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(54) **Title:** METHODS AND COMPOSITIONS FOR CLASSIFYING AND TREATING KIDNEY CANCER

(57) **Abstract:** The invention provides methods and compositions for classifying kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC); methods and compositions for treating kidney cancer in a patient, for example, by administering a treatment regimen that includes a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab) to the patient. Also provided are compositions, pharmaceutical compositions, kits, and articles of manufacture for use in classifying and treating kidney cancer in a patient.

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METHODS AND COMPOSITIONS FOR CLASSIFYING AND TREATING KIDNEY CANCER

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 5, 2021, is named 50474-241WO1_Sequence_Listing_11_3_21_ST25 and is 9,473 bytes in size.

FIELD OF THE INVENTION

This invention relates to methods and compositions for use in classifying and treating kidney cancer (e.g., renal cell carcinoma (RCC)) in a patient.

BACKGROUND OF THE INVENTION

RCC was diagnosed in more than 400,000 people and associated with approximately 175,000 deaths worldwide in 2018. Approximately 25% of patients present with metastatic disease at initial diagnosis. Clear-cell carcinoma (ccRCC) is the most common histologic subtype (75%) in RCC. About 20% of tumors from patients with advanced RCC contain sarcomatoid elements. RCC tumors that include a sarcomatoid component are highly aggressive and lead to rapid metastasis and poor clinical prognosis.

Inactivation of the *VHL* gene function by deletion of chromosome 3p, mutation, and/or promoter methylation is a predominant feature of ccRCC and leads to abnormal accumulation of hypoxia inducible factors (HIF) and activation of the angiogenesis program. However, *VHL* loss alone is insufficient for tumorigenesis, and additional genomic aberrations have been implicated in disease progression and degree of aggressiveness. ccRCC is also characterized as a highly inflamed tumor type, with one of the highest immune infiltration scores in pan-cancer analysis and high expression of immune checkpoints, such as PD-L1 and CTLA-4.

Given the distinct but variable hyper-vascularity, immune cell infiltration and PD-L1 expression in ccRCC, inhibitors of the VEGF pathway and PD-(L)1 axis as monotherapy or in combination have resulted in significant improvement in clinical outcomes in patients with advanced RCC. However, not all patients respond and these treatments can produce significant toxicities. Thus, a better understanding of the molecular basis of clinical heterogeneity in patients with advanced RCC is needed to inform treatment selection strategies and delineate resistance mechanisms. Moreover, improved methods of patient classification and treatment are needed.

SUMMARY OF THE INVENTION

The present disclosure provides, *inter alia*, methods of classifying kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC), methods of treating kidney cancer, and related kits, compositions for use, and uses.

In one aspect, the invention features a method of classifying an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the inoperable, locally advanced, or metastatic RCC is

previously untreated, the method comprising (a) assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and (b) assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative (6) stromal/proliferative; and (7) snoRNA, thereby classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient.

In another aspect, the invention features a method of treating an inoperable, locally advanced, or metastatic RCC in a human patient, the method comprising: classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient according to any one of the methods disclosed herein; and administering an anti-cancer therapy to the patient based on the classification.

In another aspect, the invention features an anti-cancer therapy for use in treating an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the previously untreated inoperable, locally advanced, or metastatic RCC in the patient has been classified according to any one of the methods disclosed herein.

In another aspect, the invention features the use of an anti-cancer therapy in the preparation of a medicament for treating an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the previously untreated inoperable, locally advanced, or metastatic RCC in the patient has been classified according to any one of the methods disclosed herein.

In some aspects, the anti-cancer therapy includes a PD-1 axis binding antagonist (e.g., an anti-PD-L1 antibody, e.g., atezolizumab). In some aspects, the anti-cancer therapy includes a VEGF antagonist (e.g., an anti-VEGF antibody, e.g., bevacizumab). In some aspects, the anti-cancer therapy includes a PD-1 axis binding antagonist and an anti-angiogenesis agent. In some aspects, the anti-cancer therapy includes atezolizumab and bevacizumab.

In another aspect, the invention features a method of treating a previously untreated inoperable, locally advanced, or metastatic RCC in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, the method comprising administering to the patient an anti-cancer therapy comprising atezolizumab and bevacizumab.

In another aspect, the present invention features a kit for classifying an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the inoperable, locally advanced, or metastatic RCC is previously untreated, the kit comprising: (a) reagents for assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and (b) instructions for assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA, thereby classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient.

In another aspect, the invention features a kit for identifying a human patient suffering from an inoperable, locally advanced, or metastatic RCC who may benefit from treatment with an anti-cancer

therapy comprising atezolizumab and bevacizumab, wherein the inoperable, locally advanced, or metastatic RCC is previously untreated, the kit comprising: (a) reagents for determining the presence of a somatic alteration in one or more of the following genes: *PBRM1, CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* in a tumor sample obtained from the patient; and (b) instructions for using the reagents to identify the patient as one who may benefit from a treatment with an anti-cancer therapy comprising atezolizumab and bevacizumab.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A is a consensus matrix depicting clusters (k=7) identified by non-negative matrix factorization (NMF) clustering of 823 patient tumors. Clusters 1-7 are shown (top, horizontal axis). The number of patient tumors in each cluster are shown in parentheses.

FIG. 1B is a heatmap representing MSigDb hallmark gene set QuSAGE enrichment scores for each NMF patient cluster compared to all other patients. Black cells represent non-significant enrichment after false discovery rate (FDR) correction.

FIG. 1C is heatmap of genes comprised in transcriptional signatures. Z-scores were calculated for each gene. Samples are grouped by NMF cluster. MSKCC, Memorial-Sloan Kettering Cancer Center clinical risk score; TMB, tumor mutation burden; FAO, fatty acid oxidation; FAS, fatty acid synthesis.

FIG. 1D is a dot plot summarizing the heatmap in Fig. 1C. Samples were aggregated by NMF group using the mean across samples for each gene, and the median z-score for each signature was calculated, resulting in one z-score per signature per NMF cluster. The horizontal bar plot on the right depicts the -log10(p-value) obtained from Kruskal-Wallis test for each signature across NMF clusters.

FIG. 1E is a bar plot representing PD-L1 expression (dark grey or light grey) by immunohistochemistry in each NMF cluster. The p-value was obtained from Pearson's Chi-squared test.

FIG. 2A is a volcano plot depicting differentially expressed genes between responders (CR/PR) and non-responders (PD) in the sunitinib arm. Genes with FDR-corrected $p<0.05$ and absolute log-fold change ≥ 0.25 are shown. CR, complete response; PR, partial response; PD, progressive disease.

FIG. 2B is a bar plot representing pathway enrichment scores for the top upregulated or downregulated MSigDb hallmark gene sets within the differentially expressed genes identified in Fig. 2A.

FIG. 2C is a volcano plot depicting differentially expressed genes in responders (CR/PR) treated with atezolizumab+bevacizumab or sunitinib. Genes with FDR-corrected $p<0.05$ and absolute log-fold change ≥ 0.25 are shown.

FIG. 2D is a bar plot representing pathway enrichment scores for the top upregulated or downregulated MSigDb hallmark gene sets within the differentially expressed genes identified in Fig. 2C.

FIG. 3A is a workflow depicting the validation strategy for Angiogenesis and T-effector signatures established in IMmotion150.

FIG. 3B are a series of Kaplan-Meier curves of progression free survival (PFS) by treatment arm (left panel, atezolizumab+bevacizumab; right panel, sunitinib) in patients with angiogenesis low (dotted line) or high (continuous line) tumors. HR, hazard ratio.

FIG. 3C are a series of Kaplan-Meier curves of PFS by treatment arm (dark grey, atezolizumab+bevacizumab; grey, sunitinib) in patients with Angiogenesis low or high and patients with T-effector low or high tumors.

FIG. 4A is a diagram showing the selection of cluster number based on consensus matrices for k=2 to k=8, and measure of cophenetic coefficient stability at various values of k. k=7, with a cophenetic coefficient of 0.90, was chosen.

FIG. 4B is a series of boxplots showing transcriptional z-scores for the 10 signatures presented in the dot plot in Fig. 1D by patient cluster.

FIG. 4C is a heatmap showing hierarchical clustering of deconvolution z-scores obtained from xCell. Samples are ordered by NMF cluster.

FIG. 4D is a graph showing the distribution of primary and metastatic tumors in NMF clusters.

FIG. 4E is a diagram showing correlations between transcriptional signatures across the IMmotion151 data set. Signature z-scores were computed for each of the 823 samples from IMmotion151 and Pearson correlations between signatures were calculated in a pairwise fashion. Positive and negative correlations are shown. The diameter of the circles is proportional to the absolute Pearson R value, which is also numerically displayed in the circles.

FIG. 4F is a bar plot representing the distribution of NMF clusters in tumors with or without *TFE* fusions. Fusions in *TFE3* and *TFEB* were grouped together. Tumors from 12 patients had *TFE3* fusions and 3 patients had *TFEB* fusions.

FIG. 4G is a Kaplan-Meier curve of PFS by treatment arm (dark grey, atezolizumab+bevacizumab; grey, sunitinib) in patients with *TFE*-fusions.

FIG. 5A is a series of heatmaps showing the IMmotion151 heatmap (left panel) in Fig. 1D which was then used to derive the IMmotion150 heatmap (right panel), following a model that was applied to assign patients from IMmotion150 into each cluster. Signature patterns across patient clusters were highly conserved between IMmotion151 and IMmotion150 datasets.

FIG. 5B is a series of X-Y graphs representing the mean aggregate z-score for the ten transcriptional signatures in IMmotion151 (x-axis) and IMmotion150 (y-axis) for each NMF group. The Pearson R value is represented on each plot.

FIG. 6A is a series of bar plots representing NMF cluster distribution by Memorial-Sloan Kettering Cancer Center (MSKCC, left panel) or International Metastatic Renal Cell Carcinoma Database Consortium (IMDC, right panel) clinical risk categories. P-values were obtained from Pearson's Chi-squared test.

FIG. 6B is a series of Kaplan-Meier curves of PFS in NMF clusters of patients treated with atezolizumab+bevacizumab or sunitinib.

FIG. 6C is a bar plot representing objective response rate by treatment arm in each NMF cluster. P-value was obtained using Pearson's Chi-squared test. NE, not evaluable; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; n.s., not statistically significant (p-value > 0.05); A/B, atezolizumab+bevacizumab; Sun., sunitinib.

FIG. 6D is a series of forest plots for PFS hazard ratios in patients treated with atezolizumab+bevacizumab (A/B) vs. sunitinib, by NMF cluster. mPFS = median PFS.

FIG. 7A is an oncoprint of genes with somatic alterations in at least 10% of 715 advanced RCC tumors. Tumor mutation burden (TMB) is represented for individual samples as a bar plot above the oncoprint.

FIG. 7B is a series of oncoprints displaying somatic alterations in NMF clusters. The horizontal bar plots to the right of each oncoprint represent the number of patients with alterations for each gene. P-values were obtained using the Pearson's Chi-squared test (**: $p<0.01$; ***: $p<0.001$).

FIG. 7C is a bar plot showing the NMF cluster distribution in patients with somatic alterations in PBRM1, KDM5C, CDKN2A/B, TP53, and BAP1

FIG. 7D is a heatmap (left panel) and a series of boxplots (right panel). Left panel: Hierarchical cluster depicting the ratio of transcriptional signature z-scores (columns) between altered and non-altered tumor samples for each gene considered (rows). Only genes with somatic alterations in ≥10% of patients and significant differences ($p<0.05$) between altered and non-altered tumors as measured by the two-side Mann-Whitney test for at least one of the transcriptional signatures considered are displayed. Right panel: Boxplots representing the z-scores of gene signatures in samples with genomic alterations in PBRM1 (n=328), KDM5C (n=100), TP53 (n=107) and/or CDKN2A/B (n=116). P-values represent the statistical significance of the comparison of signature z-scores between patients with PBRM1 and/or KDM5C alterations vs. patients with TP53 and/or CDKN2A/B alterations using the two-side Mann-Whitney test.

FIG. 8A is an oncoprint depicting the top 50 most frequently somatically altered genes in tumors from IMmotion151.

FIG. 8B is a heatmap representing the overlap proportion between pairs of the most common somatic alterations in this dataset. Proportion was calculated as the ratio of overlap between two groups over the size of the smaller group. The heatmap highlights minimal overlap between PBRM1 mutations and BAP1/CDKN2A/B alterations.

FIG. 8C is a Venn diagram representing the overlap between tumors somatically altered in PBRM1, CDKN2/B and TP53.

FIG. 8D is an oncoprint depicting somatic alterations in PBRM1, CDKN2A/B, TP53 and KDM5C.

FIG. 8E is a forest plot depicting PFS hazard ratios comparing patients treated with atezolizumab+bevacizumab vs. sunitinib by somatic alteration status for each gene. Whiskers represent 95% confidence intervals.

FIG. 9A is a series of Kaplan-Meier curves of PFS by treatment arm in patients with somatically altered or non-altered tumors for patients treated with atezolizumab+bevacizumab (dark grey) vs. sunitinib (grey).

FIG. 9B is a series of bar plots depicting objective response (OR) by arm and by somatic alteration status for the same genes as Fig. 9A. P-values were obtained from Pearson's Chi-squared test. NE, not evaluable; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete

response; n.s., not statistically significant (p-value > 0.05); A/B, atezolizumab+bevacizumab; Sun, sunitinib.

FIG. 9C is a forest plot representing PFS hazard ratios in patients with somatically altered vs. non-altered tumors, by gene and treatment arm.

FIG. 10A is a volcano plot depicting differentially expressed genes between clear cell renal cell carcinoma-sarcomatoid (ccRCC-Sarc) and ccRCC-non-sarcomatoid (ccRCC-NonSarc) tumors. Genes with FDR-corrected p<0.05 and absolute log-fold change ≥ 0.25 are shown.

FIG. 10B is a bar plot representing pathway enrichment scores for the top upregulated or downregulated MSigDb hallmark gene sets within the differentially expressed genes identified in Fig. 10A.

FIG. 10C is a volcano plot depicting differentially expressed genes between ccRCC-Sarc and non-ccRCC-Sarc tumors. Genes with FDR-corrected p<0.05 and absolute log-fold change ≥ 0.25 are shown.

FIG. 10D is a bar plot representing pathway enrichment scores for the top upregulated or downregulated MSigDb hallmark gene sets within the differentially expressed genes identified in Fig. 10C.

FIG. 10E is a bar plot representing the distribution of PD-L1 expression by immunohistochemistry (IHC) in ccRCC-Sarc, non-ccRCC-sarcomatoid (non-ccRCC-Sarc) and ccRCC-NonSarc tumors. P-values were obtained from Pearson's Chi-squared test conducted between each pair of conditions.

FIG. 10F is a bar plot representing distribution of NMF clusters in ccRCC-Sarc, non-ccRCC-Sarc and ccRCC-NonSarc tumors.

FIG. 11A is a volcano plot representing differentially expressed genes between sarcomatoid RCC (sRCC) and non-sarcomatoid RCC (non-sRCC) tumors. Genes with FDR-corrected p<0.05 and absolute log-fold change ≥ 0.25 are shown.

FIG. 11B is a bar plot representing pathway enrichment scores for the top 15 upregulated or downregulated MSigDb hallmark gene sets within the differentially expressed genes identified in Fig. 11A.

FIG. 11C is a bar plot representing the distribution of NMF defined transcriptomic subgroups.

FIG. 11D is a series of bar plots representing transcriptional signature z-scores, with p-values obtained from two-sided Mann-Whitney test.

FIG. 11E is a bar plot depicting prevalence of PD-L1 expression by immunohistochemistry.

FIG. 11F is a series of pie charts representing the distribution of somatic alterations for select genes in sRCC vs. non-sRCC tumors, with p-values obtained from Pearson's Chi-squared test.

FIG. 11G is a series of Kaplan-Meier curves of PFS in sRCC patients treated with atezolizumab+bevacizumab (dark grey) or sunitinib (grey).

FIG. 11H is a series of waterfall plots depicting the best percent reduction from baseline in sum of longest diameters (SLD). The bars indicate objective response defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Objective response rate was 49% in sRCC patients treated with atezolizumab+bevacizumab, and 14% in sRCC patients treated with sunitinib, p=7.7e-05 with Pearson's Chi-squared test. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

FIG. 12 is a schematic diagram showing a summary of molecular characteristics in transcriptomic subsets in tumors from advanced RCC patients. Radar charts in the RNA profile panel represent mean z-scores for each gene signature in the respective cluster. "DNA alts", somatic alterations.

FIG. 13A is a series of heatmaps showing gene expression comprised in transcriptional signatures from the IMmotion151 (left panel) and JAVELIN 101 (right panel) studies. Z-scores were calculated for each gene. Samples are grouped by NMF cluster. "n" indicates the number of patient tumors and "%" indicates the percentage of patient tumors in each cluster.

FIG. 13B is a series of pie charts showing the percentage of patient tumors in each NMF cluster from the IMmotion151 and JAVELIN 101 studies.

FIG. 14A is a series of Kaplan-Meier curves of PFS in NMF clusters of patients treated with sunitinib or atezolizumab+bevacizumab in the IMmotion151 study, or with sunitinib or avelumab+axitinib in the JAVELIN 101 study.

FIG. 14B is a series of forest plots for PFS hazard ratios in patients treated with atezolizumab+bevacizumab (A/B) vs. sunitinib in the IMmotion151 study (top panel) or avelumab+axitinib (Ave+Axi) or sunitinib (Sun) in the JAVELIN 101 study (bottom panel). The PFS hazard ratios for each NMF cluster are shown. mPFS = median PFS.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides diagnostic and therapeutic methods and compositions for cancer, for example, kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC). The invention is based, at least in part, on the discovery that the methods of classification described herein identify patient subgroups that have unexpectedly favorable response to anti-cancer therapies, including anti-cancer therapies that include a PD-1 axis binding antagonist (e.g., an anti-PD-L1 antibody, e.g., atezolizumab) and a VEGF antagonist (e.g., an anti-VEGF antibody, e.g., bevacizumab), as shown in Example 1. Moreover, Example 2 demonstrates that the methods of classification herein also are effective for identifying patient subgroups for other anti-cancer therapies, such as an anti-cancer therapy that includes the anti-PD-L1 antibody avelumab and the tyrosine kinase inhibitor axitinib. Based on these data, it is expected that the methods of classification described herein can also identify patient subgroups with favorable response to other anti-cancer therapies, e.g., anti-cancer therapies including an immunotherapy agent, a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent, or a combination thereof.

I. Definitions

The term "anti-cancer therapy" refers to a therapy useful in treating cancer. An anti-cancer therapy may include a treatment regimen with one or more anti-cancer therapeutic agents. Examples of anti-cancer therapeutic agents include, but are limited to, an immunotherapy agent (e.g., a PD-1 axis binding antagonist), a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism

inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent (e.g., a VEGF antagonist), and other agents to treat cancer. Combinations thereof are also included in the invention.

The term "PD-1 axis binding antagonist" refers to a molecule that inhibits the interaction of a PD-1 axis binding partner with either one or more of its binding partners, so as to remove T-cell dysfunction resulting from signaling on the PD-1 signaling axis, with a result being to restore or enhance T-cell function (e.g., proliferation, cytokine production, and/or target cell killing). As used herein, a PD-1 axis binding antagonist includes a PD-L1 binding antagonist, a PD-1 binding antagonist, and a PD-L2 binding antagonist. In some instances, the PD-1 axis binding antagonist includes a PD-L1 binding antagonist or a PD-1 binding antagonist. In a preferred aspect, the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

The term "PD-L1 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates, or interferes with signal transduction resulting from the interaction of PD-L1 with either one or more of its binding partners, such as PD-1 and/or B7-1. In some instances, a PD-L1 binding antagonist is a molecule that inhibits the binding of PD-L1 to its binding partners. In a specific aspect, the PD-L1 binding antagonist inhibits binding of PD-L1 to PD-1 and/or B7-1. In some instances, the PD-L1 binding antagonists include anti-PD-L1 antibodies, antigen-binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L1 with one or more of its binding partners, such as PD-1 and/or B7-1. In one instance, a PD-L1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L1 so as to render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some instances, the PD-L1 binding antagonist binds to PD-L1. In some instances, a PD-L1 binding antagonist is an anti-PD-L1 antibody (e.g., an anti-PD-L1 antagonist antibody). Exemplary anti-PD-L1 antagonist antibodies include atezolizumab, MDX-1105, MEDI4736 (durvalumab), MSB0010718C (avelumab), SHR-1316, CS1001, envafolimab, TQB2450, ZKAB001, LP-002, CX-072, IMC-001, KL-A167, APL-502, cosibelimab, lodapolimab, FAZ053, TG-1501, BGB-A333, BCD-135, AK-106, LDP, GR1405, HLX20, MSB2311, RC98, PDL-GEX, KD036, KY1003, YBL-007, and HS-636. In some aspects, the anti-PD-L1 antibody is atezolizumab, MDX-1105, MEDI4736 (durvalumab), or MSB0010718C (avelumab). In one specific aspect, the PD-L1 binding antagonist is MDX-1105. In another specific aspect, the PD-L1 binding antagonist is MEDI4736 (durvalumab). In another specific aspect, the PD-L1 binding antagonist is MSB0010718C (avelumab). In other aspects, the PD-L1 binding antagonist may be a small molecule, e.g., GS-4224, INCB086550, MAX-10181, INCB090244, CA-170, or ABSK041, which in some instances may be administered orally. Other exemplary PD-L1 binding antagonists include AVA-004, MT-6035, VXM10, LYN192, GB7003, and JS-003. In a preferred aspect, the PD-L1 binding antagonist is atezolizumab.

The term "PD-1 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with one or more of its binding partners, such as PD-L1 and/or PD-L2. PD-1 (programmed death 1) is also referred to in the art as "programmed cell death 1," "PDCD1," "CD279," and "SLEB2." An exemplary human PD-1 is shown

in UniProtKB/Swiss-Prot Accession No. Q15116. In some instances, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to one or more of its binding partners. In a specific aspect, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1 and/or PD-L2. For example, PD-1 binding antagonists include anti-PD-1 antibodies, antigen-binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides, and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-1 with PD-L1 and/or PD-L2. In one instance, a PD-1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-1 so as render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some instances, the PD-1 binding antagonist binds to PD-1. In some instances, the PD-1 binding antagonist is an anti-PD-1 antibody (e.g., an anti-PD-1 antagonist antibody). Exemplary anti-PD-1 antagonist antibodies include nivolumab, pembrolizumab, MEDI-0680, PDR001 (spartalizumab), REGN2810 (cemiplimab), BGB-108, prolgolimab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, retifanlimab, sasanlimab, penpulimab, CS1003, HLX10, SCT-I10A, zimberelimab, balstilimab, genolimzumab, BI 754091, cetrelimab, YBL-006, BAT1306, HX008, budigalimab, AMG 404, CX-188, JTX-4014, 609A, Sym021, LZM009, F520, SG001, AM0001, ENUM 244C8, ENUM 388D4, STI-1110, AK-103, and hAb21. In a specific aspect, a PD-1 binding antagonist is MDX-1106 (nivolumab). In another specific aspect, a PD-1 binding antagonist is MK-3475 (pembrolizumab). In another specific aspect, a PD-1 binding antagonist is a PD-L2 Fc fusion protein, e.g., AMP-224. In another specific aspect, a PD-1 binding antagonist is MED1-0680. In another specific aspect, a PD-1 binding antagonist is PDR001 (spartalizumab). In another specific aspect, a PD-1 binding antagonist is REGN2810 (cemiplimab). In another specific aspect, a PD-1 binding antagonist is BGB-108. In another specific aspect, a PD-1 binding antagonist is prolgolimab. In another specific aspect, a PD-1 binding antagonist is camrelizumab. In another specific aspect, a PD-1 binding antagonist is sintilimab. In another specific aspect, a PD-1 binding antagonist is tislelizumab. In another specific aspect, a PD-1 binding antagonist is toripalimab. Other additional exemplary PD-1 binding antagonists include BION-004, CB201, AUNP-012, ADG104, and LBL-006.

The term "PD-L2 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. PD-L2 (programmed death ligand 2) is also referred to in the art as "programmed cell death 1 ligand 2," "PDCD1LG2," "CD273," "B7-DC," "Btdc," and "PDL2." An exemplary human PD-L2 is shown in UniProtKB/Swiss-Prot Accession No. Q9BQ51. In some instances, a PD-L2 binding antagonist is a molecule that inhibits the binding of PD-L2 to one or more of its binding partners. In a specific aspect, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1. Exemplary PD-L2 antagonists include anti-PD-L2 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. In one aspect, a PD-L2 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L2 so as render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to

antigen recognition). In some aspects, the PD-L2 binding antagonist binds to PD-L2. In some aspects, a PD-L2 binding antagonist is an immunoadhesin. In other aspects, a PD-L2 binding antagonist is an anti-PD-L2 antagonist antibody.

A "stromal inhibitor" refers to any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity and/or function of a gene or gene product associated with stroma (e.g., tumor-associated stroma). In some embodiments, the stromal inhibitor partially or fully blocks, inhibits, or neutralizes a biological activity and/or function of a gene or gene product associated with fibrotic tumors. In some embodiments, treatment with a stromal inhibitor results in the reduction of stroma, thereby resulting in an increased activity of an immunotherapy; for example, by increasing the ability of activating immune cells (e.g., proinflammatory cells) to infiltrate a fibrotic tissue (e.g., a fibrotic tumor). Targets for stromal gene antagonists are known in the art; for example, see Turley et al., *Nature Reviews Immunology* 15:669-682, 2015 and Rosenbloom et al., *Biochimica et Biophysica Acta* 1832:1088–1103, 2013. In some embodiments, the stromal inhibitor is a transforming growth factor beta (TGF-β), podoplanin (PDPN), leukocyte-associated immunoglobulin-like receptor 1 (LAIR1), SMAD, anaplastic lymphoma kinase (ALK), connective tissue growth factor (CTGF/CCN2), endothelial-1 (ET-1), AP-1, interleukin (IL)-13, lysyl oxidase homolog 2 (LOXL2), endoglin (CD105), fibroblast activation protein (FAP), vascular cell adhesion protein 1 (CD106), thymocyte antigen 1 (THY1), beta 1 integrin (CD29), platelet-derived growth factor (PDGF), PDGF receptor A (PDGFRα), PDGF receptor B (PDGFRβ), vimentin, smooth muscle actin alpha (ACTA2), desmin, endosialin (CD248), or S100 calcium-binding protein A4 (S100A4) antagonist.

A "TGF-β antagonist" refers to any molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of TGF-β with one or more of its interaction partners, such as a TGF-β cellular receptor. In some embodiments, a "TGF-β binding antagonist" is a molecule that inhibits the binding of TGF-β to its binding partners. In some embodiments, the TGF-β antagonist inhibits the activation of TGF-β. In some embodiments, the TGF-β antagonist includes an anti-TGF-β antibody, antigen binding fragments thereof, an immunoadhesin, a fusion protein, an oligopeptide, and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of TGF-β with one or more of its interaction partners. In some embodiments, the TGF-β antagonist is a polypeptide, a small molecule, or a nucleic acid. In some embodiments, the TGF-β antagonist (e.g., the TGF-β binding antagonist) inhibits TGF-β1, TGF-β2, and/or TGF-β3. In some embodiments, the TGF-β antagonist (e.g., the TGF-β binding antagonist) inhibits TGF-β receptor-1 (TGFBR1), TGF-β receptor-2 (TGFBR2), and/or TGF-β receptor-3 (TGFBR3).

The terms "anti-TGF-β antibody" and "an antibody that binds to TGF-β" refer to an antibody that is capable of binding TGF-β with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting TGF-β. In one embodiment, the extent of binding of an anti-TGF-β antibody to an unrelated, non-TGF-β protein is less than about 10% of the binding of the antibody to TGF-β as measured, for example, by a RIA. In certain embodiments, an anti-TGF-β antibody binds to an epitope of TGF-β that is conserved among TGF-β from different species. In some embodiments, the anti-TGF-β antibody inhibits TGF-β1, TGF-β2, and/or TGF-β3. In some embodiments, the anti-TGF-β antibody

inhibits TGF-β1, TGF-β2, and TGF-β3. In some embodiments, the anti-TGF-β antibody is a pan-specific anti-TGF-β antibody. In some embodiments, the anti-TGF-β antibody may be any anti-TGF-β antibody disclosed in, for example, U.S. Pat. No. 5,571,714 or in International Patent Application Nos. WO 92/00330, WO 92/08480, WO 95/26203, WO 97/13844, WO 00/066631, WO 05/097832, WO 06/086469, WO 05/010049, WO 06/116002, WO 07/076391, WO 12/167143, WO 13/134365, WO 14/164709, or WO 16/201282, each of which is incorporated herein by reference in its entirety. In particular embodiments, the anti-TGF-β antibody is fresolimumab, metelimumab, lerdelimumab, 1D11, 2G7, or a derivative thereof.

An "angiogenesis inhibitor" or "anti-angiogenesis agent" refers to a small molecular weight substance (including tyrosine kinase inhibitors), a polynucleotide, a polypeptide, an isolated protein, a recombinant protein, an antibody, or conjugates or fusion proteins thereof, that inhibits angiogenesis, vasculogenesis, or undesirable vascular permeability, either directly or indirectly. It should be understood that the anti-angiogenesis agent includes those agents that bind and block the angiogenic activity of the angiogenic factor or its receptor. For example, an anti-angiogenesis agent is an antibody or other antagonist to an angiogenic agent as defined above, e.g., antibodies to VEGF-A or the VEGF-A receptor (e.g., KDR receptor or Flt-1 receptor), anti-PDGFR inhibitors such as GLEEVEC™ (imatinib mesylate). Anti-angiogenesis agents also include native angiogenesis inhibitors, e.g., angiostatin, endostatin, etc. See, for example, Klagsbrun and D'Amore, *Annu. Rev. Physiol.*, 53:217-39 (1991); Streit and Detmar, *Oncogene*, 22:3172-3179 (2003) (e.g., Table 3 listing anti-angiogenic therapy in malignant melanoma); Ferrara & Alitalo, Nature Medicine 5(12):1359-1364 (1999); Tonini et al., *Oncogene*, 22:6549-6556 (2003) and, Sato *Int. J. Clin. Oncol.*, 8:200-206 (2003).

A "VEGF antagonist" or "VEGF-specific antagonist" refers to a molecule capable of binding to VEGF, reducing VEGF expression levels, or neutralizing, blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities, including, but not limited to, VEGF binding to one or more VEGF receptors, VEGF signaling, and VEGF mediated angiogenesis and endothelial cell survival or proliferation. For example, a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities can exert its effects by binding to one or more VEGF receptor (VEGFR) (e.g., VEGFR1, VEGFR2, VEGFR3, membrane-bound VEGF receptor (mbVEGFR), or soluble VEGF receptor (sVEGFR)). Such antagonists are also referred to herein as "VEGFR inhibitors." Included as VEGF-specific antagonists useful in the methods of the invention are polypeptides that specifically bind to VEGF, anti-VEGF antibodies and antigen-binding fragments thereof, receptor molecules and derivatives which bind specifically to VEGF thereby sequestering its binding to one or more receptors, fusions proteins (e.g., VEGF-Trap (Regeneron)), and $VEGF_{121}$-gelonin (Peregrine). VEGF-specific antagonists also include antagonist variants of VEGF polypeptides, antisense nucleobase oligomers complementary to at least a fragment of a nucleic acid molecule encoding a VEGF polypeptide; small RNAs complementary to at least a fragment of a nucleic acid molecule encoding a VEGF polypeptide; ribozymes that target VEGF; peptibodies to VEGF; and VEGF aptamers. VEGF antagonists also include polypeptides that bind to VEGFR, anti-VEGFR antibodies, and antigen-binding fragments thereof, and derivatives which bind to VEGFR thereby blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities (e.g., VEGF signaling), or fusions proteins. VEGF-specific antagonists also

include nonpeptide small molecules that bind to VEGF or VEGFR and are capable of blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities. Thus, the term "VEGF activities" specifically includes VEGF mediated biological activities of VEGF. In certain embodiments, the VEGF antagonist reduces or inhibits, by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more, the expression level or biological activity of VEGF. In some embodiments, the VEGF inhibited by the VEGF-specific antagonist is VEGF (8-109), VEGF (1-109), or $VEGF_{165}$.

As used herein VEGF antagonists can include, but are not limited to, anti-VEGFR2 antibodies and related molecules (e.g., ramucirumab, tanibirumab, aflibercept), anti-VEGFR1 antibodies and related molecules (e.g., icrucumab, aflibercept (VEGF Trap-Eye; EYLEA®), and ziv-aflibercept (VEGF Trap; ZALTRAP®)), bispecific VEGF antibodies (e.g., MP-0250, vanucizumab (VEGF-ANG2), and bispecific antibodies disclosed in US 2001/0236388), bispecific antibodies including combinations of two of anti-VEGF, anti-VEGFR1, and anti-VEGFR2 arms, anti-VEGFA antibodies (e.g., bevacizumab, sevacizumab), anti-VEGFB antibodies, anti-VEGFC antibodies (e.g., VGX-100), anti-VEGFD antibodies, and nonpeptide small molecule VEGF antagonists (e.g., pazopanib, axitinib, vandetanib, stivarga, cabozantinib, lenvatinib, nintedanib, orantinib, telatinib, dovitinig, cediranib, motesanib, sulfatinib, apatinib, foretinib, famitinib, and tivozanib). In some examples, the VEGF antagonist may be a tyrosine kinase inhibitor, including a receptor tyrosine kinase inhibitors (e.g., a multi-targeted receptor tyrosine kinase inhibitor such as sunitinib or axitinib).

An "anti-VEGF antibody" is an antibody that binds to VEGF with sufficient affinity and specificity. In certain embodiments, the antibody will have a sufficiently high binding affinity for VEGF, for example, the antibody may bind hVEGF with a Kd value of between 100 nM-1 pM. Antibody affinities may be determined, e.g., by a surface plasmon resonance based assay (such as the BIAcore® assay as described in PCT Application Publication No. WO2005/012359); enzyme-linked immunoabsorbent assay (ELISA); and competition assays (e.g. radioimmunoassays (RIAs)).

In certain embodiments, the anti-VEGF antibody can be used as a therapeutic agent in targeting and interfering with diseases or conditions wherein the VEGF activity is involved. Also, the antibody may be subjected to other biological activity assays, e.g., in order to evaluate its effectiveness as a therapeutic. Such assays are known in the art and depend on the target antigen and intended use for the antibody. Examples include the HUVEC inhibition assay; tumor cell growth inhibition assays (as described in WO 89/06692, for example); antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (CDC) assays (U.S. Pat. No. 5,500,362); and agonistic activity or hematopoiesis assays (see WO 95/27062). An anti-VEGF antibody will usually not bind to other VEGF homologues such as VEGF-B or VEGF-C, nor other growth factors such as PlGF, PDGF, or bFGF. In one embodiment, anti-VEGF antibody is a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709. In another embodiment, the anti-VEGF antibody is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (*Cancer Res.* 57:4593-4599, 1997), including but not limited to the antibody known as bevacizumab (BV; AVASTIN®).

The anti-VEGF antibody "bevacizumab (BV)," also known as "rhuMAb VEGF" or "AVASTIN®," is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (*Cancer Res.* 57:4593-4599, 1997). It comprises mutated human IgG1 framework regions and antigen-binding complementarity-determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence of bevacizumab, including most of the framework regions, is derived from human IgG1, and about 7% of the sequence is derived from the murine antibody A4.6.1. Bevacizumab has a molecular mass of about 149,000 daltons and is glycosylated. Bevacizumab and other humanized anti-VEGF antibodies are further described in U.S. Pat. No. 6,884,879 issued Feb. 26, 2005, the entire disclosure of which is expressly incorporated herein by reference. Additional preferred antibodies include the G6 or B20 series antibodies (e.g., G6-31, B20-4.1), as described in PCT Application Publication No. WO 2005/012359. For additional preferred antibodies see U.S. Pat. Nos. 7,060,269, 6,582,959, 6,703,020; 6,054,297; WO98/45332; WO 96/30046; WO94/10202; EP 0666868B1; U.S. Patent Application Publication Nos. 2006009360, 20050186208, 20030206899, 20030190317, 20030203409, and 20050112126; and Popkov et al., (*Journal of Immunological Methods* 288:149-164, 2004). Other preferred antibodies include those that bind to a functional epitope on human VEGF comprising of residues F17, M18, D19, Y21, Y25, Q89, 191, K101, E103, and C104 or, alternatively, comprising residues F17, Y21, Q22, Y25, D63, 183, and Q89.

The term "immunotherapy agent" refers the use of a therapeutic agent that modulates an immune response. Exemplary, non-limiting immunotherapy agents include a PD-1 axis binding antagonist, a CTLA-4 antagonist (e.g., an anti-CTLA-4 antibody (e.g., ipilimumab)), a TIGIT antagonist (e.g., an anti-TIGIT antibody (e.g., tiragolumab)), PD1-IL2v (a fusion of an anti-PD-1 antibody and modified IL-2), PD1-LAG3, IL-15, anti-CCR8 (e.g., an anti-CCR8 antibody, e.g., FPA157), FAP-4-1BBL (fibroblast activation protein-targeted 4-1BBL agonist), or a combination thereof. In some examples, the immunotherapy agent is an immune checkpoint inhibitor. In some examples, the immunotherapy agent is a CD28, OX40, GITR, CD137, CD27, ICOS, HVEM, NKG2D, MICA, or 2B4 agonist or a CTLA-4, PD-1 axis, TIM-3, BTLA, VISTA, LAG-3, B7H4, CD96, TIGIT, or CD226 antagonist. Other particular immunotherapy agents include anti-TIGIT antibodies and antigen-binding fragments thereof, anti-CTLA-4 antibodies or antigen-binding fragments thereof, anti-CD27 antibodies or antigen-binding fragments thereof, anti-CD30 antibodies or antigen-binding fragments thereof, anti-CD40 antibodies or antigen-binding fragments thereof, anti-4-1BB antibodies or antigen-binding fragments thereof, anti-GITR antibodies or antigen-binding fragments thereof, anti-OX40 antibodies or antigen-binding fragments thereof, anti-TRAILR1 antibodies or antigen-binding fragments thereof, anti-TRAILR2 antibodies or antigen-binding fragments thereof, anti-TWEAK antibodies or antigen-binding fragments thereof, anti-TWEAKR antibodies or antigen-binding fragments thereof, anti-BRAF antibodies or antigen-binding fragments thereof, anti-MEK antibodies or antigen-binding fragments thereof, anti-CD33 antibodies or antigen-binding fragments thereof, anti-CD20 antibodies or antigen-binding fragments thereof, anti-CD52 antibodies or antigen-binding fragments thereof, anti-A33 antibodies or antigen-binding fragments thereof, anti-GD3 antibodies or antigen-binding fragments thereof, anti-PSMA antibodies or antigen-binding fragments thereof, anti-

Ceacan 1 antibodies or antigen-binding fragments thereof, anti-Galedin 9 antibodies or antigen-binding fragments thereof, anti-HVEM antibodies or antigen-binding fragments thereof, anti-VISTA antibodies or antigen-binding fragments thereof, anti-B7 H4 antibodies or antigen-binding fragments thereof, anti-HHLA2 antibodies or antigen-binding fragments thereof, anti-CD155 antibodies or antigen-binding fragments thereof, anti-CD80 antibodies or antigen-binding fragments thereof, anti-BTLA antibodies or antigen-binding fragments thereof, anti-CD160 antibodies or antigen-binding fragments thereof, anti-CD28 antibodies or antigen-binding fragments thereof, anti-CD226 antibodies or antigen-binding fragments thereof, anti-CEACAM1 antibodies or antigen-binding fragments thereof, anti-TIM3 antibodies or antigen-binding fragments thereof, anti-CD96 antibodies or antigen-binding fragments thereof, anti-CD70 antibodies or antigen-binding fragments thereof, anti-CD27 antibodies or antigen-binding fragments thereof, anti-LIGHT antibodies or antigen-binding fragments thereof, anti-CD137 antibodies or antigen-binding fragments thereof, anti-DR4 antibodies or antigen-binding fragments thereof, anti-CR5 antibodies or antigen-binding fragments thereof, anti-FAS antibodies or antigen-binding fragments thereof, anti-CD95 antibodies or antigen-binding fragments thereof, anti-TRAIL antibodies or antigen-binding fragments thereof, anti-DR6 antibodies or antigen-binding fragments thereof, anti-EDAR antibodies or antigen-binding fragments thereof, anti-NGFR antibodies or antigen-binding fragments thereof, anti-OPG antibodies or antigen-binding fragments thereof, anti-RANKL antibodies or antigen-binding fragments thereof, anti-LTβR antibodies or antigen-binding fragments thereof, anti-BCMA antibodies or antigen-binding fragments thereof, anti-TACI antibodies or antigen-binding fragments thereof, anti-BAFFR antibodies or antigen-binding fragments thereof, anti-EDAR2 antibodies or antigen-binding fragments thereof, anti-TROY antibodies or antigen-binding fragments thereof, and anti-RELT antibodies or antigen-binding fragments thereof.

