2/Ang1/Shc	angiogenesis	321
108_Tie2/SHP2	angiogenesis	323
108_vasculogenesis	angiogenesis	334
108_Tie2/Ang1/alpha5/beta1 Integrin	angiogenesis	345
23_angiogenesis	angiogenesis	403
108_Tie2/Ang1	angiogenesis	476
2_VEGFC	angiogenesis	115
108_response to hypoxia	hypoxic response	453
	calcium/calmodulin signaling	
72_mol:Ca2+	calcium/calmodulin signaling	294
95_CABIN1/MEF2D/CaM/Ca2+/CAMK IV	calcium/calmodulin signaling	332
95_CABIN1/YWHAQ/CaM/Ca2+/CAMK IV	calcium/calmodulin signaling	283
117_PRKACB	cAMP dependent protein kinase	103
	Cell cycle	
15_PLK2	cell cycle	337

15_PLK2	cell cycle	309
40_MNAT1	cell cycle	304
114_CDK4	cell cycle/G1-S	130
112_CDK4	cell cycle/G1-S	316
110_E2F1	cell cycle/G1-S	495
110_CDK4	cell cycle/G1-S	73
100_CDC2	cell cycle/mitosis	87
100_CCNB1	cell cycle/mitosis	95
51_mitosis	cell cycle/mitosis	111
90_INCENP	cell cycle/mitosis	112
100_INCENP	cell cycle/mitosis	113
77_INCENP	cell cycle/mitosis	195
77_mitotic metaphase/anaphase transition	cell cycle/mitosis	197
120_NDEL1	cell cycle/mitosis	208
47_regulation of S phase of mitotic cell cycle	cell cycle/mitosis	354
77_CDCA8	cell cycle/mitosis	393
100_SPC24	cell cycle/mitosis	396
26_NDEL1	cell cycle/mitosis	419
15_regulation of centriole replication	cell cycle/mitosis	456
100_CCNB1/CDK1	cell cycle/mitosis	491
77_Chromosomal passenger complex	cell cycle/mitosis	479
74_positive regulation of cyclin-dependent protein kinase activity	cell cycle	261
123_TIMELESS/CRY2	cell cycle/S phase	440
77_EVI5	cell cycle; G1-S	27
	chromatin remodeling	
47_KAT2B	lysine acetyltransferase; histone modification	97
52_Histones	histone	207
47_HIST2H4A	histone	117
52_HDAC6/HDAC11	histone deacetylase	139
52_HDAC11	histone deacetylase	290
52_HDAC5/BCL6/BCoR	histone deacetylase	363
63_HDAC1/Smad7	histone deacetylase	364
66_HDAC2	histone deacetylase	405
50_HDAC1	histone deacetylase	425
52_HDAC5/RFXANK	histone deacetylase	402
52_positive regulation of chromatin silencing	chromatin remodeling	106
47_SIRT1/MEF2D/HDAC4	chromatin remodeling	184
61_SIRT1	chromatin remodeling	185
106_SIRT1	chromatin remodeling	192
47_SIRT1/p300	chromatin remodeling	193
47_KU70/SIRT1	chromatin remodeling	214
47_SIRT1	chromatin remodeling	442
106_NCOA1	chromatin remodeling	165
	ECM	
23_FN1	fibronectin - ECM	292
25_LAMA5	laminin 5 - ECM	420
64_LAMA3	laminin 5 - ECM	421
78_LAMA3	laminin 5 - ECM	377
51_COL1A1	collagen 1 A1 - ECM	66
51_COL1A2	collagen 1 A2 - ECM	362
112_COL1A2	collagen 1 A2 - ECM	218
	DNA damage response	
100_BUB1	DNA damage response	173
13_PRKDC	DNA damage response	196

77_BUB1	DNA damage response	202
49_RAD50	DNA damage response	203
30_RAD50	DNA damage response	210
4_PRKDC	DNA damage response	211
49_PRKDC	DNA damage response	230
20_PRKDC	DNA damage response	300
40_TFIIH	DNA damage response	305
49_DNA-PK	DNA damage response	311
49_BARD1/DNA-PK	DNA damage response	319
20_DNA-PK	DNA damage response	329
49_FANCE	DNA damage response	338
49_FANCA	DNA damage response	435
30_ATM	DNA damage response	437
30_DNA damage response signal transduction by p53 class mediator resulting in induction of apoptosis	DNA damage response	413
	PLC Signaling	
79_PLCB1	phospholipase C b1	142
108_PLD2	phospholipase D2	186
72_PLCG1	phospholipase G1	120
	PKC signaling	
95_PRKCH	protein kinase C-eta (epithelial specifc)	94
78_GO:0007205	PKC signaling	157
72_mol:DAG	PKC signaling	158
72_mol:IP3	PKC signaling	291
43_calcium-dependent protein kinase C activity	PKC signaling	313
98_PTP4A2	**RTK signaling**	
124_PTK2	FAK family member	25
108_PTK2	FAK family member	312
104_FRS3	FGFR substrate	465
	RTK signaling	299
81_EPHA5	RTK signaling	119
108_TEK	RTK signaling	160
19_Ephrin B1/EPHB3	protein tyrosine phosphatase	164
77_RACGAP1	RTK signaling	287
104_SHC/RasGAP	RTK signaling	174
19_EPHB3	RTK signaling	175
117_proNGF (dimer)/p75(NTR)/Sortilin/MAGE-G1	RTK signaling	177
65_GPC1/NRG	RTK signaling	178
108_Crk/Dok-R	RTK signaling	189
65_NRG1	RTK signaling	190
87_NRG1	RTK signaling	200
7_RET51/GFRalpha1/GDNF/DOK/RasGAP/NCK	RTK signaling	213
94_SOS1	RTK signaling	217
72_EGFR/PI3K-beta/Gab1	RTK signaling	226
17_NRG1	RTK signaling	288
91_PDGFB-D/PDGFRB/APS/CBL	RTK signaling	367
7_RET9/GFRalpha1/GDNF/SHC	RTK signaling	368
7_RET51/GFRalpha1/GDNF/SHC	RTK signaling	369
7_RET9/GFRalpha1/GDNF/Shank3	RTK signaling	370
7_RET51/GFRalpha1/GDNF/FRS2	RTK signaling	371
7_RET9/GFRalpha1/GDNF/FRS2	RTK signaling	372
7_RET51/GFRalpha1/GDNF/GRB10	RTK signaling	373
7_RET9/GFRalpha1/GDNF/IRS1	RTK signaling	374
7_RET51/GFRalpha1/GDNF/DOK1	RTK signaling	375
7_RET51/GFRalpha1/GDNF/IRS1	RTK signaling	381

19_Ephrin B/EPHB2/RasGAP	RTK signaling	389
7_RET9/GFRalpha1/GDNF	RTK signaling	422
116_LYN/PLCgamma2	RTK signaling	426
17_ErbB4/ErbB4/neuregulin 1 beta/neuregulin 1 beta/Fyn	RTK signaling	427
17_ErbB4/EGFR/neuregulin 1 beta	RTK signaling	438
17_ErbB4 CYT2/ErbB4 CYT2/neuregulin 1 beta/neuregulin 1 beta	tyrosine kinase	26
30_ABL1	tyrosine kinase	49
84_FER	tyrosine kinase	485
108_BMX	tyrosine phosphorylation of Cbl	296
88_SORBS1	RTK signaling	492
13_MET	adaptor protein	61
72_GAB1	adaptor protein	156
7_GRB10	adaptor protein	314
108_NCK1/Dok-R	Src family kinase	280
84_FYN	Src family kinase	298
43_FYN	Src family member	310
65_HCK	**ser/thr phosphatase**	128
22_PPP3CC	ser/thr phosphatase	199
25_PPIB	ser/thr phosphatase	353
100_PPP2R1A	ser/thr phosphatase	412
100_PP2A-alpha B56	ser/thr phosphatase	
51_mol:PI-3-4-5-P3	**PI3K/AKT signaling**	99
51_AKT1	signaling/pro-survival	102
51_PI3K	signaling/pro-survival	109
4_TSC1	downstream negative regulator of AKT	69
74_PIK3R1	signaling/pro-survival	205
55_PIK3R1	signaling/pro-survival	212
108_PIK3R1	signaling/pro-survival	215
9_PIK3R1	signaling/pro-survival	221
38_PIK3R1	signaling/pro-survival	223
72_PIK3R1	signaling/pro-survival	227
43_PIK3R1	signaling/pro-survival	232
103_PIK3R1	signaling/pro-survival	233
2_PIK3R1	signaling/pro-survival	234
23_PIK3R1	signaling/pro-survival	235
88_PIK3R1	signaling/pro-survival	236
101_PIK3R1	signaling/pro-survival	237
104_PIK3R1	signaling/pro-survival	238
79_PIK3R1	signaling/pro-survival	239
51_PIK3R1	signaling/pro-survival	240
109_PIK3R1	signaling/pro-survival	241
117_PIK3R1	signaling/pro-survival	242
124_PIK3R1	signaling/pro-survival	243
7_PIK3R1	signaling/pro-survival	244
113_PIK3R1	signaling/pro-survival	245
69_PIK3R1	signaling/pro-survival	246
116_PIK3R1	signaling/pro-survival	247
119_PIK3R1	signaling/pro-survival	248
131_PIK3R1	signaling/pro-survival	249
80_PIK3R1	signaling/pro-survival	250
91_PIK3R1	signaling/pro-survival	251
135_PIK3R1	signaling/pro-survival	252
68_PIK3R1	signaling/pro-survival	253