The terms "programmed death ligand 1" and "PD-L1" refer herein to native sequence human PD-L1 polypeptide. Native sequence PD-L1 polypeptides are provided under Uniprot Accession No. Q9NZQ7. For example, the native sequence PD-L1 may have the amino acid sequence as set forth in Uniprot Accession No. Q9NZQ7-1 (isoform 1). In another example, the native sequence PD-L1 may have the amino acid sequence as set forth in Uniprot Accession No. Q9NZQ7-2 (isoform 2). In yet another example, the native sequence PD-L1 may have the amino acid sequence as set forth in Uniprot Accession No. Q9NZQ7-3 (isoform 3). PD-L1 is also referred to in the art as "programmed cell death 1 ligand 1," "PDCD1LG1," "CD274," "B7-H," and "PDL1."

The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (e.g., Kabat et al., *Sequences of Immunological Interest*. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The "EU numbering system" or "EU index" is generally used when referring to a residue in an immunoglobulin heavy chain constant region (e.g., the EU index reported in Kabat et al., *supra*). The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody.

For the purposes herein, "atezolizumab" is an Fc-engineered, humanized, non-glycosylated IgG1 kappa immunoglobulin that binds PD-L1 and comprises the heavy chain sequence of SEQ ID NO: 1 and the light chain sequence of SEQ ID NO: 2. Atezolizumab comprises a single amino acid substitution

(asparagine to alanine) at position 297 on the heavy chain (N297A) using EU numbering of Fc region amino acid residues, which results in a non-glycosylated antibody that has minimal binding to Fc receptors. Atezolizumab is also described in WHO Drug Information (International Nonproprietary Names for Pharmaceutical Substances), Proposed INN: List 112, Vol. 28, No. 4, published January 16, 2015 (see page 485).

The term "cancer" refers to a disease caused by an uncontrolled division of abnormal cells in a part of the body. In one instance, the cancer is kidney cancer e.g., an inoperable, locally advanced, or metastatic RCC. The cancer may be locally advanced or metastatic. In some instances, the cancer is locally advanced. In other instances, the cancer is metastatic. In some instances, the cancer may be unresectable (e.g., unresectable locally advanced or metastatic cancer). In some embodiments, the kidney cancer is sarcomatoid kidney cancer (e.g., sarcomatoid RCC (e.g., sarcomatoid advanced or mRCC)). In some embodiments, the kidney cancer is non-sarcomatoid kidney cancer (e.g., non-sarcomatoid RCC (e.g., non-sarcomatoid advanced or mRCC)). In some embodiments, the kidney cancer is clear cell kidney cancer (e.g., clear cell RCC (ccRCC) (e.g., advanced or metastatic ccRCC)). In some embodiments, the kidney cancer is non-clear cell kidney cancer (e.g., non-clear cell RCC (e.g., non-clear cell advanced or mRCC)).

As used herein, "cluster" refers to a subtype of a cancer (e.g., kidney cancer (e.g., inoperable, locally advanced, or metastatic RCC)) that is defined, e.g., transcriptionally (e.g., as assessed by RNA-seq or other techniques described herein) and/or by evaluation of somatic alterations. Cluster analysis can be used to identify subtypes of cancer by clustering samples (e.g., tumor samples) from patients having similar gene expression patterns and to find groups of genes that have similar expression profiles across different samples. A patient's sample (e.g., tumor sample) can be assigned into a cluster as described herein. In some examples, clusters are identified by non-negative matrix factorization (NMF); however, other clustering approaches are described herein and known in the art. In some examples, a patient's tumor sample is assigned into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA.

The term "sarcomatoid" refers to a cancer (e.g., kidney cancer (e.g., inoperable, locally advanced, or metastatic RCC)) that is characterized by sarcomatoid morphology, for example, as assessed by histology. Sarcomatoid kidney cancer (e.g., sarcomatoid RCC) is associated with aggressive behavior and poor prognosis. In some embodiments, a sarcomatoid kidney cancer includes or consists of atypical spindle-shaped cells and/or resembles any form of sarcoma. See, e.g., El Mouallem et al. *Urol. Oncol.* 36:265-271, 2018, which is incorporated herein by reference in its entirety. Sarcomatoid RCC can occur in any subtype of RCC, including clear cell RCC, chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, fumarate hydratase (FH)-deficient RCC, and succinate dehydrogenase (SDH)-deficient RCC. The incidence of sarcomatoid RCC varies among subtypes, but is typically higher in clear cell RCC (approximately 5-8%) and chromophobe RCC (approximately 8-10%). The histology of the sarcomatoid component can be variable, and may include a fibrosarcoma-like pattern, a pleomorphic undifferentiated sarcoma-like pattern, or other heterologous sarcomatoid patterns (e.g., osteosarcoma-,

chondrosarcoma-, or rhabdomyosarcoma-like patterns). Necrosis is typically present in a large majority (about 90%) of cases. In some embodiments, there is no minimum amount or percentage of sarcomatoid differentiation for an individual's kidney cancer to be classified as sarcomatoid. Sarcomatoid RCC may be assessed as described in Example 1 of U.S. Patent Application Publication No. 2021/0253710, which is incorporated by reference herein in its entirety. In other embodiments, sarcomatoid RCC may be characterized as described by the 2012 International Society of Urological Pathology (ISUP) Vancouver consensus (see Srigley et al. *Am. J. Surg. Pathol.* 37:1469-89, 2013, which is incorporated herein by reference in its entirety).

The term "Memorial Sloan Kettering Cancer Center (MSKCC) risk score" refers to a scoring system based on set of prognostic factors associated with survival in kidney cancer (e.g., RCC, e.g., mRCC) patients. See, e.g., Motzer et al. *J. Clin. Oncol.* 17(8):2530-2540, 1999 and Motzer et al. *J. Clin. Oncol.* 20(1):289-296, 2002, which are incorporated herein by reference in their entirety. In some embodiments, a MSKCC risk score can be calculated based on the following factors: (i) a time from nephrectomy to treatment (e.g., systemic treatment) of less than one year, a lack of a nephrectomy, or an initial diagnosis with metastatic disease; (ii) a hemoglobin level less than the lower limit of normal (LLN), optionally wherein the normal range for hemoglobin is between 13.5 and 17.5 g/dL for men and between 12 and 15.5 g/dL for women; (iii) a serum corrected calcium level greater than 10 mg/dL, optionally wherein the serum corrected calcium level is the serum calcium level (mg/dL) + 0.8(4 – serum albumin (g/dL)); (iv) a serum lactate dehydrogenase (LDH) level greater than 1.5 times the upper limit of normal (ULN), optionally wherein the ULN is 140 U/L; and/or (v) a Karnofsky Performance Status (KPS) score of <80. In some embodiments, an individual has a favorable MSKCC risk score if the individual has zero of the preceding characteristics. In some embodiments, an individual has an intermediate MSKCC risk score if the individual has one or two of the preceding characteristics. In some embodiments, an individual has a poor MSKCC risk score if the individual has three or more of the preceding characteristics. In some examples, an individual's MSKCC risk score may be used to identify whether the individual may benefit from an anti-cancer therapy, e.g., an anti-cancer therapy that includes a PD-L1 axis binding antagonist (e.g., an anti-PD-L1 antibody such as atezolizumab) and a VEGF antagonist (e.g., an anti-VEGF antibody such as bevacizumab), e.g., as described in U.S. Patent Application Publication No. 2021/0253710.

As used herein, "treating" comprises effective cancer treatment with an effective amount of a therapeutic agent (e.g., a PD-1 axis binding antagonist (e.g., atezolizumab) or combination of therapeutic agents (e.g., a PD-1 axis antagonist and one or more additional therapeutic agents, e.g., a VEGF antagonist). Treating herein includes, *inter alia*, adjuvant therapy, neoadjuvant therapy, non-metastatic cancer therapy (e.g., locally advanced cancer therapy), and metastatic cancer therapy. The treatment may be first-line treatment (e.g., the patient may be previously untreated or not have received prior systemic therapy), or second line or later treatment. In particular examples, the treatment may be first-line treatment (e.g., the patient may be previously untreated or not have received prior systemic therapy).

Herein, an "effective amount" refers to the amount of a therapeutic agent (e.g., a PD-1 axis binding antagonist (e.g., atezolizumab) or a combination of therapeutic agents (e.g., a PD-1 axis

antagonist and one or more additional therapeutic agents, e.g., a VEGF antagonist)), that achieves a therapeutic result. In some examples, the effective amount of a therapeutic agent or a combination of therapeutic agents is the amount of the agent or of the combination of agents that achieves a clinical endpoint of improved overall response rate (ORR), a complete response (CR), a pathological complete response (pCR), a partial response (PR), improved survival (e.g., disease-free survival (DFS), progression-free survival (PFS) and/or overall survival (OS)), and/or improved duration of response (DOR). Improvement (e.g., in terms of response rate (e.g., ORR, CR, and/or PR), survival (e.g., PFS and/or OS), or DOR) may be relative to a suitable reference treatment, for example, treatment that does not include the PD-1 axis binding antagonist and/or treatment that includes a tyrosine kinase inhibitor (e.g., sunitinib). For example, treatment with an anti-cancer therapy that includes atezolizumab and bevacizumab may be compared with a reference treatment which is treatment with sunitinib. In another example, treatment with an anti-cancer therapy that includes avelumab and axitinib may be compared with a reference treatment which is treatment with sunitinib.

As used herein, "complete response" and "CR" refers to disappearance of the cancer. In some examples, tumor response is assessed according to RECIST v1.1. For example, CR may be the disappearance of all target lesions and non-target lesions and (if applicable) normalization of tumor marker level or reduction in short axis of any pathological lymph nodes to < 10 mm.

As used herein, "partial response" and "PR" refers to at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline SLD prior to treatment. In some examples, tumor response is assessed according to RECIST v1.1. For example, PR may be a ≥ 30% decrease in the sum of diameters (SoD) of target lesions (taking as reference the baseline SoD) or persistence of ≥ 1 non-target lesions(s) and/or (if applicable) maintenance of tumor marker level above the normal limits. In some examples, the SoD may be of the longest diameters for non-nodal lesions, and the short axis for nodal lesions.

As used herein, "disease progression," "progressive disease," and "PD" refers to an increase in the size or number of target lesions. For example, PD may be a ≥ 20% relative increase in the sum of diameters (SoD) of all target lesions, taking as reference the smallest SoD on study, including baseline, and an absolute increase of ≥ 5 mm; ≥ 1 new lesion(s); and/or unequivocal progression of existing non-target lesions. In some examples, the SoD may be of the longest diameters for non-nodal lesions, and the short axis for nodal lesions.

As used herein, "overall response rate," "objective response rate," and "ORR" refer interchangeably to the sum of CR rate and PR rate. For example, ORR may refer to the percentage of participants with a documented CR or PR.

As used herein, "progression-free survival" and "PFS" refer to the length of time during and after treatment during which the cancer does not get worse. PFS may include the amount of time patients have experienced a CR or a PR, as well as the amount of time patients have experienced stable disease. For example, PFS may be the time from randomization to PD, as determined by the investigator per RECIST v1.1, or death from any cause, whichever occurred first.

As used herein, "overall survival" and "OS" refer to the length of time from either the date of diagnosis or the start of treatment for a disease (e.g., cancer) that the patient is still alive. For example, OS may be the time from randomization to death due to any cause.

As used herein, the term "duration of response" and "DOR" refer to a length of time from documentation of a tumor response until disease progression or death from any cause, whichever occurs first. For example, DOR may be the time from the first occurrence of CR/PR to PD as determined by the investigator per RECIST v1.1, or death from any cause, whichever occurred first.

As used herein, the term "chemotherapeutic agent" refers to a compound useful in the treatment of cancer, such as kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC). Examples of chemotherapeutic agents include EGFR inhibitors (including small molecule inhibitors (e.g., erlotinib (TARCEVA®, Genentech/OSI Pharm.); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA®) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); and dual EGFR/HER2 tyrosine kinase inhibitors such as lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3 fluorophenyl)methoxy]phenyl]-6[5[[[2methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine)); a tyrosine kinase inhibitor (e.g., an EGFR inhibitor; a small molecule HER2 tyrosine kinase inhibitor such as TAK165 (Takeda); CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; PKI-166 (Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 (ISIS Pharmaceuticals) which inhibit Raf-1 signaling; non-HER-targeted tyrosine kinase inhibitors such as imatinib mesylate (GLEEVEC®, Glaxo SmithKline); multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (Pharmacia); quinazolines, such as PD 153035,4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lamber); antisense molecules (e.g., those that bind to HER-encoding nucleic acid); quinoxalines (U.S. Patent No. 5,804,396); tryphostins (U.S. Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone); and rapamycin (sirolimus,

RAPAMUNE®)); proteasome inhibitors such as bortezomib (VELCADE®, Millennium Pharm.); disulfiram; epigallocatechin gallate; salinosporamide A; carfilzomib; 17-AAG (geldanamycin); radicicol; lactate dehydrogenase A (LDH-A); fulvestrant (FASLODEX®, AstraZeneca); letrozole (FEMARA®, Novartis), finasunate (VATALANIB®, Novartis); oxaliplatin (ELOXATIN®, Sanofi); 5-FU (5-fluorouracil); leucovorin; lonafamib (SCH 66336); sorafenib (NEXAVAR®, Bayer Labs); AG1478, alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including topotecan and irinotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5α-reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin, talc duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin γ1 and calicheamicin ω1); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamnol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes

(especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; etoposide (VP-16); ifosfamide; mitoxantrone; novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids, prodrugs, and derivatives of any of the above.

Chemotherapeutic agents also include (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, iodoxyfene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; buserelin, tripterelin, medroxyprogesterone acetate, diethylstilbestrol, premarin, fluoxymesterone, all transretionic acid, fenretinide, as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; (ix) growth inhibitory agents including vincas (e.g., vincristine and vinblastine), NAVELBINE® (vinorelbine), taxanes (e.g., paclitaxel, nab-paclitaxel, and docetaxel), topoisomerase II inhibitors (e.g., doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin), and DNA alkylating agents (e.g., tamoxigen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C); and (x) pharmaceutically acceptable salts, acids, prodrugs, and derivatives of any of the above.

The term "cytotoxic agent" as used herein refers to any agent that is detrimental to cells (e.g., causes cell death, inhibits proliferation, or otherwise hinders a cellular function). Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); chemotherapeutic agents; enzymes and fragments thereof such as nucleolytic enzymes; and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Exemplary cytotoxic agents can be selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, inhibitors of LDH-A, inhibitors of fatty acid biosynthesis, cell cycle signaling inhibitors, HDAC inhibitors, proteasome inhibitors, and inhibitors of cancer metabolism. In one instance, the cytotoxic agent is a platinum-based chemotherapeutic agent

(e.g., carboplatin or cisplatin). In one instance, the cytotoxic agent is an antagonist of EGFR, e.g., N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (e.g., erlotinib). In one instance the cytotoxic agent is a RAF inhibitor, e.g., a BRAF and/or CRAF inhibitor. In one instance the RAF inhibitor is vemurafenib. In one instance, the cytotoxic agent is a PI3K inhibitor.

The term "small molecule" refers to any molecule with a molecular weight of about 2000 daltons or less, preferably of about 500 daltons or less.

The term "patient" refers to a human patient. For example, the patient may be an adult.

The term "antibody" herein specifically covers monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired biological activity. In one instance, the antibody is a full-length monoclonal antibody.

The term IgG "isotype" or "subclass" as used herein is meant any of the subclasses of immunoglobulins defined by the chemical and antigenic characteristics of their constant regions.

Depending on the amino acid sequences of the constant domains of their heavy chains, antibodies (immunoglobulins) can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, γ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known and described generally in, for example, Abbas et al. *Cellular and Mol. Immunology*, 4th ed. (W.B. Saunders, Co., 2000). An antibody may be part of a larger fusion molecule, formed by covalent or non-covalent association of the antibody with one or more other proteins or peptides.

The terms "full-length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody in its substantially intact form, not antibody fragments as defined below. The terms refer to an antibody comprising an Fc region.

The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In one aspect, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, antibodies produced by host cells may undergo post-translational cleavage of one or more, particularly one or two, amino acids from the C-terminus of the heavy chain. Therefore, an antibody produced by a host cell by expression of a specific nucleic acid molecule encoding a full-length heavy chain may include the full-length heavy chain, or it may include a cleaved variant of the full-length heavy chain. This may be the case where the final two C-terminal amino acids of the heavy chain are glycine (G446) and lysine (K447). Therefore, the C-terminal lysine (Lys447), or the C-terminal glycine (Gly446) and lysine (Lys447), of the Fc region may or may not be present. Amino acid sequences of heavy chains including an Fc region are denoted herein without the C-terminal lysine (Lys447) if not indicated otherwise. In one aspect, a heavy chain including an Fc region as specified herein, comprised in an antibody disclosed herein, comprises an additional C-terminal glycine-lysine dipeptide (G446 and K447). In one aspect, a heavy chain including an Fc region as

specified herein, comprised in an antibody disclosed herein, comprises an additional C-terminal glycine residue (G446). In one aspect, a heavy chain including an Fc region as specified herein, comprised in an antibody disclosed herein, comprises an additional C-terminal lysine residue (K447). In one embodiment, the Fc region contains a single amino acid substitution N297A of the heavy chain. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.

A "naked antibody" refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical composition.

"Antibody fragments" comprise a portion of an intact antibody, preferably comprising the antigen-binding region thereof. In some instances, the antibody fragment described herein is an antigen-binding fragment. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules (e.g., scFvs); and multispecific antibodies formed from antibody fragments.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci.

The term "hypervariable region" or "HVR" as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence and which determine antigen binding specificity, for example "complementarity determining regions" ("CDRs").

Generally, antibodies comprise six CDRs: three in the VH (CDR-H1, CDR-H2, CDR-H3), and three in the VL (CDR-L1, CDR-L2, CDR-L3). Exemplary CDRs herein include:

(a) hypervariable loops occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987));

(b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991)); and

(c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al. *J. Mol. Biol.* 262: 732-745 (1996)).

Unless otherwise indicated, the CDRs are determined according to Kabat et al., *supra*. One of skill in the art will understand that the CDR designations can also be determined according to Chothia, *supra*, McCallum, *supra*, or any other scientifically accepted nomenclature system.

"Framework" or "FR" refers to variable domain residues other than complementary determining regions (CDRs). The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the CDR and FR sequences generally appear in the following sequence in VH (or VL): FR1-CDR-H1(CDR-L1)-FR2- CDR-H2(CDR-L2)-FR3- CDR-H3(CDR-L3)-FR4.

The term "variable domain residue numbering as in Kabat" or "amino acid position numbering as in Kabat," and variations thereof, refers to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat et al., *supra*. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or HVR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (e.g., residues 82a, 82b, and 82c, etc., according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

As used herein, "in combination with" refers to administration of one treatment modality in addition to another treatment modality, for example, a treatment regimen that includes administration of a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab). As such, "in combination with" refers to administration of one treatment modality before, during, or after administration of the other treatment modality to the patient.

A drug that is administered "concurrently" with one or more other drugs is administered during the same treatment cycle, on the same day of treatment, as the one or more other drugs, and, optionally, at the same time as the one or more other drugs. For instance, for cancer therapies given every 3 weeks, the concurrently administered drugs are each administered on day 1 of a 3 week cycle.

The term "detection" includes any means of detecting, including direct and indirect detection.

The term "biomarker" as used herein refers to an indicator, e.g., predictive, diagnostic, and/or prognostic, which can be detected in a sample, for example, a cluster, gene, or an alteration (e.g., a somatic alteration) disclosed herein. The biomarker may serve as an indicator of a particular subtype of a disease or disorder (e.g., cancer) characterized by certain, molecular, pathological, histological, and/or clinical features. Biomarkers include, but are not limited to, clusters, polynucleotides (e.g., DNA and/or RNA), polynucleotide copy number alterations (e.g., DNA copy numbers), polypeptides, polypeptide and polynucleotide modifications (e.g., post-translational modifications), carbohydrates, and/or glycolipid-based molecular markers. In some examples, a biomarker is a cluster, e.g., a cluster identified by NMF,

e.g., one of the following clusters: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA. In other examples, a biomarker is a gene. In yet other examples, a biomarker is an alteration (e.g., a somatic alteration).

The "amount" or "level" of a biomarker associated with an increased clinical benefit to an individual is a detectable level in a biological sample. These can be measured by methods known to one skilled in the art and also disclosed herein. The expression level or amount of biomarker assessed can be used to determine the response to the treatment.

The terms "level of expression" or "expression level" in general are used interchangeably and generally refer to the amount of a biomarker in a biological sample. "Expression" generally refers to the process by which information (e.g., gene-encoded and/or epigenetic information) is converted into the structures present and operating in the cell. Therefore, as used herein, "expression" may refer to transcription into a polynucleotide, translation into a polypeptide, or even polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide). Fragments of the transcribed polynucleotide, the translated polypeptide, or polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide) shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a post-translational processing of the polypeptide, e.g., by proteolysis. "Expressed genes" include those that are transcribed into a polynucleotide as mRNA and then translated into a polypeptide, and also those that are transcribed into RNA but not translated into a polypeptide (for example, transfer and ribosomal RNAs).

"Increased expression," "increased expression level," "increased levels," "elevated expression," "elevated expression levels," or "elevated levels" refers to an increased expression or increased levels of a biomarker in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control (e.g., a housekeeping biomarker).

"Decreased expression," "decreased expression level," "decreased levels," "reduced expression," "reduced expression levels," or "reduced levels" refers to a decrease expression or decreased levels of a biomarker in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control (e.g., a housekeeping biomarker). In some embodiments, reduced expression is little or no expression.

The term "housekeeping biomarker" refers to a biomarker or group of biomarkers (e.g., polynucleotides and/or polypeptides) which are typically similarly present in all cell types. In some embodiments, the housekeeping biomarker is a "housekeeping gene." A "housekeeping gene" refers herein to a gene or group of genes which encode proteins whose activities are essential for the maintenance of cell function and which are typically similarly present in all cell types.

The term "diagnosis" is used herein to refer to the identification or classification of a molecular or pathological state, disease or condition (e.g., cancer (e.g., kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC))). For example, "diagnosis" may refer to identification of a particular type of cancer. "Diagnosis" may also refer to the classification of a particular subtype of cancer, for instance, by histopathological criteria, or by molecular features (e.g., a subtype characterized by expression of one or a combination of biomarkers (e.g., particular genes or proteins encoded by said

genes)). In some examples, a patient may be diagnosed by classifying the patient's cancer according to the methods disclosed herein, e.g., by assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative (6) stromal/proliferative; and (7) snoRNA.

The term "sample," as used herein, refers to a composition that is obtained or derived from a subject and/or individual of interest that contains a cellular and/or other molecular entity that is to be characterized and/or identified, for example, based on physical, biochemical, chemical, and/or physiological characteristics. For example, the phrase "disease sample" and variations thereof refers to any sample obtained from a subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized. Samples include, but are not limited to, tissue samples, primary or cultured cells or cell lines, cell supernatants, cell lysates, platelets, serum, plasma, vitreous fluid, lymph fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, whole blood, blood-derived cells, urine, cerebro-spinal fluid, saliva, sputum, tears, perspiration, mucus, tumor lysates, and tissue culture medium, tissue extracts such as homogenized tissue, tumor tissue, cellular extracts, and combinations thereof.

By "tissue sample" or "cell sample" is meant a collection of similar cells obtained from a tissue of a subject or individual. The source of the tissue or cell sample may be solid tissue as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, and/or aspirate; blood or any blood constituents such as plasma; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, or interstitial fluid; cells from any time in gestation or development of the subject. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell sample is obtained from a disease tissue/organ. For instance, a "tumor sample" is a tissue sample obtained from a tumor (e.g., a liver tumor) or other cancerous tissue. The tissue sample may contain a mixed population of cell types (e.g., tumor cells and non-tumor cells, cancerous cells and non-cancerous cells). The tissue sample may contain compounds which are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

A "tumor-infiltrating immune cell," as used herein, refers to any immune cell present in a tumor or a sample thereof. Tumor-infiltrating immune cells include, but are not limited to, intratumoral immune cells, peritumoral immune cells, other tumor stroma cells (e.g., fibroblasts), or any combination thereof. Such tumor-infiltrating immune cells can be, for example, T lymphocytes (such as CD8+ T lymphocytes and/or CD4+ T lymphocytes), B lymphocytes, or other bone marrow-lineage cells, including granulocytes (e.g., neutrophils, eosinophils, and basophils), monocytes, macrophages, dendritic cells (e.g., interdigitating dendritic cells), histiocytes, and natural killer cells.

A "tumor cell" as used herein, refers to any tumor cell present in a tumor or a sample thereof. Tumor cells may be distinguished from other cells that may be present in a tumor sample, for example, stromal cells and tumor-infiltrating immune cells, using methods known in the art and/or described herein.

A "reference sample," "reference cell," "reference tissue," "control sample," "control cell," "control tissue," or "reference level," as used herein, refers to a sample, cell, tissue, standard, or level that is used

for comparison purposes. In one embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or reference level is obtained from a healthy and/or non-diseased part of the body (e.g., tissue or cells) of the same subject or individual. For example, the reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or reference level may be healthy and/or non-diseased cells or tissue adjacent to the diseased cells or tissue (e.g., cells or tissue adjacent to a tumor). In another embodiment, a reference sample is obtained from an untreated tissue and/or cell of the body of the same subject or individual. In yet another embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or reference level is obtained from a healthy and/or non-diseased part of the body (e.g., tissues or cells) of an individual who is not the subject or individual. In even another embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or reference level is obtained from an untreated tissue and/or cell of the body of an individual who is not the subject or individual.

For the purposes herein a "section" of a tissue sample is meant a single part or piece of a tissue sample, for example, a thin slice of tissue or cells cut from a tissue sample (e.g., a tumor sample). It is to be understood that multiple sections of tissue samples may be taken and subjected to analysis, provided that it is understood that the same section of tissue sample may be analyzed at both morphological and molecular levels, or analyzed with respect to polypeptides (e.g., by immunohistochemistry) and/or polynucleotides (e.g., by in situ hybridization).

The phrase "based on" when used herein means that the information about one or more biomarkers is used to inform a treatment decision, information provided on a package insert, or marketing/promotional guidance, and the like. For example, a patient may be selected for an anti-cancer therapy and/or treated with an anti-cancer therapy based on classification of the patient as disclosed herein, e.g., by assignment of the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative (6) stromal/proliferative; and (7) snoRNA. In another example, a patient may be selected for an anti-cancer therapy and/or treated with an anti-cancer therapy based on (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*.

The term "multiplex-PCR" refers to a single PCR reaction carried out on nucleic acid obtained from a single source (e.g., an individual) using more than one primer set for the purpose of amplifying two or more DNA sequences in a single reaction.

The technique of "polymerase chain reaction" or "PCR" as used herein generally refers to a procedure wherein minute amounts of a specific piece of nucleic acid, RNA and/or DNA, are amplified as described, for example, in U.S. Pat. No. 4,683,195. Generally, sequence information from the ends of the region of interest or beyond needs to be available, such that oligonucleotide primers can be designed; these primers will be identical or similar in sequence to opposite strands of the template to be amplified. The 5' terminal nucleotides of the two primers may coincide with the ends of the amplified material. PCR can be used to amplify specific RNA sequences, specific DNA sequences from total genomic DNA, and

cDNA transcribed from total cellular RNA, bacteriophage, or plasmid sequences, etc. See generally Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.* 51:263 (1987) and Erlich, ed., *PCR Technology*, (Stockton Press, NY, 1989). As used herein, PCR is considered to be one, but not the only, example of a nucleic acid polymerase reaction method for amplifying a nucleic acid test sample, comprising the use of a known nucleic acid (DNA or RNA) as a primer and utilizes a nucleic acid polymerase to amplify or generate a specific piece of nucleic acid or to amplify or generate a specific piece of nucleic acid which is complementary to a particular nucleic acid.

"Quantitative real-time polymerase chain reaction" or "qRT-PCR" refers to a form of PCR wherein the amount of PCR product is measured at each step in a PCR reaction. This technique has been described in various publications including, for example, Cronin et al., *Am. J. Pathol.* 164(1):35-42 (2004) and Ma et al., *Cancer Cell* 5:607-616 (2004).

The term "microarray" refers to an ordered arrangement of hybridizable array elements, preferably polynucleotide probes, on a substrate.

The term "RNA-seq," also called "Whole Transcriptome Shotgun Sequencing (WTSS)," refers to the use of high-throughput sequencing technologies to sequence and/or quantify cDNA to obtain information about a sample's RNA content. Publications describing RNA-seq include: Wang et al. *Nature Reviews Genetics* 10(1):57-63, 2009; Ryan et al. *BioTechniques* 45(1):81-94, 2008; and Maher et al. *Nature* 458(7234):97-101, 2009.

II. Methods of Classifying Kidney Cancer

Provided herein are methods for classifying kidney cancer (e.g., an inoperable, locally advanced, or metastatic RCC), which may involve assigning a sample (e.g., a tumor sample) from the patient into a cluster as disclosed herein.

In one example, provided herein is a method of classifying a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, the method comprising assigning a sample obtained from the patient into one of the following seven clusters based on a transcriptional profile of the patient's sample: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA, thereby classifying the kidney cancer in the patient. In some examples, the transcriptional profile has been provided by assaying mRNA in a sample (e.g., a tumor sample) from the patient.

In another example, provided herein is a method of classifying a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, the method comprising: (a) assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and (b) assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA, thereby classifying the kidney cancer in the patient.

In some examples, the kidney cancer is previously untreated.

In one example, provided herein is a method of classifying a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer is previously untreated, the method comprising assigning the patient's tumor sample into one of the following seven clusters based on a transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA, thereby classifying the kidney cancer in the patient. In some examples, the transcriptional profile has been provided by assaying mRNA in a sample (e.g., a tumor sample) from the patient.

In another example, provided herein is a method of classifying a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer is previously untreated, the method comprising: (a) assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and (b) assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA, thereby classifying the kidney cancer in the patient.

Any suitable approach for assaying mRNA may be used. In some examples, assaying mRNA in the tumor sample from the patient comprises RNA sequencing (RNA-seq), reverse transcription-quantitative polymerase chain reaction (RT-qPCR), qPCR, multiplex qPCR or RT-qPCR, microarray analysis, serial analysis of gene expression (SAGE), MassARRAY technique, in situ hybridization (ISH), or a combination thereof. In some particular examples, assaying mRNA in the tumor sample from the patient comprises RNA-seq.

Any suitable approach can be used to identify clusters into which a patient's sample (e.g., tumor sample) may be assigned. For example, in some examples, clusters are identified by non-negative matrix factorization (NMF; see, e.g., Lee et al. *Nature* 401(6755):788-791, 1999 and Brunet et al. *Proc. Nat'l Acad. Sci. USA* 101:4164-4169, 2004), hierarchical clustering (see, e.g., Eisen et al. *Proc. Nat'l Acad. Sci. USA* 95(25):14863-8, 1998), partition clustering (e.g., K-means clustering, K-mediods clustering, or partitioning around medioids (PAM, see, e.g., Kaufman et al. *Finding Groups in Data:* John Wiley and Sons, Inc. 2008, pages 68-125)), model-based clustering (e.g., gaussian mixture models), principal component analysis, clustering with deep learning (see, e.g., Li et al. *Nat. Commun.* 11:2338, 2020), self-organizing map (see, e.g., Kohonen et al. *Biol. Cybernet.* 43(1):59-69, 1982), density-based spatial clustering of applications with noise (DBSCAN, see, e.g., Ester et al. *Proceedings of the Second International Conference on Knowledge Discovery and Data Mining*; Portland, Oregon: 3001507: AAAI Press; 1996. p. 226–31), and the like. In some examples, hierarchical clustering may include single-linkage, average-linkage, or complete-linkage hierarchical clustering algorithms. Reviews of exemplary clustering approaches are provided, e.g., in Oyalade et al. *Bioinform. And Biol. Insights* 10:237-253, 2016; Vidman et al. *PLoS One* 14(12)e0219102, 2019; and Jamail and Moussa, IntechOpen (DOI: 10.5772/intechopen.94069). In particular examples, clusters are identified by non-negative NMF, e.g., as described herein in Example 1.

In some examples, RNA-seq count data may be transformed prior to cluster analysis. Any suitable transformation approach can be used, e.g., logarithmic transformation (e.g., log2-transformation), variance stabilizing transformation, eight data transformation, and the like.

In some examples, the seven clusters are identified by NMF. In some examples, the seven clusters identified by NMF are based on a set of genes representing the top 10% most variable genes in a population of patients having previously untreated kidney cancer (e.g., an inoperable, locally advanced, or metastatic RCC). In some examples, the set of genes is set forth in Table 1.

Table 1. Genes Representing Top 10% Most Variable Transcripts in Previously Untreated Kidney Cancer

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
100	ADA	adenosine deaminase	4329	ALDH6A1	aldehyde dehydrogenase 6 family member A1
100033413	SNORD116-1	small nucleolar RNA, C/D box 116-1	4332	MNDA	myeloid cell nuclear differentiation antigen
100033414	SNORD116-2	small nucleolar RNA, C/D box 116-2	4337	MOCS1	molybdenum cofactor synthesis 1
100033418	SNORD116-6	small nucleolar RNA, C/D box 116-6	4345	CD200	CD200 molecule
100033420	SNORD116-8	small nucleolar RNA, C/D box 116-8	4360	MRC1	mannose receptor C-type 1
100033423	SNORD116-11	small nucleolar RNA, C/D box 116-11	439921	MXRA7	matrix remodeling associated 7
100033425	SNORD116-13	small nucleolar RNA, C/D box 116-13	440050	KRTAP5-7	keratin associated protein 5-7
100033426	SNORD116-14	small nucleolar RNA, C/D box 116-14	440270	GOLGA8B	golgin A8 family member B
100033427	SNORD116-15	small nucleolar RNA, C/D box 116-15	440348	NPIPB15	nuclear pore complex interacting protein family member B15
100033428	SNORD116-16	small nucleolar RNA, C/D box 116-16	440482	ANKRD20A5P	ankyrin repeat domain 20 family member A5, pseudogene
100033431	SNORD116-20	small nucleolar RNA, C/D box 116-20	440567	UQCRHL	ubiquinol-cytochrome c reductase hinge protein like
100033432	SNORD116-21	small nucleolar RNA, C/D box 116-21	440585	FAM183A	family with sequence similarity 183 member A
100033433	SNORD116-22	small nucleolar RNA, C/D box 116-22	440689	HIST2H2BF	histone cluster 2 H2B family member f
100033434	SNORD116-23	small nucleolar RNA, C/D box 116-23	440712	RHEX	regulator of hemoglobinization and erythroid cell expansion
100033435	SNORD116-24	small nucleolar RNA, C/D box 116-24	441027	TMEM150C	transmembrane protein 150C
100033436	SNORD116-25	small nucleolar RNA, C/D box 116-25	441054	C4orf47	chromosome 4 open reading frame 47
100033438	SNORD116-26	small nucleolar RNA, C/D box 116-26	441124	GTF2IP20	general transcription factor IIi pseudogene 20
100033439	SNORD116-27	small nucleolar RNA, C/D box 116-27	441168	CALHM6	calcium homeostasis modulator family member 6
100033804	SNORD115-30	small nucleolar RNA, C/D box 115-30	441294	CTAGE15	CTAGE family member 15
100033806	SNORD115-32	small nucleolar RNA, C/D box 115-32	441528	NA	NA
100033807	SNORD115-33	small nucleolar RNA, C/D box 115-33	442213	PTCHD4	patched domain containing 4
100033812	SNORD115-38	small nucleolar RNA, C/D box 115-38	442319	ZNF727	zinc finger protein 727
100033818	SNORD115-44	small nucleolar RNA, C/D box 115-44	443	ASPA	aspartoacylase
100033821	SNORD116-29	small nucleolar RNA, C/D box 116-29	445	ASS1	argininosuccinate synthase 1

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
100049587	SIGLEC14	sialic acid binding Ig like lectin 14	445347	TARP	TCR gamma alternate reading frame protein
10008	KCNE3	potassium voltage-gated channel subfamily E regulatory subunit 3	4485	MST1	macrophage stimulating 1
1001	CDH3	cadherin 3	4489	MT1A	metallothionein 1A
100113393	SNORD12B	small nucleolar RNA, C/D box 12B	4493	MT1E	metallothionein 1E
100124536	SNORA38B	small nucleolar RNA, H/ACA box 38B	4494	MT1F	metallothionein 1F
100124539	SNORA11B	small nucleolar RNA, H/ACA box 11B	4495	MT1G	metallothionein 1G
100126299	VTRNA2-1	vault RNA 2-1	4496	MT1H	metallothionein 1H
100127983	C8orf88	chromosome 8 open reading frame 88	4499	MT1M	metallothionein 1M
100129543	ZNF730	zinc finger protein 730	4500	MT1L	metallothionein 1L, pseudogene
100129697	LOC100129697	uncharacterized LOC100129697	4501	MT1X	metallothionein 1X
100132116	ACTA2-AS1	ACTA2 antisense RNA 1	4502	MT2A	metallothionein 2A
100132287	LOC100132287	uncharacterized LOC100132287	4504	MT3	metallothionein 3
100132417	FCGR1CP	Fc fragment of IgG receptor Ic, pseudogene	4508	ATP6	ATP synthase F0 subunit 6
100151683	RNU4ATAC	RNA, U4atac small nuclear (U12-dependent splicing)	4509	ATP8	ATP synthase F0 subunit 8
100151684	RNU6ATAC	RNA, U6atac small nuclear (U12-dependent splicing)	4512	COX1	cytochrome c oxidase subunit I
100192204	PPIAP30	peptidylprolyl isomerase A pseudogene 30	4513	COX2	cytochrome c oxidase subunit II
1002	CDH4	cadherin 4	4514	COX3	cytochrome c oxidase III
100233156	LOC100233156	tektin 4 pseudogene	4515	MTCP1	mature T-cell proliferation 1
10024	TROAP	trophinin associated protein	4519	CYTB	cytochrome b
100240734	LOC100240734	uncharacterized LOC100240734	4535	ND1	NADH dehydrogenase, subunit 1 (complex I)
100271927	RASA4B	RAS p21 protein activator 4B	4536	ND2	MTND2
100272147	CMC4	C-X9-C motif containing 4	4537	ND3	NADH dehydrogenase, subunit 3 (complex I)
100287171	WASHC1	WASH complex subunit 1	4538	ND4	NADH dehydrogenase, subunit 4 (complex I)
100287569	LINC00173	long intergenic non-protein coding RNA 173	4539	ND4L	NADH dehydrogenase, subunit 4L (complex I)
100288152	SLC9A3-AS1	SLC9A3 antisense RNA 1	4540	ND5	NADH dehydrogenase, subunit 5 (complex I)
100288332	NPIPA5	nuclear pore complex interacting protein family member A5	4541	ND6	NADH dehydrogenase, subunit 6 (complex I)
100288778	LOC100288778	WASH complex subunit 1 pseudogene	4543	MTNR1A	melatonin receptor 1A
100289333	LOC100289333	uncharacterized LOC100289333	4547	MTTP	microsomal triglyceride transfer protein
100293211	NA	NA	4564	TRNH	tRNA
100294362	LOC100294362	uncharacterized LOC100294362	4569	TRNM	tRNA
1003	CDH5	cadherin 5	4582	MUC1	mucin 1, cell surface associated
100302743	SNORA80B	small nucleolar RNA, H/ACA box 80B	4584	MUC3A	mucin 3A, cell surface associated
100303491	ZEB2-AS1	ZEB2 antisense RNA 1	4605	MYBL2	MYB proto-oncogene like 2
100313769	MIR320B2	microRNA 320b-2	4616	GADD45B	growth arrest and DNA damage inducible beta
1004	CDH6	cadherin 6	4629	MYH11	myosin heavy chain 11
100423062	IGLL5	immunoglobulin lambda like polypeptide 5	4634	MYL3	myosin light chain 3

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
10050	SLC17A4	solute carrier family 17 member 4	4645	MYO5B	myosin VB
100505679	UBE2Q2L	ubiquitin conjugating enzyme E2 Q2 like	4647	MYO7A	myosin VIIA
100506658	OCLN	occludin	4648	MYO7B	myosin VIIB
100506736	SLFN12L	schlafen family member 12 like	467	ATF3	activating transcription factor 3
100506755	MIR497HG	mir-497-195 cluster host gene	4674	NAP1L2	nucleosome assembly protein 1 like 2
100506898	MAGOH2P	mago homolog 2, pseudogene	4684	NCAM1	neural cell adhesion molecule 1
100507203	SMLR1	small leucine rich protein 1	4688	NCF2	neutrophil cytosolic factor 2
100507421	TMEM178B	transmembrane protein 178B	4689	NCF4	neutrophil cytosolic factor 4
100509457	NA	NA	4703	NEB	Nebulin
100510710	LOC100510710	glucosylceramidase-like	4739	NEDD9	neural precursor cell expressed, developmentally down-regulated 9
10053	AP1M2	adaptor related protein complex 1 mu 2 subunit	4741	NEFM	neurofilament medium
100652781	SNX29P1	sorting nexin 29 pseudogene 1	4747	NEFL	neurofilament light
10071	MUC12	mucin 12, cell surface associated	4751	NEK2	NIMA related kinase 2
10076	PTPRU	protein tyrosine phosphatase, receptor type U	4753	NELL2	neural EGFL like 2
10083	USH1C	USH1 protein network component harmonin	477	ATP1A2	ATPase Na+/K+ transporting subunit alpha 2
10085	EDIL3	EGF like repeats and discoidin domains 3	478	ATP1A3	ATPase Na+/K+ transporting subunit alpha 3
100874323	HOXA10-AS	HOXA10 antisense RNA	4803	NGF	nerve growth factor
1009	CDH11	cadherin 11	4804	NGFR	nerve growth factor receptor
100996809	NA	NA	481	ATP1B1	ATPase Na+/K+ transporting subunit beta 1
10100	TSPAN2	tetraspanin 2	4818	NKG7	natural killer cell granule protein 7
10103	TSPAN1	tetraspanin 1	482	ATP1B2	ATPase Na+/K+ transporting subunit beta 2
101059918	GOLGA8R	golgin A8 family member R	4828	NMB	neuromedin B
101060026	NA	NA	4837	NNMT	nicotinamide N-methyltransferase
101060789	NA	NA	4854	NOTCH3	notch 3
101060846	NA	NA	4855	NOTCH4	notch 4
10107	TRIM10	tripartite motif containing 10	4856	NOV	nephroblastoma overexpressed
10110	SGK2	SGK2, serine/threonine kinase 2	4857	NOVA1	NOVA alternative splicing regulator 1
10112	KIF20A	kinesin family member 20A	486	FXYD2	FXYD domain containing ion transport regulator 2
10117	ENAM	enamelin	487	ATP2A1	ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 1
1012	CDH13	cadherin 13	4881	NPR1	natriuretic peptide receptor 1
10123	ARL4C	ADP ribosylation factor like GTPase 4C	4883	NPR3	natriuretic peptide receptor 3
10125	RASGRP1	RAS guanyl releasing protein 1	4885	NPTX2	neuronal pentraxin 2
10129	FRY	FRY microtubule binding protein	4886	NPY1R	neuropeptide Y receptor Y1
1014	CDH16	cadherin 16	4888	NPY6R	neuropeptide Y receptor Y6 (pseudogene)
10141	LINC01587	long intergenic non-protein coding RNA 1587	4897	NRCAM	neuronal cell adhesion molecule
10144	FAM13A	family with sequence similarity 13 member A	4907	NT5E	5'-nucleotidase ecto
10149	ADGRG2	adhesion G protein-coupled receptor G2	4908	NTF3	neurotrophin 3

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
10158	PDZK1IP1	PDZK1 interacting protein 1	491	ATP2B2	ATPase plasma membrane Ca2+ transporting 2
10178	TENM1	teneurin transmembrane protein 1	4915	NTRK2	neurotrophic receptor tyrosine kinase 2
10186	LHFPL6	LHFPL tetraspan subfamily member 6	4916	NTRK3	neurotrophic receptor tyrosine kinase 3
101927594	NA	NA	4920	ROR2	receptor tyrosine kinase like orphan receptor 2
101927733	NA	NA	492307	PPDPFL	pancreatic progenitor cell differentiation and proliferation factor like
101927746	LOC101927746	uncharacterized LOC101927746	4929	NR4A2	nuclear receptor subfamily 4 group A member 2
101927905	LINC02449	long intergenic non-protein coding RNA 2449	4935	GPR143	G protein-coupled receptor 143
101927960	LOC101927960	uncharacterized LOC101927960	4948	OCA2	OCA2 melanosomal transmembrane protein
101927999	LOC101927999	putative uncharacterized protein FLJ44672	4958	OMD	osteomodulin
101928149	LOC101928149	nascent polypeptide-associated complex alpha subunit pseudogene	4969	OGN	osteoglycin
101928281	NA	NA	497190	CLEC18B	C-type lectin domain family 18 member B
101928706	NA	NA	4973	OLR1	oxidized low density lipoprotein receptor 1
101929206	NA	NA	4982	TNFRSF11B	TNF receptor superfamily member 11b
101929335	ADAMTS9-AS1	ADAMTS9 antisense RNA 1	5003	SLC22A18AS	solute carrier family 22 member 18 antisense
101929560	LOC101929560	uncharacterized LOC101929560	5004	ORM1	orosomucoid 1
101929773	LOC101929773	UDP-glucuronosyltransferase 2B10-like	5010	CLDN11	claudin 11
101930013	LOC101930013	polycystin-1-like	5046	PCSK6	proprotein convertase subtilisin/kexin type 6
101930662	NA	NA	50486	G0S2	G0/G1 switch 2
101930669	NA	NA	50507	NOX4	NADPH oxidase 4
10203	CALCRL	calcitonin receptor like receptor	50509	COL5A3	collagen type V alpha 3 chain
10216	PRG4	proteoglycan 4	50512	PODXL2	podocalyxin like 2
10225	CD96	CD96 molecule	5053	PAH	phenylalanine hydroxylase
10231	RCAN2	regulator of calcineurin 2	5054	SERPINE1	serpin family E member 1
10234	LRRC17	leucine rich repeat containing 17	50614	GALNT9	polypeptide N-acetylgalactosaminyltransferase 9
10246	SLC17A2	solute carrier family 17 member 2	5063	PAK3	p21 (RAC1) activated kinase 3
102465485	MIR6809	microRNA 6809	5071	PRKN	parkin RBR E3 ubiquitin protein ligase
102467147	LINC01948	long intergenic non-protein coding RNA 1948	5076	PAX2	paired box 2
10247	RIDA	reactive intermediate imine deaminase A homolog	50852	TRAT1	T-cell receptor associated transmembrane adaptor 1
10249	GLYAT	glycine-N-acyltransferase	50861	STMN3	stathmin 3
10252	SPRY1	sprouty RTK signaling antagonist 1	5087	PBX1	PBX homeobox 1
10256	CNKSR1	connector enhancer of kinase suppressor of Ras 1	5091	PC	pyruvate carboxylase
1026	CDKN1A	cyclin dependent kinase inhibitor 1A	50937	CDON	cell adhesion associated, oncogene regulated
10261	IGSF6	immunoglobulin superfamily member 6	50940	PDE11A	phosphodiesterase 11A
10265	IRX5	iroquois homeobox 5	5099	PCDH7	protocadherin 7

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
10266	RAMP2	receptor activity modifying protein 2	5104	SERPINA5	serpin family A member 5
10268	RAMP3	receptor activity modifying protein 3	5105	PCK1	phosphoenolpyruvate carboxykinase 1
10272	FSTL3	follistatin like 3	51084	CRYL1	crystallin lambda 1
102723407	LOC102723407	putative V-set and immunoglobulin domain-containing-like protein IGHV4OR15-8	51085	MLXIPL	MLX interacting protein like
102723493	LOC102723493	uncharacterized LOC102723493	51087	YBX2	Y-box binding protein 2
102723647	RPL23AP97	ribosomal protein L23a pseudogene 97	51090	PLLP	plasmolipin
102724058	LOC102724058	uncharacterized LOC102724058	51129	ANGPTL4	angiopoietin like 4
102724343	NA	NA	51162	EGFL7	EGF like domain multiple 7
102724424	NA	NA	51171	HSD17B14	hydroxysteroid 17-beta dehydrogenase 14
102724436	NA	NA	51176	LEF1	lymphoid enhancer binding factor 1
102724660	LOC102724660	uncharacterized LOC102724660	51179	HAO2	hydroxyacid oxidase 2
102724668	DPY19L1P2	DPY19L1 pseudogene 2	5118	PCOLCE	procollagen C-endopeptidase enhancer
102724788	LOC102724788	proline dehydrogenase 1, mitochondrial	51200	CPA4	carboxypeptidase A4
102724850	LOC102724850	uncharacterized LOC102724850	51206	GP6	glycoprotein VI platelet
102724880	LOC102724880	uncharacterized LOC102724880	51232	CRIM1	cysteine rich transmembrane BMP regulator 1
102725001	NA	NA	51233	DRICH1	aspartate rich 1
102725018	NA	NA	51237	MZB1	marginal zone B and B1 cell specific protein
102725414	NA	NA	5125	PCSK5	proprotein convertase subtilisin/kexin type 5
10276	NET1	neuroepithelial cell transforming 1	51268	PIPOX	pipecolic acid and sarcosine oxidase
10288	LILRB2	leukocyte immunoglobulin like receptor B2	51284	TLR7	toll like receptor 7
10319	LAMC3	laminin subunit gamma 3	5129	CDK18	cyclin dependent kinase 18
10326	SIRPB1	signal regulatory protein beta 1	51294	PCDH12	protocadherin 12
1033	CDKN3	cyclin dependent kinase inhibitor 3	51299	NRN1	neuritin 1
10331	B3GNT3	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 3	51302	CYP39A1	cytochrome P450 family 39 subfamily A member 1
10335	MRVI1	murine retrovirus integration site 1 homolog	51305	KCNK9	potassium two pore domain channel subfamily K member 9
10350	ABCA9	ATP binding cassette subfamily A member 9	51310	SLC22A17	solute carrier family 22 member 17
10351	ABCA8	ATP binding cassette subfamily A member 8	51311	TLR8	toll like receptor 8
10370	CITED2	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2	51316	PLAC8	placenta specific 8
10371	SEMA3A	semaphorin 3A	5133	PDCD1	programmed cell death 1
103752587	FOXC2-AS1	FOXC2 antisense RNA 1	51330	TNFRSF12A	TNF receptor superfamily member 12A
10381	TUBB3	tubulin beta 3 class III	51338	MS4A4A	membrane spanning 4-domains A4A

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
10382	TUBB4A	tubulin beta 4A class IVa	51339	DACT1	dishevelled binding antagonist of beta catenin 1
103908605	LOC103908605	uncharacterized LOC103908605	51351	ZNF117	zinc finger protein 117
10397	NDRG1	N-myc downstream regulated 1	5136	PDE1A	phosphodiesterase 1A
1040	CDS1	CDP-diacylglycerol synthase 1	51361	HOOK1	hook microtubule tethering protein 1
10406	WFDC2	WAP four-disulfide core domain 2	51365	PLA1A	phospholipase A1 member A
10409	BASP1	brain abundant membrane attached signal protein 1	5137	PDE1C	phosphodiesterase 1C
10411	RAPGEF3	Rap guanine nucleotide exchange factor 3	5138	PDE2A	phosphodiesterase 2A
10417	SPON2	spondin 2	5139	PDE3A	phosphodiesterase 3A
10418	SPON1	spondin 1	5140	PDE3B	phosphodiesterase 3B
1043	CD52	CD52 molecule	51411	BIN2	bridging integrator 2
10437	IFI30	IFI30, lysosomal thiol reductase	51421	AMOTL2	angiomotin like 2
10439	OLFM1	olfactomedin 1	51435	SCARA3	scavenger receptor class A member 3
10449	ACAA2	acetyl-CoA acyltransferase 2	51454	GULP1	GULP, engulfment adaptor PTB domain containing 1
10457	GPNMB	glycoprotein nmb	51471	NAT8B	N-acetyltransferase 8B (putative, gene/pseudogene)
10462	CLEC10A	C-type lectin domain containing 10A	51473	DCDC2	doublecortin domain containing 2
1047	CLGN	calmegin	51513	ETV7	ETS variant 7
10489	LRRC41	leucine rich repeat containing 41	5152	PDE9A	phosphodiesterase 9A
1050	CEBPA	CCAAT/enhancer binding protein alpha	51559	NT5DC3	5'-nucleotidase domain containing 3
10509	SEMA4B	semaphorin 4B	5156	PDGFRA	platelet derived growth factor receptor alpha
1051	CEBPB	CCAAT/enhancer binding protein beta	51560	RAB6B	RAB6B, member RAS oncogene family
10512	SEMA3C	semaphorin 3C	5157	PDGFRL	platelet derived growth factor receptor like
10516	FBLN5	fibulin 5	5158	PDE6B	phosphodiesterase 6B
10529	NEBL	nebulette	5159	PDGFRB	platelet derived growth factor receptor beta
10536	P3H3	prolyl 3-hydroxylase 3	5164	PDK2	pyruvate dehydrogenase kinase 2
10537	UBD	ubiquitin D	51655	RASD1	ras related dexamethasone induced 1
10538	BATF	basic leucine zipper ATF-like transcription factor	51659	GINS2	GINS complex subunit 2
10563	CXCL13	C-X-C motif chemokine ligand 13	5166	PDK4	pyruvate dehydrogenase kinase 4
10568	SLC34A2	solute carrier family 34 member 2	5167	ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
10578	GNLY	granulysin	51673	TPPP3	tubulin polymerization promoting protein family member 3
10579	TACC2	transforming acidic coiled-coil containing protein 2	51678	MPP6	membrane palmitoylated protein 6
10580	SORBS1	sorbin and SH3 domain containing 1	5168	ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2
10590	SCGN	secretagogin, EF-hand calcium binding protein	5169	ENPP3	ectonucleotide pyrophosphatase/phosphodiesterase 3
10610	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	51700	CYB5R2	cytochrome b5 reductase 2

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
10615	SPAG5	sperm associated antigen 5	51703	ACSL5	acyl-CoA synthetase long chain family member 5
1062	CENPE	centromere protein E	51704	GPRC5B	G protein-coupled receptor class C group 5 member B
1063	CENPF	centromere protein F	51705	EMCN	endomucin
10630	PDPN	podoplanin	51733	UPB1	beta-ureidopropionase 1
10631	POSTN	periostin	5174	PDZK1	PDZ domain containing 1
10642	IGF2BP1	insulin like growth factor 2 mRNA binding protein 1	51751	HIGD1B	HIG1 hypoxia inducible domain family member 1B
10643	IGF2BP3	insulin like growth factor 2 mRNA binding protein 3	5176	SERPINF1	serpin family F member 1
10644	IGF2BP2	insulin like growth factor 2 mRNA binding protein 2	51760	SYT17	synaptotagmin 17
10647	SCGB1D2	secretoglobin family 1D member 2	5187	PER1	period circadian regulator 1
1066	CES1	carboxylesterase 1	5197	PF4V1	platelet factor 4 variant 1
10663	CXCR6	C-X-C motif chemokine receptor 6	5222	PGA5	pepsinogen 5, group I (pepsinogen A)
10669	CGREF1	cell growth regulator with EF-hand domain 1	5224	PGAM2	phosphoglycerate mutase 2
10673	TNFSF13B	TNF superfamily member 13b	5228	PGF	placental growth factor
10687	PNMA2	PNMA family member 2	5239	PGM5	phosphoglucomutase 5
1071	CETP	cholesteryl ester transfer protein	5243	ABCB1	ATP binding cassette subfamily B member 1
10718	NRG3	neuregulin 3	5244	ABCB4	ATP binding cassette subfamily B member 4
10742	RAI2	retinoic acid induced 2	5255	PHKA1	phosphorylase kinase regulatory subunit alpha 1
10752	CHL1	cell adhesion molecule L1 like	5265	SERPINA1	serpin family A member 1
10763	NES	nestin	5266	PI3	peptidase inhibitor 3
10786	SLC17A3	solute carrier family 17 member 3	5270	SERPINE2	serpin family E member 2
108	ADCY2	adenylate cyclase 2	5274	SERPINI1	serpin family I member 1
10819	OR7E14P	olfactory receptor family 7 subfamily E member 14 pseudogene	5284	PIGR	polymeric immunoglobulin receptor
10826	FAXDC2	fatty acid hydroxylase domain containing 2	5307	PITX1	paired like homeodomain 1
10840	ALDH1L1	aldehyde dehydrogenase 1 family member L1	5313	PKLR	pyruvate kinase L/R
10841	FTCD	formimidoyltransferase cyclodeaminase	5314	PKHD1	PKHD1, fibrocystin/polyductin
10846	PDE10A	phosphodiesterase 10A	5317	PKP1	plakophilin 1
10870	HCST	hematopoietic cell signal transducer	5318	PKP2	plakophilin 2
10874	NMU	neuromedin U	5319	PLA2G1B	phospholipase A2 group IB
10878	CFHR3	complement factor H related 3	5320	PLA2G2A	phospholipase A2 group IIA
10882	C1QL1	complement C1q like 1	5327	PLAT	plasminogen activator, tissue type
10891	PPARGC1A	PPARG coactivator 1 alpha	5328	PLAU	plasminogen activator, urokinase
10893	MMP24	matrix metallopeptidase 24	5329	PLAUR	plasminogen activator, urokinase receptor
10894	LYVE1	lymphatic vessel endothelial hyaluronan receptor 1	5332	PLCB4	phospholipase C beta 4
10903	MTMR11	myotubularin related protein 11	5334	PLCL1	phospholipase C like 1 (inactive)
10911	UTS2	urotensin 2	53345	TM6SF2	transmembrane 6 superfamily member 2
10924	SMPDL3A	sphingomyelin phosphodiesterase acid like 3A	53347	UBASH3A	ubiquitin associated and SH3 domain containing A

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
10936	GPR75	G protein-coupled receptor 75	53354	PANK1	pantothenate kinase 1
10954	PDIA5	protein disulfide isomerase family A member 5	5341	PLEK	pleckstrin
10964	IFI44L	interferon induced protein 44 like	5345	SERPINF2	serpin family F member 2
10974	ADIRF	adipogenesis regulatory factor	5347	PLK1	polo like kinase 1
10990	LILRB5	leukocyte immunoglobulin like receptor B5	5348	FXYD1	FXYD domain containing ion transport regulator 1
10993	SDS	serine dehydratase	5350	PLN	phospholamban
11001	SLC27A2	solute carrier family 27 member 2	5352	PLOD2	procollagen-lysine,2-oxoglutarate 5-dioxygenase 2
11004	KIF2C	kinesin family member 2C	5355	PLP2	proteolipid protein 2
11005	SPINK5	serine peptidase inhibitor, Kazal type 5	5357	PLS1	plastin 1
11006	LILRB4	leukocyte immunoglobulin like receptor B4	5360	PLTP	phospholipid transfer protein
11013	TMSB15A	thymosin beta 15a	53616	ADAM22	ADAM metallopeptidase domain 22
11015	KDELR3	KDEL endoplasmic reticulum protein retention receptor 3	53630	BCO1	beta-carotene oxygenase 1
11040	PIM2	Pim-2 proto-oncogene, serine/threonine kinase	5365	PLXNB3	plexin B3
11065	UBE2C	ubiquitin conjugating enzyme E2 C	5367	PMCH	pro-melanin concentrating hormone
11067	DEPP1	DEPP1, autophagy regulator	5380	PMS2P2	PMS1 homolog 2, mismatch repair system component pseudogene 2
11069	RAPGEF4	Rap guanine nucleotide exchange factor 4	53829	P2RY13	purinergic receptor P2Y13
11078	TRIOBP	TRIO and F-actin binding protein	53833	IL20RB	interleukin 20 receptor subunit beta
11082	ESM1	endothelial cell specific molecule 1	53841	CDHR5	cadherin related family member 5
111	ADCY5	adenylate cyclase 5	53904	MYO3A	myosin IIIA
11113	CIT	citron rho-interacting serine/threonine kinase	5396	PRRX1	paired related homeobox 1
11117	EMILIN1	elastin microfibril interfacer 1	54	ACP5	acid phosphatase 5, tartrate resistant
11118	BTN3A2	butyrophilin subfamily 3 member A2	540	ATP7B	ATPase copper transporting beta
11136	SLC7A9	solute carrier family 7 member 9	54039	PCBP3	poly(rC) binding protein 3
11148	HHLA2	HERV-H LTR-associating 2	54101	RIPK4	receptor interacting serine/threonine kinase 4
11151	CORO1A	coronin 1A	54102	CLIC6	chloride intracellular channel 6
11155	LDB3	LIM domain binding 3	5414	SEPT4	septin 4
1116	CHI3L1	chitinase 3 like 1	5420	PODXL	podocalyxin like
11167	FSTL1	follistatin like 1	54206	ERRFI1	ERBB receptor feedback inhibitor 1
1117	CHI3L2	chitinase 3 like 2	54209	TREM2	triggering receptor expressed on myeloid cells 2
1118	CHIT1	chitinase 1	54210	TREM1	triggering receptor expressed on myeloid cells 1
11184	MAP4K1	mitogen-activated protein kinase kinase kinase kinase 1	54345	SOX18	SRY-box 18
11185	INMT	indolethylamine N-methyltransferase	54360	CYTL1	cytokine like 1
11227	GALNT5	polypeptide N-acetylgalactosaminyltransferase 5	54437	SEMA5B	semaphorin 5B

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
112399	EGLN3	egl-9 family hypoxia inducible factor 3	54443	ANLN	anillin actin binding protein
11240	PADI2	peptidyl arginine deiminase 2	5446	PON3	paraoxonase 3
11247	NXPH4	neurexophilin 4	54463	RETREG1	reticulophagy regulator 1
11259	FILIP1L	filamin A interacting protein 1 like	54507	ADAMTSL4	ADAMTS like 4
11262	SP140	SP140 nuclear body protein	54509	RHOF	ras homolog family member F, filopodia associated
112724	RDH13	retinol dehydrogenase 13	54510	PCDH18	protocadherin 18
112817	HOGA1	4-hydroxy-2-oxoglutarate aldolase 1	54538	ROBO4	roundabout guidance receptor 4
113026	PLCD3	phospholipase C delta 3	54541	DDIT4	DNA damage inducible transcript 4
113146	AHNAK2	AHNAK nucleoprotein 2	54546	RNF186	ring finger protein 186
113220	KIF12	kinesin family member 12	5455	POU3F3	POU class 3 homeobox 3
11326	VSIG4	V-set and immunoglobulin domain containing 4	54550	NECAB2	N-terminal EF-hand calcium binding protein 2
113278	SLC52A3	solute carrier family 52 member 3	54567	DLL4	delta like canonical Notch ligand 4
11346	SYNPO	synaptopodin	54575	UGT1A10	UDP glucuronosyltransferase family 1 member A10
113835	ZNF257	zinc finger protein 257	54576	UGT1A8	UDP glucuronosyltransferase family 1 member A8
1140	CHRNB1	cholinergic receptor nicotinic beta 1 subunit	54577	UGT1A7	UDP glucuronosyltransferase family 1 member A7
114088	TRIM9	tripartite motif containing 9	54578	UGT1A6	UDP glucuronosyltransferase family 1 member A6
114569	MAL2	mal, T-cell differentiation protein 2 (gene/pseudogene)	54579	UGT1A5	UDP glucuronosyltransferase family 1 member A5
114757	CYGB	cytoglobin	54587	MXRA8	matrix remodeling associated 8
114800	CCDC85A	coiled-coil domain containing 85A	5460	POU5F1	POU class 5 homeobox 1
114804	RNF157	ring finger protein 157	54600	UGT1A9	UDP glucuronosyltransferase family 1 member A9
114827	FHAD1	forkhead associated phosphopeptide binding domain 1	5462	POU5F1B	POU class 5 homeobox 1B
114836	SLAMF6	SLAM family member 6	54657	UGT1A4	UDP glucuronosyltransferase family 1 member A4
114897	C1QTNF1	C1q and TNF related 1	54658	UGT1A1	UDP glucuronosyltransferase family 1 member A1
1152	CKB	creatine kinase B	54659	UGT1A3	UDP glucuronosyltransferase family 1 member A3
115265	DDIT4L	DNA damage inducible transcript 4 like	54660	PCDHB18P	protocadherin beta 18 pseudogene
115273	RAB42	RAB42, member RAS oncogene family	54661	PCDHB17P	protocadherin beta 17 pseudogene
115290	FBXO17	F-box protein 17	5468	PPARG	peroxisome proliferator activated receptor gamma
115352	FCRL3	Fc receptor like 3	54682	MANSC1	MANSC domain containing 1
115361	GBP4	guanylate binding protein 4	5473	PPBP	pro-platelet basic protein
115362	GBP5	guanylate binding protein 5	54757	FAM20A	FAM20A, golgi associated secretory pathway pseudokinase
115677	NOSTRIN	nitric oxide synthase trafficking	54762	GRAMD1C	GRAM domain containing 1C
115701	ALPK2	alpha kinase 2	54768	HYDIN	HYDIN, axonemal central pair apparatus protein
115908	CTHRC1	collagen triple helix repeat containing 1	54769	DIRAS2	DIRAS family GTPase 2
1160	CKMT2	creatine kinase, mitochondrial 2	54798	DCHS2	dachsous cadherin-related 2
116085	SLC22A12	solute carrier family 22 member 12	54810	GIPC2	GIPC PDZ domain containing family member 2

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
116159	CYYR1	cysteine and tyrosine rich 1	54825	CDHR2	cadherin related family member 2
116238	TLCD1	TLC domain containing 1	54829	ASPN	asporin
116362	RBP7	retinol binding protein 7	54830	NUP62CL	nucleoporin 62 C-terminal like
1164	CKS2	CDC28 protein kinase regulatory subunit 2	54843	SYTL2	synaptotagmin like 2
116441	TM4SF18	transmembrane 4 L six family member 18	54845	ESRP1	epithelial splicing regulatory protein 1
116449	CLNK	cytokine dependent hematopoietic cell linker	54848	ARHGEF38	Rho guanine nucleotide exchange factor 38
116832	RPL39L	ribosomal protein L39 like	54852	PAQR5	progestin and adipoQ receptor family member 5
116842	LEAP2	liver enriched antimicrobial peptide 2	54855	FAM46C	family with sequence similarity 46 member C
116844	LRG1	leucine rich alpha-2-glycoprotein 1	54866	PPP1R14D	protein phosphatase 1 regulatory inhibitor subunit 14D
116937	SNORD83A	small nucleolar RNA, C/D box 83A	54869	EPS8L1	EPS8 like 1
116938	SNORD83B	small nucleolar RNA, C/D box 83B	54873	PALMD	palmdelphin
116966	WDR17	WD repeat domain 17	54900	LAX1	lymphocyte transmembrane adaptor 1
117153	NA	NA	54922	RASIP1	Ras interacting protein 1
117177	RAB3IP	RAB3A interacting protein	54923	LIME1	Lck interacting transmembrane adaptor 1
117247	SLC16A10	solute carrier family 16 member 10	5493	PPL	periplakin
117248	GALNT15	polypeptide N-acetylgalactosaminyltransferase 15	54972	TMEM132A	transmembrane protein 132A
117283	IP6K3	inositol hexakisphosphate kinase 3	54979	HRASLS2	HRAS like suppressor 2
117289	TAGAP	T-cell activation RhoGTPase activating protein	54988	ACSM5	acyl-CoA synthetase medium chain family member 5
1184	CLCN5	chloride voltage-gated channel 5	54996	MTARC2	mitochondrial amidoxime reducing component 2
118471	PRAP1	proline rich acidic protein 1	54997	TESC	tescalcin
118663	BTBD16	BTB domain containing 16	55001	TTC22	tetratricopeptide repeat domain 22
1187	CLCNKA	chloride voltage-gated channel Ka	5502	PPP1R1A	protein phosphatase 1 regulatory inhibitor subunit 1A
118788	PIK3AP1	phosphoinositide-3-kinase adaptor protein 1	55026	TMEM255A	transmembrane protein 255A
1188	CLCNKB	chloride voltage-gated channel Kb	55034	MOCOS	molybdenum cofactor sulfurase
118932	ANKRD22	ankyrin repeat domain 22	55036	CCDC40	coiled-coil domain containing 40
1191	CLU	clusterin	55064	SPATA6L	spermatogenesis associated 6 like
119385	AGAP11	ArfGAP with GTPase domain, ankyrin repeat and PH domain 11	5507	PPP1R3C	protein phosphatase 1 regulatory subunit 3C
119391	GSTO2	glutathione S-transferase omega 2	55073	LRRC37A4P	leucine rich repeat containing 37 member A4, pseudogene
119467	CLRN3	clarin 3	55076	TMEM45A	transmembrane protein 45A
119587	CPXM2	carboxypeptidase X, M14 family member 2	55083	KIF26B	kinesin family member 26B
12	SERPINA3	serpin family A member 3	55084	SOBP	sine oculis binding protein homolog
120071	LARGE2	LARGE xylosyl- and glucuronyltransferase 2	55086	CXorf57	chromosome X open reading frame 57
120224	TMEM45B	transmembrane protein 45B	55107	ANO1	anoctamin 1
120376	COLCA2	colorectal cancer associated 2	55118	CRTAC1	cartilage acidic protein 1
120425	JAML	junction adhesion molecule like	55138	FAM90A1	family with sequence similarity 90 member A1

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
120892	LRRK2	leucine rich repeat kinase 2	55143	CDCA8	cell division cycle associated 8
121551	BTBD11	BTB domain containing 11	55151	TMEM38B	transmembrane protein 38B
121601	ANO4	anoctamin 4	55165	CEP55	centrosomal protein 55
122402	TDRD9	tudor domain containing 9	55195	CCDC198	coiled-coil domain containing 198
122481	AK7	adenylate kinase 7	55214	P3H2	prolyl 3-hydroxylase 2
122618	PLD4	phospholipase D family member 4	55224	ETNK2	ethanolamine kinase 2
122622	ADSSL1	adenylosuccinate synthase like 1	55228	PNMA8A	PNMA family member 8A
122970	ACOT4	acyl-CoA thioesterase 4	55240	STEAP3	STEAP3 metalloreductase
123	PLIN2	perilipin 2	55244	SLC47A1	solute carrier family 47 member 1
1230	CCR1	C-C motif chemokine receptor 1	55247	NEIL3	nei like DNA glycosylase 3
1233	CCR4	C-C motif chemokine receptor 4	55258	THNSL2	threonine synthase like 2
1234	CCR5	C-C motif chemokine receptor 5 (gene/pseudogene)	55259	CASC1	cancer susceptibility 1
1235	CCR6	C-C motif chemokine receptor 6	55282	LRRC36	leucine rich repeat containing 36
123872	DNAAF1	dynein axonemal assembly factor 1	55286	C4orf19	chromosome 4 open reading frame 19
123876	ACSM2A	acyl-CoA synthetase medium chain family member 2A	55304	SPTLC3	serine palmitoyltransferase long chain base subunit 3
1244	ABCC2	ATP binding cassette subfamily C member 2	55329	MNS1	meiosis specific nuclear structural 1
124872	B4GALNT2	beta-1,4-N-acetyl-galactosaminyltransferase 2	55349	CHDH	choline dehydrogenase
124976	SPNS2	sphingolipid transporter 2	55351	STK32B	serine/threonine kinase 32B
125	ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	55355	HJURP	Holliday junction recognition protein
125050	RN7SK	RNA, 7SK small nuclear	55365	TMEM176A	transmembrane protein 176A
125206	SLC5A10	solute carrier family 5 member 10	55423	SIRPG	signal regulatory protein gamma
126	ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	554236	DPY19L2P1	DPY19L2 pseudogene 1
126353	MISP	mitotic spindle positioning	55450	CAMK2N1	calcium/calmodulin dependent protein kinase II inhibitor 1
126393	HSPB6	heat shock protein family B (small) member 6	5549	PRELP	proline and arginine rich end leucine rich repeat protein
1264	CNN1	calponin 1	55504	TNFRSF19	TNF receptor superfamily member 19
126433	FBXO27	F-box protein 27	5551	PRF1	perforin 1
126868	MAB21L3	mab-21 like 3	55510	DDX43	DEAD-box helicase 43
126969	SLC44A3	solute carrier family 44 member 3	5553	PRG2	proteoglycan 2, pro eosinophil major basic protein
127069	OR2T10	olfactory receptor family 2 subfamily T member 10	55540	IL17RB	interleukin 17 receptor B
127077	OR2T11	olfactory receptor family 2 subfamily T member 11 (gene/pseudogene)	55553	SOX6	SRY-box 6
1272	CNTN1	contactin 1	55559	HAUS7	HAUS augmin like complex subunit 7
127294	MYOM3	myomesin 3	55586	MIOX	myo-inositol oxygenase
127435	PODN	podocan	55612	FERMT1	fermitin family member 1
1277	COL1A1	collagen type I alpha 1 chain	55616	ASAP3	ArfGAP with SH3 domain, ankyrin repeat and PH domain 3
127707	KLHDC7A	kelch domain containing 7A	55620	STAP2	signal transducing adaptor family member 2
1278	COL1A2	collagen type I alpha 2 chain	5563	PRKAA2	protein kinase AMP-activated catalytic subunit alpha 2
127845	GOLT1A	golgi transport 1A	55638	SYBU	syntabulin

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
1281	COL3A1	collagen type III alpha 1 chain	55655	NLRP2	NLR family pyrin domain containing 2
1282	COL4A1	collagen type IV alpha 1 chain	55679	LIMS2	LIM zinc finger domain containing 2
128239	IQGAP3	IQ motif containing GTPase activating protein 3	55713	ZNF334	zinc finger protein 334
128312	HIST3H2BB	histone cluster 3 H2B family member b	55714	TENM3	teneurin transmembrane protein 3
128344	PIFO	primary cilia formation	55748	CNDP2	carnosine dipeptidase 2
128346	C1orf162	chromosome 1 open reading frame 162	55753	OGDHL	oxoglutarate dehydrogenase like
128414	NKAIN4	sodium/potassium transporting ATPase interacting 4	55765	C1orf106	chromosome 1 open reading frame 106
1285	COL4A3	collagen type IV alpha 3 chain	55786	ZNF415	zinc finger protein 415
128553	TSHZ2	teashirt zinc finger homeobox 2	5579	PRKCB	protein kinase C beta
1286	COL4A4	collagen type IV alpha 4 chain	55790	CSGALNACT1	chondroitin sulfate N-acetylgalactosaminyltransferase 1
1287	COL4A5	collagen type IV alpha 5 chain	55799	CACNA2D3	calcium voltage-gated channel auxiliary subunit alpha2delta 3
1289	COL5A1	collagen type V alpha 1 chain	55825	PECR	peroxisomal trans-2-enoyl-CoA reductase
1290	COL5A2	collagen type V alpha 2 chain	5583	PRKCH	protein kinase C eta
129049	SGSM1	small G protein signaling modulator 1	55867	SLC22A11	solute carrier family 22 member 11
1292	COL6A2	collagen type VI alpha 2 chain	55872	PBK	PDZ binding kinase
1293	COL6A3	collagen type VI alpha 3 chain	5588	PRKCQ	protein kinase C theta
1294	COL7A1	collagen type VII alpha 1 chain	55893	ZNF395	zinc finger protein 395
1295	COL8A1	collagen type VIII alpha 1 chain	5592	PRKG1	protein kinase, cGMP-dependent, type I
129530	LYG1	lysozyme g1	5593	PRKG2	protein kinase, cGMP-dependent, type II
129804	FBLN7	fibulin 7	55937	APOM	apolipoprotein M
129881	CCDC173	coiled-coil domain containing 173	55959	SULF2	sulfatase 2
130	ADH6	alcohol dehydrogenase 6 (class V)	55966	AJAP1	adherens junctions associated protein 1
1300	COL10A1	collagen type X alpha 1 chain	55971	BAIAP2L1	BAI1 associated protein 2 like 1
130013	ACMSD	aminocarboxymuconate semialdehyde decarboxylase	56062	KLHL4	kelch like family member 4
130075	OR9A4	olfactory receptor family 9 subfamily A member 4	56099	PCDHGB7	protocadherin gamma subfamily B, 7
1301	COL11A1	collagen type XI alpha 1 chain	56100	PCDHGB6	protocadherin gamma subfamily B, 6
130106	CIB4	calcium and integrin binding family member 4	56101	PCDHGB5	protocadherin gamma subfamily B, 5
130132	RFTN2	raftlin family member 2	56102	PCDHGB3	protocadherin gamma subfamily B, 3
130271	PLEKHH2	pleckstrin homology, MyTH4 and FERM domain containing H2	56103	PCDHGB2	protocadherin gamma subfamily B, 2
1303	COL12A1	collagen type XII alpha 1 chain	56104	PCDHGB1	protocadherin gamma subfamily B, 1
130340	AP1S3	adaptor related protein complex 1 sigma 3 subunit	56106	PCDHGA10	protocadherin gamma subfamily A, 10
1306	COL15A1	collagen type XV alpha 1 chain	56107	PCDHGA9	protocadherin gamma subfamily A, 9