84_PIK3R1	signaling/pro-survival	254
46_PIK3R1	signaling/pro-survival	255
3_PIK3R1	signaling/pro-survival	256
57_PIK3R1	signaling/pro-survival	257
19_PIK3R1	signaling/pro-survival	258
45_PIK3R1	signaling/pro-survival	259
22_PIK3R1	signaling/pro-survival	260
70_PIK3R1	signaling/pro-survival	262
94_PIK3R1	signaling/pro-survival	263
93_PIK3R1	signaling/pro-survival	266
122_PIK3R1	signaling/pro-survival	268
72_mol:PIP3	signaling/pro-survival	279
4_AKT1	signaling/pro-survival	330
4_AKT1/RAF1	signaling/pro-survival	335
4_AKT1/ASK1	signaling/pro-survival	339
108_AKT1	signaling/pro-survival	445
108_PI3K	signaling/pro-survival	475
51_RPS6KB1	signaling/pro-survival	141
4_mTOR/RHEB/GDP/Raptor/GBL/PRAS40	ribosomal protein S6 kinase - signaling	384
74_SMPD1	signaling/translational control	270
4_AKT1S1	AKA: mTOR - signaling	366
44_NDRG1	AKT substrate	342
	sphingosine 1 phosphate	
83_S1P/S1P3/Gq	sphingomyelinase; generates ceramide	159
112_SP1	sphingosine 1 phosphate	224
1_S1P/S1P5/G12	sphingosine 1 phosphate	338
1_mol:S1P	sphingosine 1 phosphate	337
61_SP1	sphingosine 1 phosphate	265
1_S1P/S1P3/Gq	sphingosine 1 phosphate	315
51_SP1	sphingosine 1 phosphate	487
14_SP1	sphingosine 1 phosphate	488
44_SP1	sphingosine 1 phosphate	489
51_JAK1	sphingosine 1 phosphate	5
105_BAMBI	**TGFb signaling**	8
65_TGFBR1 (dimer)	TGFb signaling	104
105_BMP2-4/BMPR2/BMPR1A-1B/RGM/ENDOFIN/GADD34/PP1CA	TGFb signaling	162
65_GPC1/TGFB/TGFBR1/TGFBR2	TGFb signaling	180
23_TGFBR2	TGFb signaling	181
65_TGFBR2	TGFb signaling	182
65_TGFBR2 (dimer)	TGFb signaling	183
105_BMP2-4/BMPR2/BMPR1A-1B/RGM/XIAP	TGFb signaling	326
105_SMAD7/SMURF1	TGFb signaling	350
105_SMAD7	TGFb signaling	443
63_SMAD7	TGFb signaling	444
105_BMPR2 (homodimer)	TGFb signaling	474
	TGFb signaling	
56_JAM3	**cell adhesion**	410
78_positive regulation of cell-cell adhesion	cell adhesion	343
23_cell adhesion	cell adhesion	309
51_ITGB3	integrin beta 3	88
11_ITGB7	integrin beta 7	89
124_ITGB7	integrin beta 7	90
45_ITGB7	integrin beta 7	91
57_ITGB7	integrin beta 7	179

56_JAM3 homodimer	tight junctional protein	411
	tight junctional protein	
47_FOXO3	**Transcription factor**	7
47_FOXO1/FHL2/SIRT1	transcription factor	110
47_SIRT1/FOXO3a	transcription factor	116
123_NPAS2	transcription factor	166
106_JUN	transcription factor	222
7_JUN	transcription factor	271
126_MYC	transcription factor	318
108_FOXO1	transcription factor	356
50_MYC	transcription factor	379
92_FOXO3A/14-3-3	transcription factor	382
75_NFAT1/CK1 alpha	transcription factor	383
4_FOXO1-3a-4/14-3-3 family	transcription factor	408
4_FOXO1	transcription factor	415
4_FOXO3	transcription factor	416
4_FOXO4	transcription factor	417
113_AP1	transcription factor	432
30_MYC	transcription factor	449
50_HNF1A	transcription factor	486
20_PATZ1	transcription factor	499
51_EGR2	transcription factor	52
	transcription factor; regulates ErbB2 exspression	
72_GNA11	**G protein signaling**	78
33_mol:GTP	GTP function	281
16_mol:GDP	GTP function	295
72_mol:GTP	GTP function	322
24_Gi family/GNB1/GNG2/GDP	GTP function	309
4_mol:GDP	GTP function	481
63_mol:GTP	GTP function	28
79_GNB1/GNG2	G protein	385
97_Rac/GTP	G protein - cell motility	191
32_EntrezGene:2778	G protein signaling	428
58_GNB1	G regulatory protein function	496
24_GNB1	G regulatory protein function	451
29_CENTA1/KIF3B	ARF protein - trafficking	216
1_ABCC1	ARF-GAP	458
14_NF1	negatively regulates Ras pathway	477
78_NF1	negatively regulates Ras pathway	478
135_NF1	negatively regulates Ras pathway	92
116_RAPGEF1	Rac GAP protein	188
7_HRAS/GTP	RAP GEF	441
5_RAN	Ras family member	324
63_RAN	Ras family member/nucleocytoplasmic transport	351
97_ARF1/GTP	Ras family member/nucleocytoplasmic transport	169
108_RasGAP/Dok-R	Ras family member/protein trafficking	127
43_RasGAP/p62DOK	Ras signaling	390
108_RASA1	RasGAP	143
19_RASA1	Ras-GAP	144
109_RASA1	Ras-GAP	145
78_RASA1	Ras-GAP	146
43_RASA1	Ras-GAP	147
77_RASA1	Ras-GAP	148
88_RASA1	Ras-GAP	149

7_RASA1	Ras-GAP	150
26_RASA1	Ras-GAP	151
104_RASA1	Ras-GAP	152
22_RASA1	Ras-GAP	153
92_SOD2	Ras-GAP	457
29_GNA11	trimeric G protein	82
1_GNA11	trimeric G protein	83
83_GNA11	trimeric G protein	84
58_GNA11	trimeric G protein	85
79_GNA11	trimeric G protein	86
32_GNA11	trimeric G protein	93
58_Gq family/GTP	trimeric G protein	114
79_Gq family/GTP	trimeric G protein	140
58_Gq family/GTP/EBP50	trimeric G protein	194
79_Gq family/GDP/Gbeta gamma	trimeric G protein	278
1_GNA12	trimeric G protein	336
89_GNAT1	trimeric G protein	407
19_PAK1	trimeric G protein	198
88_TC10/GDP	Rho effector kinase	167
103_CDC42	Rho family member; cell motility	289
33_RHOQ	Rho family member; cell motility	467
59_ARHGEF6	Rho family member; cell motility	399
19_KALRN	Rho GEF	365
	Rho GEF kinase	
	Ubiquitination	284
77_Chromosomal passenger complex/Cul3 protein complex	ubiquitinitation	361
63_ubiquitin-dependent protein catabolic process	ubiquitinitation	107
133_MDM2	ubiquitinitation of p53	59
51_CBL	ubiquitinitation of RTKs	
	metabolism	
47_ACSS2	acyl CoA synthetase	206
52_NPC	cholesterol trafficking	134
44_PFKFB3	glucose metabolism	378
47_SIRT1/PGC1A	metabolism	358
108_mol:NADP	metabolism	360
108_mol:L-citrulline	metabolism	446
123_mol:NADPH	metabolism	297
	Other	482
51_AICDA	activation-induced cytidine deaminase	81
	alpha/beta hydrolase	301
129_APP	amyloid beta precursor protein	461
117_APP	amyloid beta precursor protein	462
65_APP	amyloid beta precursor protein	98
125_ARF1	arachidonate 15-lipoxygenase	418
82_ABCC1	ATP transporter; multi drug resistance	460
4_BAD/BCL-XL	ATP transporter; multi drug resistance	424
127_mol:Bile acids	bile acid	201
56_PLAT	blood coagulation	387
88_F2RL2	blood coagulation	484
108_PLG	blood coagulation	136
37_bone resorption	bone remodeling	163
123_mol:CO	carbon monoxide	154
86_JAK1	stat signaling	310
92_GADD45A	cell cycle arrest and apoptosis (p53 inducible)	80