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
1307	COL16A1	collagen type XVI alpha 1 chain	56108	PCDHGA7	protocadherin gamma subfamily A, 7
130749	CPO	carboxypeptidase O	56109	PCDHGA6	protocadherin gamma subfamily A, 6
130752	MDH1B	malate dehydrogenase 1B	56110	PCDHGA5	protocadherin gamma subfamily A, 5
130940	CCDC148	coiled-coil domain containing 148	56111	PCDHGA4	protocadherin gamma subfamily A, 4
1311	COMP	cartilage oligomeric matrix protein	56112	PCDHGA3	protocadherin gamma subfamily A, 3
131450	CD200R1	CD200 receptor 1	56113	PCDHGA2	protocadherin gamma subfamily A, 2
131566	DCBLD2	discoidin, CUB and LCCL domain containing 2	56114	PCDHGA1	protocadherin gamma subfamily A, 1
1316	KLF6	Kruppel like factor 6	56120	PCDHGB8P	protocadherin gamma subfamily B, 8 pseudogene
132430	PABPC4L	poly(A) binding protein cytoplasmic 4 like	56121	PCDHB15	protocadherin beta 15
132671	SPATA18	spermatogenesis associated 18	56122	PCDHB14	protocadherin beta 14
132864	CPEB2	cytoplasmic polyadenylation element binding protein 2	56123	PCDHB13	protocadherin beta 13
133	ADM	adrenomedullin	56124	PCDHB12	protocadherin beta 12
133418	EMB	embigin	56125	PCDHB11	protocadherin beta 11
133584	EGFLAM	EGF like, fibronectin type III and laminin G domains	56126	PCDHB10	protocadherin beta 10
133688	UGT3A1	UDP glycosyltransferase family 3 member A1	56127	PCDHB9	protocadherin beta 9
134147	CMBL	carboxymethylenebutenolidase homolog	56128	PCDHB8	protocadherin beta 8
134265	AFAP1L1	actin filament associated protein 1 like 1	56129	PCDHB7	protocadherin beta 7
134285	TMEM171	transmembrane protein 171	56130	PCDHB6	protocadherin beta 6
1346	COX7A1	cytochrome c oxidase subunit 7A1	56131	PCDHB4	protocadherin beta 4
1356	CP	ceruloplasmin	56132	PCDHB3	protocadherin beta 3
135656	DPCR1	diffuse panbronchiolitis critical region 1	56133	PCDHB2	protocadherin beta 2
1359	CPA3	carboxypeptidase A3	56136	PCDHA13	protocadherin alpha 13
135932	TMEM139	transmembrane protein 139	56137	PCDHA12	protocadherin alpha 12
136	ADORA2B	adenosine A2b receptor	56138	PCDHA11	protocadherin alpha 11
1363	CPE	carboxypeptidase E	56139	PCDHA10	protocadherin alpha 10
1364	CLDN4	claudin 4	56140	PCDHA8	protocadherin alpha 8
1365	CLDN3	claudin 3	56141	PCDHA7	protocadherin alpha 7
1366	CLDN7	claudin 7	56142	PCDHA6	protocadherin alpha 6
1368	CPM	carboxypeptidase M	56143	PCDHA5	protocadherin alpha 5
1373	CPS1	carbamoyl-phosphate synthase 1	56144	PCDHA4	protocadherin alpha 4
1378	CR1	complement C3b/C4b receptor 1 (Knops blood group)	56154	TEX15	testis expressed 15, meiosis and synapsis associated
137872	ADHFE1	alcohol dehydrogenase, iron containing 1	56159	TEX11	testis expressed 11
1379	CR1L	complement C3b/C4b receptor 1 like	5616	PRKY	protein kinase, Y-linked, pseudogene
137902	PXDNL	peroxidasin like	56171	DNAH7	dynein axonemal heavy chain 7
138162	C9orf116	chromosome 9 open reading frame 116	56241	SUSD2	sushi domain containing 2
139065	SLITRK4	SLIT and NTRK like family member 4	56253	CRTAM	cytotoxic and regulatory T-cell molecule
139170	DCAF12L1	DDB1 and CUL4 associated factor 12 like 1	56256	SERTAD4	SERTA domain containing 4

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1396	CRIP1	cysteine rich protein 1	56265	CPXM1	carboxypeptidase X, M14 family member 1
139728	PNCK	pregnancy up-regulated nonubiquitous CaM kinase	5627	PROS1	protein S
140	ADORA3	adenosine A3 receptor	56271	BEX4	brain expressed X-linked 4
140686	WFDC3	WAP four-disulfide core domain 3	563	AZGP1	alpha-2-glycoprotein 1, zinc-binding
140733	MACROD2	MACRO domain containing 2	56477	CCL28	C-C motif chemokine ligand 28
140738	TMEM37	transmembrane protein 37	5648	MASP1	mannan binding lectin serine peptidase 1
140766	ADAMTS14	ADAM metallopeptidase with thrombospondin type 1 motif 14	5649	RELN	reelin
140862	ISM1	isthmin 1	5652	PRSS8	protease, serine 8
140876	RIPOR3	RIPOR family member 3	56521	DNAJC12	DnaJ heat shock protein family (Hsp40) member C12
1410	CRYAB	crystallin alpha B	5654	HTRA1	HtrA serine peptidase 1
1415	CRYBB2	crystallin beta B2	56606	SLC2A9	solute carrier family 2 member 9
1428	CRYM	crystallin mu	56664	VTRNA1-1	vault RNA 1-1
143425	SYT9	synaptotagmin 9	56667	MUC13	mucin 13, cell surface associated
143872	ARHGAP42	Rho GTPase activating protein 42	56670	SUCNR1	succinate receptor 1
1441	CSF3R	colony stimulating factor 3 receptor	56833	SLAMF8	SLAM family member 8
144100	PLEKHA7	pleckstrin homology domain containing A7	56892	TCIM	transcriptional and immune response regulator
144165	PRICKLE1	prickle planar cell polarity protein 1	56898	BDH2	3-hydroxybutyrate dehydrogenase 2
144193	AMDHD1	amidohydrolase domain containing 1	56899	ANKS1B	ankyrin repeat and sterile alpha motif domain containing 1B
144406	WDR66	WD repeat domain 66	56901	NDUFA4L2	NDUFA4, mitochondrial complex associated like 2
144455	E2F7	E2F transcription factor 7	56911	MAP3K7CL	MAP3K7 C-terminal like
144501	KRT80	keratin 80	56937	PMEPA1	prostate transmembrane protein, androgen induced 1
145200	LINC00239	long intergenic non-protein coding RNA 239	56938	ARNTL2	aryl hydrocarbon receptor nuclear translocator like 2
145270	PRIMA1	proline rich membrane anchor 1	56944	OLFML3	olfactomedin like 3
145864	HAPLN3	hyaluronan and proteoglycan link protein 3	56969	RPL23AP32	ribosomal protein L23a pseudogene 32
1462	VCAN	versican	570	BAAT	bile acid-CoA:amino acid N-acyltransferase
1464	CSPG4	chondroitin sulfate proteoglycan 4	57007	ACKR3	atypical chemokine receptor 3
146439	BICDL2	BICD family like cargo adaptor 2	57016	AKR1B10	aldo-keto reductase family 1 member B10
146456	TMED6	transmembrane p24 trafficking protein 6	57094	CPA6	carboxypeptidase A6
1466	CSRP2	cysteine and glycine rich protein 2	57101	ANO2	anoctamin 2
147	ADRA1B	adrenoceptor alpha 1B	57105	CYSLTR2	cysteinyl leukotriene receptor 2
1470	CST2	cystatin SA	57110	HRASLS	HRAS like suppressor
147138	TMC8	transmembrane channel like 8	57124	CD248	CD248 molecule
147495	APCDD1	APC down-regulated 1	57125	PLXDC1	plexin domain containing 1
1475	CSTA	cystatin A	57139	RGL3	ral guanine nucleotide dissociation stimulator like 3
147686	ZNF418	zinc finger protein 418	57158	JPH2	junctophilin 2
147798	TMC4	transmembrane channel like 4	57165	GJC2	gap junction protein gamma 2
147968	CAPN12	calpain 12	57167	SALL4	spalt like transcription factor 4

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148229	ATP8B3	ATPase phospholipid transporting 8B3	57172	CAMK1G	calcium/calmodulin dependent protein kinase IG
148523	CIART	circadian associated repressor of transcription	57188	ADAMTSL3	ADAMTS like 3
148641	SLC35F3	solute carrier family 35 member F3	57194	ATP10A	ATPase phospholipid transporting 10A (putative)
148979	GLIS1	GLIS family zinc finger 1	57211	ADGRG6	adhesion G protein-coupled receptor G6
1490	CTGF	connective tissue growth factor	57214	CEMIP	cell migration inducing hyaluronan binding protein
149175	MANEAL	mannosidase endo-alpha like	57216	VANGL2	VANGL planar cell polarity protein 2
1493	CTLA4	cytotoxic T-lymphocyte associated protein 4	57221	ARFGEF3	ARFGEF family member 3
149466	C1orf210	chromosome 1 open reading frame 210	5730	PTGDS	prostaglandin D2 synthase
149628	PYHIN1	pyrin and HIN domain family member 1	5733	PTGER3	prostaglandin E receptor 3
150468	CKAP2L	cytoskeleton associated protein 2 like	57381	RHOJ	ras homolog family member J
151	ADRA2B	adrenoceptor alpha 2B	57393	TMEM27	transmembrane protein 27
1510	CTSE	cathepsin E	5740	PTGIS	prostaglandin I2 synthase
1511	CTSG	cathepsin G	574042	SNORA10	small nucleolar RNA, H/ACA box 10
151126	ZNF385B	zinc finger protein 385B	57405	SPC25	SPC25, NDC80 kinetochore complex component
151258	SLC38A11	solute carrier family 38 member 11	57406	ABHD6	abhydrolase domain containing 6
151295	SLC23A3	solute carrier family 23 member 3	57419	SLC24A3	solute carrier family 24 member 3
1513	CTSK	cathepsin K	5742	PTGS1	prostaglandin-endoperoxide synthase 1
151507	MSL3P1	MSL complex subunit 3 pseudogene 1	5743	PTGS2	prostaglandin-endoperoxide synthase 2
151651	EFHB	EF-hand domain family member B	5744	PTHLH	parathyroid hormone like hormone
151827	LRRC34	leucine rich repeat containing 34	57447	NDRG2	NDRG family member 2
151887	CCDC80	coiled-coil domain containing 80	5745	PTH1R	parathyroid hormone 1 receptor
152	ADRA2C	adrenoceptor alpha 2C	57451	TENM2	teneurin transmembrane protein 2
1520	CTSS	cathepsin S	57452	GALNT16	polypeptide N-acetylgalactosaminyltransferase 16
152078	PQLC2L	PQ loop repeat containing 2 like	57453	DSCAML1	DS cell adhesion molecule like 1
1521	CTSW	cathepsin W	57463	AMIGO1	adhesion molecule with Ig like domain 1
152273	FGD5	FYVE, RhoGEF and PH domain containing 5	57464	STRIP2	striatin interacting protein 2
152330	CNTN4	contactin 4	57502	NLGN4X	neuroligin 4, X-linked
1524	CX3CR1	C-X3-C motif chemokine receptor 1	57520	HECW2	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 2
1525	CXADR	CXADR, Ig-like cell adhesion molecule	57530	CGN	cingulin
152573	SHISA3	shisa family member 3	57537	SORCS2	sortilin related VPS10 domain containing receptor 2
152789	JAKMIP1	janus kinase and microtubule interacting protein 1	57538	ALPK3	alpha kinase 3
1528	CYB5A	cytochrome b5 type A	5754	PTK7	protein tyrosine kinase 7 (inactive)
153218	SPINK13	serine peptidase inhibitor, Kazal type 13 (putative)	57552	NCEH1	neutral cholesterol ester hydrolase 1

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153562	MARVELD2	MARVEL domain containing 2	57554	LRRC7	leucine rich repeat containing 7
153579	BTNL9	butyrophilin like 9	57556	SEMA6A	semaphorin 6A
1536	CYBB	cytochrome b-245 beta chain	57561	ARRDC3	arrestin domain containing 3
153643	FAM81B	family with sequence similarity 81 member B	57572	DOCK6	dedicator of cytokinesis 6
153768	PRELID2	PRELI domain containing 2	57573	ZNF471	zinc finger protein 471
153769	SH3RF2	SH3 domain containing ring finger 2	57575	PCDH10	protocadherin 10
154	ADRB2	adrenoceptor beta 2	57586	SYT13	synaptotagmin 13
154043	CNKSR3	CNKSR family member 3	57593	EBF4	early B-cell factor 4
1545	CYP1B1	cytochrome P450 family 1 subfamily B member 1	57619	SHROOM3	shroom family member 3
154661	RUNDC3B	RUN domain containing 3B	57639	CCDC146	coiled-coil domain containing 146
154796	AMOT	angiomotin	5764	PTN	pleiotrophin
154865	IQUB	IQ motif and ubiquitin domain containing	57643	ZSWIM5	zinc finger SWIM-type containing 5
155368	METTL27	methyltransferase like 27	57662	CAMSAP3	calmodulin regulated spectrin associated protein family member 3
1557	CYP2C19	cytochrome P450 family 2 subfamily C member 19	5768	QSOX1	quiescin sulfhydryl oxidase 1
1558	CYP2C8	cytochrome P450 family 2 subfamily C member 8	57715	SEMA4G	semaphorin 4G
1559	CYP2C9	cytochrome P450 family 2 subfamily C member 9	57717	PCDHB16	protocadherin beta 16
1573	CYP2J2	cytochrome P450 family 2 subfamily J member 2	57722	IGDCC4	immunoglobulin superfamily DCC subclass member 4
157313	CDCA2	cell division cycle associated 2	57733	GBA3	glucosylceramidase beta 3 (gene/pseudogene)
1577	CYP3A5	cytochrome P450 family 3 subfamily A member 5	57761	TRIB3	tribbles pseudokinase 3
157869	SBSPON	somatomedin B and thrombospondin type 1 domain containing	5778	PTPN7	protein tyrosine phosphatase, non-receptor type 7
1579	CYP4A11	cytochrome P450 family 4 subfamily A member 11	57817	HAMP	hepcidin antimicrobial peptide
158067	AK8	adenylate kinase 8	57823	SLAMF7	SLAM family member 7
158158	RASEF	RAS and EF-hand domain containing	57830	KRTAP5-8	keratin associated protein 5-8
1582	CYP8B1	cytochrome P450 family 8 subfamily B member 1	57834	CYP4F11	cytochrome P450 family 4 subfamily F member 11
158326	FREM1	FRAS1 related extracellular matrix 1	57863	CADM3	cell adhesion molecule 3
158376	SPAAR	small regulatory polypeptide of amino acid response	5787	PTPRB	protein tyrosine phosphatase, receptor type B
158399	ZNF483	zinc finger protein 483	5788	PTPRC	protein tyrosine phosphatase, receptor type C
158471	PRUNE2	prune homolog 2	5789	PTPRD	protein tyrosine phosphatase, receptor type D
1586	CYP17A1	cytochrome P450 family 17 subfamily A member 1	5790	PTPRCAP	protein tyrosine phosphatase, receptor type C associated protein
1589	CYP21A2	cytochrome P450 family 21 subfamily A member 2	5794	PTPRH	protein tyrosine phosphatase, receptor type H
1590	CYP21A1P	cytochrome P450 family 21 subfamily A member 1, pseudogene	5797	PTPRM	protein tyrosine phosphatase, receptor type M
1591	CYP24A1	cytochrome P450 family 24 subfamily A member 1	5806	PTX3	pentraxin 3
1593	CYP27A1	cytochrome P450 family 27 subfamily A member 1	58189	WFDC1	WAP four-disulfide core domain 1
159963	SLC5A12	solute carrier family 5 member 12	5827	PXMP2	peroxisomal membrane protein 2

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1602	DACH1	dachshund family transcription factor 1	5831	PYCR1	pyrroline-5-carboxylate reductase 1
160364	CLEC12A	C-type lectin domain family 12 member A	5837	PYGM	glycogen phosphorylase, muscle associated
160428	ALDH1L2	aldehyde dehydrogenase 1 family member L2	58475	MS4A7	membrane spanning 4-domains A7
160728	SLC5A8	solute carrier family 5 member 8	58494	JAM2	junctional adhesion molecule 2
1610	DAO	D-amino acid oxidase	58510	PRODH2	proline dehydrogenase 2
161198	CLEC14A	C-type lectin domain containing 14A	58528	RRAGD	Ras related GTP binding D
162417	NAGS	N-acetylglutamate synthase	586	BCAT1	branched chain amino acid transaminase 1
162461	TMEM92	transmembrane protein 92	5880	RAC2	Rac family small GTPase 2
162632	USP32P1	ubiquitin specific peptidase 32 pseudogene 1	5896	RAG1	recombination activating 1
162967	ZNF320	zinc finger protein 320	58985	IL22RA1	interleukin 22 receptor subunit alpha 1
163059	ZNF433	zinc finger protein 433	59	ACTA2	actin, alpha 2, smooth muscle, aorta
163071	ZNF114	zinc finger protein 114	590	BCHE	butyrylcholinesterase
163175	LGI4	leucine rich repeat LGI family member 4	59084	ENPP5	ectonucleotide pyrophosphatase/phosphodiester ase 5 (putative)
163223	ZNF676	zinc finger protein 676	5909	RAP1GAP	RAP1 GTPase activating protein
1634	DCN	decorin	5918	RARRES1	retinoic acid receptor responder 1
163404	PLPPR5	phospholipid phosphatase related 5	5919	RARRES2	retinoic acid receptor responder 2
1636	ACE	angiotensin I converting enzyme	5920	RARRES3	retinoic acid receptor responder 3
164312	LRRN4	leucine rich repeat neuronal 4	5924	RASGRF2	Ras protein specific guanine nucleotide releasing factor 2
1644	DDC	dopa decarboxylase	59272	ACE2	angiotensin I converting enzyme 2
1645	AKR1C1	aldo-keto reductase family 1 member C1	59277	NTN4	netrin 4
1646	AKR1C2	aldo-keto reductase family 1 member C2	59341	TRPV4	transient receptor potential cation channel subfamily V member 4
164668	APOBEC3H	apolipoprotein B mRNA editing enzyme catalytic subunit 3H	59350	RXFP1	relaxin/insulin like family peptide receptor 1
1647	GADD45A	growth arrest and DNA damage inducible alpha	5947	RBP1	retinol binding protein 1
165	AEBP1	AE binding protein 1	594838	SNORD100	small nucleolar RNA, C/D box 100
165631	PARP15	poly(ADP-ribose) polymerase family member 15	594839	SNORA33	small nucleolar RNA, H/ACA box 33
166824	RASSF6	Ras association domain family member 6	595	CCND1	cyclin D1
1672	DEFB1	defensin beta 1	5950	RBP4	retinol binding protein 4
1674	DES	desmin	595101	SMG1P5	SMG1 pseudogene 5
167465	ZNF366	zinc finger protein 366	5959	RDH5	retinol dehydrogenase 5
1675	CFD	complement factor D	596	BCL2	BCL2, apoptosis regulator
168537	GIMAP7	GTPase, IMAP family member 7	5967	REG1A	regenerating family member 1 alpha
168620	BHLHA15	basic helix-loop-helix family member a15	597	BCL2A1	BCL2 related protein A1
168667	BMPER	BMP binding endothelial regulator	5972	REN	renin
1687	GSDME	gasdermin E	5973	RENBP	renin binding protein
1690	COCH	cochlin	5996	RGS1	regulator of G protein signaling 1
169044	COL22A1	collagen type XXII alpha 1 chain	5997	RGS2	regulator of G protein signaling 2
169611	OLFML2A	olfactomedin like 2A	5999	RGS4	regulator of G protein signaling 4

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169693	TMEM252	transmembrane protein 252	6004	RGS16	regulator of G protein signaling 16
169834	ZNF883	zinc finger protein 883	6029	RN7SL1	RNA, 7SL, cytoplasmic 1
170063	NA	NA	6035	RNASE1	ribonuclease A family member 1, pancreatic
170679	PSORS1C1	psoriasis susceptibility 1 candidate 1	6036	RNASE2	ribonuclease A family member 2
170690	ADAMTS16	ADAM metallopeptidase with thrombospondin type 1 motif 16	6038	RNASE4	ribonuclease A family member 4
170692	ADAMTS18	ADAM metallopeptidase with thrombospondin type 1 motif 18	6044	SNORA62	small nucleolar RNA, H/ACA box 62
171024	SYNPO2	synaptopodin 2	606500	SNORD68	small nucleolar RNA, C/D box 68
1718	DHCR24	24-dehydrocholesterol reductase	60681	FKBP10	FK506 binding protein 10
1728	NQO1	NAD(P)H quinone dehydrogenase 1	608	TNFRSF17	TNF receptor superfamily member 17
1731	SEPT1	septin 1	6083	SNORD21	small nucleolar RNA, C/D box 21
1749	DLX5	distal-less homeobox 5	6084	RNY1	RNA, Ro-associated Y1
1755	DMBT1	deleted in malignant brain tumors 1	6086	RNY4	RNA, Ro-associated Y4
1756	DMD	dystrophin	6090	RNY5	RNA, Ro-associated Y5
1759	DNM1	dynamin 1	6091	ROBO1	roundabout guidance receptor 1
176	ACAN	aggrecan	6092	ROBO2	roundabout guidance receptor 2
1767	DNAH5	dynein axonemal heavy chain 5	6097	RORC	RAR related orphan receptor C
1768	DNAH6	dynein axonemal heavy chain 6	6101	RP1	RP1, axonemal microtubule associated
1776	DNASE1L3	deoxyribonuclease 1 like 3	6133	RPL9	ribosomal protein L9
1794	DOCK2	dedicator of cytokinesis 2	6192	RPS4Y1	ribosomal protein S4, Y-linked 1
1800	DPEP1	dipeptidase 1	619279	ZNF704	zinc finger protein 704
1803	DPP4	dipeptidyl peptidase 4	619498	SNORD74	small nucleolar RNA, C/D box 74
1805	DPT	dermatopontin	619505	SNORA21	small nucleolar RNA, H/ACA box 21
1807	DPYS	dihydropyrimidinase	619562	SNORA3A	small nucleolar RNA, H/ACA box 3A
1809	DPYSL3	dihydropyrimidinase like 3	619569	SNORA41	small nucleolar RNA, H/ACA box 41
1824	DSC2	desmocollin 2	619570	SNORD95	small nucleolar RNA, C/D box 95
1829	DSG2	desmoglein 2	619571	SNORD96A	small nucleolar RNA, C/D box 96A
183	AGT	angiotensinogen	6236	RRAD	RRAD, Ras related glycolysis inhibitor and calcium channel regulator
1831	TSC22D3	TSC22 domain family member 3	6241	RRM2	ribonucleotide reductase regulatory subunit M2
1832	DSP	desmoplakin	6261	RYR1	ryanodine receptor 1
1837	DTNA	dystrobrevin alpha	6262	RYR2	ryanodine receptor 2
1839	HBEGF	heparin binding EGF like growth factor	6271	S100A1	S100 calcium binding protein A1
1842	ECM2	extracellular matrix protein 2	6279	S100A8	S100 calcium binding protein A8
1843	DUSP1	dual specificity phosphatase 1	6280	S100A9	S100 calcium binding protein A9
1844	DUSP2	dual specificity phosphatase 2	6283	S100A12	S100 calcium binding protein A12
185	AGTR1	angiotensin II receptor type 1	6285	S100B	S100 calcium binding protein B
187	APLNR	apelin receptor	6288	SAA1	serum amyloid A1
1879	EBF1	early B-cell factor 1	6289	SAA2	serum amyloid A2
1880	GPR183	G protein-coupled receptor 183	629	CFB	complement factor B
1893	ECM1	extracellular matrix protein 1	6296	ACSM3	acyl-CoA synthetase medium chain family member 3

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
1894	ECT2	epithelial cell transforming 2	6300	MAPK12	mitogen-activated protein kinase 12
1901	S1PR1	sphingosine-1-phosphate receptor 1	6319	SCD	stearoyl-CoA desaturase
1903	S1PR3	sphingosine-1-phosphate receptor 3	6324	SCN1B	sodium voltage-gated channel beta subunit 1
1906	EDN1	endothelin 1	6326	SCN2A	sodium voltage-gated channel alpha subunit 2
1907	EDN2	endothelin 2	6328	SCN3A	sodium voltage-gated channel alpha subunit 3
1909	EDNRA	endothelin receptor type A	633	BGN	biglycan
1910	EDNRB	endothelin receptor type B	6330	SCN4B	sodium voltage-gated channel beta subunit 4
1917	EEF1A2	eukaryotic translation elongation factor 1 alpha 2	6334	SCN8A	sodium voltage-gated channel alpha subunit 8
1942	EFNA1	ephrin A1	6335	SCN9A	sodium voltage-gated channel alpha subunit 9
1946	EFNA5	ephrin A5	6337	SCNN1A	sodium channel epithelial 1 alpha subunit
1948	EFNB2	ephrin B2	6338	SCNN1B	sodium channel epithelial 1 beta subunit
1950	EGF	epidermal growth factor	634	CEACAM1	carcinoembryonic antigen related cell adhesion molecule 1
1952	CELSR2	cadherin EGF LAG seven-pass G-type receptor 2	6340	SCNN1G	sodium channel epithelial 1 gamma subunit
1956	EGFR	epidermal growth factor receptor	6347	CCL2	C-C motif chemokine ligand 2
1958	EGR1	early growth response 1	6348	CCL3	C-C motif chemokine ligand 3
1959	EGR2	early growth response 2	6349	CCL3L1	C-C motif chemokine ligand 3 like 1
1962	EHHADH	enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase	635	BHMT	betaine--homocysteine S-methyltransferase
196410	METTL7B	methyltransferase like 7B	6351	CCL4	C-C motif chemokine ligand 4
196446	MYRFL	myelin regulatory factor-like	6352	CCL5	C-C motif chemokine ligand 5
196883	ADCY4	adenylate cyclase 4	6355	CCL8	C-C motif chemokine ligand 8
197135	PATL2	PAT1 homolog 2	6356	CCL11	C-C motif chemokine ligand 11
199	AIF1	allograft inflammatory factor 1	6357	CCL13	C-C motif chemokine ligand 13
199731	CADM4	cell adhesion molecule 4	6358	CCL14	C-C motif chemokine ligand 14
1999	ELF3	E74 like ETS transcription factor 3	6362	CCL18	C-C motif chemokine ligand 18
200010	SLC5A9	solute carrier family 5 member 9	6363	CCL19	C-C motif chemokine ligand 19
200162	SPAG17	sperm associated antigen 17	6364	CCL20	C-C motif chemokine ligand 20
2003	ELK2AP	ELK2A, member of ETS oncogene family, pseudogene	6366	CCL21	C-C motif chemokine ligand 21
200373	CFAP221	cilia and flagella associated protein 221	6368	CCL23	C-C motif chemokine ligand 23
200420	ALMS1P1	ALMS1, centrosome and basal body associated protein pseudogene 1	6372	CXCL6	C-X-C motif chemokine ligand 6
2006	ELN	elastin	6373	CXCL11	C-X-C motif chemokine ligand 11
200634	KRTCAP3	keratinocyte associated protein 3	6374	CXCL5	C-X-C motif chemokine ligand 5
200879	LIPH	lipase H	6376	CX3CL1	C-X3-C motif chemokine ligand 1
200916	RPL22L1	ribosomal protein L22 like 1	6382	SDC1	syndecan 1
200931	SLC51A	solute carrier family 51 alpha subunit	6387	CXCL12	C-X-C motif chemokine ligand 12
200958	MUC20	mucin 20, cell surface associated	63895	PIEZO2	piezo type mechanosensitive ion channel component 2
201161	CENPV	centromere protein V	63910	SLC17A9	solute carrier family 17 member 9

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
2012	EMP1	epithelial membrane protein 1	63917	GALNT11	polypeptide N-acetylgalactosaminyltransferase 11
201232	SLC16A13	solute carrier family 16 member 13	63951	DMRTA1	DMRT like family A1
2015	ADGRE1	adhesion G protein-coupled receptor E1	63982	ANO3	anoctamin 3
201501	ZBTB7C	zinc finger and BTB domain containing 7C	640	BLK	BLK proto-oncogene, Src family tyrosine kinase
2018	EMX2	empty spiracles homeobox 2	64005	MYO1G	myosin IG
202134	FAM153B	family with sequence similarity 153 member B	6402	SELL	selectin L
202333	CMYA5	cardiomyopathy associated 5	6403	SELP	selectin P
2026	ENO2	enolase 2	6405	SEMA3F	semaphorin 3F
2028	ENPEP	glutamyl aminopeptidase	64073	C19orf33	chromosome 19 open reading frame 33
203100	HTRA4	HtrA serine peptidase 4	64081	PBLD	phenazine biosynthesis like protein domain containing
203111	ERICH5	glutamate rich 5	64084	CLSTN2	calsyntenin 2
2034	EPAS1	endothelial PAS domain protein 1	64092	SAMSN1	SAM domain, SH3 domain and nuclear localization signals 1
203562	TMEM31	transmembrane protein 31	64093	SMOC1	SPARC related modular calcium binding 1
203859	ANO5	anoctamin 5	64094	SMOC2	SPARC related modular calcium binding 2
2039	DMTN	dematin actin binding protein	64097	EPB41L4A	erythrocyte membrane protein band 4.1 like 4A
2042	EPHA3	EPH receptor A3	64108	RTP4	receptor transporter protein 4
2043	EPHA4	EPH receptor A4	64122	FN3K	fructosamine 3 kinase
2045	EPHA7	EPH receptor A7	64123	ADGRL4	adhesion G protein-coupled receptor L4
2048	EPHB2	EPH receptor B2	64127	NOD2	nucleotide binding oligomerization domain containing 2
204962	SLC44A5	solute carrier family 44 member 5	64129	TINAGL1	tubulointerstitial nephritis antigen like 1
2053	EPHX2	epoxide hydrolase 2	641371	ACOT1	acyl-CoA thioesterase 1
2064	ERBB2	erb-b2 receptor tyrosine kinase 2	6414	SELENOP	selenoprotein P
2065	ERBB3	erb-b2 receptor tyrosine kinase 3	641451	SNORA19	small nucleolar RNA, H/ACA box 19
2066	ERBB4	erb-b2 receptor tyrosine kinase 4	641648	SNORD87	small nucleolar RNA, C/D box 87
2070	EYA4	EYA transcriptional coactivator and phosphatase 4	641649	TMEM91	transmembrane protein 91
2078	ERG	ERG, ETS transcription factor	64167	ERAP2	endoplasmic reticulum aminopeptidase 2
2104	ESRRG	estrogen related receptor gamma	641700	ECSCR	endothelial cell surface expressed chemotaxis and apoptosis regulator
2115	ETV1	ETS variant 1	64218	SEMA4A	semaphorin 4A
2124	EVI2B	ecotropic viral integration site 2B	6422	SFRP1	secreted frizzled related protein 1
213	ALB	albumin	642236	FRG1JP	FSHD region gene 1 family member J, pseudogene
2138	EYA1	EYA transcriptional coactivator and phosphatase 1	6423	SFRP2	secreted frizzled related protein 2
2139	EYA2	EYA transcriptional coactivator and phosphatase 2	64231	MS4A6A	membrane spanning 4-domains A6A
2147	F2	coagulation factor II, thrombin	6424	SFRP4	secreted frizzled related protein 4

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
2149	F2R	coagulation factor II thrombin receptor	642517	AGAP9	ArfGAP with GTPase domain, ankyrin repeat and PH domain 9
2150	F2RL1	F2R like trypsin receptor 1	64283	ARHGEF28	Rho guanine nucleotide exchange factor 28
2152	F3	coagulation factor III, tissue factor	64284	RAB17	RAB17, member RAS oncogene family
2153	F5	coagulation factor V	64288	ZSCAN31	zinc finger and SCAN domain containing 31
2157	F8	coagulation factor VIII	642987	TMEM232	transmembrane protein 232
2159	F10	coagulation factor X	64321	SOX17	SRY-box 17
216	ALDH1A1	aldehyde dehydrogenase 1 family member A1	643236	TMEM72	transmembrane protein 72
2162	F13A1	coagulation factor XIII A chain	64332	NFKBIZ	NFKB inhibitor zeta
2166	FAAH	fatty acid amide hydrolase	64333	ARHGAP9	Rho GTPase activating protein 9
2167	FABP4	fatty acid binding protein 4	644165	BCRP3	breakpoint cluster region pseudogene 3
2168	FABP1	fatty acid binding protein 1	6442	SGCA	sarcoglycan alpha
2170	FABP3	fatty acid binding protein 3	644246	KANSL1-AS1	KANSL1 antisense RNA 1
2171	FABP5	fatty acid binding protein 5	6447	SCG5	secretogranin V
2172	FABP6	fatty acid binding protein 6	645090	NA	NA
2173	FABP7	fatty acid binding protein 7	645367	GGT8P	gamma-glutamyltransferase 8 pseudogene
2180	ACSL1	acyl-CoA synthetase long chain family member 1	645432	ARRDC5	arrestin domain containing 5
2184	FAH	fumarylacetoacetate hydrolase	64577	ALDH8A1	aldehyde dehydrogenase 8 family member A1
2191	FAP	fibroblast activation protein alpha	645784	ANKRD36BP2	ankyrin repeat domain 36B pseudogene 2
2192	FBLN1	fibulin 1	64581	CLEC7A	C-type lectin domain containing 7A
219285	SAMD9L	sterile alpha motif domain containing 9 like	646023	ADORA2A-AS1	ADORA2A antisense RNA 1
219348	PLAC9	placenta specific 9	646396	REREP3	arginine-glutamic acid dipeptide repeats pseudogene 3
219621	CABCOCO1	ciliary associated calcium binding coiled-coil 1	64641	EBF2	early B-cell factor 2
219736	STOX1	storkhead box 1	64651	CSRNP1	cysteine and serine rich nuclear protein 1
2199	FBLN2	fibulin 2	6469	SHH	sonic hedgehog
220	ALDH1A3	aldehyde dehydrogenase 1 family member A3	64699	TMPRSS3	transmembrane protease, serine 3
2200	FBN1	fibrillin 1	6470	SHMT1	serine hydroxymethyltransferase 1
220001	VWCE	von Willebrand factor C and EGF domains	647024	C6orf132	chromosome 6 open reading frame 132
2201	FBN2	fibrillin 2	64757	MTARC1	mitochondrial amidoxime reducing component 1
2202	EFEMP1	EGF containing fibulin extracellular matrix protein 1	64762	GAREM1	GRB2 associated regulator of MAPK1 subtype 1
2203	FBP1	fructose-bisphosphatase 1	647859	LOC647859	occludin pseudogene
2205	FCER1A	Fc fragment of IgE receptor Ia	6480	ST6GAL1	ST6 beta-galactoside alpha-2,6-sialyltransferase 1
220594	USP32P2	ubiquitin specific peptidase 32 pseudogene 2	64805	P2RY12	purinergic receptor P2Y12
2206	MS4A2	membrane spanning 4-domains A2	64838	FNDC4	fibronectin type III domain containing 4
2207	FCER1G	Fc fragment of IgE receptor Ig	64849	SLC13A3	solute carrier family 13 member 3
2209	FCGR1A	Fc fragment of IgG receptor Ia	64866	CDCP1	CUB domain containing protein 1
220963	SLC16A9	solute carrier family 16 member 9	64901	RANBP17	RAN binding protein 17