51_JAK2	stat signaling	336
109_cell morphogenesis	cell shape	155
78_Syndecan-2/Syntenin/PI-4-5-P2	cell surface proteoglycan	108
108_mol:Choline	choline	72
123_CLOCK	circadian rythym	67
5_EntrezGene:9972	component of the nuclear pore complex	282
5_EntrezGene:23636	component of the nuclear pore complex	161
44_EDN1	endothelin 1 - vasoconstriction	400
123_mol:HEME	erythropoeisis	450
79_ESR1	estrogen signaling	96
131_GRIN2B	glutamate receptor	459
17_GRIN2B	glutamate receptor	264
89_GUCA1A	guanylate cyclase	433
20_PIAS3	inhibits Stat signaling	414
24_IFT88	intraflagellar transport	331
20_FHL2	LIM domain containing protein	325
23_MFGE8	milk fat globule-EGF factor 8 protein	500
20_HNRNPA1	mRNA processing	76
47_muscle cell differentiation	muscle cell differentiation	77
47_SIRT1/PCAF/MYOD	muscle cell differentiation	429
105_RGMB	neuronal function	132
19_neuron projection morphogenesis	neuronal function	176
65_neuron differentiation	neuronal function	391
7_GFRalpha1/GDNF	neurotrophic receptor	32
51_OPRM1	opioid receptor	171
85_hyperosmotic response	osmosis	455
79_MAPK11	phosphatidic acid	187
89_PDE6G/GNAT1/GTP	phosphodiesterase	344
84_Prolactin Receptor/Prolactin	pregnancy hormone	340
17_Prolactin receptor/Prolactin receptor/Prolactin	pregnancy hormone	464
78_TRAPPC4	protein trafficking	37
27_MAP3K12	reactive oxygen species	480
51_SOCS3	regulates Stat signaling	70
51_SOCS5	regulates Stat signaling	129
51_RETNLB	regulates Stat signaling	60
40_CRBP1/9-cic-RA	resistin like beta	9
40_RBP1	retinol binding protein	17
51_TFF3	secreted protein normally found in the GI mucosa	65
68_DHH N/PTCH1	sonic hedgehog receptor	
74_EIF3A	translation	468
78_Syndecan-2/CASK/Protein 4.1	transmembrane proteoglycan	48
66_VIPR1	vasoconstriction	293
32_ETB receptor/Endothelin-3	vasoconstriction	320
45_E-cadherin/Ca2+/beta catenin/alpha catenin	Wnt signaling	18

[0033] **Table 3** lists pathway entities (individual proteins or complexes) that are located in immune related pathways and that are differentially regulated relative to healthy tissue. These entities were from a subgroup of positive outcome patients.

Table 3

MicMa Immune-Related PathwayEntity	Function	Rank
	Anti-tumor Immunity (NK cell, CTL, M1 macrophage function)	
86_IL12B	important for Th1 differentiation	18
51_T-helper 1 cell differentiation	important for Th1 differentiation	35
9_IL12B	important for Th1 differentiation	55
10_IL12B	important for Th1 differentiation	144
86_IFNG	anti-tumor immunity	145
77_PSMA3	immunoproteasome	203
39_IFNG	anti-tumor immunity	403
	Pan T Cell Function	
51_T cell proliferation	T cell proliferation	6
51_THY1	T cell surface antigen	9
51_CCL17	chemotactic for T cells	70
95_PRKCQ	PKC theta - important for T cell activation	178
110_PRKCQ	PKC theta - important for T cell activation	179
114_NFATC3	nuclear factor of activated T cells	210
42_EntrezGene:6957	TCR beta	385
39_NFATC2	nuclear factor of activated T cells	458
	Pro-inflammatory signaling/Innate Immunity	
51_CCL11	chemotactic for eosinophils	12
51_CCL26	chemotactic for eosinphils and basophils	17
30_IFNAR2	IFN alpha/beta receptor - proinflammatory	25
80_SQSTM1	regulates NFkB activation - inflammatory	26
104_SQSTM1	regulates NFkB activation - inflammatory	27
117_SQSTM1	regulates NFkB activation - inflammatory	28
80_IRAK4	activates NFkB - inflammatory	37
12_NFKBIA	pro-inflammatory	59
28_NFKBIA	pro-inflammatory	120
118_NFKBIA	pro-inflammatory	121
93_IL6ST	pro-inflammatory	168
9_NFKBIA	pro-inflammatory	175
86_IL6ST	pro-inflammatory	206
85_MAP3K1	binds TRAF2; stimulates NFkB	231
95_MAP3K1	binds TRAF2; stimulates NFkB	232
115_MAP3K1	binds TRAF2; stimulates NFkB	233
30_IRF1	activates IFN alpha and beta transcription - inflammatory	343
70_IRF9	IFN alpha responsive gene - inflammatory	345
41_NFKBIA	pro-inflammatory	358
2_MAP3K13	binds TRAF2; stimulates NFkB	409
63_NFKBIA	pro-inflammatory	452
16_PTGS2	prostaglandin synthase - proinflammatory	487
30_IFN-gamma/IRF1	activates IFN alpha and beta transcription - inflammatory	488
	B cell/Humoral Immunity	
51_IL4	B cell/humoral immunity	1
51_IL5	differentiation factor for B cells (eosinophils)	3
51_STAT6 (cleaved dimer)	activated by IL4; Th2 differentiation	7
51_IGHG3	heavy chain of IgG3	8
51_IL4R	B cell/humoral immunity	10
51_IL13RA2	B cell/humoral immunity	11
51_STAT6 (dimer)/PARP14	activated by IL4; Th2 differentiation	13
51_IL4/IL4R/JAK1	B cell/humoral immunity	16
51_IL4R/JAK1	B cell/humoral immunity	44
51_PIGR	polymeric immunoglobulin receptor	96

51_IL13RA1	B cell/humoral immunity	100
110_T-helper 2 cell lineage commitment	B cell/humoral immunity	111
51_STAT6 (dimer)/ETS1	activated by IL4; Th2 differentiation	142
10_IL4	B cell/humoral immunity	155
22_PI3K/BCAP/CD19	B cell marker	165
51_T-helper 2 cell differentiation	B cell/humoral immunity	170
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/DOK2	B cell/humoral immunity	171
51_STAT6	activated by IL4; Th2 differentiation	176
51_STAT6 (dimer)	activated by IL4; Th2 differentiation	189
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHIP	B cell/humoral immunity	190
51_FCER2	Fc fragment of IgE receptor	194
51_IL4/IL4R/JAK1/IL13RA1/JAK2	B cell/humoral immunity	195
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHC/SHIP	B cell/humoral immunity	207
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/FES/IRS2	B cell/humoral immunity	230
51_IL4/IL4R/JAK1/IL2R gamma/JAK3	B cell/humoral immunity	236
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHC/SHIP/GRB2	B cell/humoral immunity	280
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/IRS1	B cell/humoral immunity	315
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/FES	B cell/humoral immunity	316
51_IL4/IL4R/JAK1/IL2R gamma/JAK3/SHP1	B cell/humoral immunity	319
112_IGHV3OR16-13	Ig variable chain	356
39_IL4	B cell/humoral immunity	386
51_IGHG1	IgG1 heavy chain	401
	Immunosuppression	
51_IL10	immunosuppressive cytokine	43
	Macrophage Function	
42_PRKCE	protein kinase C-epsilon-impt for LPS-mediated function in M1 macrophage	342
84_CSF1R	macrophage differentiation	445
51_ARG1	M2 macrophage marker	447
	Pan Immune Cell Function	
51_LTA	cytokine produced by lymphocytes	15
51_SELP	role in platelet activation	58
63_FKBP3	protein folding; immunoregulation	62
94_STAT5A (dimer)	induced by many cytokines; pro-tumorigenic properties	450
53_LCP2	lymphocyte specific adaptor protein	456
43_LCP2	lymphocyte specific adaptor protein	457
42_LCP2	lymphocyte specific adaptor protein	459
108_DOK2	adaptor protein expressed in hematopoeitic progenitors	492
51_DOK2	adaptor protein expressed in hematopoeitic progenitors	493
62_platelet activation	platelet function	243

[0034] **Table 4** lists pathway entities (individual proteins or complexes) that are located in non-immune related pathways and that are differentially regulated relative to healthy tissue these entities are from a subgroup of positive outcome patients. These entities were from a subgroup of positive outcome patients.