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
220965	FAM13C	family with sequence similarity 13 member C	64902	AGXT2	alanine--glyoxylate aminotransferase 2
221002	RASGEF1A	RasGEF domain family member 1A	6492	SIM1	single-minded family bHLH transcription factor 1
2213	FCGR2B	Fc fragment of IgG receptor IIb	64922	LRRC19	leucine rich repeat containing 19
221395	ADGRF5	adhesion G protein-coupled receptor F5	64926	RASAL3	RAS protein activator like 3
2214	FCGR3A	Fc fragment of IgG receptor IIIa	650	BMP2	bone morphogenetic protein 2
221416	C6orf223	chromosome 6 open reading frame 223	6503	SLA	Src like adaptor
221421	RSPH9	radial spoke head 9 homolog	650368	TSSC2	tumor suppressing subtransferable candidate 2 pseudogene
2215	FCGR3B	Fc fragment of IgG receptor IIIb	6504	SLAMF1	signaling lymphocytic activation molecule family member 1
221806	VWDE	von Willebrand factor D and EGF domains	6505	SLC1A1	solute carrier family 1 member 1
2219	FCN1	ficolin 1	6507	SLC1A3	solute carrier family 1 member 3
221935	SDK1	sidekick cell adhesion molecule 1	65078	RTN4R	reticulon 4 receptor
221981	THSD7A	thrombospondin type 1 domain containing 7A	6508	SLC4A3	solute carrier family 4 member 3
222223	KIAA1324L	KIAA1324 like	6513	SLC2A1	solute carrier family 2 member 1
222256	CDHR3	cadherin related family member 3	6514	SLC2A2	solute carrier family 2 member 2
222643	UNC5CL	unc-5 family C-terminal like	6515	SLC2A3	solute carrier family 2 member 3
222865	TMEM130	transmembrane protein 130	6517	SLC2A4	solute carrier family 2 member 4
222962	SLC29A4	solute carrier family 29 member 4	6518	SLC2A5	solute carrier family 2 member 5
223117	SEMA3D	semaphorin 3D	6519	SLC3A1	solute carrier family 3 member 1
2239	GPC4	glypican 4	652	BMP4	bone morphogenetic protein 4
224	ALDH3A2	aldehyde dehydrogenase 3 family member A2	6523	SLC5A1	solute carrier family 5 member 1
2243	FGA	fibrinogen alpha chain	6526	SLC5A3	solute carrier family 5 member 3
2244	FGB	fibrinogen beta chain	65266	WNK4	WNK lysine deficient protein kinase 4
2245	FGD1	FYVE, RhoGEF and PH domain containing 1	6527	SLC5A4	solute carrier family 5 member 4
2247	FGF2	fibroblast growth factor 2	6529	SLC6A1	solute carrier family 6 member 1
2252	FGF7	fibroblast growth factor 7	6531	SLC6A3	solute carrier family 6 member 3
2256	FGF11	fibroblast growth factor 11	653113	FAM86FP	family with sequence similarity 86, member A pseudogene
225689	MAPK15	mitogen-activated protein kinase 15	653190	ABCC6P1	ATP binding cassette subfamily C member 6 pseudogene 1
2259	FGF14	fibroblast growth factor 14	653316	FAM153C	family with sequence similarity 153 member C
2261	FGFR3	fibroblast growth factor receptor 3	653361	NCF1	neutrophil cytosolic factor 1
2263	FGFR2	fibroblast growth factor receptor 2	6535	SLC6A8	solute carrier family 6 member 8
2264	FGFR4	fibroblast growth factor receptor 4	653604	HIST2H3D	histone cluster 2 H3 family member d
2266	FGG	fibrinogen gamma chain	653689	GSTT2B	glutathione S-transferase theta 2B (gene/pseudogene)
2273	FHL1	four and a half LIM domains 1	653720	GOLGA8M	golgin A8 family member M
2274	FHL2	four and a half LIM domains 2	6539	SLC6A12	solute carrier family 6 member 12
22795	NID2	nidogen 2	6540	SLC6A13	solute carrier family 6 member 13
22797	TFEC	transcription factor EC	6542	SLC7A2	solute carrier family 7 member 2
22801	ITGA11	integrin subunit alpha 11	654321	SNORA75	small nucleolar RNA, H/ACA box 75

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
22806	IKZF3	IKAROS family zinc finger 3	654322	SNORA13	small nucleolar RNA, H/ACA box 13
22822	PHLDA1	pleckstrin homology like domain family A member 1	6555	SLC10A2	solute carrier family 10 member 2
22829	NLGN4Y	neuroligin 4, Y-linked	6556	SLC11A1	solute carrier family 11 member 1
22836	RHOBTB3	Rho related BTB domain containing 3	6561	SLC13A1	solute carrier family 13 member 1
22871	NLGN1	neuroligin 1	6563	SLC14A1	solute carrier family 14 member 1 (Kidd blood group)
22885	ABLIM3	actin binding LIM protein family member 3	6564	SLC15A1	solute carrier family 15 member 1
2289	FKBP5	FK506 binding protein 5	6568	SLC17A1	solute carrier family 17 member 1
22899	ARHGEF15	Rho guanine nucleotide exchange factor 15	6578	SLCO2A1	solute carrier organic anion transporter family member 2A1
229	ALDOB	aldolase, fructose-bisphosphate B	6581	SLC22A3	solute carrier family 22 member 3
22915	MMRN1	multimerin 1	6582	SLC22A2	solute carrier family 22 member 2
22932	POMZP3	POM121 and ZP3 fusion	6583	SLC22A4	solute carrier family 22 member 4
22936	ELL2	elongation factor for RNA polymerase II 2	6584	SLC22A5	solute carrier family 22 member 5
2294	FOXF1	forkhead box F1	6586	SLIT3	slit guidance ligand 3
22941	SHANK2	SH3 and multiple ankyrin repeat domains 2	6590	SLPI	secretory leukocyte peptidase inhibitor
22949	PTGR1	prostaglandin reductase 1	6591	SNAI2	snail family transcriptional repressor 2
2297	FOXD1	forkhead box D1	65975	STK33	serine/threonine kinase 33
22974	TPX2	TPX2, microtubule nucleation factor	660	BMX	BMX non-receptor tyrosine kinase
22977	AKR7A3	aldo-keto reductase family 7 member A3	66002	CYP4F12	cytochrome P450 family 4 subfamily F member 12
22986	SORCS3	sortilin related VPS10 domain containing receptor 3	6614	SIGLEC1	sialic acid binding Ig like lectin 1
22996	TTC39A	tetratricopeptide repeat domain 39A	6616	SNAP25	synaptosome associated protein 25
230	ALDOC	aldolase, fructose-bisphosphate C	6622	SNCA	synuclein alpha
2300	FOXL1	forkhead box L1	6623	SNCG	synuclein gamma
23015	GOLGA8A	golgin A8 family member A	6624	FSCN1	fascin actin-bundling protein 1
23024	PDZRN3	PDZ domain containing ring finger 3	664	BNIP3	BCL2 interacting protein 3
2303	FOXC2	forkhead box C2	6640	SNTA1	syntrophin alpha 1
23037	PDZD2	PDZ domain containing 2	664701	ZNF826P	zinc finger protein 826, pseudogene
2305	FOXM1	forkhead box M1	6648	SOD2	superoxide dismutase 2
2307	FOXS1	forkhead box S1	6662	SOX9	SRY-box 9
23072	HECW1	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1	6688	SPI1	Spi-1 proto-oncogene
23086	EXPH5	exophilin 5	6690	SPINK1	serine peptidase inhibitor, Kazal type 1
23089	PEG10	paternally expressed 10	6692	SPINT1	serine peptidase inhibitor, Kunitz type 1
231	AKR1B1	aldo-keto reductase family 1 member B	6695	SPOCK1	SPARC/osteonectin, cwcv and kazal like domains proteoglycan 1
23114	NFASC	neurofascin	6696	SPP1	secreted phosphoprotein 1
23149	FCHO1	FCH domain only 1	6712	SPTBN2	spectrin beta, non-erythrocytic 2
23151	GRAMD4	GRAM domain containing 4	6752	SSTR2	somatostatin receptor 2
2318	FLNC	filamin C	6768	ST14	suppression of tumorigenicity 14
23189	KANK1	KN motif and ankyrin repeat domains 1	6769	STAC	SH3 and cysteine rich domain
2321	FLT1	fms related tyrosine kinase 1	6772	STAT1	signal transducer and activator of transcription 1

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
23213	SULF1	sulfatase 1	677679	SCARNA3	small Cajal body-specific RNA 3
23236	PLCB1	phospholipase C beta 1	677681	SCARNA20	small Cajal body-specific RNA 20
2324	FLT4	fms related tyrosine kinase 4	677765	SCARNA18	small Cajal body-specific RNA 18
23242	COBL	cordon-bleu WH2 repeat protein	677770	SCARNA22	small Cajal body-specific RNA 22
23245	ASTN2	astrotactin 2	677771	SCARNA4	small Cajal body-specific RNA 4
23250	ATP11A	ATPase phospholipid transporting 11A	677772	SCARNA6	small Cajal body-specific RNA 6
23255	MTCL1	microtubule crosslinking factor 1	677773	SCARNA23	small Cajal body-specific RNA 23
2326	FMO1	flavin containing monooxygenase 1	677775	SCARNA5	small Cajal body-specific RNA 5
23263	MCF2L	MCF.2 cell line derived transforming sequence like	677776	SCARNA8	small Cajal body-specific RNA 8
2327	FMO2	flavin containing monooxygenase 2	677780	SCARNA11	small Cajal body-specific RNA 11
2328	FMO3	flavin containing monooxygenase 3	677792	SNORA1	small nucleolar RNA, H/ACA box 1
23284	ADGRL3	adhesion G protein-coupled receptor L3	677793	SNORA2A	small nucleolar RNA, H/ACA box 2A
23286	WWC1	WW and C2 domain containing 1	677794	SNORA2B	small nucleolar RNA, H/ACA box 2B
23302	WSCD1	WSC domain containing 1	677796	SNORA5C	small nucleolar RNA, H/ACA box 5C
2331	FMOD	fibromodulin	677798	SNORA9	small nucleolar RNA, H/ACA box 9
23314	SATB2	SATB homeobox 2	677799	SNORA11	small nucleolar RNA, H/ACA box 11
2335	FN1	fibronectin 1	677801	SNORA14A	small nucleolar RNA, H/ACA box 14A
23362	PSD3	pleckstrin and Sec7 domain containing 3	677802	SNORA14B	small nucleolar RNA, H/ACA box 14B
23363	OBSL1	obscurin like 1	677803	SNORA15	small nucleolar RNA, H/ACA box 15
23414	ZFPM2	zinc finger protein, FOG family member 2	677806	SNORA20	small nucleolar RNA, H/ACA box 20
23417	MLYCD	malonyl-CoA decarboxylase	677810	SNORA26	small nucleolar RNA, H/ACA box 26
23426	GRIP1	glutamate receptor interacting protein 1	677811	SNORA28	small nucleolar RNA, H/ACA box 28
23428	SLC7A8	solute carrier family 7 member 8	677812	SNORA29	small nucleolar RNA, H/ACA box 29
23430	TPSD1	tryptase delta 1	677813	SNORA30	small nucleolar RNA, H/ACA box 30
23452	ANGPTL2	angiopoietin like 2	677814	SNORA31	small nucleolar RNA, H/ACA box 31
2346	FOLH1	folate hydrolase 1	677815	SNORA2C	small nucleolar RNA, H/ACA box 2C
23460	ABCA6	ATP binding cassette subfamily A member 6	677818	SNORA36B	small nucleolar RNA, H/ACA box 36B
23462	HEY1	hes related family bHLH transcription factor with YRPW motif 1	677821	SNORA71E	small nucleolar RNA, H/ACA box 71E
2348	FOLR1	folate receptor 1	677823	SNORA80E	small nucleolar RNA, H/ACA box 80E
23491	CES3	carboxylesterase 3	677825	SNORA44	small nucleolar RNA, H/ACA box 44
23493	HEY2	hes related family bHLH transcription factor with YRPW motif 2	677826	SNORA3B	small nucleolar RNA, H/ACA box 3B
23498	HAAO	3-hydroxyanthranilate 3,4-dioxygenase	677827	SNORA46	small nucleolar RNA, H/ACA box 46

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
2350	FOLR2	folate receptor beta	677828	SNORA47	small nucleolar RNA, H/ACA box 47
23500	DAAM2	dishevelled associated activator of morphogenesis 2	677830	SNORA50A	small nucleolar RNA, H/ACA box 50A
23516	SLC39A14	solute carrier family 39 member 14	677831	SNORA51	small nucleolar RNA, H/ACA box 51
2353	FOS	Fos proto-oncogene, AP-1 transcription factor subunit	677833	SNORA54	small nucleolar RNA, H/ACA box 54
23532	PRAME	preferentially expressed antigen in melanoma	677834	SNORA55	small nucleolar RNA, H/ACA box 55
2354	FOSB	FosB proto-oncogene, AP-1 transcription factor subunit	677836	SNORA58	small nucleolar RNA, H/ACA box 58
23547	LILRA4	leukocyte immunoglobulin like receptor A4	677837	SNORA60	small nucleolar RNA, H/ACA box 60
23551	RASD2	RASD family member 2	677838	SNORA61	small nucleolar RNA, H/ACA box 61
23554	TSPAN12	tetraspanin 12	677839	SNORA71C	small nucleolar RNA, H/ACA box 71C
2357	FPR1	formyl peptide receptor 1	677840	SNORA71D	small nucleolar RNA, H/ACA box 71D
23576	DDAH1	dimethylarginine dimethylaminohydrolase 1	677842	SNORA50C	small nucleolar RNA, H/ACA box 50C
2358	FPR2	formyl peptide receptor 2	677843	SNORA77	small nucleolar RNA, H/ACA box 77
23584	VSIG2	V-set and immunoglobulin domain containing 2	677844	SNORA78	small nucleolar RNA, H/ACA box 78
23594	ORC6	origin recognition complex subunit 6	677845	SNORA79	small nucleolar RNA, H/ACA box 79
23596	OPN3	opsin 3	677846	SNORA80A	small nucleolar RNA, H/ACA box 80A
23600	AMACR	alpha-methylacyl-CoA racemase	677850	SNORD1C	small nucleolar RNA, C/D box 1C
23643	LY96	lymphocyte antigen 96	6781	STC1	stanniocalcin 1
23704	KCNE4	potassium voltage-gated channel subfamily E regulatory subunit 4	6790	AURKA	aurora kinase A
23705	CADM1	cell adhesion molecule 1	6799	SULT1A2	sulfotransferase family 1A member 2
23743	BHMT2	betaine--homocysteine S-methyltransferase 2	6812	STXBP1	syntaxin binding protein 1
23767	FLRT3	fibronectin leucine rich transmembrane protein 3	6817	SULT1A1	sulfotransferase family 1A member 1
240	ALOX5	arachidonate 5-lipoxygenase	6819	SULT1C2	sulfotransferase family 1C member 2
241	ALOX5AP	arachidonate 5-lipoxygenase activating protein	684959	SNORA25	small nucleolar RNA, H/ACA box 25
24137	KIF4A	kinesin family member 4A	6876	TAGLN	transgelin
24141	LAMP5	lysosomal associated membrane protein family member 5	688	KLF5	Kruppel like factor 5
246126	TXLNGY	taxilin gamma pseudogene, Y-linked	6887	TAL2	TAL bHLH transcription factor 2
246181	AKR7L	aldo-keto reductase family 7 like (gene/pseudogene)	6907	TBL1X	transducin beta like 1 X-linked
246721	POLR2J2	RNA polymerase II subunit J2	6909	TBX2	T-box 2
246744	STH	saitohin	6913	TBX15	T-box 15
246777	SPESP1	sperm equatorial segment protein 1	6920	TCEA3	transcription elongation factor A3
247	ALOX15B	arachidonate 15-lipoxygenase, type B	692053	SNORD9	small nucleolar RNA, C/D box 9
2487	FRZB	frizzled related protein	692057	SNORD12	small nucleolar RNA, C/D box 12
249	ALPL	alkaline phosphatase, liver/bone/kidney	692063	SNORA32	small nucleolar RNA, H/ACA box 32

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
2528	FUT6	fucosyltransferase 6	692073	SNORA16A	small nucleolar RNA, H/ACA box 16A
2532	ACKR1	atypical chemokine receptor 1 (Duffy blood group)	692076	SNORD7	small nucleolar RNA, C/D box 7
2533	FYB1	FYN binding protein 1	692084	SNORD13	small nucleolar RNA, C/D box 13
253650	ANKRD18A	ankyrin repeat domain 18A	692085	SNORD45C	small nucleolar RNA, C/D box 45C
253738	EBF3	early B-cell factor 3	692090	SNORD59B	small nucleolar RNA, C/D box 59B
253982	ASPHD1	aspartate beta-hydroxylase domain containing 1	692106	SNORD65	small nucleolar RNA, C/D box 65
2542	SLC37A4	solute carrier family 37 member 4	692107	SNORD66	small nucleolar RNA, C/D box 66
254295	PHYHD1	phytanoyl-CoA dioxygenase domain containing 1	692108	SNORD67	small nucleolar RNA, C/D box 67
255027	MPV17L	MPV17 mitochondrial inner membrane protein like	692109	SNORD69	small nucleolar RNA, C/D box 69
255231	MCOLN2	mucolipin 2	692111	SNORD71	small nucleolar RNA, C/D box 71
255631	COL24A1	collagen type XXIV alpha 1 chain	692149	SCARNA14	small Cajal body-specific RNA 14
255743	NPNT	nephronectin	692196	SNORD76	small nucleolar RNA, C/D box 76
255877	BCL6B	B-cell CLL/lymphoma 6B	692199	SNORD84	small nucleolar RNA, C/D box 84
2562	GABRB3	gamma-aminobutyric acid type A receptor beta3 subunit	692200	SNORD103C	small nucleolar RNA, C/D box 103C
256236	NAPSB	napsin B aspartic peptidase, pseudogene	692204	SNORD88C	small nucleolar RNA, C/D box 88C
2563	GABRD	gamma-aminobutyric acid type A receptor delta subunit	692205	SNORD89	small nucleolar RNA, C/D box 89
2564	GABRE	gamma-aminobutyric acid type A receptor epsilon subunit	692206	SNORD90	small nucleolar RNA, C/D box 90
256691	MAMDC2	MAM domain containing 2	692208	SNORD91B	small nucleolar RNA, C/D box 91B
256714	MAP7D2	MAP7 domain containing 2	692209	SNORD92	small nucleolar RNA, C/D box 92
256764	WDR72	WD repeat domain 72	692212	SNORD99	small nucleolar RNA, C/D box 99
257019	FRMD3	FERM domain containing 3	692213	SNORD110	small nucleolar RNA, C/D box 110
2571	GAD1	glutamate decarboxylase 1	692225	SNORD94	small nucleolar RNA, C/D box 94
257106	ARHGAP30	Rho GTPase activating protein 30	692227	SNORD104	small nucleolar RNA, C/D box 104
257177	CFAP126	cilia and flagella associated protein 126	692229	SNORD105	small nucleolar RNA, C/D box 105
257194	NEGR1	neuronal growth regulator 1	692233	SNORD117	small nucleolar RNA, C/D box 117
257407	C2orf72	chromosome 2 open reading frame 72	6926	TBX3	T-box 3
25759	SHC2	SHC adaptor protein 2	6927	HNF1A	HNF1 homeobox A
257629	ANKS4B	ankyrin repeat and sterile alpha motif domain containing 4B	6928	HNF1B	HNF1 homeobox B
25787	DGCR9	DiGeorge syndrome critical region gene 9 (non-protein coding)	693197	MIR612	microRNA 612
25791	NGEF	neuronal guanine nucleotide exchange factor	6943	TCF21	transcription factor 21
25797	QPCT	glutaminyl-peptide cyclotransferase	6947	TCN1	transcobalamin 1
25802	LMOD1	leiomodin 1	6948	TCN2	transcobalamin 2
25805	BAMBI	BMP and activin membrane bound inhibitor	695	BTK	Bruton tyrosine kinase
25825	BACE2	beta-site APP-cleaving enzyme 2	699	BUB1	BUB1 mitotic checkpoint serine/threonine kinase
25826	SNORD82	small nucleolar RNA, C/D box 82	6999	TDO2	tryptophan 2,3-dioxygenase
2583	B4GALNT1	beta-1,4-N-acetyl-galactosaminyltransferase 1	70	ACTC1	actin, alpha, cardiac muscle 1

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
25840	METTL7A	methyltransferase like 7A	701	BUB1B	BUB1 mitotic checkpoint serine/threonine kinase B
25841	ABTB2	ankyrin repeat and BTB domain containing 2	7010	TEK	TEK receptor tyrosine kinase
25849	PARM1	prostate androgen-regulated mucin-like protein 1	7018	TF	transferrin
25854	FAM149A	family with sequence similarity 149 member A	7020	TFAP2A	transcription factor AP-2 alpha
25878	MXRA5	matrix remodeling associated 5	7025	NR2F1	nuclear receptor subfamily 2 group F member 1
25890	ABI3BP	ABI family member 3 binding protein	7033	TFF3	trefoil factor 3
25891	PAMR1	peptidase domain containing associated with muscle regeneration 1	7035	TFPI	tissue factor pathway inhibitor
25894	PLEKHG4	pleckstrin homology and RhoGEF domain containing G4	7039	TGFA	transforming growth factor alpha
259	AMBP	alpha-1-microglobulin/bikunin precursor	7045	TGFBI	transforming growth factor beta induced
25903	OLFML2B	olfactomedin like 2B	7049	TGFBR3	transforming growth factor beta receptor 3
2591	GALNT3	polypeptide N-acetylgalactosaminyltransferase 3	7051	TGM1	transglutaminase 1
259232	NALCN	sodium leak channel, non-selective	7052	TGM2	transglutaminase 2
25925	ZNF521	zinc finger protein 521	7057	THBS1	thrombospondin 1
259266	ASPM	abnormal spindle microtubule assembly	7058	THBS2	thrombospondin 2
259289	TAS2R43	taste 2 receptor member 43	7060	THBS4	thrombospondin 4
2593	GAMT	guanidinoacetate N-methyltransferase	7066	THPO	thrombopoietin
259307	IL4I1	interleukin 4 induced 1	7070	THY1	Thy-1 cell surface antigen
25975	EGFL6	EGF like domain multiple 6	7075	TIE1	tyrosine kinase with immunoglobulin like and EGF like domains 1
25976	TIPARP	TCDD inducible poly(ADP-ribose) polymerase	7078	TIMP3	TIMP metallopeptidase inhibitor 3
25987	TSKU	tsukushi, small leucine rich proteoglycan	7079	TIMP4	TIMP metallopeptidase inhibitor 4
26	AOC1	amine oxidase, copper containing 1	7083	TK1	thymidine kinase 1
26002	MOXD1	monooxygenase DBH like 1	7089	TLE2	transducin like enhancer of split 2
26011	TENM4	teneurin transmembrane protein 4	7092	TLL1	tolloid like 1
26022	TMEM98	transmembrane protein 98	7098	TLR3	toll like receptor 3
260293	CYP4X1	cytochrome P450 family 4 subfamily X member 1	7102	TSPAN7	tetraspanin 7
26033	ATRNL1	attractin like 1	7103	TSPAN8	tetraspanin 8
26050	SLITRK5	SLIT and NTRK like family member 5	7108	TM7SF2	transmembrane 7 superfamily member 2
26053	AUTS2	AUTS2, activator of transcription and developmental regulator	7111	TMOD1	tropomodulin 1
26084	ARHGEF26	Rho guanine nucleotide exchange factor 26	712	C1QA	complement C1q A chain
26095	PTPN20	protein tyrosine phosphatase, non-receptor type 20	7123	CLEC3B	C-type lectin domain family 3 member B
2615	LRRC32	leucine rich repeat containing 32	713	C1QB	complement C1q B chain
26150	RIBC2	RIB43A domain with coiled-coils 2	7130	TNFAIP6	TNF alpha induced protein 6

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
26154	ABCA12	ATP binding cassette subfamily A member 12	7134	TNNC1	troponin C1, slow skeletal and cardiac type
26167	PCDHB5	protocadherin beta 5	7138	TNNT1	troponin T1, slow skeletal type
261729	STEAP2	STEAP2 metalloreductase	7139	TNNT2	troponin T2, cardiac type
26191	PTPN22	protein tyrosine phosphatase, non-receptor type 22	714	C1QC	complement C1q C chain
2620	GAS2	growth arrest specific 2	7140	TNNT3	troponin T3, fast skeletal type
26207	PITPNC1	phosphatidylinositol transfer protein, cytoplasmic 1	7145	TNS1	tensin 1
26219	OR1J4	olfactory receptor family 1 subfamily J member 4	7148	TNXB	tenascin XB
26223	FBXL21	F-box and leucine rich repeat protein 21 (gene/pseudogene)	715	C1R	complement C1r
26227	PHGDH	phosphoglycerate dehydrogenase	7153	TOP2A	DNA topoisomerase II alpha
26247	OR2L1P	olfactory receptor family 2 subfamily L member 1 pseudogene	716	C1S	complement C1s
2625	GATA3	GATA binding protein 3	7164	TPD52L1	tumor protein D52 like 1
26253	CLEC4E	C-type lectin domain family 4 member E	717	C2	complement C2
2627	GATA6	GATA binding protein 6	718	C3	complement C3
26279	PLA2G2D	phospholipase A2 group IID	72	ACTG2	actin, gamma 2, smooth muscle, enteric
2628	GATM	glycine amidinotransferase	720	C4A	complement C4A (Rodgers blood group)
2633	GBP1	guanylate binding protein 1	721	C4B	complement C4B (Chido blood group)
2635	GBP3	guanylate binding protein 3	7216	TRO	trophinin
26353	HSPB8	heat shock protein family B (small) member 8	7225	TRPC6	transient receptor potential cation channel subfamily C member 6
2638	GC	GC, vitamin D binding protein	723778	MIR650	microRNA 650
26470	SEZ6L2	seizure related 6 homolog like 2	7253	TSHR	thyroid stimulating hormone receptor
26499	PLEK2	pleckstrin 2	7262	PHLDA2	pleckstrin homology like domain family A member 2
26508	HEYL	hes related family bHLH transcription factor with YRPW motif-like	7263	TST	thiosulfate sulfurtransferase
26575	RGS17	regulator of G protein signaling 17	7272	TTK	TTK protein kinase
26577	PCOLCE2	procollagen C-endopeptidase enhancer 2	7273	TTN	titin
26579	MYEOV	myeloma overexpressed	7275	TUB	tubby bipartite transcription factor
26585	GREM1	gremlin 1, DAN family BMP antagonist	727800	RNF208	ring finger protein 208
2669	GEM	GTP binding protein overexpressed in skeletal muscle	727936	GXYLT2	glucoside xylosyltransferase 2
267010	RNU12	RNA, U12 small nuclear	727956	SDHAP2	succinate dehydrogenase complex flavoprotein subunit A pseudogene 2
2674	GFRA1	GDNF family receptor alpha 1	7280	TUBB2A	tubulin beta 2A class IIa
26751	SH3YL1	SH3 and SYLF domain containing 1	728053	NA	NA
26762	HAVCR1	hepatitis A virus cellular receptor 1	728233	PI4KAP1	phosphatidylinositol 4-kinase alpha pseudogene 1
26765	SNORD12C	small nucleolar RNA, C/D box 12C	728464	METTL24	methyltransferase like 24
26773	SNORD4A	small nucleolar RNA, C/D box 4A	728609	SDHAP3	succinate dehydrogenase complex flavoprotein subunit A pseudogene 3

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
26774	SNORD80	small nucleolar RNA, C/D box 80	728640	FAM133CP	family with sequence similarity 133, member A pseudogene
26775	SNORA72	small nucleolar RNA, H/ACA box 72	728747	ANKRD20A4	ankyrin repeat domain 20 family member A4
26776	SNORA71B	small nucleolar RNA, H/ACA box 71B	729	C6	complement C6
26777	SNORA71A	small nucleolar RNA, H/ACA box 71A	729162	FAM239B	zinc finger protein 839 pseudogene
26779	SNORA69	small nucleolar RNA, H/ACA box 69	729171	ANKRD20A8P	ankyrin repeat domain 20 family member A8, pseudogene
2678	GGT1	gamma-glutamyltransferase 1	729230	CCR2	C-C motif chemokine receptor 2
26782	SNORA66	small nucleolar RNA, H/ACA box 66	729359	PLIN4	perilipin 4
26783	SNORA65	small nucleolar RNA, H/ACA box 65	729648	ZNF812P	zinc finger protein 812, pseudogene
26785	SNORD63	small nucleolar RNA, C/D box 63	729737	LOC729737	uncharacterized LOC729737
26787	SNORD61	small nucleolar RNA, C/D box 61	729970	LOC729970	hCG2028352-like
26788	SNORD60	small nucleolar RNA, C/D box 60	729993	SHISA9	shisa family member 9
26791	SNORD58A	small nucleolar RNA, C/D box 58A	730	C7	complement C7
26792	SNORD57	small nucleolar RNA, C/D box 57	730005	SEC14L6	SEC14 like lipid binding 6
26793	SNORD56	small nucleolar RNA, C/D box 56	730013	ABCC6P2	ATP binding cassette subfamily C member 6 pseudogene 2
26795	SNORD54	small nucleolar RNA, C/D box 54	730087	ZNF726	zinc finger protein 726
26796	SNORD53	small nucleolar RNA, C/D box 53	7305	TYROBP	TYRO protein tyrosine kinase binding protein
26799	SNORD50A	small nucleolar RNA, C/D box 50A	731220	RFX8	RFX family member 8, lacking RFX DNA binding domain
26800	SNORD49A	small nucleolar RNA, C/D box 49A	7345	UCHL1	ubiquitin C-terminal hydrolase L1
26801	SNORD48	small nucleolar RNA, C/D box 48	735	C9	complement C9
26802	SNORD47	small nucleolar RNA, C/D box 47	7351	UCP2	uncoupling protein 2
26805	SNORD45A	small nucleolar RNA, C/D box 45A	7364	UGT2B7	UDP glucuronosyltransferase family 2 member B7
2681	GGTA1P	glycoprotein, alpha-galactosyltransferase 1 pseudogene	7368	UGT8	UDP glycosyltransferase 8
26810	SNORD41	small nucleolar RNA, C/D box 41	7373	COL14A1	collagen type XIV alpha 1 chain
26811	SNORD55	small nucleolar RNA, C/D box 55	7388	UQCRH	ubiquinol-cytochrome c reductase hinge protein
26813	SNORD36C	small nucleolar RNA, C/D box 36C	7404	UTY	ubiquitously transcribed tetratricopeptide repeat containing, Y-linked
26814	SNORD36B	small nucleolar RNA, C/D box 36B	7409	VAV1	vav guanine nucleotide exchange factor 1
26815	SNORD36A	small nucleolar RNA, C/D box 36A	7412	VCAM1	vascular cell adhesion molecule 1
26816	SNORD35A	small nucleolar RNA, C/D box 35A	7422	VEGFA	vascular endothelial growth factor A
26817	SNORD34	small nucleolar RNA, C/D box 34	7424	VEGFC	vascular endothelial growth factor C
26818	SNORD33	small nucleolar RNA, C/D box 33	7429	VIL1	villin 1
26819	SNORD32A	small nucleolar RNA, C/D box 32A	745	MYRF	myelin regulatory factor

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
26820	SNORD24	small nucleolar RNA, C/D box 24	7450	VWF	von Willebrand factor
26822	SNORD14A	small nucleolar RNA, C/D box 14A	7482	WNT2B	Wnt family member 2B
26824	RNU11	RNA, U11 small nuclear	7490	WT1	Wilms tumor 1
26829	RNU5E-1	RNA, U5E small nuclear 1	7498	XDH	xanthine dehydrogenase
26831	RNU5A-1	RNA, U5A small nuclear 1	7503	XIST	X inactive specific transcript (non-protein coding)
26832	RNU5B-1	RNA, U5B small nuclear 1	7512	XPNPEP2	X-prolyl aminopeptidase 2
26834	RNU4-2	RNA, U4 small nuclear 2	7535	ZAP70	zeta chain of T-cell receptor associated protein kinase 70
26835	RNU4-1	RNA, U4 small nuclear 1	7538	ZFP36	ZFP36 ring finger protein
26851	SNORD3B-1	small nucleolar RNA, C/D box 3B-1	7544	ZFY	zinc finger protein, Y-linked
26855	RNU2-2P	RNA, U2 small nuclear 2, pseudogene	7552	ZNF711	zinc finger protein 711
26860	RNU1-13P	RNA, U1 small nuclear 13, pseudogene	760	CA2	carbonic anhydrase 2
2687	GGT5	gamma-glutamyltransferase 5	762	CA4	carbonic anhydrase 4
26872	STEAP1	STEAP family member 1	7643	ZNF90	zinc finger protein 90
2690	GHR	growth hormone receptor	767	CA8	carbonic anhydrase 8
2697	GJA1	gap junction protein alpha 1	768	CA9	carbonic anhydrase 9
26996	GPR160	G protein-coupled receptor 160	768206	PRCD	photoreceptor disc component
270	AMPD1	adenosine monophosphate deaminase 1	7694	ZNF135	zinc finger protein 135
2701	GJA4	gap junction protein alpha 4	7704	ZBTB16	zinc finger and BTB domain containing 16
27019	DNAI1	dynein axonemal intermediate chain 1	771	CA12	carbonic anhydrase 12
2702	GJA5	gap junction protein alpha 5	7710	ZNF154	zinc finger protein 154
2705	GJB1	gap junction protein beta 1	775	CACNA1C	calcium voltage-gated channel subunit alpha1 C
2706	GJB2	gap junction protein beta 2	7754	ZNF204P	zinc finger protein 204, pseudogene
27063	ANKRD1	ankyrin repeat domain 1	7757	ZNF208	zinc finger protein 208
27074	LAMP3	lysosomal associated membrane protein 3	776	CACNA1D	calcium voltage-gated channel subunit alpha1 D
27075	TSPAN13	tetraspanin 13	7772	ZNF229	zinc finger protein 229
27122	DKK3	dickkopf WNT signaling pathway inhibitor 3	778	CACNA1F	calcium voltage-gated channel subunit alpha1 F
27128	CYTH4	cytohesin 4	7784	ZP3	zona pellucida glycoprotein 3
27132	CPNE7	copine 7	7802	DNALI1	dynein axonemal light intermediate chain 1
27141	CIDEB	cell death-inducing DFFA-like effector b	7804	LRP8	LDL receptor related protein 8
27145	FILIP1	filamin A interacting protein 1	780851	SNORD3A	small nucleolar RNA, C/D box 3A
27147	DENND2A	DENN domain containing 2A	780853	SNORD3C	small nucleolar RNA, C/D box 3C
27156	RSPH14	radial spoke head 14 homolog	780854	SNORD3D	small nucleolar RNA, C/D box 3D
27181	SIGLEC8	sialic acid binding Ig like lectin 8	781	CACNA2D1	calcium voltage-gated channel auxiliary subunit alpha2delta 1
2719	GPC3	glypican 3	783	CACNB2	calcium voltage-gated channel auxiliary subunit beta 2
27202	C5AR2	complement component 5a receptor 2	7837	PXDN	peroxidasin
27233	SULT1C4	sulfotransferase family 1C member 4	7849	PAX8	paired box 8
27237	ARHGEF16	Rho guanine nucleotide exchange factor 16	7850	IL1R2	interleukin 1 receptor type 2
27242	TNFRSF21	TNF receptor superfamily member 21	7851	MALL	mal, T-cell differentiation protein like

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
27253	PCDH17	protocadherin 17	7857	SCG2	secretogranin II
27283	TINAG	tubulointerstitial nephritis antigen	7869	SEMA3B	semaphorin 3B
27285	TEKT2	tektin 2	7881	KCNAB1	potassium voltage-gated channel subfamily A member regulatory beta subunit 1
27286	SRPX2	sushi repeat containing protein, X-linked 2	78989	COLEC11	collectin subfamily member 11
27293	SMPDL3B	sphingomyelin phosphodiesterase acid like 3B	79083	MLPH	melanophilin
27295	PDLIM3	PDZ and LIM domain 3	79168	LILRA6	leukocyte immunoglobulin like receptor A6
27299	ADAMDEC1	ADAM like decysin 1	79191	IRX3	iroquois homeobox 3
2731	GLDC	glycine decarboxylase	79365	BHLHE41	basic helix-loop-helix family member e41
27324	TOX3	TOX high mobility group box family member 3	79369	B3GNT4	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 4
27329	ANGPTL3	angiopoietin like 3	7940	LST1	leukocyte specific transcript 1
27334	P2RY10	P2Y receptor family member 10	7941	PLA2G7	phospholipase A2 group VII
27344	PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor	79411	GLB1L	galactosidase beta 1 like
27347	STK39	serine/threonine kinase 39	79444	BIRC7	baculoviral IAP repeat containing 7
2743	GLRB	glycine receptor beta	79589	RNF128	ring finger protein 128, E3 ubiquitin protein ligase
27445	PCLO	piccolo presynaptic cytomatrix protein	79605	PGBD5	piggyBac transposable element derived 5
2745	GLRX	glutaredoxin	79611	ACSS3	acyl-CoA synthetase short chain family member 3
2791	GNG11	G protein subunit gamma 11	79623	GALNT14	polypeptide N-acetylgalactosaminyltransferase 14
28	ABO	ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase	79625	NDNF	neuron derived neurotrophic factor
280	AMY2B	amylase, alpha 2B (pancreatic)	79632	FAM184A	family with sequence similarity 184 member A
2805	GOT1	glutamic-oxaloacetic transaminase 1	79633	FAT4	FAT atypical cadherin 4
2810	SFN	stratifin	79652	TMEM204	transmembrane protein 204
2819	GPD1	glycerol-3-phosphate dehydrogenase 1	79656	BEND5	BEN domain containing 5
2823	GPM6A	glycoprotein M6A	79669	C3orf52	chromosome 3 open reading frame 52
28231	SLCO4A1	solute carrier organic anion transporter family member 4A1	79674	VEPH1	ventricular zone expressed PH domain containing 1
2828	GPR4	G protein-coupled receptor 4	79689	STEAP4	STEAP4 metalloreductase
2829	XCR1	X-C motif chemokine receptor 1	79729	SH3D21	SH3 domain containing 21
282969	FUOM	fucose mutarotase	79730	NSUN7	NOP2/Sun RNA methyltransferase family member 7
282996	RBM20	RNA binding motif protein 20	79733	E2F8	E2F transcription factor 8
283	ANG	angiogenin	79739	TTLL7	tubulin tyrosine ligase like 7
283120	H19	H19, imprinted maternally expressed transcript (non-protein coding)	79742	CXorf36	chromosome X open reading frame 36
283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	79745	CLIP4	CAP-Gly domain containing linker protein family member 4