MicMa (non-immune)	Rank

	Cytoskeletal (actin/microtulule)	
45_actin cytoskeleton organization	actin dynamics	254
131_MAPT	AKA: Tau - microtubule associated protein	204
120_DYNC1H1	dynein - microtubule dynamics	331
24_KIF3A	kinesin; microtubule dynamics	123
77_KIF2C	kinesin; microtubule dynamics	159
100_KIF2A	kinesin; microtubule dynamics	369
100_positive regulation of microtubule depolymerization	microtubule dynamics	367
73_STMN1	microtubule dynamics	451
	Mitogenic signaling	
32_MAP2K1	activates ERK pathway	477
87_MAPK3	AKA: ERK1	443
40_MAPK1	AKA: ERK2	31
115_MAPK1	AKA: ERK2	32
126_MAPK1	AKA: ERK2	33
105_MAPK1	AKA: ERK2	34
66_MAPK1	AKA: ERK2	38
62_MAPK1	AKA: ERK2	182
98_MAPK1	AKA: ERK2	225
27_DUSP1	dual specificity phosphatase; suppresses MAPK	317
43_DUSP1	dual specificity phosphatase; suppresses MAPK	318
	Stress signaling	
19_MAP4K4	activates JNK pathway	467
2_MAP2K3	activates p38MAPK - stress signaling	413
95_MAPK14	MAPK: role in stress response and cell cycle	193
69_MAPK14	MAPK: role in stress response and cell cycle	200
40_MAPK14	MAPK: role in stress response and cell cycle	201
85_MAPK14	MAPK: role in stress response and cell cycle	202
66_MAPK14	MAPK: role in stress response and cell cycle	226
16_MAPK14	MAPK: role in stress response and cell cycle	240
67_MAPK14	MAPK: role in stress response and cell cycle	373
51_MAPK14	MAPK: role in stress response and cell cycle	375
51_MAPKKK cascade	regulates JNK and ERK pathways	213
19_JNK cascade	JNK signaling	473
	Angiogenesis	
2_VEGFR2 homodimer/VEGFA homodimer/GRB10/NEDD4	angiogenesis	408
2_VEGFR2 homodimer/VEGFA homodimer/alphaV beta3 Integrin	angiogenesis	415
2_VEGFR2 homodimer/VEGFA homodimer	angiogenesis	475
2_NRP2	regulates angiogenesis	198
3_NRP2	regulates angiogenesis	199
44_HIF1A	hypoxic response	140
23_EDIL3	integrin ligand; role in angiogenesis	101
108_blood circulation	hemovascular	235
	Apoptosis	
114_BIRC5	anti-apoptotic function	172
130_TNFRSF10C	anti-apoptotic function	314
23_apoptosis	apoptosis	219
51_BCL2L1	AKA: anti-apoptotic Bcl2 family member	20
130_TRAILR3 (trimer)	pro-apoptotic	313
39_FASLG	Fas ligand - pro-apoptotic	391
	Nuclear Hormone Receptor	
106_ZMIZ2	binds nuclear hormone receptors	417

127_PPARD	nuclear hormone receptor	23
126_PPARD	nuclear hormone receptor	24
40_RAR alpha/9cRA/Cyclin H	nuclear hormone receptor	137
40_RAR alpha/9cRA	nuclear hormone receptor	205
52_NR3C1	nuclear hormone receptor	334
106_NR3C1	nuclear hormone receptor	335
112_NR3C1	nuclear hormone receptor	351
52_Glucocorticoid receptor/Hsp90/HDAC6	nuclear hormone receptor	399
40_RXRA	nuclear hormone receptor	400
	Calcium/Calmodulin signaling	
95_CALM1	calmodulin	61
70_CALM1	calmodulin	71
3_CALM1	calmodulin	83
85_CALM1	calmodulin	84
120_CALM1	calmodulin	85
62_CALM1	calmodulin	86
33_CALM1	calmodulin	87
115_CALM1	calmodulin	88
74_CALM1	calmodulin	89
2_CALM1	calmodulin	90
39_CALM1	calmodulin	99
95_CaM/Ca2+/Calcineurin A alpha-beta B1	calmodulin	117
95_CaM/Ca2+	calmodulin	118
33_AS160/CaM/Ca2+	calmodulin	129
33_CaM/Ca2+	calmodulin	130
120_CaM/Ca2+	calmodulin	131
51_mast cell activation	calmodulin	133
95_CaM/Ca2+/CAMK IV	calmodulin	160
39_CaM/Ca2+	calmodulin	162
39_CaM/Ca2+/Calcineurin A alpha-beta B1	calmodulin	164
110_CALM1	calmodulin	188
110_CaM/Ca2+/Calcineurin A alpha-beta B1	calmodulin	424
3_CaM/Ca2+	calmodulin	489
52_CAMK4	calmodulin signaling	270
95_CAMK4	calmodulin signaling	271
	cAMP signaling	
16_CREB1	cAMP response element	158
112_CREB1	cAMP response element	402
62_mol:cAMP	cAMP signaling	252
95_AKAP5	PKA signaling	344
	Casein kinase	
95_CSNK1A1	casein kinase 1, alpha 1	93
92_CSNK1A1	casein kinase 1, alpha 1	125
75_CSNK1A1	casein kinase 1, alpha 1	126
24_CSNK1A1	casein kinase 1, alpha 1	127
126_CSNK1A1	casein kinase 1, alpha 1	128
50_CSNK1A1	casein kinase 1, alpha 1	184
92_CSNK1G3	casein kinase 1, gamma 3	52
24_CSNK1G3	casein kinase 1, gamma 3	53
	Cell Cycle	
51_mitosis	cell cycle/mitosis	48
22_re-entry into mitotic cell cycle	cell cycle/mitosis	166

114_CDC2	cell cycle/mitosis	169
114_NEK2	cell cycle/mitosis	173
114_CKS1B	cell cycle	180
114_CENPF	cell cycle/mitosis	181
114_CENPA	cell cycle/mitosis	187
77_Aurora B/RasGAP	cell cycle/mitosis	234
100_CDC20	cell cycle/mitosis	251
77_CDCA8	cell cycle/mitosis	261
20_Cyclin D3/CDK11 p58	cell cycle/G1-S	446
100_PRC1	cell cycle/mitosis	354
114_CENPB	cell cycle/mitosis	359
100_APC/C/CDC20	cell cycle/mitosis	394
77_Centraspindlin	cell cycle/mitosis	412
114_PLK1	cell cycle/mitosis	421
77_cytokinesis	cell cycle/mitosis	442
100_CENPE	cell cycle/mitosis	474
114_CDC25B	cell cycle/mitosis	491
49_PCNA	cell cycle/replication	363
30_RBBP7	cell cycle-Rb binding protein	379
40_MNAT1	component of CAK - cell cycle	92
114_CCNB2	cell cycle/mitosis	186
40_CCNH	cyclin H; transcriptional regulation/cell cycle	19
	DNA damage response	
114_CHEK2	DNA damage response	132
49_RAD50	DNA damage response	215
30_RAD50	DNA damage response	216
49_DNA repair	DNA damage response	260
114_BRCA2	DNA damage response	388
49_FA complex/FANCD2/Ubiquitin	DNA damage response	432
49_BRCA1/BARD1/RAD51/PCNA	DNA damage response	449
40_TFIIH	nucleotide DNA excision repair	30
49_FANCE	involved in DSB repair	22
49_FANCA	involved in DSB repair	47
	chromatin remodelling	
114_HIST1H2BA	histone	347
112_KAT2B	histone acetyltransferase function	406
106_HDAC1	histone acetyltransferase function	418
106_KAT2B	histone acetyltransferase function	423
63_KAT2B	histone acetyltransferase function	425
47_KAT2B	histone acetyltransferase function	426
40_KAT2B	histone acetyltransferase function	427
63_I kappa B alpha/HDAC3	histone deacetylase	185
52_HDAC7/HDAC3	histone deacetylase	208
52_HDAC5/ANKRA2	histone deacetylase	278
40_HDAC3	histone deacetylase	440
52_HDAC3	histone deacetylase	441
63_HDAC3	histone deacetylase	472
63_HDAC3/SMRT (N-CoR2)	chromatin remodelling	370
63_I kappa B alpha/HDAC1	chromatin remodelling	454
	Cell Adhesion	
23_alphaV/beta3 Integrin/Caspase 8	integrin	220
113_ITGAV	integrin	221
23_ITGAV	integrin	222
2_ITGAV	integrin	223

103_ITGAV	integrin	224
23_alphaV/beta3 Integrin/Del1	integrin	338
51_ITGB3	integrin beta 3	36
29_alphaIIb/beta3 Integrin	FN receptor expressed in platelets	393
101_alphaIIb/beta3 Integrin	FN receptor expressed in platelets	395
84_alphaIIb/beta3 Integrin	FN receptor expressed in platelets	430
	Proteolysis	
126_PSEN1	presinilin 1 - protease	323
76_PSEN1	presinilin 1 - protease	324
117_PSEN1	presinilin 1 - protease	325
	G protein signaling	
16_GDI1	Rab GDP dissociation inhibitor	478
98_RABGGTA	Rab geranylgeranyltransferase	340
45_RAP1B	Ras family member	434
103_RAP1B	Ras family member	435
56_RAP1B	Ras family member	436
104_RAP1B	Ras family member	437
70_RAP1B	Ras family member	438
19_RAP1B	Ras family member	439
22_RASA1	Ras-GAP	72
108_RASA1	Ras-GAP	73
19_RASA1	Ras-GAP	74
109_RASA1	Ras-GAP	75
78_RASA1	Ras-GAP	76
43_RASA1	Ras-GAP	77
77_RASA1	Ras-GAP	78
88_RASA1	Ras-GAP	79
7_RASA1	Ras-GAP	80
26_RASA1	Ras-GAP	81
104_RASA1	Ras-GAP	82
91_RASA1	Ras-GAP	398
72_GNG2	gamma subunit of a trimeric G protein	51
58_GNG2	gamma subunit of a trimeric G protein	60
119_GNG2	gamma subunit of a trimeric G protein	63
75_GNG2	gamma subunit of a trimeric G protein	64
24_GNG2	gamma subunit of a trimeric G protein	65
79_GNG2	gamma subunit of a trimeric G protein	66
67_GNG2	gamma subunit of a trimeric G protein	67
52_GNG2	gamma subunit of a trimeric G protein	68
79_GNB1/GNG2	gamma subunit of a trimeric G protein	414
72_GNB1/GNG2	gamma subunit of a trimeric G protein	431
67_G-protein coupled receptor activity	GPCR signaling	348
128_mol:GTP	GTP function	218
42_mol:GDP	GTP signaling	336
	RTK/non-RTK signaling	
103_PDGFB-D/PDGFRB	RTK signaling	112
83_PDGFB-D/PDGFRB	RTK signaling	113
83_PDGFRB	RTK signaling	114
103_PDGFRB	RTK signaling	115
84_PDGFRB	RTK signaling	116
91_PDGFRB	RTK signaling	134
82_PDGFB-D/PDGFRB	RTK signaling	135
82_PDGFRB	RTK signaling	136
104_KIDINS220/CRKL	RTK signaling	146

113_CRKL	RTK signaling	147
104_CRKL	RTK signaling	148
53_CRKL	RTK signaling	149
57_CRKL	RTK signaling	150
124_CRKL	RTK signaling	151
131_CRKL	RTK signaling	152
70_CRKL	RTK signaling	153
91_Bovine Papilomavirus E5/PDGFRB	RTK signaling	161
46_GRB10	RTK signaling	380
7_GRB10	RTK signaling	381
88_GRB10	RTK signaling	382
91_GRB10	RTK signaling	383
88_GRB14	RTK signaling	404
108_GRB14	RTK signaling	405
2_GRB10	RTK signaling	471
135_EGFR	RTK signaling	479
48_EGFR	RTK signaling	480
38_EGFR	RTK signaling	481
71_EGFR	RTK signaling	482
58_EGFR	RTK signaling	483
17_EGFR	RTK signaling	484
76_EGFR	RTK signaling	485
29_EGFR	RTK signaling	486
72_EGFR	RTK signaling	497
84_EGFR	RTK signaling	499
84_FER	tyrosine kinase	217
46_PTK2	FAK homologue - cell motility	156
109_PTK2	FAK homologue - cell motility	157
72_PTK2	FAK homologue - cell motility	397
119_PTK2	FAK homologue - cell motility	411
7_FRS2	fibroblast growth factor substrate	461
2_FRS2	fibroblast growth factor substrate	462
104_FRS2	fibroblast growth factor substrate	463
87_ERBB2IP	negatively regulates ErbB2	228
	PI3K/AKT signaling	
51_AKT1	signaling; tumor cell survival	91
44_AKT1	signaling; tumor cell survival	143
108_PIK3R1	signaling; tumor cell survival	269
72_PIK3R1	signaling; tumor cell survival	274
94_PIK3R1	signaling; tumor cell survival	275
122_PIK3R1	signaling; tumor cell survival	276
22_PIK3R1	signaling; tumor cell survival	277
45_PIK3R1	signaling; tumor cell survival	279
103_PIK3R1	signaling; tumor cell survival	281
2_PIK3R1	signaling; tumor cell survival	282
23_PIK3R1	signaling; tumor cell survival	283
88_PIK3R1	signaling; tumor cell survival	284
101_PIK3R1	signaling; tumor cell survival	285
104_PIK3R1	signaling; tumor cell survival	286
79_PIK3R1	signaling; tumor cell survival	287
51_PIK3R1	signaling; tumor cell survival	288
109_PIK3R1	signaling; tumor cell survival	289
117_PIK3R1	signaling; tumor cell survival	290
124_PIK3R1	signaling; tumor cell survival	291

7_PIK3R1	signaling; tumor cell survival	292
113_PIK3R1	signaling; tumor cell survival	293
69_PIK3R1	signaling; tumor cell survival	294
116_PIK3R1	signaling; tumor cell survival	295
119_PIK3R1	signaling; tumor cell survival	296
131_PIK3R1	signaling; tumor cell survival	297
80_PIK3R1	signaling; tumor cell survival	298
91_PIK3R1	signaling; tumor cell survival	299
135_PIK3R1	signaling; tumor cell survival	300
68_PIK3R1	signaling; tumor cell survival	301
84_PIK3R1	signaling; tumor cell survival	302
46_PIK3R1	signaling; tumor cell survival	303
3_PIK3R1	signaling; tumor cell survival	304
57_PIK3R1	signaling; tumor cell survival	305
19_PIK3R1	signaling; tumor cell survival	306
43_PIK3R1	signaling; tumor cell survival	307
70_PIK3R1	signaling; tumor cell survival	311
38_PIK3R1	signaling; tumor cell survival	320
93_PIK3R1	signaling; tumor cell survival	321
55_PIK3R1	signaling; tumor cell survival	339
74_PIK3R1	signaling; tumor cell survival	444
9_PIK3R1	signaling; tumor cell survival	460
51_RPS6KB1	ribosomal protein S6 kinase - signaling	50
16_RPS6KA4	ribosomal protein S6 kinase - signaling	378
51_FRAP1	AKA: mTOR - signaling	98
51_mol:PI-3-4-5-P3	pro-survival	97
51_PI3K	pro-survival	138
	TGFb signaling	
105_SMAD5	TGFb signaling	174
105_SMAD5/SMAD5/SMAD4	TGFb signaling	197
105_SMAD6/SMURF1/SMAD5	TGFb signaling	214
105_BMP4	TGFb signaling	229
105_SMAD9	TGFb signaling	310
105_SMAD5/SKI	TGFb signaling	322
105_SMAD8A/SMAD8A/SMAD4	TGFb signaling	346
105_CHRDL1	BMP4 antagonist	498
	ser/thr phosphatase	
131_mol:PP2	ser/thr phosphatase	312
43_PPAP2A	ser/thr phosphatase	500
120_PPP2R5D	PP2A - ser/thr phosphatase	40
77_PPP2R5D	PP2A - ser/thr phosphatase	41
26_PPP2R5D	PP2A - ser/thr phosphatase	42
100_PPP2CA	PP2A - ser/thr phosphatase	122
105_PPM1A	PP2C family member - ser/thr phosphatase	272
115_PPM1A	PP2C family member - ser/thr phosphatase	273
	Transcription Factor	
106_positive regulation of transcription	transcription	256
30_MAX	transcription factor	39
63_MAX	transcription factor	46
112_MAX	transcription factor	119
95_NFAT1/CK1 alpha	transcription factor	191
114_ETV5	transcription factor	211
95_NFAT4/CK1 alpha	transcription factor	241
63_GATA2	transcription factor	257