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
283208	P4HA3	prolyl 4-hydroxylase subunit alpha 3	79746	ECHDC3	enoyl-CoA hydratase domain containing 3
283316	CD163L1	CD163 molecule like 1	79750	ZNF385D	zinc finger protein 385D
283358	B4GALNT3	beta-1,4-N-acetyl-galactosaminyltransferase 3	79774	GRTP1	growth hormone regulated TBC protein 1
283375	SLC39A5	solute carrier family 39 member 5	79776	ZFHX4	zinc finger homeobox 4
283383	ADGRD1	adhesion G protein-coupled receptor D1	79781	IQCA1	IQ motif containing with AAA domain 1
283392	TRHDE-AS1	TRHDE antisense RNA 1	79783	SUGCT	succinyl-CoA:glutarate-CoA transferase
283417	DPY19L2	dpy-19 like 2	79784	MYH14	myosin heavy chain 14
283422	LINC01559	long intergenic non-protein coding RNA 1559	79785	RERGL	RERG like
283431	GAS2L3	growth arrest specific 2 like 3	79799	UGT2A3	UDP glucuronosyltransferase family 2 member A3
283755	HERC2P3	hect domain and RLD 2 pseudogene 3	7980	TFPI2	tissue factor pathway inhibitor 2
283796	GOLGA8IP	golgin A8 family member I, pseudogene	79801	SHCBP1	SHC binding and spindle associated 1
283848	CES4A	carboxylesterase 4A	79812	MMRN2	multimerin 2
283849	EXOC3L1	exocyst complex component 3 like 1	79814	AGMAT	agmatinase
283971	CLEC18C	C-type lectin domain family 18 member C	79817	MOB3B	MOB kinase activator 3B
284	ANGPT1	angiopoietin 1	79820	CATSPERB	cation channel sperm associated auxiliary subunit beta
284047	CCDC144B	coiled-coil domain containing 144B (pseudogene)	79822	ARHGAP28	Rho GTPase activating protein 28
284076	TTLL6	tubulin tyrosine ligase like 6	79827	CLMP	CXADR like membrane protein
284217	LAMA1	laminin subunit alpha 1	79839	CCDC102B	coiled-coil domain containing 102B
284297	SSC5D	scavenger receptor cysteine rich family member with 5 domains	79849	PDZD3	PDZ domain containing 3
284339	TMEM145	transmembrane protein 145	79883	PODNL1	podocan like 1
284422	SMIM24	small integral membrane protein 24	79888	LPCAT1	lysophosphatidylcholine acyltransferase 1
284612	SYPL2	synaptophysin like 2	799	CALCR	calcitonin receptor
2847	MCHR1	melanin concentrating hormone receptor 1	79931	TNIP3	TNFAIP3 interacting protein 3
284716	RIMKLA	ribosomal modification protein rimK like family member A	79953	SYNDIG1	synapse differentiation inducing 1
284904	SEC14L4	SEC14 like lipid binding 4	79971	WLS	wntless Wnt ligand secretion mediator
285	ANGPT2	angiopoietin 2	79983	POF1B	POF1B, actin binding protein
285016	ALKAL2	ALK and LTK ligand 2	79986	ZNF702P	zinc finger protein 702, pseudogene
285025	CCDC141	coiled-coil domain containing 141	79987	SVEP1	sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1
28514	DLL1	delta like canonical Notch ligand 1	79993	ELOVL7	ELOVL fatty acid elongase 7
2852	GPER1	G protein-coupled estrogen receptor 1	80000	GREB1L	growth regulation by estrogen in breast cancer 1 like
285220	EPHA6	EPH receptor A6	80008	TMEM156	transmembrane protein 156
285498	RNF212	ring finger protein 212	80022	MYO15B	myosin XVB
285590	SH3PXD2B	SH3 and PX domains 2B	80031	SEMA6D	semaphorin 6D
285596	FAM153A	family with sequence similarity 153 member A	80036	TRPM3	transient receptor potential cation channel subfamily M member 3
2857	GPR34	G protein-coupled receptor 34	80039	FAM106A	family with sequence similarity 106 member A

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
2859	GPR35	G protein-coupled receptor 35	80086	TUBA4B	tubulin alpha 4b
286	ANK1	ankyrin 1	80115	BAIAP2L2	BAI1 associated protein 2 like 2
286077	FAM83H	family with sequence similarity 83 member H	8013	NR4A3	nuclear receptor subfamily 4 group A member 3
2861	GPR37	G protein-coupled receptor 37	80144	FRAS1	Fraser extracellular matrix complex subunit 1
286464	CFAP47	cilia and flagella associated protein 47	80150	ASRGL1	asparaginase like 1
286676	ILDR1	immunoglobulin like domain containing receptor 1	80162	PGGHG	protein-glucosylgalactosylhydroxylysine glucosidase
287	ANK2	ankyrin 2	80164	PRR36	proline rich 36
2875	GPT	glutamic--pyruvic transaminase	80177	MYCT1	MYC target 1
2878	GPX3	glutathione peroxidase 3	80183	RUBCNL	RUN and cysteine rich domain containing beclin 1 interacting protein like
288	ANK3	ankyrin 3	80201	HKDC1	hexokinase domain containing 1
2886	GRB7	growth factor receptor bound protein 7	80217	CFAP43	cilia and flagella associated protein 43
2888	GRB14	growth factor receptor bound protein 14	80221	ACSF2	acyl-CoA synthetase family member 2
2892	GRIA3	glutamate ionotropic receptor AMPA type subunit 3	80243	PREX2	phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2
2894	GRID1	glutamate ionotropic receptor delta type subunit 1	80258	EFHC2	EF-hand domain containing 2
28951	TRIB2	tribbles pseudokinase 2	80270	HSD3B7	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 7
28968	SLC6A16	solute carrier family 6 member 16	8029	CUBN	cubilin
28970	C11orf54	chromosome 11 open reading frame 54	80303	EFHD1	EF-hand domain family member D1
28984	RGCC	regulator of cell cycle	80307	FER1L4	fer-1 like family member 4, pseudogene
2899	GRIK3	glutamate ionotropic receptor kainate type subunit 3	80310	PDGFD	platelet derived growth factor D
28999	KLF15	Kruppel like factor 15	80323	CCDC68	coiled-coil domain containing 68
290	ANPEP	alanyl aminopeptidase, membrane	80328	ULBP2	UL16 binding protein 2
2903	GRIN2A	glutamate ionotropic receptor NMDA type subunit 2A	80333	KCNIP4	potassium voltage-gated channel interacting protein 4
2904	GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B	80339	PNPLA3	patatin like phospholipase domain containing 3
29089	UBE2T	ubiquitin conjugating enzyme E2 T	80342	TRAF3IP3	TRAF3 interacting protein 3
29108	PYCARD	PYD and CARD domain containing	8038	ADAM12	ADAM metallopeptidase domain 12
2918	GRM8	glutamate metabotropic receptor 8	80380	PDCD1LG2	programmed cell death 1 ligand 2
2919	CXCL1	C-X-C motif chemokine ligand 1	8061	FOSL1	FOS like 1, AP-1 transcription factor subunit
2920	CXCL2	C-X-C motif chemokine ligand 2	80704	SLC19A3	solute carrier family 19 member 3
2938	GSTA1	glutathione S-transferase alpha 1	80726	IQCN	IQ motif containing N
2939	GSTA2	glutathione S-transferase alpha 2	80731	THSD7B	thrombospondin type 1 domain containing 7B
2944	GSTM1	glutathione S-transferase mu 1	80736	SLC44A4	solute carrier family 44 member 4
2947	GSTM3	glutathione S-transferase mu 3	8076	MFAP5	microfibril associated protein 5

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
2949	GSTM5	glutathione S-transferase mu 5	80760	ITIH5	inter-alpha-trypsin inhibitor heavy chain family member 5
29760	BLNK	B-cell linker	80763	SPX	spexin hormone
29763	PACSIN3	protein kinase C and casein kinase substrate in neurons 3	80816	ASXL3	additional sex combs like 3, transcriptional regulator
29802	VPREB3	V-set pre-B cell surrogate light chain 3	80832	APOL4	apolipoprotein L4
29851	ICOS	inducible T-cell costimulator	80896	NPL	N-acetylneuraminate pyruvate lyase
29909	GPR171	G protein-coupled receptor 171	81029	WNT5B	Wnt family member 5B
29923	HILPDA	hypoxia inducible lipid droplet associated	81030	ZBP1	Z-DNA binding protein 1
29943	PADI1	peptidyl arginine deiminase 1	81031	SLC2A10	solute carrier family 2 member 10
29944	PNMA3	PNMA family member 3	81035	COLEC12	collectin subfamily member 12
29948	OSGIN1	oxidative stress induced growth inhibitor 1	8120	AP3B2	adaptor related protein complex 3 beta 2 subunit
29953	TRHDE	thyrotropin releasing hormone degrading enzyme	81285	OR51E2	olfactory receptor family 51 subfamily E member 2
29958	DMGDH	dimethylglycine dehydrogenase	8140	SLC7A5	solute carrier family 7 member 5
29968	PSAT1	phosphoserine aminotransferase 1	81466	OR2L5	olfactory receptor family 2 subfamily L member 5
29974	A1CF	APOBEC1 complementation factor	81575	APOLD1	apolipoprotein L domain containing 1
2999	GZMH	granzyme H	81578	COL21A1	collagen type XXI alpha 1 chain
3001	GZMA	granzyme A	81615	TMEM163	transmembrane protein 163
3002	GZMB	granzyme B	81624	DIAPH3	diaphanous related formin 3
3003	GZMK	granzyme K	81693	AMN	amnion associated transmembrane protein
3007	HIST1H1D	histone cluster 1 H1 family member d	81706	PPP1R14C	protein phosphatase 1 regulatory inhibitor subunit 14C
3009	HIST1H1B	histone cluster 1 H1 family member b	81792	ADAMTS12	ADAM metallopeptidase with thrombospondin type 1 motif 12
3012	HIST1H2AE	histone cluster 1 H2A family member e	81794	ADAMTS10	ADAM metallopeptidase with thrombospondin type 1 motif 10
3013	HIST1H2AD	histone cluster 1 H2A family member d	81831	NETO2	neuropilin and tolloid like 2
3018	HIST1H2BB	histone cluster 1 H2B family member b	8263	F8A1	coagulation factor VIII associated 1
3024	HIST1H1A	histone cluster 1 H1 family member a	827	CAPN6	calpain 6
3026	HABP2	hyaluronan binding protein 2	8284	KDM5D	lysine demethylase 5D
3037	HAS2	hyaluronan synthase 2	8287	USP9Y	ubiquitin specific peptidase 9, Y-linked
3039	HBA1	hemoglobin subunit alpha 1	8294	HIST1H4I	histone cluster 1 H4 family member i
3040	HBA2	hemoglobin subunit alpha 2	8302	KLRC4	killer cell lectin like receptor C4
3043	HBB	hemoglobin subunit beta	8309	ACOX2	acyl-CoA oxidase 2
3048	HBG2	hemoglobin subunit gamma 2	8320	EOMES	eomesodermin
306	ANXA3	annexin A3	8321	FZD1	frizzled class receptor 1
3067	HDC	histidine decarboxylase	8322	FZD4	frizzled class receptor 4
307	ANXA4	annexin A4	8329	HIST1H2AI	histone cluster 1 H2A family member i
3071	NCKAP1L	NCK associated protein 1 like	8331	HIST1H2AJ	histone cluster 1 H2A family member j
3075	CFH	complement factor H	8332	HIST1H2AL	histone cluster 1 H2A family member l
3078	CFHR1	complement factor H related 1	8335	HIST1H2AB	histone cluster 1 H2A family member b
3081	HGD	homogentisate 1,2-dioxygenase	8336	HIST1H2AM	histone cluster 1 H2A family member m

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
30818	KCNIP3	potassium voltage-gated channel interacting protein 3	8339	HIST1H2BG	histone cluster 1 H2B family member g
3082	HGF	hepatocyte growth factor	8340	HIST1H2BL	histone cluster 1 H2B family member l
30832	ZNF354C	zinc finger protein 354C	83416	FCRL5	Fc receptor like 5
30835	CD209	CD209 molecule	8342	HIST1H2BM	histone cluster 1 H2B family member m
3084	NRG1	neuregulin 1	8343	HIST1H2BF	histone cluster 1 H2B family member f
3099	HK2	hexokinase 2	8345	HIST1H2BH	histone cluster 1 H2B family member h
3101	HK3	hexokinase 3	83450	DRC3	dynein regulatory complex subunit 3
3111	HLA-DOA	major histocompatibility complex, class II, DO alpha	8346	HIST1H2BI	histone cluster 1 H2B family member i
3112	HLA-DOB	major histocompatibility complex, class II, DO beta	83468	GLT8D2	glycosyltransferase 8 domain containing 2
3116	HLA-DPB2	major histocompatibility complex, class II, DP beta 2 (pseudogene)	83478	ARHGAP24	Rho GTPase activating protein 24
3119	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	8348	HIST1H2BO	histone cluster 1 H2B family member o
312	ANXA13	annexin A13	83481	EPPK1	epiplakin 1
3120	HLA-DQB2	major histocompatibility complex, class II, DQ beta 2	83483	PLVAP	plasmalemma vesicle associated protein
3123	HLA-DRB1	major histocompatibility complex, class II, DR beta 1	8350	HIST1H3A	histone cluster 1 H3 family member a
3125	HLA-DRB3	major histocompatibility complex, class II, DR beta 3	8352	HIST1H3C	histone cluster 1 H3 family member c
3126	HLA-DRB4	major histocompatibility complex, class II, DR beta 4	8353	HIST1H3E	histone cluster 1 H3 family member e
3128	HLA-DRB6	major histocompatibility complex, class II, DR beta 6 (pseudogene)	83539	CHST9	carbohydrate sulfotransferase 9
313	AOAH	acyloxyacyl hydrolase	8354	HIST1H3I	histone cluster 1 H3 family member i
3131	HLF	HLF, PAR bZIP transcription factor	83540	NUF2	NUF2, NDC80 kinetochore complex component
3134	HLA-F	major histocompatibility complex, class I, F	83543	AIF1L	allograft inflammatory factor 1 like
3135	HLA-G	major histocompatibility complex, class I, G	8355	HIST1H3G	histone cluster 1 H3 family member g
3136	HLA-H	major histocompatibility complex, class I, H (pseudogene)	8356	HIST1H3J	histone cluster 1 H3 family member j
3137	HLA-J	major histocompatibility complex, class I, J (pseudogene)	8357	HIST1H3H	histone cluster 1 H3 family member h
3158	HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2	8358	HIST1H3B	histone cluster 1 H3 family member b
3159	HMGA1	high mobility group AT-hook 1	83592	AKR1E2	aldo-keto reductase family 1 member E2
316	AOX1	aldehyde oxidase 1	8361	HIST1H4F	histone cluster 1 H4 family member f
3161	HMMR	hyaluronan mediated motility receptor	83660	TLN2	talin 2
3162	HMOX1	heme oxygenase 1	8368	HIST1H4L	histone cluster 1 H4 family member l
3164	NR4A1	nuclear receptor subfamily 4 group A member 1	83690	CRISPLD1	cysteine rich secretory protein LCCL domain containing 1
3170	FOXA2	forkhead box A2	83706	FERMT3	fermitin family member 3
3172	HNF4A	hepatocyte nuclear factor 4 alpha	83714	NRIP2	nuclear receptor interacting protein 2

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3174	HNF4G	hepatocyte nuclear factor 4 gamma	83715	ESPN	espin
3177	SLC29A2	solute carrier family 29 member 2	83716	CRISPLD2	cysteine rich secretory protein LCCL domain containing 2
319103	SNORD8	small nucleolar RNA, C/D box 8	83758	RBP5	retinol binding protein 5
3199	HOXA2	homeobox A2	838	CASP5	caspase 5
3201	HOXA4	homeobox A4	8382	NME5	NME/NM23 family member 5
3203	HOXA6	homeobox A6	83872	HMCN1	hemicentin 1
3204	HOXA7	homeobox A7	83879	CDCA7	cell division cycle associated 7
3206	HOXA10	homeobox A10	83935	TMEM133	transmembrane protein 133
3207	HOXA11	homeobox A11	8395	PIP5K1B	phosphatidylinositol-4-phosphate 5-kinase type 1 beta
3209	HOXA13	homeobox A13	83953	FCAMR	Fc fragment of IgA and IgM receptor
321	APBA2	amyloid beta precursor protein binding family A member 2	83987	CCDC8	coiled-coil domain containing 8
3226	HOXC10	homeobox C10	83992	CTTNBP2	cortactin binding protein 2
3233	HOXD4	homeobox D4	84033	OBSCN	obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF
3235	HOXD9	homeobox D9	8404	SPARCL1	SPARC like 1
3236	HOXD10	homeobox D10	84054	PCDHB19P	protocadherin beta 19 pseudogene
3237	HOXD11	homeobox D11	8406	SRPX	sushi repeat containing protein, X-linked
3240	HP	haptoglobin	84109	QRFPR	pyroglutamylated RFamide peptide receptor
3241	HPCAL1	hippocalcin like 1	84125	LRRIQ1	leucine rich repeats and IQ motif containing 1
3242	HPD	4-hydroxyphenylpyruvate dioxygenase	84129	ACAD11	acyl-CoA dehydrogenase family member 11
3248	HPGD	15-hydroxyprostaglandin dehydrogenase	84144	SYDE2	synapse defective Rho GTPase homolog 2
3249	HPN	hepsin	8416	ANXA9	annexin A9
326342	ADGRE4P	adhesion G protein-coupled receptor E4, pseudogene	84166	NLRC5	NLR family CARD domain containing 5
3270	HRC	histidine rich calcium binding protein	84168	ANTXR1	anthrax toxin receptor 1
3274	HRH2	histamine receptor H2	84171	LOXL4	lysyl oxidase like 4
3280	HES1	hes family bHLH transcription factor 1	84174	SLA2	Src like adaptor 2
3284	HSD3B2	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2	84217	ZMYND12	zinc finger MYND-type containing 12
3290	HSD11B1	hydroxysteroid 11-beta dehydrogenase 1	84239	ATP13A4	ATPase 13A4
3291	HSD11B2	hydroxysteroid 11-beta dehydrogenase 2	8424	BBOX1	gamma-butyrobetaine hydroxylase 1
3293	HSD17B3	hydroxysteroid 17-beta dehydrogenase 3	8425	LTBP4	latent transforming growth factor beta binding protein 4
3294	HSD17B2	hydroxysteroid 17-beta dehydrogenase 2	84251	SGIP1	SH3 domain GRB2 like endophilin interacting protein 1
3299	HSF4	heat shock transcription factor 4	84264	HAGHL	hydroxyacylglutathione hydrolase like
33	ACADL	acyl-CoA dehydrogenase long chain	84302	TMEM246	transmembrane protein 246
330	BIRC3	baculoviral IAP repeat containing 3	8436	CAVIN2	caveolae associated protein 2
3303	HSPA1A	heat shock protein family A (Hsp70) member 1A	8437	RASAL1	RAS protein activator like 1
3304	HSPA1B	heat shock protein family A (Hsp70) member 1B	8438	RAD54L	RAD54 like

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
3306	HSPA2	heat shock protein family A (Hsp70) member 2	84417	C2orf40	chromosome 2 open reading frame 40
3311	HSPA7	heat shock protein family A (Hsp70) member 7	84419	C15orf48	chromosome 15 open reading frame 48
3316	HSPB2	heat shock protein family B (small) member 2	84433	CARD11	caspase recruitment domain family member 11
332	BIRC5	baculoviral IAP repeat containing 5	84451	MAP3K21	mitogen-activated protein kinase kinase kinase 21
333	APLP1	amyloid beta precursor like protein 1	84457	PHYHIPL	phytanoyl-CoA 2-hydroxylase interacting protein like
3339	HSPG2	heparan sulfate proteoglycan 2	84465	MEGF11	multiple EGF like domains 11
3357	HTR2B	5-hydroxytryptamine receptor 2B	8447	DOC2B	double C2 domain beta
3371	TNC	tenascin C	8448	DOC2A	double C2 domain alpha
3373	HYAL1	hyaluronoglucosaminidase 1	845	CASQ2	calsequestrin 2
337875	HIST2H2BA	histone cluster 2 H2B family member a (pseudogene)	84546	SNORD35B	small nucleolar RNA, C/D box 35B
338	APOB	apolipoprotein B	84561	SLC12A8	solute carrier family 12 member 8
338094	FAM151A	family with sequence similarity 151 member A	84612	PARD6B	par-6 family cell polarity regulator beta
3381	IBSP	integrin binding sialoprotein	84624	FNDC1	fibronectin type III domain containing 1
338328	GPIHBP1	glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1	84626	KRBA1	KRAB-A domain containing 1
338440	ANO9	anoctamin 9	84627	ZNF469	zinc finger protein 469
338442	HCAR2	hydroxycarboxylic acid receptor 2	84631	SLITRK2	SLIT and NTRK like family member 2
338596	ST8SIA6	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 6	84634	KISS1R	KISS1 receptor
338707	B4GALNT4	beta-1,4-N-acetyl-galactosaminyltransferase 4	84636	GPR174	G protein-coupled receptor 174
338773	TMEM119	transmembrane protein 119	84647	PLA2G12B	phospholipase A2 group XIIB
339400	FLG-AS1	FLG antisense RNA 1	84675	TRIM55	tripartite motif containing 55
3397	ID1	inhibitor of DNA binding 1, HLH protein	84689	MS4A14	membrane spanning 4-domains A14
339778	C2orf70	chromosome 2 open reading frame 70	84699	CREB3L3	cAMP responsive element binding protein 3 like 3
3399	ID3	inhibitor of DNA binding 3, HLH protein	8470	SORBS2	sorbin and SH3 domain containing 2
339965	CCDC158	coiled-coil domain containing 158	84701	COX4I2	cytochrome c oxidase subunit 4I2
3400	ID4	inhibitor of DNA binding 4, HLH protein	84706	GPT2	glutamic--pyruvic transaminase 2
340267	COL28A1	collagen type XXVIII alpha 1 chain	84707	BEX2	brain expressed X-linked 2
340307	CTAGE6	CTAGE family member 6	84708	LNX1	ligand of numb-protein X 1
340348	TSPAN33	tetraspanin 33	84709	MGARP	mitochondria localized glutamic acid rich protein
340351	AGBL3	ATP/GTP binding protein like 3	8477	GPR65	G protein-coupled receptor 65
340542	BEX5	brain expressed X-linked 5	84803	GPAT3	glycerol-3-phosphate acyltransferase 3
340547	VSIG1	V-set and immunoglobulin domain containing 1	84808	PERM1	PPARGC1 and ESRR induced regulator, muscle 1
341	APOC1	apolipoprotein C1	84812	PLCD4	phospholipase C delta 4
341019	DCDC1	doublecortin domain containing 1	84866	TMEM25	transmembrane protein 25
341640	FREM2	FRAS1 related extracellular matrix protein 2	84868	HAVCR2	hepatitis A virus cellular receptor 2

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
341676	NEK5	NIMA related kinase 5	84879	MFSD2A	major facilitator superfamily domain containing 2A
342527	SMTNL2	smoothelin like 2	84894	LINGO1	leucine rich repeat and Ig domain containing 1
3426	CFI	complement factor I	8490	RGS5	regulator of G protein signaling 5
3429	IFI27	interferon alpha inducible protein 27	8492	PRSS12	protease, serine 12
342908	ZNF404	zinc finger protein 404	84935	MEDAG	mesenteric estrogen dependent adipogenesis
342979	PALM3	paralemmin 3	84952	CGNL1	cingulin like 1
3434	IFIT1	interferon induced protein with tetratricopeptide repeats 1	84960	CCDC183	coiled-coil domain containing 183
343413	FCRL6	Fc receptor like 6	8497	PPFIA4	PTPRF interacting protein alpha 4
343450	KCNT2	potassium sodium-activated channel subfamily T member 2	8499	PPFIA2	PTPRF interacting protein alpha 2
345079	SOWAHB	sosondowah ankyrin repeat domain family member B	85004	RERG	RAS like estrogen regulated growth inhibitor
346171	ZFP57	ZFP57 zinc finger protein	85016	C11orf70	chromosome 11 open reading frame 70
346389	MACC1	MACC1, MET transcriptional regulator	85027	SMIM3	small integral membrane protein 3
346606	MOGAT3	monoacylglycerol O-acyltransferase 3	8503	PIK3R3	phosphoinositide-3-kinase regulatory subunit 3
347	APOD	apolipoprotein D	8515	ITGA10	integrin subunit alpha 10
347475	CCDC160	coiled-coil domain containing 160	8516	ITGA8	integrin subunit alpha 8
347733	TUBB2B	tubulin beta 2B class IIb	85235	HIST1H2AH	histone cluster 1 H2A family member h
347735	SERINC2	serine incorporator 2	8530	CST7	cystatin F
3479	IGF1	insulin like growth factor 1	8532	CPZ	carboxypeptidase Z
348	APOE	apolipoprotein E	85329	LGALS12	galectin 12
348093	RBPMS2	RNA binding protein with multiple splicing 2	85358	SHANK3	SH3 and multiple ankyrin repeat domains 3
348158	ACSM2B	acyl-CoA synthetase medium chain family member 2B	8538	BARX2	BARX homeobox 2
348174	CLEC18A	C-type lectin domain family 18 member A	85388	SNORD14B	small nucleolar RNA, C/D box 14B
348249	CCL15-CCL14	CCL15-CCL14 readthrough (NMD candidate)	85389	SNORD14C	small nucleolar RNA, C/D box 14C
3484	IGFBP1	insulin like growth factor binding protein 1	85390	SNORD14D	small nucleolar RNA, C/D box 14D
348487	FAM131C	family with sequence similarity 131 member C	85409	NKD2	naked cuticle homolog 2
3485	IGFBP2	insulin like growth factor binding protein 2	8542	APOL1	apolipoprotein L1
3486	IGFBP3	insulin like growth factor binding protein 3	85439	STON2	stonin 2
348738	C2orf48	chromosome 2 open reading frame 48	85442	KNDC1	kinase non-catalytic C-lobe domain containing 1
3488	IGFBP5	insulin like growth factor binding protein 5	85453	TSPYL5	TSPY like 5
3489	IGFBP6	insulin like growth factor binding protein 6	8547	FCN3	ficolin 3
3491	CYR61	cysteine rich angiogenic inducer 61	85477	SCIN	scinderin
349152	DPY19L2P2	DPY19L2 pseudogene 2	85479	DNAJC5B	DnaJ heat shock protein family (Hsp40) member C5 beta
350	APOH	apolipoprotein H	85495	RPPH1	ribonuclease P RNA component H1
3512	JCHAIN	joining chain of multimeric IgA and IgM	8564	KMO	kynurenine 3-monooxygenase

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
353189	SLCO4C1	solute carrier organic anion transporter family member 4C1	8572	PDLIM4	PDZ and LIM domain 4
353514	LILRA5	leukocyte immunoglobulin like receptor A5	860	RUNX2	runt related transcription factor 2
3549	IHH	indian hedgehog	8611	PLPP1	phospholipid phosphatase 1
3553	IL1B	interleukin 1 beta	8612	PLPP2	phospholipid phosphatase 2
3557	IL1RN	interleukin 1 receptor antagonist	8613	PLPP3	phospholipid phosphatase 3
3559	IL2RA	interleukin 2 receptor subunit alpha	8614	STC2	stanniocalcin 2
356	FASLG	Fas ligand	8622	PDE8B	phosphodiesterase 8B
3560	IL2RB	interleukin 2 receptor subunit beta	8635	RNASET2	ribonuclease T2
3561	IL2RG	interleukin 2 receptor subunit gamma	8638	OASL	2'-5'-oligoadenylate synthetase like
3563	IL3RA	interleukin 3 receptor subunit alpha	8639	AOC3	amine oxidase, copper containing 3
3569	IL6	interleukin 6	8641	PCDHGB4	protocadherin gamma subfamily B, 4
3575	IL7R	interleukin 7 receptor	8642	DCHS1	dachsous cadherin-related 1
3576	CXCL8	C-X-C motif chemokine ligand 8	8645	KCNK5	potassium two pore domain channel subfamily K member 5
358	AQP1	aquaporin 1 (Colton blood group)	8646	CHRD	chordin
3580	CXCR2P1	C-X-C motif chemokine receptor 2 pseudogene 1	8653	DDX3Y	DEAD-box helicase 3, Y-linked
3586	IL10	interleukin 10	8659	ALDH4A1	aldehyde dehydrogenase 4 family member A1
3587	IL10RA	interleukin 10 receptor subunit alpha	866	SERPINA6	serpin family A member 6
3594	IL12RB1	interleukin 12 receptor subunit beta 1	8660	IRS2	insulin receptor substrate 2
3595	IL12RB2	interleukin 12 receptor subunit beta 2	8671	SLC4A4	solute carrier family 4 member 4
3598	IL13RA2	interleukin 13 receptor subunit alpha 2	8685	MARCO	macrophage receptor with collagenous structure
360	AQP3	aquaporin 3 (Gill blood group)	8701	DNAH11	dynein axonemal heavy chain 11
3604	TNFRSF9	TNF receptor superfamily member 9	8722	CTSF	cathepsin F
3606	IL18	interleukin 18	8736	MYOM1	myomesin 1
361	AQP4	aquaporin 4	8743	TNFSF10	TNF superfamily member 10
3613	IMPA2	inositol monophosphatase 2	8787	RGS9	regulator of G protein signaling 9
3620	IDO1	indoleamine 2,3-dioxygenase 1	8792	TNFRSF11A	TNF receptor superfamily member 11a
3623	INHA	inhibin alpha subunit	8794	TNFRSF10C	TNF receptor superfamily member 10c
3624	INHBA	inhibin beta A subunit	88	ACTN2	actinin alpha 2
3625	INHBB	inhibin beta B subunit	8808	IL1RL2	interleukin 1 receptor like 2
3627	CXCL10	C-X-C motif chemokine ligand 10	8824	CES2	carboxylesterase 2
364	AQP7	aquaporin 7	8825	LIN7A	lin-7 homolog A, crumbs cell polarity complex component
3643	INSR	insulin receptor	8839	WISP2	WNT1 inducible signaling pathway protein 2
3659	IRF1	interferon regulatory factor 1	8842	PROM1	prominin 1
366	AQP9	aquaporin 9	8854	ALDH1A2	aldehyde dehydrogenase 1 family member A2
3662	IRF4	interferon regulatory factor 4	8857	FCGBP	Fc fragment of IgG binding protein
3664	IRF6	interferon regulatory factor 6	8862	APLN	apelin
3667	IRS1	insulin receptor substrate 1	8863	PER3	period circadian regulator 3
367	AR	androgen receptor	8870	IER3	immediate early response 3

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
3671	ISLR	immunoglobulin superfamily containing leucine rich repeat	8875	VNN2	vanin 2
3675	ITGA3	integrin subunit alpha 3	8876	VNN1	vanin 1
3679	ITGA7	integrin subunit alpha 7	890	CCNA2	cyclin A2
368	ABCC6	ATP binding cassette subfamily C member 6	891	CCNB1	cyclin B1
3681	ITGAD	integrin subunit alpha D	8912	CACNA1H	calcium voltage-gated channel subunit alpha1 H
3683	ITGAL	integrin subunit alpha L	8942	KYNU	kynureninase
3687	ITGAX	integrin subunit alpha X	8968	HIST1H3F	histone cluster 1 H3 family member f
3690	ITGB3	integrin subunit beta 3	8969	HIST1H2AG	histone cluster 1 H2A family member g
3691	ITGB4	integrin subunit beta 4	8970	HIST1H2BJ	histone cluster 1 H2B family member j
3694	ITGB6	integrin subunit beta 6	8972	MGAM	maltase-glucoamylase
3696	ITGB8	integrin subunit beta 8	89765	RSPH1	radial spoke head 1 homolog
3699	ITIH3	inter-alpha-trypsin inhibitor heavy chain 3	89790	SIGLEC10	sialic acid binding Ig like lectin 10
3700	ITIH4	inter-alpha-trypsin inhibitor heavy chain family member 4	89795	NAV3	neuron navigator 3
3702	ITK	IL2 inducible T-cell kinase	89858	SIGLEC12	sialic acid binding Ig like lectin 12 (gene/pseudogene)
3710	ITPR3	inositol 1,4,5-trisphosphate receptor type 3	89870	TRIM15	tripartite motif containing 15
3714	JAG2	jagged 2	89876	MAATS1	MYCBP associated and testis expressed 1
3718	JAK3	Janus kinase 3	8989	TRPA1	transient receptor potential cation channel subfamily A member 1
3725	JUN	Jun proto-oncogene, AP-1 transcription factor subunit	89932	PAPLN	papilin, proteoglycan like sulfated glycoprotein
3726	JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	89944	GLB1L2	galactosidase beta 1 like 2
3730	ANOS1	anosmin 1	8996	NOL3	nucleolar protein 3
3732	CD82	CD82 molecule	8999	CDKL2	cyclin dependent kinase like 2
374	AREG	amphiregulin	9002	F2RL3	F2R like thrombin or trypsin receptor 3
3741	KCNA5	potassium voltage-gated channel subfamily A member 5	90139	TSPAN18	tetraspanin 18
374383	NCR3LG1	natural killer cell cytotoxicity receptor 3 ligand 1	9021	SOCS3	suppressor of cytokine signaling 3
374407	DNAJB13	DnaJ heat shock protein family (Hsp40) member B13	9027	NAT8	N-acetyltransferase 8 (putative)
374618	TEX9	testis expressed 9	9032	TM4SF5	transmembrane 4 L six family member 5
374666	WASH3P	WAS protein family homolog 3 pseudogene	90332	EXOC3L2	exocyst complex component 3 like 2
3748	KCNC3	potassium voltage-gated channel subfamily C member 3	90381	TICRR	TOPBP1 interacting checkpoint and replication regulator
374864	CCDC178	coiled-coil domain containing 178	9047	SH2D2A	SH2 domain containing 2A
375033	PEAR1	platelet endothelial aggregation receptor 1	9051	PSTPIP1	proline-serine-threonine phosphatase interacting protein 1
3752	KCND3	potassium voltage-gated channel subfamily D member 3	9052	GPRC5A	G protein-coupled receptor class C group 5 member A
375298	CERKL	ceramide kinase like	9053	MAP7	microtubule associated protein 7
375449	MAST4	microtubule associated serine/threonine kinase family member 4	9056	SLC7A7	solute carrier family 7 member 7
375616	KCP	kielin/chordin-like protein	90649	ZNF486	zinc finger protein 486

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
375775	PNPLA7	patatin like phospholipase domain containing 7	9071	CLDN10	claudin 10
3759	KCNJ2	potassium voltage-gated channel subfamily J member 2	9075	CLDN2	claudin 2
3760	KCNJ3	potassium voltage-gated channel subfamily J member 3	9076	CLDN1	claudin 1
3764	KCNJ8	potassium voltage-gated channel subfamily J member 8	9079	LDB2	LIM domain binding 2
3772	KCNJ15	potassium voltage-gated channel subfamily J member 15	9086	EIF1AY	eukaryotic translation initiation factor 1A, Y-linked
3773	KCNJ16	potassium voltage-gated channel subfamily J member 16	90865	IL33	interleukin 33
3776	KCNK2	potassium two pore domain channel subfamily K member 2	90952	ESAM	endothelial cell adhesion molecule
3777	KCNK3	potassium two pore domain channel subfamily K member 3	9099	USP2	ubiquitin specific peptidase 2
3778	KCNMA1	potassium calcium-activated channel subfamily M alpha 1	90993	CREB3L1	cAMP responsive element binding protein 3 like 1
3782	KCNN3	potassium calcium-activated channel subfamily N member 3	9103	FCGR2C	Fc fragment of IgG receptor IIc (gene/pseudogene)
378706	RN7SL2	RNA, 7SL, cytoplasmic 2	9104	RGN	regucalcin
379	ARL4D	ADP ribosylation factor like GTPase 4D	91156	IGFN1	immunoglobulin-like and fibronectin type III domain containing 1
3791	KDR	kinase insert domain receptor	9122	SLC16A4	solute carrier family 16 member 4
3795	KHK	ketohexokinase	91316	GUSBP11	glucuronidase, beta pseudogene 11
3796	KIF2A	kinesin family member 2A	9133	CCNB2	cyclin B2
38	ACAT1	acetyl-CoA acetyltransferase 1	914	CD2	CD2 molecule
3805	KIR2DL4	killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 4	915	CD3D	CD3d molecule
3815	KIT	KIT proto-oncogene receptor tyrosine kinase	91522	COL23A1	collagen type XXIII alpha 1 chain
3818	KLKB1	kallikrein B1	9154	SLC28A1	solute carrier family 28 member 1
3820	KLRB1	killer cell lectin like receptor B1	9156	EXO1	exonuclease 1
3821	KLRC1	killer cell lectin like receptor C1	916	CD3E	CD3e molecule
3822	KLRC2	killer cell lectin like receptor C2	91614	DEPDC7	DEP domain containing 7
3823	KLRC3	killer cell lectin like receptor C3	9162	DGKI	diacylglycerol kinase iota
3833	KIFC1	kinesin family member C1	91624	NEXN	nexilin F-actin binding protein
384	ARG2	arginase 2	91683	SYT12	synaptotagmin 12
3846	KRTAP5-9	keratin associated protein 5-9	917	CD3G	CD3g molecule
3855	KRT7	keratin 7	91703	ACY3	aminoacylase 3
3856	KRT8	keratin 8	9173	IL1RL1	interleukin 1 receptor like 1
3872	KRT17	keratin 17	91768	CABLES1	Cdk5 and Abl enzyme substrate 1
387357	THEMIS	thymocyte selection associated	9182	RASSF9	Ras association domain family member 9
387496	RASL11A	RAS like family 11 member A	91828	EXOC3L4	exocyst complex component 3 like 4
3875	KRT18	keratin 18	9185	REPS2	RALBP1 associated Eps domain containing 2

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
387597	ILDR2	immunoglobulin like domain containing receptor 2	91851	CHRDL1	chordin like 1
387638	C10orf113	chromosome 10 open reading frame 113	919	CD247	CD247 molecule
387646	LRRC37A6P	leucine rich repeat containing 37 member A6, pseudogene	91937	TIMD4	T-cell immunoglobulin and mucin domain containing 4
387695	C10orf99	chromosome 10 open reading frame 99	91975	ZNF300	zinc finger protein 300
387700	SLC16A12	solute carrier family 16 member 12	9201	DCLK1	doublecortin like kinase 1
387748	OR56B1	olfactory receptor family 56 subfamily B member 1	921	CD5	CD5 molecule
387751	GVINP1	GTPase, very large interferon inducible pseudogene 1	9212	AURKB	aurora kinase B
387763	C11orf96	chromosome 11 open reading frame 96	92126	DSEL	dermatan sulfate epimerase-like
387804	VSTM5	V-set and transmembrane domain containing 5	9214	FCMR	Fc fragment of IgM receptor
387882	C12orf75	chromosome 12 open reading frame 75	92162	TMEM88	transmembrane protein 88
388	RHOB	ras homolog family member B	92211	CDHR1	cadherin related family member 1
3880	KRT19	keratin 19	92291	CAPN13	calpain 13
388011	LINC01550	long intergenic non-protein coding RNA 1550	92292	GLYATL1	glycine-N-acyltransferase like 1
388335	TMEM220	transmembrane protein 220	923	CD6	CD6 molecule
388372	CCL4L1	C-C motif chemokine ligand 4 like 1	9232	PTTG1	pituitary tumor-transforming 1
388512	CLEC17A	C-type lectin domain containing 17A	92359	CRB3	crumbs 3, cell polarity complex component
388559	ZNF888	zinc finger protein 888	924	CD7	CD7 molecule
388630	TRABD2B	TraB domain containing 2B	9242	MSC	musculin
388886	LRRC75B	leucine rich repeat containing 75B	9244	CRLF1	cytokine receptor like factor 1
389336	C5orf46	chromosome 5 open reading frame 46	9245	GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin type
389337	ARHGEF37	Rho guanine nucleotide exchange factor 37	925	CD8A	CD8a molecule
389643	NUGGC	nuclear GTPase, germinal center associated	92558	BICDL1	BICD family like cargo adaptor 1
389668	XKR9	XK related 9	92737	DNER	delta/notch like EGF repeat containing
3897	L1CAM	L1 cell adhesion molecule	92745	SLC38A5	solute carrier family 38 member 5
3898	LAD1	ladinin 1	92815	HIST3H2A	histone cluster 3 H2A
389840	MAP3K15	mitogen-activated protein kinase kinase kinase 15	9289	ADGRG1	adhesion G protein-coupled receptor G1
389860	PAGE2B	PAGE family member 2B	9297	SNORD29	small nucleolar RNA, C/D box 29
3899	AFF3	AF4/FMR2 family member 3	930	CD19	CD19 molecule
390072	OR52N4	olfactory receptor family 52 subfamily N member 4 (gene/pseudogene)	9300	SNORD28	small nucleolar RNA, C/D box 28
3902	LAG3	lymphocyte activating 3	9301	SNORD27	small nucleolar RNA, C/D box 27
390649	OR4F15	olfactory receptor family 4 subfamily F member 15	9302	SNORD26	small nucleolar RNA, C/D box 26
390651	OR4F13P	olfactory receptor family 4 subfamily F member 13 pseudogene	9308	CD83	CD83 molecule
3908	LAMA2	laminin subunit alpha 2	93099	DMKN	dermokine
3909	LAMA3	laminin subunit alpha 3	931	MS4A1	membrane spanning 4-domains A1
391190	OR2L8	olfactory receptor family 2 subfamily L member 8 (gene/pseudogene)	9314	KLF4	Kruppel like factor 4