106_GATA2	transcription factor	258
52_GATA2	transcription factor	259
112_FOXG1	transcription factor	262
112_GSC	transcription factor	328
63_GATA2/HDAC3	transcription factor	337
52_MEF2C	transcription factor	341
14_FOXA1	transcription factor	349
112_MYC	transcription factor	357
30_MYC	transcription factor	362
63_GATA1/HDAC3	transcription factor	368
52_GATA2/HDAC5	transcription factor	371
105_ENDOFIN/SMAD1	transcription factor	372
52_GATA1	transcription factor	377
106_EGR1	transcription factor	453
16_USF1	transcription factor	468
114_MYC	transcription factor	470
114_FOXM1	transcription factor	490
39_FOS	transcription factor - mitogenic signaling	212
37_FOS	transcription factor - mitogenic signaling	227
30_FOS	transcription factor - mitogenic signaling	237
72_FOS	transcription factor - mitogenic signaling	242
43_FOS	transcription factor - mitogenic signaling	246
126_FOS	transcription factor - mitogenic signaling	247
109_FOS	transcription factor - mitogenic signaling	248
93_FOS	transcription factor - mitogenic signaling	249
70_CAMK2A	transcription factor - mitogenic signaling	250
87_FOS	transcription factor - mitogenic signaling	267
110_FOS	transcription factor - mitogenic signaling	407
10_FOS	transcription factor - mitogenic signaling	419
112_FOS	transcription factor - mitogenic signaling	476
22_AP-1	transcription factor; mitogenic response	154
51_EGR2	transcription factor; regulates ErbB2 exspression	45
40_CDK7	transcription initiation; DNA repair	29
	ubiquitination	
41_beta TrCP1/SCF ubiquitin ligase complex	ubiquitination	56
41_FBXW11	ubiquitination	57
69_beta TrCP1/SCF ubiquitin ligase complex	ubiquitination	102
63_beta TrCP1/SCF ubiquitin ligase complex	ubiquitination	103
35_beta TrCP1/SCF ubiquitin ligase complex	ubiquitination	104
126_FBXW11	ubiquitination	105
63_FBXW11	ubiquitination	106
50_FBXW11	ubiquitination	107
100_FBXW11	ubiquitination	108
35_FBXW11	ubiquitination	109
69_FBXW11	ubiquitination	110
106_proteasomal ubiquitin-dependent protein catabolic process	ubiquitination	177
41_proteasomal ubiquitin-dependent protein catabolic process	ubiquitination	355
63_proteasomal ubiquitin-dependent protein catabolic process	ubiquitination	448
51_CBL	adaptor protein; regulates ubiquitination of RTKs	183
	Wnt signaling	
38_CTNNA1	Wnt signaling	263

45_CTNNA1	Wnt signaling	264
103_CTNNA1	Wnt signaling	265
71_CTNNA1	Wnt signaling	266
75_FZD6	Wnt signaling	360
111_FZD6	Wnt signaling	361
126_DKK1/LRP6/Kremen 2	Wnt signaling	389
50_DKK1/LRP6/Kremen 2	Wnt signaling	390
126_Axin1/APC/beta catenin	Wnt signaling	392
126_WNT1	Wnt signaling	464
50_WNT1	Wnt signaling	466
	Other	
51_AICDA	activation-induced cytidine deaminase	2
44_ABCB1	ABC transporter - multidrug resistance	428
131_LRP8	apolipoprotein E receptor	332
120_LRP8	apolipoprotein E receptor	333
51_ALOX15	arachidonate 15-lipoxygenase	5
14_TTR	carrier protein	495
87_CHRNA1	cholinergic receptor	455
33_LNPEP	cleaves peptide hormones	416
88_F2RL2	coagulation factor	245
51_COL1A1	collagen 1A1; ECM	192
51_COL1A2	collagen 1A2; ECM	209
95_NUP214	component of the nuclear pore complex	327
105_NUP214	component of the nuclear pore complex	329
115_NUP214	component of the nuclear pore complex	330
40_positive regulation of DNA binding	DNA binding??	124
77_Chromosomal passenger complex	DNA function	352
77_Chromosomal passenger complex/EVI5	DNA function	410
30_BLM	DNA helicase	350
24_RAB23	endocytosis; vesicular transport	196
48_EDN1	endothelin 1 - vasoconstriction	364
10_GADD45B	growth arrest and DNA damage inducible gene	422
89_GUCA1B	guanylate cyclase	429
114_HSPA1B	heat shock protein	54
47_mol:Lysophosphatidic acid	LPA signaling	465
87_myelination	mucscle function	353
105_RGMB	neuronal function	255
7_GFRA1	neurotrophic factor	374
51_OPRM1	opioid receptor	14
62_negative regulation of phagocytosis	phagocytosis	244
23_PI4KA	phosphatidylinositol 4-kinase	163
89_PDE6A/B	phosphodiesterase	433
89_PDE6A	phosphodiesterase	469
43_GO:0007205	PKC signaling	387
95_PRKCH	PKC-eta (epithelial specifc)	253
45_KLHL20	pleoitrophic	384
58_PTGDR	prostaglandin D2 receptor	239
58_PGD2/DP	prostaglandin D2 synthase	326
105_ZFYVE16	protein trafficking	69
33_VAMP2	protein trafficking	238
21_VAMP2	protein trafficking	308
102_EXOC5	protein trafficking	309
71_CYFIP2	putative role in adhesion/apoptosis	94
45_CYFIP2	putative role in adhesion/apoptosis	95

52_ANKRA2	putative role in endocytosis	49
108_mol:ROS	reactive oxygen species	167
31_oxygen homeostasis	redox	268
54_NPHS1	renal function	496
51_RETNLB	resistin like beta	4
51_TFF3	secreted protein normally found in the GI mucosa	21
52_SRF	serum response factor; immediate early gene	141
51_SOCS1	Stat signaling	139
51_SOCS3	Stat signaling	376
106_SENP1	sumoylation	494
16_EIF4EBP1	translation	366

[0035] While all of the above pathway entities, when differentially expressed relative to normal (overexpressed or underexpressed) may serve as indicators for an immune suppressed tumor, it is contemplated that only a fraction may be analyzed. For example, suitable tests may analyze at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 60%, or at least 70%, or at least 80%, or at least 90% of the genes/pathway entities listed in Tables 1-4. Alternatively, contemplated tests may also use specific genes of the genes/pathway entities listed in Tables 1-4, and especially one or more of pathway elements selected form the group consisting of IL12B, IFNG, PSMA3, THY1, CCL17, PRKCQ, NFATC3, NFATC2, CCL11, CCL26, IFNAR2, SQSTM1, IRAK4, NFKBIA, IL6ST, MAP3K1, IRF1, IRF9, PTGS2, IL4, IL5, IGHG3, IL4R, IL13RA2, PIGR, IL13RA1, STAT6, FCER2, IGHG1, IL10, STAT5A, PRKCE, CSF1R, ARG1, LTA, SELP, FKBP3, LCP2, and DOK2. For example, such list may include at least two, at least three, at least four, at least five, at least ten, at least 15, or at least 20 of IL12B, IFNG, PSMA3, THY1, CCL17, PRKCQ, NFATC3, NFATC2, CCL11, CCL26, IFNAR2, SQSTM1, IRAK4, NFKBIA, IL6ST, MAP3K1, IRF1, IRF9, PTGS2, IL4, IL5, IGHG3, IL4R, IL13RA2, PIGR, IL13RA1, STAT6, FCER2, IGHG1, IL10, STAT5A, PRKCE, CSF1R, ARG1, LTA, SELP, FKBP3, LCP2, and DOK2.

[0036] In addition, contemplated assays need not only be limited to single pathway elements, but may also include complexes of pathway elements, and especially one or more complexes selected from the group consisting of IFN-gamma/IRF1, STAT6 (dimer)/PARP14, IL4/IL4R/JAK1, IL4R/JAK1, STAT6 (dimer)/ETS1, PI3K/BCAP/CD19, IL4/IL4R/JAK1/IL2Rgamma/JAK3/DOK2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHIP, IL4/IL4R/JAK1/IL13RA1/JAK2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHC/SHIP, IL4/IL4R/JAK1/IL2Rgamma/JAK3/FES/IRS2, IL4/IL4R/JAK1/IL2Rgamma/JAK3,

IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHC/SHIP/GRB2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/IRS1, IL4/IL4R/JAK1/IL2Rgamma/JAK3/FES, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHP1 (or any combination of at least two, at least three, at least four, at least five, or at least ten complexes).

[0037] In addition, the differentially expressed genes may include highly expressed genes, and especially FOXM1. Still further contemplated differentially expressed genes include non-immune genes that encode a protein involved in at least one of mitogenic signaling, stress signaling, apoptosis, calcium/calmodulin signaling, G-protein signaling, PI3K/AKT signaling, RTK signaling, Wnt signaling, and cAMP signaling, or non-immune genes encoding a protein that is involved in at least one of cell cycle control, DNA damage response, and chromatin remodeling as shown in Tables 2 and 4 above. For example, suitable contemplated non-immune genes include at least one, at least two, at least three, at least four, at least five, at least ten MAPK1, MAPK14, NRP2, HIF1A, CALM1, CREB1, CSNK1A1, CSNK1G3, CCNH, FANCE, FANCA, TFIIH, ITGB3, RASA1, GNG2, PDGFRB, AKT1, and PIK3R1.

[0038] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms “comprises” and “comprising” should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C …. and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

CLAIMS

What is claimed is:

1. A method of predicting a likely therapeutic outcome for immune therapy of a cancer with a checkpoint inhibitor, comprising:
   obtaining omics data from a tumor of the patient, wherein the omics data comprise at least one of whole genome sequencing data and RNA sequencing data;
   using pathway analysis to identify from the omics data a plurality of highly expressed genes in a plurality of immune related pathways having a plurality of respective pathway elements;
   associating the highly expressed genes with likely response of the cancer to treatment with the checkpoint inhibitor when the highly expressed genes are indicative of a Th2/humoral response and a low Th1/Th2 ratio; and
   updating or generating a patient record with an indication of the likely response of the cancer to treatment with the checkpoint inhibitor when the highly expressed genes are indicative of a Th2/humoral response and a low Th1/Th2 ratio.

2. The method of claim 1 wherein the immune related pathways are selected from the group consisting of an immune cell function pathway, a pro-inflammatory signaling pathway, and an immune suppression pathway.

3. The method of claim 1 wherein the pathway element control activity of at least one of Th1 differentiation, Th2 differentiation, B cell differentiation, macrophage differentiation, T cell activation, and an immunoproteasome.

4. The method of claim 1 wherein the pathway element control activity of at least one of NFkB, an IFNalpha responsive gene.

5. The method of claim 1 wherein the pathway element is a cytokine.

6. The method of claim 1 wherein the cytokine is selected form the group consisting of IL12 beta, IFNgamma, IL4, IL5, and IL10.

7. The method of claim 1 wherein the pathway element is a chemokine.

8. The method of claim 1 wherein the chemokine is selected from the group consisting of CCL17, CCL11, and CCL26.

9. The method of claim 1 wherein the pathway element is selected form the group consisting of IL12B, IFNG, PSMA3, THY1, CCL17, PRKCQ, NFATC3, NFATC2, CCL11, CCL26, IFNAR2, SQSTM1, IRAK4, NFKBIA, IL6ST, MAP3K1, IRF1, IRF9, PTGS2, IL4, IL5, IGHG3, IL4R, IL13RA2, PIGR, IL13RA1, STAT6, FCER2, IGHG1, IL10, STAT5A, PRKCE, CSF1R, ARG1, LTA, SELP, FKBP3, LCP2, and DOK2.

10. The method of claim 1 wherein the pathway element is a complex selected form the group consisting of IFN-gamma/IRF1, STAT6 (dimer)/PARP14, IL4/IL4R/JAK1, IL4R/JAK1, STAT6 (dimer)/ETS1, PI3K/BCAP/CD19, IL4/IL4R/JAK1/IL2Rgamma/JAK3/DOK2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHIP, IL4/IL4R/JAK1/IL13RA1/JAK2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHC/SHIP, IL4/IL4R/JAK1/IL2Rgamma/JAK3/FES/IRS2, IL4/IL4R/JAK1/IL2Rgamma/JAK3, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHC/SHIP/GRB2, IL4/IL4R/JAK1/IL2Rgamma/JAK3/IRS1, IL4/IL4R/JAK1/IL2Rgamma/JAK3/FES, IL4/IL4R/JAK1/IL2Rgamma/JAK3/SHP1.

11. The method of claim 1 wherein the omics data further comprise at least one of siRNA data, DNA methylation status data, transcription level data, and proteomics data.

12. The method of claim 1 wherein the pathway analysis comprises PARADIGM analysis.

13. The method of claim 1 wherein the omics data are normalized against the same patient.

14. The method of claim 1 wherein the checkpoint inhibitor is a CTLA-4 inhibitor or a PD-1 inhibitor.

15. The method of claim 1 wherein the cancer is a breast cancer, and wherein the highly expressed genes further include FOXM1.

16. The method of claim 1 wherein the highly expressed genes further include non-immune genes encoding a protein involved in at least one of mitogenic signaling, stress signaling, apoptosis, calcium/calmodulin signaling, G-protein signaling, PI3K/AKT signaling, RTK signaling, Wnt signaling, and cAMP signaling.

17. The method of claim 1 wherein the highly expressed genes further include non-immune genes encoding a protein involved in at least one of cell cycle control, DNA damage response, and chromatin remodeling.

18. The method of claim 1 wherein the highly expressed genes further include non-immune genes selected from the group consisting of MAPK1, MAPK14, NRP2, HIF1A, CALM1, CREB1, CSNK1A1, CSNK1G3, CCNH, FANCE, FANCA, TFIIH, ITGB3, RASA1, GNG2, PDGFRB, AKT1, and PIK3R1.

19. The method of claim 1 wherein the likely therapeutic outcome is predicted prior to therapy with the checkpoint inhibitor.

20. The method of claim 1 wherein the immune therapy further comprises administration of at least one of a genetically modified virus and a genetically modified NK cell.