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
391267	ANKRD20A11P	ankyrin repeat domain 20 family member A11, pseudogene	93145	OLFM2	olfactomedin 2
3914	LAMB3	laminin subunit beta 3	9317	PTER	phosphotriesterase related
3918	LAMC2	laminin subunit gamma 2	933	CD22	CD22 molecule
392255	GDF6	growth differentiation factor 6	9332	CD163	CD163 molecule
392360	CTSL3P	cathepsin L family member 3, pseudogene	93432	MGAM2	maltase-glucoamylase 2 (putative)
392364	LOC392364	nuclear pore associated protein 1 pseudogene	9351	SLC9A3R2	SLC9A3 regulator 2
392636	AGMO	alkylglycerol monooxygenase	93517	SDR42E1	short chain dehydrogenase/reductase family 42E, member 1
3929	LBP	lipopolysaccharide binding protein	9353	SLIT2	slit guidance ligand 2
3932	LCK	LCK proto-oncogene, Src family tyrosine kinase	9358	ITGBL1	integrin subunit beta like 1
3934	LCN2	lipocalin 2	9365	KL	klotho
3936	LCP1	lymphocyte cytosolic protein 1	9379	NRXN2	neurexin 2
3949	LDLR	low density lipoprotein receptor	9388	LIPG	lipase G, endothelial type
3957	LGALS2	galectin 2	939	CD27	CD27 molecule
3958	LGALS3	galectin 3	93953	GCNA	germ cell nuclear acidic peptidase
3960	LGALS4	galectin 4	93986	FOXP2	forkhead box P2
3976	LIF	LIF, interleukin 6 family cytokine	94	ACVRL1	activin A receptor like type 1
3977	LIFR	LIF receptor alpha	94031	HTRA3	HtrA serine peptidase 3
3984	LIMK1	LIM domain kinase 1	9415	FADS2	fatty acid desaturase 2
3990	LIPC	lipase C, hepatic type	94161	SNORD46	small nucleolar RNA, C/D box 46
400566	C17orf97	chromosome 17 open reading frame 97	94162	SNORD38A	small nucleolar RNA, C/D box 38A
400759	GBP1P1	guanylate binding protein 1 pseudogene 1	942	CD86	CD86 molecule
400916	CHCHD10	coiled-coil-helix-coiled-coil-helix domain containing 10	94234	FOXQ1	forkhead box Q1
401124	DTHD1	death domain containing 1	94240	EPSTI1	epithelial stromal interaction 1
401190	RGS7BP	regulator of G protein signaling 7 binding protein	94274	PPP1R14A	protein phosphatase 1 regulatory inhibitor subunit 14A
401409	RAB19	RAB19, member RAS oncogene family	9429	ABCG2	ATP binding cassette subfamily G member 2 (Junior blood group)
401427	OR2A7	olfactory receptor family 2 subfamily A member 7	9437	NCR1	natural cytotoxicity triggering receptor 1
4015	LOX	lysyl oxidase	9447	AIM2	absent in melanoma 2
4016	LOXL1	lysyl oxidase like 1	9450	LY86	lymphocyte antigen 86
4017	LOXL2	lysyl oxidase like 2	9452	ITM2A	integral membrane protein 2A
4023	LPL	lipoprotein lipase	9457	FHL5	four and a half LIM domains 5
4033	LRMP	lymphoid restricted membrane protein	947	CD34	CD34 molecule
4036	LRP2	LDL receptor related protein 2	9472	AKAP6	A-kinase anchoring protein 6
4038	LRP4	LDL receptor related protein 4	9476	NAPSA	napsin A aspartic peptidase
404550	C16orf74	chromosome 16 open reading frame 74	9478	CABP1	calcium binding protein 1
4046	LSP1	lymphocyte-specific protein 1	9479	MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1
4050	LTB	lymphotoxin beta	948	CD36	CD36 molecule
4051	CYP4F3	cytochrome P450 family 4 subfamily F member 3	9481	SLC25A27	solute carrier family 25 member 27
4052	LTBP1	latent transforming growth factor beta binding protein 1	949	SCARB1	scavenger receptor class B member 1

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
4053	LTBP2	latent transforming growth factor beta binding protein 2	9493	KIF23	kinesin family member 23
4056	LTC4S	leukotriene C4 synthase	9499	MYOT	myotilin
4057	LTF	lactotransferrin	9507	ADAMTS4	ADAM metallopeptidase with thrombospondin type 1 motif 4
4059	BCAM	basal cell adhesion molecule (Lutheran blood group)	9509	ADAMTS2	ADAM metallopeptidase with thrombospondin type 1 motif 2
4060	LUM	lumican	9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif 1
4061	LY6E	lymphocyte antigen 6 family member E	9514	GAL3ST1	galactose-3-O-sulfotransferase 1
4063	LY9	lymphocyte antigen 9	9518	GDF15	growth differentiation factor 15
4064	CD180	CD180 molecule	952	CD38	CD38 molecule
4068	SH2D1A	SH2 domain containing 1A	9536	PTGES	prostaglandin E synthase
4069	LYZ	lysozyme	954	ENTPD2	ectonucleoside triphosphate diphosphohydrolase 2
4070	TACSTD2	tumor associated calcium signal transducer 2	9547	CXCL14	C-X-C motif chemokine ligand 14
4071	TM4SF1	transmembrane 4 L six family member 1	9560	CCL4L2	C-C motif chemokine ligand 4 like 2
4072	EPCAM	epithelial cell adhesion molecule	957	ENTPD5	ectonucleoside triphosphate diphosphohydrolase 5
408186	OVOS	ovostatin	9572	NR1D1	nuclear receptor subfamily 1 group D member 1
4093	SMAD9	SMAD family member 9	9580	SOX13	SRY-box 13
4118	MAL	mal, T-cell differentiation protein	9582	APOBEC3B	apolipoprotein B mRNA editing enzyme catalytic subunit 3B
4128	MAOA	monoamine oxidase A	9586	CREB5	cAMP responsive element binding protein 5
4129	MAOB	monoamine oxidase B	959	CD40LG	CD40 ligand
4133	MAP2	microtubule associated protein 2	9590	AKAP12	A-kinase anchoring protein 12
4137	MAPT	microtubule associated protein tau	9595	CYTIP	cytohesin 1 interacting protein
414157	C10orf62	chromosome 10 open reading frame 62	960	CD44	CD44 molecule (Indian blood group)
414194	CCNYL2	cyclin Y-like 2 (pseudogene)	9615	GDA	guanine deaminase
414224	AGAP12P	ArfGAP with GTPase domain, ankyrin repeat and PH domain 12, pseudogene	962	CD48	CD48 molecule
414235	PRR26	proline rich 26	969	CD69	CD69 molecule
4143	MAT1A	methionine adenosyltransferase 1A	970	CD70	CD70 molecule
4147	MATN2	matrilin 2	9708	PCDHGA8	protocadherin gamma subfamily A, 8
4148	MATN3	matrilin 3	971	CD72	CD72 molecule
415	ARSE	arylsulfatase E (chondrodysplasia punctata 1)	9719	ADAMTSL2	ADAMTS like 2
4162	MCAM	melanoma cell adhesion molecule	9720	CCDC144A	coiled-coil domain containing 144A
4192	MDK	midkine	9727	RAB11FIP3	RAB11 family interacting protein 3
420	ART4	ADP-ribosyltransferase 4 (Dombrock blood group)	973	CD79A	CD79a molecule
4210	MEFV	MEFV, pyrin innate immunity regulator	974	CD79B	CD79b molecule
4223	MEOX2	mesenchyme homeobox 2	9744	ACAP1	ArfGAP with coiled-coil, ankyrin repeat and PH domains 1
4232	MEST	mesoderm specific transcript	9750	RIPOR2	RHO family interacting cell polarization regulator 2
4237	MFAP2	microfibril associated protein 2	9760	TOX	thymocyte selection associated high mobility group box

Gene ID	Symbol	Gene Name	Gene ID	Symbol	Gene Name
4239	MFAP4	microfibril associated protein 4	978	CDA	cytidine deaminase
4241	MELTF	melanotransferrin	9787	DLGAP5	DLG associated protein 5
4248	MGAT3	mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase	9805	SCRN1	secernin 1
4254	KITLG	KIT ligand	9828	ARHGEF17	Rho guanine nucleotide exchange factor 17
4256	MGP	matrix Gla protein	983	CDK1	cyclin dependent kinase 1
4257	MGST1	microsomal glutathione S-transferase 1	9833	MELK	maternal embryonic leucine zipper kinase
4261	CIITA	class II major histocompatibility complex transactivator	9848	MFAP3L	microfibril associated protein 3 like
4281	MID1	midline 1	9886	RHOBTB1	Rho related BTB domain containing 1
4283	CXCL9	C-X-C motif chemokine ligand 9	990	CDC6	cell division cycle 6
4288	MKI67	marker of proliferation Ki-67	9902	MRC2	mannose receptor C type 2
4306	NR3C2	nuclear receptor subfamily 3 group C member 2	991	CDC20	cell division cycle 20
4311	MME	membrane metalloendopeptidase	9915	ARNT2	aryl hydrocarbon receptor nuclear translocator 2
4312	MMP1	matrix metallopeptidase 1	9928	KIF14	kinesin family member 14
4313	MMP2	matrix metallopeptidase 2	9934	P2RY14	purinergic receptor P2Y14
4316	MMP7	matrix metallopeptidase 7	9945	GFPT2	glutamine-fructose-6-phosphate transaminase 2
4318	MMP9	matrix metallopeptidase 9	9956	HS3ST2	heparan sulfate-glucosamine 3-sulfotransferase 2
4320	MMP11	matrix metallopeptidase 11	9963	SLC23A1	solute carrier family 23 member 1
4321	MMP12	matrix metallopeptidase 12	9971	NR1H4	nuclear receptor subfamily 1 group H member 4
4325	MMP16	matrix metallopeptidase 16	9976	CLEC2B	C-type lectin domain family 2 member B
4327	MMP19	matrix metallopeptidase 19	999	CDH1	cadherin 1

Any of the methods described herein may include classification of a patient's sample into a cluster, e.g., any cluster identified herein. For example, machine learning algorithms can be used to develop a classifier from gene expression data. Any suitable machine learning algorithm can be used, including supervised learning (e.g., decision tree, random forest, gradient boost machine (GBM), CATBOOST, XGBOOST, support vector machine (SVM), PCA, K-nearest neighbor, and naïve Bayes) and unsupervised learning approaches. In particular instances, the machine learning algorithm is a random forest algorithm, as described, e.g., in Examples 1 and 2. For example, a classifier can be developed using the random forest machine learning algorithm (e.g., using the R package *randomForest*). The random forest classifier can be learned on a training gene set and then used to predict the cluster (e.g., NMF classes) in a second gene set. In other instances, K-means clustering, K-mediods clustering, or PAM can be used for classification.

Any of the methods disclosed herein may further include determining the expression level (e.g., the mRNA expression level) of one or more genes or gene signatures.

In some examples, the method further comprises determining the mRNA expression level of one or more of the following gene signatures in the tumor sample from the patient: (a) a T-effector signature comprising one or more (e.g., one, two, three, or four), or all, of CD8A, IFNG, EOMES, PRF1, and PD-L1;

(b) an angiogenesis signature comprising one or more (e.g., one, two, three, four, or five), or all, of VEGFA, KDR, ESM1, CD34, PECAM1, and ANGPTL4; (c) a fatty acid oxidation (FAO)/AMPK signature comprising one or more (e.g., one, two, three, four, or five), or all, of CPT2, PPARA, CPT1A, PRKAA2, PDK2, and PRKAB1; (d) a cell cycle signature comprising one or more (e.g., one, two, three, four, five, six, seven, eight, or nine), or all, of CDK2, CDK4, CDK6, BUB1, BUB1B, CCNE1, POLQ, AURKA, MKI67, and CCNB2; (e) a fatty acid synthesis (FAS)/pentose phosphate signature comprising one or more (e.g., one, two, three, four, five, or six), or all, of FASN, PARP1, ACACA, G6PD, TKT, TALDO1, and PGD; (f) a stroma signature comprising one or more (e.g., one, two, three, four, five, six, or seven), or all, of FAP, FN1, COL5A1, COL5A2, POSTN, COL1A1, COL1A2, and MMP2; (g) a myeloid inflammation signature comprising one or more (e.g., one, two, three, four, or five), or all, of CXCL1, CXCL2, CXCL3, CXCL8, IL6, and PTGS2; (h) a complement cascade signature comprising one or more (e.g., one, two, three, four, or five), or all, of F2, C1S, C9, C1R, CFB, and C3; (i) an Ω-oxidation signature comprising one or more (e.g., one, two, three, four, five, six, or seven), or all, of CYP4F3, CYP8B1, NNMT, MGST1, MAOA, CYP4F11, CYP4F2, CYP4F12; and/or (j) a snoRNA signature comprising one or more (e.g., one, two, three, four, or five), or all, of SNORD38A, SNORD104, SNORD32A, SNORD68, SNORD66, and SNORD100.

In some examples, the patient's tumor sample is assigned into the angiogenic/stromal cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the angiogenesis signature and the stroma signature, optionally wherein the patient's tumor sample has decreased expression levels, relative to reference expression levels, of the T-effector signature, the cell cycle signature, and/or the FAS/pentose phosphate signature.

In some examples, the patient's tumor sample is assigned into the angiogenic cluster, and the patient's tumor sample has increased expression levels, relative to a reference expression levels, of the angiogenesis signature and the FAO/AMPK signature, optionally wherein the patient's tumor has decreased expression levels, relative to reference expression levels, of the cell cycle signature, the FAS/pentose phosphate signature, the stroma signature, the myeloid inflammation signature, and/or the complement cascade signature.

In some examples, the patient's tumor sample is assigned into the complement/Ω-oxidation cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the complement cascade signature and the Ω-oxidation signature, optionally wherein the patient's tumor sample has an increased expression level, relative to a reference expression level, of the myeloid inflammation signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature and/or the T-effector signature.

In some examples, the patient's tumor sample is assigned into the T-effector/proliferative cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the cell cycle signature and the T-effector signature, optionally wherein the patient's tumor sample has increased expression levels, relative to reference expression levels, of the FAS/pentose phosphate signature, the myeloid inflammation signature, and/or the complement cascade signature, and/or

decreased expression levels, relative to reference expression levels, of the angiogenesis signature, the FAO/AMP signature, and/or the snoRNA signature.

In some examples, the patient's tumor sample is assigned into the proliferative cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the cell cycle signature and the FAS/pentose phosphate signature, optionally wherein the patient's tumor sample has increased expression levels, relative to reference expression levels, of the myeloid inflammation signature and/or the FAO/AMPK signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature, the T-effector signature, the stroma signature, the complement cascade signature, the Ω-oxidation signature, and/or the snoRNA signature.

In some examples, the patient's tumor sample is assigned into the stromal/proliferative cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the cell cycle signature and the stromal signature, optionally wherein the patient's tumor sample has increased expression levels, relative to reference expression levels, of the FAS/pentose phosphate signature and/or the myeloid inflammation signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature, the FAO/AMPK signature, the complement cascade signature, the Ω-oxidation signature, and/or the snoRNA signature.

In some examples, the patient's tumor sample is assigned into the snoRNA cluster, and the patient's tumor sample has an increased expression level, relative to a reference expression level, of the snoRNA signature, optionally wherein the patient's tumor sample has decreased expression levels, relative to reference expression levels, of the FOA/AMPK signature, the cell cycle signature, and the FAS/pentose phosphate signature.

Any suitable reference expression level for a signature may be used. In some examples, the reference expression level is determined from a population of patients having a previously untreated kidney cancer (e.g., an inoperable, locally advanced, or metastatic RCC). In some examples, the reference expression level of a signature is the median Z-score of the signature in a population of patients having a previously untreated inoperable, locally advanced, or metastatic RCC.

In some examples, assignment of the patient's tumor sample into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (7) snoRNA indicates that the patient is likely to have an increased clinical benefit from treatment with an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a VEGF antagonist (e.g., bevacizumab or axitinib) compared to treatment with a tyrosine kinase inhibitor (e.g., sunitinib). In some examples, assignment of the patient's tumor sample into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (7) snoRNA indicates that the patient is likely to have an increased clinical benefit from treatment with an anti-cancer therapy comprising atezolizumab and bevacizumab compared to treatment with sunitinib. In some examples, assignment of the patient's tumor sample into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (7) snoRNA indicates that the patient is likely to have an increased clinical benefit from treatment with an anti-cancer therapy comprising avelumab and axitinib compared to treatment with sunitinib. In some examples, the patient's tumor sample is assigned into cluster (4). In other examples, the patient's tumor is assigned into cluster (5). In yet other examples, the

patient's tumor sample is assigned into cluster (7). In some examples, increased clinical benefit comprises a relative increase in one or more of the following: objective response rate (ORR), overall survival (OS), progression-free survival (PFS), compete response (CR), partial response (PR), or a combination thereof. In some examples, increased clinical benefit comprises a relative increase in ORR or PFS.

In some examples, the patient's tumor sample is assigned into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (7) snoRNA, and the method further comprises selecting an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a VEGF antagonist (e.g., bevacizumab or axitinib) for the patient. In some examples, the method further comprises selecting an anti-cancer therapy comprising atezolizumab and bevacizumab. In other examples, the method further comprises selecting an anti-cancer therapy comprising avelumab and axitinib.

In some examples, the patient's tumor sample is assigned into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (7) snoRNA, and the method further comprises treating the patient by administering an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a VEGF antagonist (e.g., bevacizumab or axitinib) to the patient. In some examples, the method further comprises administering an anti-cancer therapy comprising atezolizumab and bevacizumab to the patient. In other examples, the method further comprises administering an anti-cancer therapy comprising avelumab and axitinib to the patient.

In some examples, the patient's tumor is assigned into one of the following clusters: (1) angiogenic/stromal; or (2) angiogenic, and the method further comprises selecting an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a next-generation anti-angiogenic agent (e.g., XL092 (a next generation tyrosine kinase inhibitor from Exilixis, which targets VEGF receptors; MET, TYRO3, AXL and MERTK (TAM) kinases; and other kinases implicated in cancer's growth and spread) or a HIF2A inhibitor (e.g., belzutifan (also known as MK-6482) or PT2385)) for the patient.

In some examples, the patient's tumor is assigned into one of the following clusters: (1) angiogenic/stromal; or (2) angiogenic, and the method further comprises treating the patient by administering an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a next-generation anti-angiogenic agent (e.g., XL092 or a HIF2A inhibitor (e.g., belzutifan (also known as MK-6482) or PT2385)).

In some examples, the patient's tumor is assigned into one of the following clusters: (2) angiogenic; or (3) complement/Ω-oxidation, and the method further comprises selecting an anti-cancer therapy comprising an AMP-activated protein kinase (AMPK) inhibitor (e.g., SBI-0206965, 5′-hydroxy-staurosporine, or compound C (also known as dorsomorphin)) for the patient. Exemplary AMPK inhibitors are described, e.g., in Das et al. *Sci. Rep.* 8:3770, 2018; Vara-Ciruelos et al. *Open Biol.* 9(7):190099, 2019; Scott et al. *Chem. Biol.* 22:705-711, 2015; and Dite et al. *J. Biol. Chem.* 293:8874-8885, 2018..

In some examples, the patient's tumor is assigned into one of the following clusters: (2) angiogenic; or (3) complement/Ω-oxidation, and the method further comprises treating the patient by

administering an anti-cancer therapy comprising an AMPK inhibitor (e.g., SBI-0206965, 5′-hydroxy-staurosporine, or compound C (also known as dorsomorphin)) to the patient.

In some examples, the patient's tumor is assigned into the following cluster: (4) T-effector/proliferative, and the method further comprises selecting an anti-cancer therapy comprising an immunotherapy (e.g., an anti-TIGIT antibody (e.g., tiragolumab), PD1-IL2v (a fusion of an anti-PD-1 antibody and modified IL-2), PD1-LAG3, IL-15, anti-CCR8 (e.g., an anti-CCR8 antibody, e.g., FPA157), FAP-4-1BBL (fibroblast activation protein-targeted 4-1BBL agonist), or a combination thereof for the patient.

In some examples, the patient's tumor is assigned into the following cluster: (4) T-effector/proliferative, and the method further comprises treating the patient by administering an anti-cancer therapy comprising an immunotherapy (e.g., an anti-TIGIT antibody (e.g., tiragolumab), PD1-IL2v, PD1-LAG3, IL-15, anti-CCR8 (e.g., an anti-CCR8 antibody, e.g., FPA157 or HBM1022), FAP-4-1BBL, or a combination thereof to the patient.

In some examples, the immunotherapy agent is an immune checkpoint inhibitor. In some examples, the immunotherapy agent is a CD28, OX40, GITR, CD137, CD27, ICOS, HVEM, NKG2D, MICA, or 2B4 agonist or a CTLA-4, PD-1 axis, TIM-3, BTLA, VISTA, LAG-3, B7H4, CD96, TIGIT, or CD226 antagonist. Other particular immunotherapy agents that may be used include anti-CTLA-4 antibodies or antigen-binding fragments thereof, anti-CD27 antibodies or antigen-binding fragments thereof, anti-CD30 antibodies or antigen-binding fragments thereof, anti-CD40 antibodies or antigen-binding fragments thereof, anti-4-1BB antibodies or antigen-binding fragments thereof, anti-GITR antibodies or antigen-binding fragments thereof, anti-OX40 antibodies or antigen-binding fragments thereof, anti-TRAILR1 antibodies or antigen-binding fragments thereof, anti-TRAILR2 antibodies or antigen-binding fragments thereof, anti-TWEAK antibodies or antigen-binding fragments thereof, anti-TWEAKR antibodies or antigen-binding fragments thereof, anti-BRAF antibodies or antigen-binding fragments thereof, anti-MEK antibodies or antigen-binding fragments thereof, anti-CD33 antibodies or antigen-binding fragments thereof, anti-CD20 antibodies or antigen-binding fragments thereof, anti-CD52 antibodies or antigen-binding fragments thereof, anti-A33 antibodies or antigen-binding fragments thereof, anti-GD3 antibodies or antigen-binding fragments thereof, anti-PSMA antibodies or antigen-binding fragments thereof, anti-Ceacan 1 antibodies or antigen-binding fragments thereof, anti-Galedin 9 antibodies or antigen-binding fragments thereof, anti-HVEM antibodies or antigen-binding fragments thereof, anti-VISTA antibodies or antigen-binding fragments thereof, anti-B7 H4 antibodies or antigen-binding fragments thereof, anti-HHLA2 antibodies or antigen-binding fragments thereof, anti-CD155 antibodies or antigen-binding fragments thereof, anti-CD80 antibodies or antigen-binding fragments thereof, anti-BTLA antibodies or antigen-binding fragments thereof, anti-CD160 antibodies or antigen-binding fragments thereof, anti-CD28 antibodies or antigen-binding fragments thereof, anti-CD226 antibodies or antigen-binding fragments thereof, anti-CEACAM1 antibodies or antigen-binding fragments thereof, anti-TIM3 antibodies or antigen-binding fragments thereof, anti-CD96 antibodies or antigen-binding fragments thereof, anti-CD70 antibodies or antigen-binding fragments thereof, anti-CD27 antibodies or antigen-binding fragments thereof, anti-LIGHT antibodies or antigen-binding fragments

thereof, anti-CD137 antibodies or antigen-binding fragments thereof, anti-DR4 antibodies or antigen-binding fragments thereof, anti-CR5 antibodies or antigen-binding fragments thereof, anti-FAS antibodies or antigen-binding fragments thereof, anti-CD95 antibodies or antigen-binding fragments thereof, anti-TRAIL antibodies or antigen-binding fragments thereof, anti-DR6 antibodies or antigen-binding fragments thereof, anti-EDAR antibodies or antigen-binding fragments thereof, anti-NGFR antibodies or antigen-binding fragments thereof, anti-OPG antibodies or antigen-binding fragments thereof, anti-RANKL antibodies or antigen-binding fragments thereof, anti-LTβR antibodies or antigen-binding fragments thereof, anti-BCMA antibodies or antigen-binding fragments thereof, anti-TACI antibodies or antigen-binding fragments thereof, anti-BAFFR antibodies or antigen-binding fragments thereof, anti-EDAR2 antibodies or antigen-binding fragments thereof, anti-TROY antibodies or antigen-binding fragments thereof, and anti-RELT antibodies or antigen-binding fragments thereof.

In some examples, the patient's tumor is assigned into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (6) stromal/proliferative, and the method further comprises selecting an anti-cancer therapy comprising an anti-proliferative agent or a growth inhibitory agent (e.g., a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, or abemaciclib)) for the patient.

In some examples, the patient's tumor is assigned into one of the following clusters: (4) T-effector/proliferative; (5) proliferative; or (6) stromal/proliferative, and the method further comprises treating the patient by administering an anti-cancer therapy comprising an anti-proliferative agent or a growth inhibitory agent (e.g., a cyclin dependent kinase (CDK)4/6 inhibitor (e.g., palbociclib, ribociclib, or abemaciclib)) to the patient.

In some examples, the patient's tumor is assigned into the following cluster: (3) complement/Ω-oxidation, and the method further comprises selecting an anti-cancer therapy comprising a complement antagonist (e.g., a C1 inhibitor (e.g., CINRYZE® C1 esterase inhibitor)), a C3 inhibitor (e.g., a PEGylated pentadecapeptide (e.g., pegcetacoplan) or an anti-C3 antibody (e.g., H17)), a C5 inhibitor (e.g., an anti-C5 antibody (e.g., eculizumab, ABP959, ALXN1210, ALXN5500, SKY59, or LFG 316), an anti-C5 antibody fragment (e.g., MUBODINA®, a neutralizing mini antibody against C5), an siRNA (e.g., ALNCC5), a recombinant protein (e.g., coversin), or a small molecule (e.g., RA101348)), a C5a receptor antagonist (e.g., PMX53, CCX168, or MP-435)), an FD inhibitor (e.g., an anti-FD antibody (e.g., lampalizumab) or a small molecule (e.g., ACH-3856, ACH-4100, or ACH-4471)), an FB inhibitor (e.g., an anti-FB antibody, e.g., TA106), a small molecule (e.g., LNP023), an siRNA (e.g., anti-FB siRNA, Alnylam), or an antisense (e.g., Ionis-FB-L_{Rx})), a properdin inhibitor (e.g., an anti-properdin antibody (e.g., NM9401)), a C3 convertase (C3bBb) inhibitor (e.g., an FFH-based protein such as TT30 (CR2/CFH) or mini-FH (Amyndas)), or a C3 convertase (C4bC3B and C3bBb) inhibitor (e.g., mirococept (APT070)) for the patient. Other exemplary complement antagonists are described, e.g., in Risitano et al. *Am. J. Hematol.* 93:564-577, 2018.

In some examples, the patient's tumor is assigned into the following cluster: (3) complement/Ω-oxidation, and the method further comprises treating the patient by administering an anti-cancer therapy a complement antagonist (e.g., a C1 inhibitor (e.g., CINRYZE® C1 esterase inhibitor)), a C3 inhibitor (e.g., a PEGylated pentadecapeptide (e.g., pegcetacoplan) or an anti-C3 antibody (e.g., H17)), a C5 inhibitor

(e.g., an anti-C5 antibody (e.g., eculizumab, ABP959, ALXN1210, ALXN5500, SKY59, or LFG 316), an anti-C5 antibody fragment (e.g., MUBODINA®, a neutralizing mini antibody against C5), an siRNA (e.g., ALNCC5), a recombinant protein (e.g., coversin), or a small molecule (e.g., RA101348)), a C5a receptor antagonist (e.g., PMX53, CCX168, or MP-435)), an FD inhibitor (e.g., an anti-FD antibody (e.g., lampalizumab) or a small molecule (e.g., ACH-3856, ACH-4100, or ACH-4471)), an FB inhibitor (e.g., an anti-FB antibody, e.g., TA106), a small molecule (e.g., LNP023), an siRNA (e.g., anti-FB siRNA, Alnylam), or an antisense (e.g., Ionis-FB-L_{Rx})), a properdin inhibitor (e.g., an anti-properdin antibody (e.g., NM9401)), a C3 convertase (C3bBb) inhibitor (e.g., an FFH-based protein such as TT30 (CR2/CFH) or mini-FH (Amyndas)), or a C3 convertase (C4bC3B and C3bBb) inhibitor (e.g., mirococept (APT070)) to the patient.

In some examples, the patient's tumor is assigned into one of the following clusters: (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; or (6) stromal/proliferative, and the method further comprises selecting an anti-cancer therapy comprising a metabolism inhibitor (e.g., a proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitor (e.g., an anti-PCSK9 antibody, e.g., alirocumab or evolocumab) or a fatty acid synthase (FAS) inhibitor (e.g., cerulenin, C75, isoniazid, or orlistat (tetrahydrolipstatin)) for the patient.

In some examples, the patient's tumor is assigned into one of the following clusters: (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; or (6) stromal/proliferative, and the method further comprises treating the patient by administering an anti-cancer therapy comprising a metabolism inhibitor (e.g., a proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitor (e.g., an anti-PCSK9 antibody, e.g., alirocumab or evolocumab) or a fatty acid synthase (FAS) inhibitor (e.g., cerulenin, C75, isoniazid, or orlistat (tetrahydrolipstatin)) to the patient.

In some examples, the patient's tumor is assigned into one of the following clusters: (1) angiogenic/stromal; or (6) stromal/proliferative, and the method further comprises selecting an anti-cancer therapy comprising a stromal inhibitor (e.g., a transforming growth factor beta (TGF-β), podoplanin (PDPN), leukocyte-associated immunoglobulin-like receptor 1 (LAIR1), SMAD, anaplastic lymphoma kinase (ALK), connective tissue growth factor (CTGF/CCN2), endothelial-1 (ET-1), AP-1, interleukin (IL)-13, lysyl oxidase homolog 2 (LOXL2), endoglin (CD105), fibroblast activation protein (FAP), vascular cell adhesion protein 1 (CD106), thymocyte antigen 1 (THY1), beta 1 integrin (CD29), platelet-derived growth factor (PDGF), PDGF receptor A (PDGFRα), PDGF receptor B (PDGFRβ), vimentin, smooth muscle actin alpha (ACTA2), desmin, endosialin (CD248), or S100 calcium-binding protein A4 (S100A4) antagonist) for the patient. In some examples, the stromal inhibitor is a TGF-β antagonist (e.g., an anti-TGF-β antibody, e.g., any anti-TGF-β antibody disclosed herein).

In some examples, the patient's tumor is assigned into one of the following clusters: (1) angiogenic/stromal; or (6) stromal/proliferative, and the method further comprises treating the patient by administering an anti-cancer therapy comprising a stromal inhibitor (e.ga transforming growth factor beta (TGF-β), podoplanin (PDPN), leukocyte-associated immunoglobulin-like receptor 1 (LAIR1), SMAD, anaplastic lymphoma kinase (ALK), connective tissue growth factor (CTGF/CCN2), endothelial-1 (ET-1), AP-1, interleukin (IL)-13, lysyl oxidase homolog 2 (LOXL2), endoglin (CD105), fibroblast activation protein

(FAP), vascular cell adhesion protein 1 (CD106), thymocyte antigen 1 (THY1), beta 1 integrin (CD29), platelet-derived growth factor (PDGF), PDGF receptor A (PDGFRα), PDGF receptor B (PDGFRβ), vimentin, smooth muscle actin alpha (ACTA2), desmin, endosialin (CD248), or S100 calcium-binding protein A4 (S100A4) antagonist) to the patient. In some examples, the stromal inhibitor is a TGF-β antagonist (e.g., an anti-TGF-β antibody, e.g., any anti-TGF-β antibody disclosed herein).

Any of the methods disclosed herein may comprise assaying for somatic alterations in the patient's genotype in the tumor sample obtained from the patient. Any suitable somatic alterations may be assayed. In some examples, the method comprises assaying for somatic alterations in *PBRM1, CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and/or *KMT2C.*

In some examples, (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1* indicates that the patient is likely to have an increased clinical benefit from treatment with an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab) compared to treatment with a tyrosine kinase inhibitor (e.g., sunitinib).

In some examples, the patient's genotype is determined to comprise a somatic alteration in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C*, and the method further comprises selecting an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab) for the patient.

In some examples, the patient's genotype is determined to comprise a somatic alteration in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C*, and the method further comprises administering to the patient an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab).

In some examples, the presence of a somatic alteration in the patient's genotype in *PBRM1* indicates that the patient is likely to have an increased clinical benefit from treatment with sunitinib compared a patient whose genotype lacks a somatic alteration in *PBRM1*.

In some examples, the patient's genotype is determined to comprise a somatic alteration in *PBRM1*, and the method further comprises administering a tyrosine kinase inhibitor (e.g., sunitinib) to the patient.

Any suitable somatic alterations may be assessed. In some examples, the somatic alteration is a short variant, a loss, an amplification, a deletion, a duplication, a rearrangement, or a truncation.

Any suitable sample may be used for patient classification in the methods described herein. In some examples, the sample is a tumor sample. In some examples, the tumor sample is a formalin-fixed and paraffin-embedded (FFPE) sample, an archival sample, a fresh sample, or a frozen sample. In some examples, the tumor sample is a pre-treatment tumor sample. In some examples, the tumor sample from the patient has a clear cell histology. In other examples, the tumor sample from the patient has a non-clear cell histology. In some examples, the tumor sample from the patient has a sarcomatoid component. In some examples, the tumor sample lacks a sarcomatoid component.

In some examples, the method further comprises determining the patient's Memorial Sloan

Kettering Cancer Center (MSKCC) risk score.

In some examples, the method further comprises selecting an additional therapeutic agent to the patient.

In some examples, the method further comprises administering an additional therapeutic agent to the patient.

In some examples, the additional therapeutic agent is an immunotherapy agent, a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent, or a combination thereof. In some examples, the growth inhibitory agent is a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, or abemaciclib). In some examples, the anti-angiogenic agent is a VEGF antagonist (e.g., any VEGF antagonist disclosed herein, e.g., an anti-VEGF antibody (e.g., bevacizumab) or a tyrosine kinase inhibitor (e.g., sunitinib or axitinib)) or a HIF2A inhibitor (e.g., belzutifan (also known as MK-6482) or PT2385). In some examples, the stromal inhibitor is a TGF-β antagonist (e.g., an anti-TGF-β antibody, e.g., any anti-TGF-β antibody disclosed herein). In some examples, the metabolism inhibitor is a PCSK9 inhibitor (e.g., an anti-PCSK9 antibody, e.g., alirocumab or evolocumab), a FAS inhibitor (e.g., cerulenin, C75, isoniazid, or orlistat (tetrahydrolipstatin)), or an AMPK inhibitor (e.g., SBI-0206965, 5′-hydroxy-staurosporine, or compound C (also known as dorsomorphin)). In some embodiments, the complement antagonist is a C1 inhibitor (e.g., CINRYZE® C1 esterase inhibitor), a C3 inhibitor (e.g., a PEGylated pentadecapeptide (e.g., pegcetacoplan) or an anti-C3 antibody (e.g., H17)), a C5 inhibitor (e.g., an anti-C5 antibody (e.g., eculizumab, ABP959, ALXN1210, ALXN5500, SKY59, or LFG 316), an anti-C5 antibody fragment (e.g., MUBODINA®, a neutralizing mini antibody against C5), an siRNA (e.g., ALNCC5), a recombinant protein (e.g., coversin), or a small molecule (e.g., RA101348)), a C5a receptor antagonist (e.g., PMX53, CCX168, or MP-435), an FD inhibitor (e.g., an anti-FD antibody (e.g., lampalizumab) or a small molecule (e.g., ACH-3856, ACH-4100, or ACH-4471)), an FB inhibitor (e.g., an anti-FB antibody, e.g., TA106), a small molecule (e.g., LNP023), an siRNA (e.g., anti-FB siRNA, Alnylam), or an antisense (e.g., Ionis-FB-L_{Rx})), a properdin inhibitor (e.g., an anti-properdin antibody (e.g., NM9401)), a C3 convertase (C3bBb) inhibitor (e.g., an FFH-based protein such as TT30 (CR2/CFH) or mini-FH (Amyndas)), or a C3 convertase (C4bC3B and C3bBb) inhibitor (e.g., mirococept (APT070)).

Any of the methods of classifying a kidney cancer in a patient may further include treating the patient, e.g., using any approach described below in Section III.

III. Therapeutic Methods, Compositions, and Uses for Kidney Cancer

In one example, provided herein is a method of treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, the method comprising: classifying the cancer in the patient according to any one of the methods disclosed herein; and administering an anti-cancer therapy to the patient based on the classification.

In another example, provided herein is an anti-cancer therapy for use in treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer in the patient has been classified according to any one of the methods disclosed herein.

In another example, provided herein is the use of an anti-cancer therapy in the preparation of a medicament for treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer in the patient has been classified according to any one of the methods disclosed herein.

In some examples, the kidney cancer is previously untreated.

For example, provided herein is a method of treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer is untreated, the method comprising: classifying the cancer in the patient according to any one of the methods disclosed herein; and administering an anti-cancer therapy to the patient based on the classification.

In another example, provided herein is an anti-cancer therapy for use in treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer is untreated, wherein the kidney cancer in the patient has been classified according to any one of the methods disclosed herein.

In another example, provided herein is the use of an anti-cancer therapy in the preparation of a medicament for treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer is previously untreated, wherein the kidney cancer in the patient has been classified according to any one of the methods disclosed herein.

In one example, provided herein is a method of treating an inoperable, locally advanced, or metastatic RCC in a human patient, the method comprising: classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient according to any one of the methods disclosed herein; and administering an anti-cancer therapy to the patient based on the classification.

In another example, provided herein is an anti-cancer therapy for use in treating an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the previously untreated inoperable, locally advanced, or metastatic RCC in the patient has been classified according to any one of the methods disclosed herein.