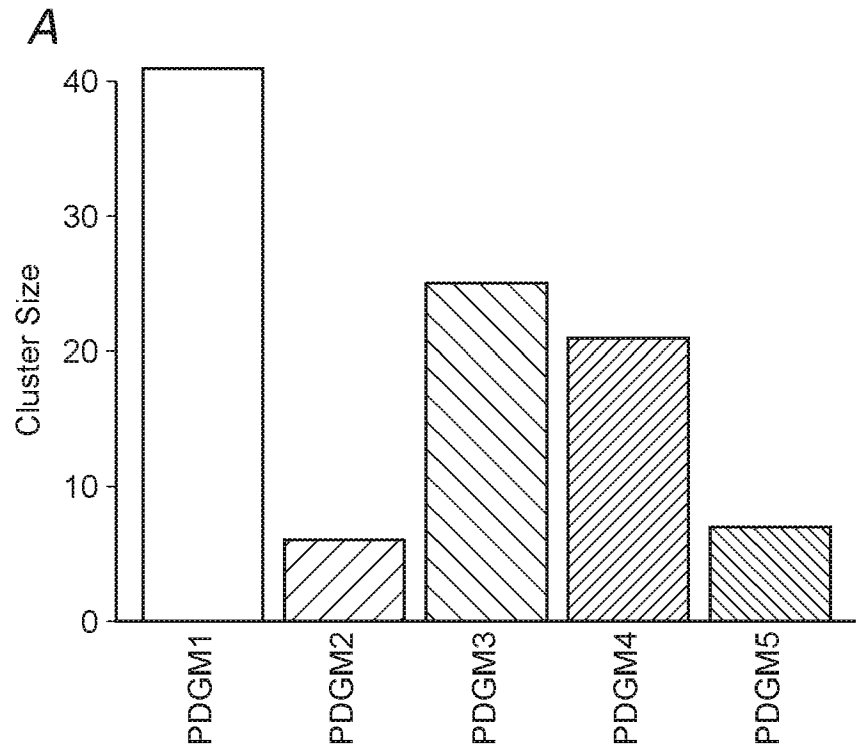
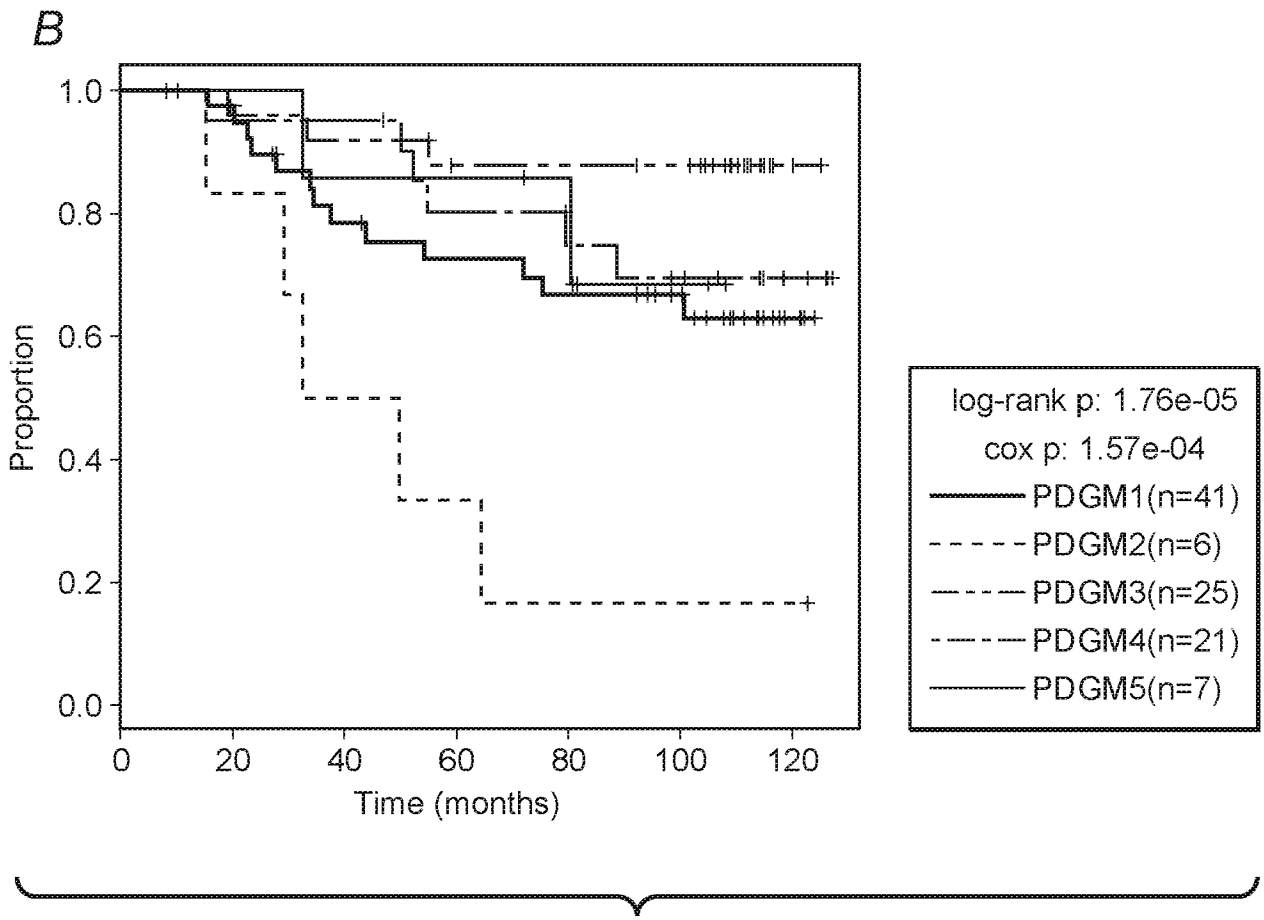

A
Cluster Size
40
30
20
10
0
PDGM1
PDGM2
PDGM3
PDGM4
PDGM5

FIG. 1


B
Proportion
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
Time (months)
log-rank p: 1.76e-05
cox p: 1.57e-04
PDGM1(n=41)
PDGM2(n=6)
PDGM3(n=25)
PDGM4(n=21)
PDGM5(n=7)

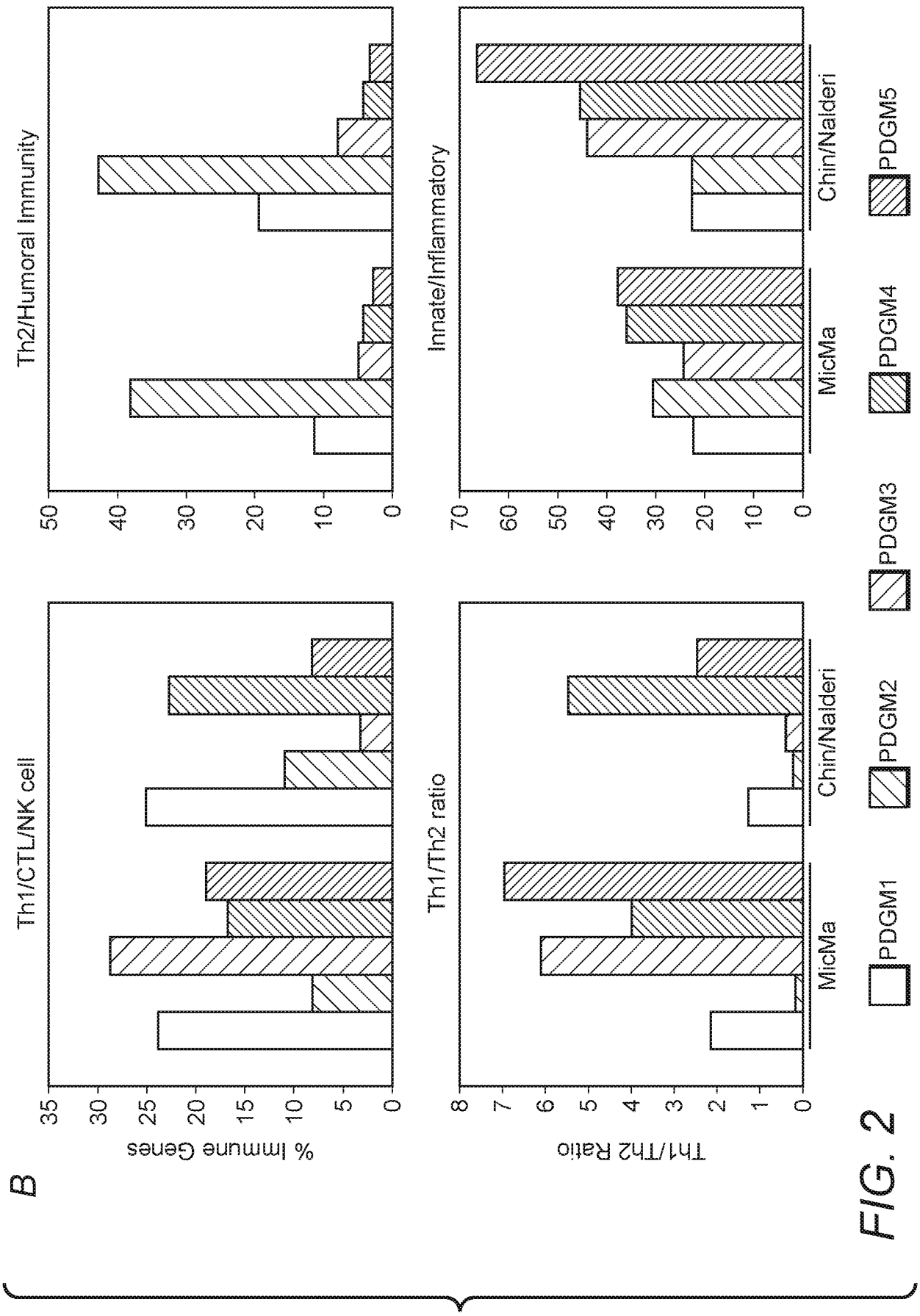

B
Th1/CTL/NK cell
% Immune Genes
0
5
10
15
20
25
30
35
Th2/Humoral Immunity
0
10
20
30
40
50
Th1/Th2 ratio
Th1/Th2 Ratio
0
1
2
3
4
5
6
7
8
Innate/Inflammatory
0
10
20
30
40
50
60
70
MicMa
Chin/Nalderi
MicMa
Chin/Nalderi
PDGM1
PDGM2
PDGM3
PDGM4
PDGM5

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/031418

A. CLASSIFICATION OF SUBJECT MATTER

G06F 19/12(2011.01)i, G06F 19/26(2011.01)i, C12Q 1/68(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F 19/12; A61K 39/00; G01N 33/53; G06F 19/26; C12Q 1/68

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: immune therapy, prediction, cancer, checkpoint inhibitor, Th1/Th2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	SANTOS et al., `Model-based genotype-phenotype mapping used to investigate gene signatures of immune sensitivity and resistance in melanoma micrometastasis`, Scientific Reports, 26 April 2016(online), vol. 6, article no. 24967, internal pages 1-14 See abstract; and pages 2, 10, 13.	1-20
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 August 2017 (08.08.2017)	**08 August 2017 (08.08.2017)**

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Information on patent family members

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PCT/US2017/031418

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