In another example, provided herein is the use of an anti-cancer therapy in the preparation of a medicament for treating an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the previously untreated inoperable, locally advanced, or metastatic RCC in the patient has been classified according to any one of the methods disclosed herein.

Any suitable anti-cancer therapy may be administered to the patient based on the classification. For example, in some embodiments, a PD-1 axis binding antagonist (e.g., an anti-PD-L1 antibody, e.g., atezolizumab or avelumab) is administered to the patient. In some examples, a VEGF antagonist (e.g., an anti-VEGF antibody (e.g., bevacizumab) or a tyrosine kinase inhibitor (e.g., sunitinib or axitinib) is administered to the patient. In some examples, the anti-cancer therapy comprises atezolizumab and bevacizumab. In other examples, the anti-cancer therapy comprises avelumab and axitinib. In some examples, the method further comprises administering an additional therapeutic agent to the patient.

In another example, provided herein is a method of treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient whose genotype has been determined to

comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, the method comprising administering to the patient an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a VEGF antagonist (e.g., bevacizumab or axitinib).

In another example, provided herein is a PD-1 axis binding antagonist (e.g., atezolizumab or axitinib) for use in treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, wherein the PD-1 axis binding antagonist is administered in combination with a VEGF antagonist (e.g., bevacizumab or axitinib).

In another example, provided herein is the use of a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) in the preparation of a medicament for treating a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, wherein the medicament is administered in combination with a VEGF antagonist (e.g., bevacizumab or axitinib).

In some examples, the kidney cancer is previously untreated.

For example, provided herein is a method of treating a previously untreated kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, the method comprising administering to the patient an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) and a VEGF antagonist (e.g., bevacizumab or axitinib).

In another example, provided herein is a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) for use in treating a previously untreated kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, wherein the PD-1 axis binding antagonist is administered in combination with a VEGF antagonist (e.g., bevacizumab or axitinib).

In another example, provided herein is the use of a PD-1 axis binding antagonist (e.g., atezolizumab or avelumab) in the preparation of a medicament for treating a previously untreated kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a

somatic alteration in the patient's genotype in *PBRM1*, wherein the medicament is administered in combination with a VEGF antagonist (e.g., bevacizumab or axitinib).

In some examples, the kidney cancer is RCC. In some examples, the kidney cancer is an inoperable, locally advanced, or metastatic RCC.

In another example, provided herein is a method of treating a previously untreated inoperable, locally advanced, or metastatic RCC in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, the method comprising administering to the patient an anti-cancer therapy comprising atezolizumab or bevacizumab.

In another example, provided herein is atezolizumab for use in treating a previously untreated inoperable, locally advanced, or metastatic RCC in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, wherein the atezolizumab is administered in combination with bevacizumab.

In another example, provided herein is the use of atezolizumab in the preparation of a medicament for treating a previously untreated inoperable, locally advanced, or metastatic RCC in a patient whose genotype has been determined to comprise a somatic alteration in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C*, wherein the medicament is administered in combination bevacizumab.

In some examples, the PD-1 axis binding antagonist and/or the VEGF antagonist is administered in combination with an effective amount of one or more additional therapeutic agents. In some examples, the PD-1 axis binding antagonist is administered in combination with an effective amount of a VEGF antagonist. In some examples, the additional therapeutic agent is an immunotherapy agent, a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent, or a combination thereof. In some examples, the growth inhibitory agent is a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, or abemaciclib). In some examples, the anti-angiogenic agent is a VEGF antagonist (e.g., any VEGF antagonist disclosed herein, e.g., an anti-VEGF antibody (e.g., bevacizumab) or a tyrosine kinase inhibitor (e.g., sunitinib or axitinib)) or a HIF2A inhibitor (e.g., belzutifan (also known as MK-6482) or PT2385). In some examples, the stromal inhibitor is a TGF-β antagonist (e.g., an anti-TGF-β antibody, e.g., any anti-TGF-β antibody disclosed herein). In some examples, the metabolism inhibitor is a PCSK9 inhibitor (e.g., an anti-PCSK9 antibody, e.g., alirocumab or evolocumab), a FAS inhibitor (e.g., cerulenin, C75, isoniazid, or orlistat (tetrahydrolipstatin)), or an AMPK inhibitor (e.g., SBI-0206965, 5'-hydroxy-staurosporine, or compound C (also known as dorsomorphin)). In some embodiments, the complement antagonist is a C1 inhibitor (e.g., CINRYZE® C1 esterase inhibitor), a C3 inhibitor (e.g., a PEGylated pentadecapeptide (e.g., pegcetacoplan) or an anti-C3 antibody (e.g., H17)), a C5 inhibitor (e.g., an anti-C5 antibody (e.g., eculizumab, ABP959, ALXN1210, ALXN5500, SKY59, or LFG 316), an anti-C5 antibody fragment (e.g.,

MUBODINA®, a neutralizing mini antibody against C5), an siRNA (e.g., ALNCC5), a recombinant protein (e.g., coversin), or a small molecule (e.g., RA101348)), a C5a receptor antagonist (e.g., PMX53, CCX168, or MP-435), an FD inhibitor (e.g., an anti-FD antibody (e.g., lampalizumab) or a small molecule (e.g., ACH-3856, ACH-4100, or ACH-4471)), an FB inhibitor (e.g., an anti-FB antibody, e.g., TA106), a small molecule (e.g., LNP023), an siRNA (e.g., anti-FB siRNA, Alnylam), or an antisense (e.g., Ionis-FB-L_{Rx})), a properdin inhibitor (e.g., an anti-properdin antibody (e.g., NM9401)), a C3 convertase (C3bBb) inhibitor (e.g., an FFH-based protein such as TT30 (CR2/CFH) or mini-FH (Amyndas)), or a C3 convertase (C4bC3B and C3bBb) inhibitor (e.g., mirococept (APT070)).

In any of the preceding examples, each dosing cycle may have any suitable length, e.g., about 7 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, or longer. In some instances, each dosing cycle is about 21 days. In some instances, each dosing cycle is about 42 days.

As a general proposition, the therapeutically effective amount of a PD-1 axis binding antagonist (e.g., atezolizumab) administered to a human will be in the range of about 0.01 to about 50 mg/kg of patient body weight, whether by one or more administrations.

In some exemplary embodiments, the PD-1 axis binding antagonist is administered in a dose of about 0.01 to about 45 mg/kg, about 0.01 to about 40 mg/kg, about 0.01 to about 35 mg/kg, about 0.01 to about 30 mg/kg, about 0.01 to about 25 mg/kg, about 0.01 to about 20 mg/kg, about 0.01 to about 15 mg/kg, about 0.01 to about 10 mg/kg, about 0.01 to about 5 mg/kg, or about 0.01 to about 1 mg/kg administered daily, weekly, every two weeks, every three weeks, or every four weeks, for example.

In one instance, a PD-1 axis binding antagonist is administered to a human at a dose of about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, or about 1500 mg. In some instances, the PD-1 axis binding antagonist may be administered at a dose of about 1000 mg to about 1400 mg every three weeks (e.g., about 1100 mg to about 1300 mg every three weeks, e.g., about 1150 mg to about 1250 mg every three weeks). In some instances, the PD-1 axis binding antagonist may be administered at a dose of 1200 mg every three weeks.

In some instances, a patient is administered a total of 1 to 50 doses of a PD-1 axis binding antagonist, e.g., 1 to 50 doses, 1 to 45 doses, 1 to 40 doses, 1 to 35 doses, 1 to 30 doses, 1 to 25 doses, 1 to 20 doses, 1 to 15 doses, 1 to 10 doses, 1 to 5 doses, 2 to 50 doses, 2 to 45 doses, 2 to 40 doses, 2 to 35 doses, 2 to 30 doses, 2 to 25 doses, 2 to 20 doses, 2 to 15 doses, 2 to 10 doses, 2 to 5 doses, 3 to 50 doses, 3 to 45 doses, 3 to 40 doses, 3 to 35 doses, 3 to 30 doses, 3 to 25 doses, 3 to 20 doses, 3 to 15 doses, 3 to 10 doses, 3 to 5 doses, 4 to 50 doses, 4 to 45 doses, 4 to 40 doses, 4 to 35 doses, 4 to 30 doses, 4 to 25 doses, 4 to 20 doses, 4 to 15 doses, 4 to 10 doses, 4 to 5 doses, 5 to 50 doses, 5 to 45 doses, 5 to 40 doses, 5 to 35 doses, 5 to 30 doses, 5 to 25 doses, 5 to 20 doses, 5 to 15 doses, 5 to 10 doses, 10 to 50 doses, 10 to 45 doses, 10 to 40 doses, 10 to 35 doses, 10 to 30 doses, 10 to 25 doses, 10 to 20 doses, 10 to 15 doses, 15 to 50 doses, 15 to 45 doses, 15 to 40 doses, 15 to 35 doses, 15 to 30 doses, 15 to 25 doses, 15 to 20 doses, 20 to 50 doses, 20 to 45 doses, 20 to 40 doses, 20 to 35 doses, 20 to 30 doses, 20 to 25 doses, 25 to 50 doses, 25 to 45 doses, 25 to 40 doses, 25 to 35 doses, 25 to 30 doses, 30 to 50 doses, 30 to 45 doses, 30 to 40 doses, 30 to 35 doses, 35 to 50 doses, 35 to 45 doses,

35 to 40 doses, 40 to 50 doses, 40 to 45 doses, or 45 to 50 doses. In particular instances, the doses may be administered intravenously.

In some instances, atezolizumab is administered to the patient intravenously at a dose of about 840 mg every 2 weeks, about 1200 mg every 3 weeks, or about 1680 mg of every 4 weeks.

In some instances, atezolizumab is administered at a fixed dose of 1200 mg via intravenous infusion on Days 1 and 22 of each 42-day cycle.

In some instances, atezolizumab is administered at a fixed dose of 1200 mg via intravenous (IV) infusion on Days 1 and 22 of each 42-day cycle, and bevacizumab is administered at a dose of 15 mg/kg via IV infusion on Days 1 and 22 of each 42-day cycle.

In some instances, avelumab is administered at a dose of 10 mg/kg IV every two weeks.

In some instances, axitinib is administered at a dose of 5 mg orally twice a day (PO BID).

In some instances, avelumab is administered at a dose of 10 mg/kg IV every two weeks, and axitinib is administered at a dose of 5 mg PO BID for a 6-week cycle.

In some instances, sunitinib is administered at a dose of 50 mg PO every day (QD).

The PD-1 axis binding antagonist, the VEGF antagonist, and/or any additional therapeutic agent(s), including an immunotherapy agent, a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent (e.g., a VEGF antagonist), or a combination thereof, may be administered in any suitable manner known in the art.

For example, the PD-1 axis binding antagonist, the VEGF antagonist, and/or any additional therapeutic agent(s) may be administered sequentially (on different days) or concurrently (on the same day or during the same treatment cycle). In some instances, the PD-1 axis binding antagonist is administered prior to the additional therapeutic agent. In other instances, the PD-1 axis binding antagonist is administered after the additional therapeutic agent. In some instances, the PD-1 axis binding antagonist and/or any additional therapeutic agent(s) may be administered on the same day. In some instances, the PD-1 axis binding antagonist may be administered prior to an additional therapeutic agent that is administered on the same day. For example, the PD-1 axis binding antagonist may be administered prior to chemotherapy on the same day. In another example, the PD-1 axis binding antagonist may be administered prior to both chemotherapy and another drug (e.g., bevacizumab) on the same day. In other instances, the PD-1 axis binding antagonist may be administered after an additional therapeutic agent that is administered on the same day. In yet other instances, the PD-1 axis binding antagonist is administered at the same time as the additional therapeutic agent. In some instances, the PD-1 axis binding antagonist is in a separate composition as the additional therapeutic agent. In some instances, the PD-1 axis binding antagonist is in the same composition as the additional therapeutic agent. In some instances, the PD-1 axis binding antagonist is administered through a separate intravenous line from any other therapeutic agent administered to the patient on the same day.

The PD-1 axis binding antagonist, the VEGF antagonist, and any additional therapeutic agent(s) may be administered by the same route of administration or by different routes of administration. In some instances, the PD-1 axis binding antagonist is administered intravenously, intramuscularly,

subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some instances, the additional therapeutic agent is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

In a preferred embodiment, the PD-1 axis binding antagonist is administered intravenously. In one example, atezolizumab may be administered intravenously over 60 minutes; if the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. In some examples, the PD-1 axis binding antagonist is not administered as an intravenous push or bolus.

Also provided herein are methods for treating kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient comprising administering to the patient a treatment regimen comprising an effective amount of a PD-1 axis binding antagonist (e.g., atezolizumab) and/or a VEGF antagonist (e.g., bevacizumab) in combination with another anti-cancer agent or cancer therapy. For example, a PD-1 axis binding antagonist may be administered in combination with an additional chemotherapy or chemotherapeutic agent (see definition above); a targeted therapy or targeted therapeutic agent; an immunotherapy or immunotherapeutic agent, for example, a monoclonal antibody; one or more cytotoxic agents (see definition above); or combinations thereof. For example, the PD-1 axis binding antagonist may be administered in combination with bevacizumab, paclitaxel, paclitaxel protein-bound (e.g., nab-paclitaxel), carboplatin, cisplatin, pemetrexed, gemcitabine, etoposide, cobimetinib, vemurafenib, or a combination thereof. The PD-1 axis binding antagonist may be an anti-PD-L1 antibody (e.g., atezolizumab) or an anti-PD-1 antibody.

For example, when administering with chemotherapy with or without bevacizumab, atezolizumab may be administered at a dose of 1200 mg every 3 weeks prior to chemotherapy and bevacizumab. In another example, following completion of 4-6 cycles of chemotherapy, and if bevacizumab is discontinued, atezolizumab may be administered at a dose of 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every four weeks. In another example, atezolizumab may be administered at a dose of 840 mg, followed by 100 mg/m^2 of paclitaxel protein-bound (e.g., nab-paclitaxel); for each 28 day cycle, atezolizumab is administered on days 1 and 15, and paclitaxel protein-bound is administered on days 1, 8, and 15. In another example, when administering with carboplatin and etoposide, atezolizumab can be administered at a dose of 1200 mg every 3 weeks prior to chemotherapy. In yet another example, following completion of 4 cycles of carboplatin and etoposide, atezolizumab may be administered at a dose of 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. In another example, following completion of a 28-day cycle of cobimenitib and vemurafenib, atezolizumab may be administered at a dose of 840 mg every 2 weeks with cobimetinib at a dose of 60 mg orally once daily (21 days on, 7 days off) and vemurafenib at a dose of 720 mg orally twice daily.

In some instances, the treatment may further comprise an additional therapy. Any suitable additional therapy known in the art or described herein may be used. The additional therapy may be radiation therapy, surgery, gene therapy, DNA therapy, viral therapy, RNA therapy, immunotherapy, bone marrow transplantation, nanotherapy, monoclonal antibody therapy, gamma irradiation, or a combination

of the foregoing.

In some instances, the additional therapy is the administration of side-effect limiting agents (e.g., agents intended to lessen the occurrence and/or severity of side effects of treatment, such as anti-nausea agents, a corticosteroid (e.g., prednisone or an equivalent, e.g., at a dose of 1-2 mg/kg/day), hormone replacement medicine(s), and the like).

IV. Assessment of PD-L1 Expression

The expression of PD-L1 may be assessed in a patient treated according to any of the methods, compositions for use, and uses described herein. The methods, compositions for use, and uses may include determining the expression level of PD-L1 in a biological sample (e.g., a tumor sample) obtained from the patient. In other examples, the expression level of PD-L1 in a biological sample (e.g., a tumor sample) obtained from the patient has been determined prior to initiation of treatment or after initiation of treatment. PD-L1 expression may be determined using any suitable approach. For example, PD-L1 expression may be determined as described in U.S. Patent Application Nos. 15/787,988 and 15/790,680. Any suitable tumor sample may be used, e.g., a formalin-fixed and paraffin-embedded (FFPE) tumor sample, an archival tumor sample, a fresh tumor sample, or a frozen tumor sample.

For example, PD-L1 expression may be determined in terms of the percentage of a tumor sample comprised by tumor-infiltrating immune cells expressing a detectable expression level of PD-L1, as the percentage of tumor-infiltrating immune cells in a tumor sample expressing a detectable expression level of PD-L1, and/or as the percentage of tumor cells in a tumor sample expressing a detectable expression level of PD-L1. It is to be understood that in any of the preceding examples, the percentage of the tumor sample comprised by tumor-infiltrating immune cells may be in terms of the percentage of tumor area covered by tumor-infiltrating immune cells in a section of the tumor sample obtained from the patient, for example, as assessed by IHC using an anti-PD-L1 antibody (e.g., the SP142 antibody). Any suitable anti-PD-L1 antibody may be used, including, e.g., SP142 (Ventana), SP263 (Ventana), 22C3 (Dako), 28-8 (Dako), E1L3N (Cell Signaling Technology), 4059 (ProSci, Inc.), h5H1 (Advanced Cell Diagnostics), and 9A11. In some examples, the anti-PD-L1 antibody is SP142. In other examples, the anti-PD-L1 antibody is SP263.

In some examples, a tumor sample obtained from the patient has a detectable expression level of PD-L1 in less than 1% of the tumor cells in the tumor sample, in 1% or more of the tumor cells in the tumor sample, in from 1% to less than 5% of the tumor cells in the tumor sample, in 5% or more of the tumor cells in the tumor sample, in from 5% to less than 50% of the tumor cells in the tumor sample, or in 50% or more of the tumor cells in the tumor sample.

In some examples, a tumor sample obtained from the patient has a detectable expression level of PD-L1 in tumor-infiltrating immune cells that comprise less than 1% of the tumor sample, more than 1% of the tumor sample, from 1% to less than 5% of the tumor sample, more than 5% of the tumor sample, from 5% to less than 10% of the tumor sample, or more than 10% of the tumor sample.

In some examples, tumor samples may be scored for PD-L1 positivity in tumor-infiltrating immune cells and/or in tumor cells according to the criteria for diagnostic assessment shown in Table 2 and/or Table 3, respectively.

Table 2. Tumor-infiltrating immune cell (IC) IHC diagnostic criteria

PD-L1 Diagnostic Assessment	IC Score
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering <1% of tumor area occupied by tumor cells, associated intratumoral stroma, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥1% to <5% of tumor area occupied by tumor cells, associated intratumoral stroma, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥5% to <10% of tumor area occupied by tumor cells, associated intratumoral stroma, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥10% of tumor area occupied by tumor cells, associated intratumoral stroma, and contiguous peri-tumoral desmoplastic stroma	IC3

Table 3. Tumor cell (TC) IHC diagnostic criteria

PD-L1 Diagnostic Assessment	TC Score
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in <1% of tumor cells	TC0
Presence of discernible PD-L1 staining of any intensity in ≥1% to <5% of tumor cells	TC1
Presence of discernible PD-L1 staining of any intensity in ≥5% to <50% of tumor cells	TC2
Presence of discernible PD-L1 staining of any intensity in ≥50% of tumor cells	TC3

V. PD-1 Axis Binding Antagonists

PD-1 axis binding antagonists may include PD-L1 binding antagonists, PD-1 binding antagonists, and PD-L2 binding antagonists. Any suitable PD-1 axis binding antagonist may be used.

A. PD-L1 Binding Antagonists

In some instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to one or more of its ligand binding partners. In other instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In yet other instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1. The PD-L1 binding antagonist may be, without limitation, an antibody, an antigen-binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or a small molecule. In some instances, the PD-L1

binding antagonist is a small molecule that inhibits PD-L1 (e.g., GS-4224, INCB086550, MAX-10181, INCB090244, CA-170, or ABSK041). In some instances, the PD-L1 binding antagonist is a small molecule that inhibits PD-L1 and VISTA. In some instances, the PD-L1 binding antagonist is CA-170 (also known as AUPM-170). In some instances, the PD-L1 binding antagonist is a small molecule that inhibits PD-L1 and TIM3. In some instances, the small molecule is a compound described in WO 2015/033301 and/or WO 2015/033299.

In some instances, the PD-L1 binding antagonist is an anti-PD-L1 antibody. A variety of anti-PD-L1 antibodies are contemplated and described herein. In any of the instances herein, the isolated anti-PD-L1 antibody can bind to a human PD-L1, for example a human PD-L1 as shown in UniProtKB/Swiss-Prot Accession No. Q9NZQ7-1, or a variant thereof. In some instances, the anti-PD-L1 antibody is capable of inhibiting binding between PD-L1 and PD-1 and/or between PD-L1 and B7-1. In some instances, the anti-PD-L1 antibody is a monoclonal antibody. In some instances, the anti-PD-L1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragments. In some instances, the anti-PD-L1 antibody is a humanized antibody. In some instances, the anti-PD-L1 antibody is a human antibody. Exemplary anti-PD-L1 antibodies include atezolizumab, MDX-1105, MEDI4736 (durvalumab), MSB0010718C (avelumab), SHR-1316, CS1001, envafolimab, TQB2450, ZKAB001, LP-002, CX-072, IMC-001, KL-A167, APL-502, cosibelimab, lodapolimab, FAZ053, TG-1501, BGB-A333, BCD-135, AK-106, LDP, GR1405, HLX20, MSB2311, RC98, PDL-GEX, KD036, KY1003, YBL-007, and HS-636. Examples of anti-PD-L1 antibodies useful in the methods of this invention and methods of making them are described in International Patent Application Publication No. WO 2010/077634 and U.S. Patent No. 8,217,149, each of which is incorporated herein by reference in its entirety.

In some instances, the anti-PD-L1 antibody comprises:

(a) an HVR-H1, HVR-H2, and HVR-H3 sequence of GFTFSDSWIH (SEQ ID NO: 3), AWISPYGGSTYYADSVKG (SEQ ID NO: 4) and RHWPGGFDY (SEQ ID NO: 5), respectively, and

(b) an HVR-L1, HVR-L2, and HVR-L3 sequence of RASQDVSTAVA (SEQ ID NO: 6), SASFLYS (SEQ ID NO: 7) and QQYLYHPAT (SEQ ID NO: 8), respectively.

In one embodiment, the anti-PD-L1 antibody comprises:

(a) a heavy chain variable region (VH) comprising the amino acid sequence: EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRF TISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ ID NO: 9), and

(b) the light chain variable region (VL) comprising the amino acid sequence: DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO: 10).

In some instances, the anti-PD-L1 antibody comprises (a) a VH comprising an amino acid sequence comprising having at least 95% sequence identity (e.g., at least 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of SEQ ID NO: 9; (b) a VL comprising an amino acid sequence comprising having at least 95% sequence identity (e.g., at least 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of SEQ ID NO: 10; or (c) a VH as in (a) and a VL as in (b).

In one embodiment, the anti-PD-L1 antibody comprises atezolizumab, which comprises:

(a) the heavy chain amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRF
TISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1), and

(b) the light chain amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR
GEC (SEQ ID NO: 2).

In some instances, the anti-PD-L1 antibody is avelumab (CAS Registry Number: 1537032-82-8). Avelumab, also known as MSB0010718C, is a human monoclonal IgG1 anti-PD-L1 antibody (Merck KGaA, Pfizer).

In some instances, the anti-PD-L1 antibody is durvalumab (CAS Registry Number: 1428935-60-7). Durvalumab, also known as MEDI4736, is an Fc-optimized human monoclonal IgG1 kappa anti-PD-L1 antibody (MedImmune, AstraZeneca) described in WO 2011/066389 and US 2013/034559.

In some instances, the anti-PD-L1 antibody is MDX-1105 (Bristol Myers Squibb). MDX-1105, also known as BMS-936559, is an anti-PD-L1 antibody described in WO 2007/005874.

In some instances, the anti-PD-L1 antibody is LY3300054 (Eli Lilly).

In some instances, the anti-PD-L1 antibody is STI-A1014 (Sorrento). STI-A1014 is a human anti-PD-L1 antibody.

In some instances, the anti-PD-L1 antibody is KN035 (Suzhou Alphamab). KN035 is single-domain antibody (dAB) generated from a camel phage display library.

In some instances, the anti-PD-L1 antibody comprises a cleavable moiety or linker that, when cleaved (e.g., by a protease in the tumor microenvironment), activates an antibody antigen binding domain to allow it to bind its antigen, e.g., by removing a non-binding steric moiety. In some instances, the anti-PD-L1 antibody is CX-072 (CytomX Therapeutics).

In some instances, the anti-PD-L1 antibody comprises the six HVR sequences (e.g., the three heavy chain HVRs and the three light chain HVRs) and/or the heavy chain variable domain and light chain variable domain from an anti-PD-L1 antibody described in US 20160108123, WO 2016/000619, WO 2012/145493, U.S. Pat. No. 9,205,148, WO 2013/181634, or WO 2016/061142.

In a still further specific aspect, the anti-PD-L1 antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from an "effector-less Fc mutation" or aglycosylation mutation. In still a further instance, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region. In still a further instance, the effector-less Fc mutation

is an N297A substitution in the constant region. In some instances, the isolated anti-PD-L1 antibody is aglycosylated. Glycosylation of antibodies is typically either N-linked or O- linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. Removal of glycosylation sites from an antibody is conveniently accomplished by altering the amino acid sequence such that one of the above-described tripeptide sequences (for N-linked glycosylation sites) is removed. The alteration may be made by substitution of an asparagine, serine or threonine residue within the glycosylation site with another amino acid residue (e.g., glycine, alanine, or a conservative substitution).

B. PD-1 Binding Antagonists

In some instances, the PD-1 axis binding antagonist is a PD-1 binding antagonist. For example, in some instances, the PD-1 binding antagonist inhibits the binding of PD-1 to one or more of its ligand binding partners. In some instances, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In other instances, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In yet other instances, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. The PD-1 binding antagonist may be, without limitation, an antibody, an antigen-binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or a small molecule. In some instances, the PD-1 binding antagonist is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). For example, in some instances, the PD-1 binding antagonist is an Fc-fusion protein. In some instances, the PD-1 binding antagonist is AMP-224. AMP-224, also known as B7-DCIg, is a PD-L2-Fc fusion soluble receptor described in WO 2010/027827 and WO 2011/066342. In some instances, the PD-1 binding antagonist is a peptide or small molecule compound. In some instances, the PD-1 binding antagonist is AUNP-12 (PierreFabre/Aurigene). See, e.g., WO 2012/168944, WO 2015/036927, WO 2015/044900, WO 2015/033303, WO 2013/144704, WO 2013/132317, and WO 2011/161699. In some instances, the PD-1 binding antagonist is a small molecule that inhibits PD-1.

In some instances, the PD-1 binding antagonist is an anti-PD-1 antibody. A variety of anti-PD-1 antibodies can be utilized in the methods and uses disclosed herein. In any of the instances herein, the PD-1 antibody can bind to a human PD-1 or a variant thereof. In some instances the anti-PD-1 antibody is a monoclonal antibody. In some instances, the anti-PD-1 antibody is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments. In some instances, the anti-PD-1 antibody is a humanized antibody. In other instances, the anti-PD-1 antibody is a human antibody. Exemplary anti-PD-1 antagonist antibodies include nivolumab, pembrolizumab, MEDI-0680, PDR001 (spartalizumab), REGN2810 (cemiplimab), BGB-108, prolgolimab, camrelizumab, sintilimab,

tislelizumab, toripalimab, dostarlimab, retifanlimab, sasanlimab, penpulimab, CS1003, HLX10, SCT-I10A, zimberelimab, balstilimab, genolimzumab, BI 754091, cetrelimab, YBL-006, BAT1306, HX008, budigalimab, AMG 404, CX-188, JTX-4014, 609A, Sym021, LZM009, F520, SG001, AM0001, ENUM 244C8, ENUM 388D4, STI-1110, AK-103, and hAb21.

In some instances, the anti-PD-1 antibody is nivolumab (CAS Registry Number: 946414-94-4). Nivolumab (Bristol-Myers Squibb/Ono), also known as MDX-1106-04, MDX-1106, ONO-4538, BMS-936558, and OPDIVO®, is an anti-PD-1 antibody described in WO 2006/121168.

In some instances, the anti-PD-1 antibody is pembrolizumab (CAS Registry Number: 1374853-91-4). Pembrolizumab (Merck), also known as MK-3475, Merck 3475, lambrolizumab, SCH-900475, and KEYTRUDA®, is an anti-PD-1 antibody described in WO 2009/114335.

In some instances, the anti-PD-1 antibody is MEDI-0680 (AMP-514; AstraZeneca). MEDI-0680 is a humanized IgG4 anti-PD-1 antibody.

In some instances, the anti-PD-1 antibody is PDR001 (CAS Registry No. 1859072-53-9; Novartis). PDR001 is a humanized IgG4 anti-PD-1 antibody that blocks the binding of PD-L1 and PD-L2 to PD-1.

In some instances, the anti-PD-1 antibody is REGN2810 (Regeneron). REGN2810 is a human anti-PD-1 antibody.

In some instances, the anti-PD-1 antibody is BGB-108 (BeiGene).

In some instances, the anti-PD-1 antibody is BGB-A317 (BeiGene).

In some instances, the anti-PD-1 antibody is JS-001 (Shanghai Junshi). JS-001 is a humanized anti-PD-1 antibody.

In some instances, the anti-PD-1 antibody is STI-A1110 (Sorrento). STI-A1110 is a human anti-PD-1 antibody.

In some instances, the anti-PD-1 antibody is INCSHR-1210 (Incyte). INCSHR-1210 is a human IgG4 anti-PD-1 antibody.

In some instances, the anti-PD-1 antibody is PF-06801591 (Pfizer).

In some instances, the anti-PD-1 antibody is TSR-042 (also known as ANB011; Tesaro/AnaptysBio).

In some instances, the anti-PD-1 antibody is AM0001 (ARMO Biosciences).

In some instances, the anti-PD-1 antibody is ENUM 244C8 (Enumeral Biomedical Holdings). ENUM 244C8 is an anti-PD-1 antibody that inhibits PD-1 function without blocking binding of PD-L1 to PD-1.

In some instances, the anti-PD-1 antibody is ENUM 388D4 (Enumeral Biomedical Holdings). ENUM 388D4 is an anti-PD-1 antibody that competitively inhibits binding of PD-L1 to PD-1.

In some instances, the anti-PD-1 antibody comprises the six HVR sequences (e.g., the three heavy chain HVRs and the three light chain HVRs) and/or the heavy chain variable domain and light chain variable domain from an anti-PD-1 antibody described in WO 2015/112800, WO 2015/112805, WO 2015/112900, US 20150210769 , WO2016/089873, WO 2015/035606, WO 2015/085847, WO

2014/206107, WO 2012/145493, US 9,205,148, WO 2015/119930, WO 2015/119923, WO 2016/032927, WO 2014/179664, WO 2016/106160, and WO 2014/194302.

In a still further specific aspect, the anti-PD-1 antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from an "effector-less Fc mutation" or aglycosylation mutation. In still a further instance, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region. In some instances, the isolated anti-PD-1 antibody is aglycosylated.

C. PD-L2 Binding Antagonists

In some instances, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some instances, the PD-L2 binding antagonist is a molecule that inhibits the binding of PD-L2 to its ligand binding partners. In a specific aspect, the PD-L2 binding ligand partner is PD-1. The PD-L2 binding antagonist may be, without limitation, an antibody, an antigen-binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or a small molecule.

In some instances, the PD-L2 binding antagonist is an anti-PD-L2 antibody. In any of the instances herein, the anti-PD-L2 antibody can bind to a human PD-L2 or a variant thereof. In some instances, the anti-PD-L2 antibody is a monoclonal antibody. In some instances, the anti-PD-L2 antibody is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments. In some instances, the anti-PD-L2 antibody is a humanized antibody. In other instances, the anti-PD-L2 antibody is a human antibody. In a still further specific aspect, the anti-PD-L2 antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from an "effector-less Fc mutation" or aglycosylation mutation. In still a further instance, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region. In some instances, the isolated anti-PD-L2 antibody is aglycosylated.

VI. VEGF Antagonists

Provided herein are methods for treating kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient comprising administering to the patient a treatment regimen comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab). Also provided are related compositions (e.g., pharmaceutical compositions) for use, kits, and articles of manufacture. Any of the methods, compositions for use, kits, or articles of manufacture described herein may include or involve any of the agents described below.

VEGF antagonists include any molecule capable of binding VEGF, reducing VEGF expression levels, or neutralizing, blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities. An exemplary human VEGF is shown under UniProtKB/Swiss-Prot Accession No. P15692, Gene ID (NCBI): 7422.

In some instances, the VEGF antagonist is an anti-VEGF antibody. In some embodiments, the anti-VEGF antibody is bevacizumab, also known as "rhuMab VEGF" or "AVASTIN®." Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (*Cancer*

Res. 57:4593-4599, 1997). It comprises mutated human IgG1 framework regions and antigen-binding complementarity-determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence of bevacizumab, including most of the framework regions, is derived from human IgG1, and about 7% of the sequence is derived from the murine antibody A4.6.1. Bevacizumab has a molecular mass of about 149,000 daltons and is glycosylated. Bevacizumab and other humanized anti-VEGF antibodies are further described in U.S. Pat. No. 6,884,879 issued Feb. 26, 2005, the entire disclosure of which is expressly incorporated herein by reference. Additional preferred antibodies include the G6 or B20 series antibodies (e.g., G6-31, B20-4.1), as described in PCT Application Publication No. WO 2005/012359. For additional preferred antibodies see U.S. Pat. Nos. 7,060,269, 6,582,959, 6,703,020; 6,054,297; WO98/45332; WO 96/30046; WO94/10202; EP 0666868B1; U.S. Patent Application Publication Nos. 2006009360, 20050186208, 20030206899, 20030190317, 20030203409, and 20050112126; and Popkov et al. (*Journal of Immunological Methods* 288:149-164, 2004). Other preferred antibodies include those that bind to a functional epitope on human VEGF comprising of residues F17, M18, D19, Y21, Y25, Q89, 191, K101, E103, and C104 or, alternatively, comprising residues F17, Y21, Q22, Y25, D63, 183, and Q89.

In other instances, the VEGF antagonist is an anti-VEGFR2 antibody or related molecule (e.g., ramucirumab, tanibirumab, aflibercept); an anti-VEGFR1 antibody or related molecules (e.g., icrucumab, aflibercept (VEGF Trap-Eye; EYLEA®), or ziv-aflibercept (VEGF Trap; ZALTRAP®)); a bispecific VEGF antibody (e.g., MP-0250, vanucizumab (VEGF-ANG2), or bispecific antibodies disclosed in US 2001/0236388); a bispecific antibody including a combination of two of anti-VEGF, anti-VEGFR1, and anti-VEGFR2 arms; an anti-VEGFA antibody (e.g., bevacizumab, sevacizumab); an anti-VEGFB antibody; an anti-VEGFC antibody (e.g., VGX-100), an anti-VEGFD antibody; or a nonpeptide small molecule VEGF antagonist (e.g., pazopanib, axitinib, vandetanib, stivarga, cabozantinib, lenvatinib, nintedanib, orantinib, telatinib, dovitinib, cediranib, motesanib, sulfatinib, apatinib, foretinib, famitinib, or tivozanib). In some examples, the VEGF antagonist may be a tyrosine kinase inhibitor, including a receptor tyrosine kinase inhibitors (e.g., a multi-targeted receptor tyrosine kinase inhibitor such as sunitinib or axitinib).

VII. Pharmaceutical Compositions and Formulations

Also provided herein are pharmaceutical compositions and formulations comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and, optionally, a pharmaceutically acceptable carrier. The disclosure also provides pharmaceutical compositions and formulations comprising a VEGF antagonist (e.g., bevacizumab), and optionally, a pharmaceutically acceptable carrier. Any of the additional therapeutic agents described herein may also be included in a pharmaceutical composition or formulation.

Pharmaceutical compositions and formulations as described herein can be prepared by mixing the active ingredients (e.g., a PD-1 axis binding antagonist) having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (see, e.g., *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), e.g., in the form of lyophilized formulations or aqueous solutions.

An exemplary atezolizumab formulation comprises glacial acetic acid, L-histidine, polysorbate 20, and sucrose, with a pH of 5.8. For example, atezolizumab may be provided in a 20 mL vial containing

1200 mg of atezolizumab that is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. In another example, atezolizumab may be provided in a 14 mL vial containing 840 mg of atezolizumab that is formulated in glacial acetic acid (11.5 mg), L-histidine (43.4 mg), polysorbate 20 (5.6 mg), and sucrose (575.1 mg) with a pH of 5.8.

VIII. Articles of Manufacture or Kits

Also provided herein are articles of manufacture and kits, which may be used for classifying a patient according to any of the methods disclosed herein.

In one example, provided herein is a kit for classifying a kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a human patient, wherein the kidney cancer is previously untreated, the kit comprising: (a) reagents for assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and (b) instructions for assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor: (1) angiogenic/stromal; (2) angiogenic; (3) complement/Ω-oxidation; (4) T-effector/proliferative; (5) proliferative; (6) stromal/proliferative; and (7) snoRNA, thereby classifying the kidney cancer in the patient. Any suitable reagents for assaying mRNA may be included in the kit, e.g., nucleic acids, enzymes, buffers, and the like.

In one example, provided herein is a kit for identifying a human patient suffering from an kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) who may benefit from treatment with an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab), wherein the kidney cancer is previously untreated, the kit comprising: (a) reagents for determining the presence of a somatic alteration in one or more of the following genes: *PBRM1, CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* in a tumor sample obtained from the patient; and (b) instructions for using the reagents to identify the patient as one who may benefit from a treatment with an anti-cancer therapy comprising a PD-1 axis binding antagonist and a VEGF antagonist. In some examples, (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1* indicates that the patient is likely to have an increased clinical benefit from treatment with an anti-cancer therapy comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and a VEGF antagonist (e.g., bevacizumab) compared to treatment with a tyrosine kinase inhibitor (e.g., sunitinib).

In another aspect, provided herein is an article of manufacture or a kit comprising a PD-1 axis binding antagonist (e.g., atezolizumab) and/or a VEGF antagonist (e.g., bevacizumab). In some instances, the article of manufacture or kit further comprises package insert comprising instructions for using the PD-1 axis binding antagonist to treat or delay progression of kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient, e.g., for a patient who has been classified according to any of the methods disclosed herein. In some instances, the article of manufacture or kit further comprises package insert comprising instructions for using the PD-1 axis binding antagonist in combination with a VEGF antagonist to treat or delay progression of kidney cancer (e.g., RCC, e.g., an inoperable, locally advanced, or metastatic RCC) in a patient. Any of the PD-1 axis binding antagonists,

VEGF antagonists, and/or any additional therapeutic agents described herein may be included in the article of manufacture or kits.

In some instances, the PD-1 axis binding antagonist, the VEGF antagonist, and/or any additional therapeutic agent are in the same container or separate containers. Suitable containers include, for example, bottles, vials, bags and syringes. The container may be formed from a variety of materials such as glass, plastic (such as polyvinyl chloride or polyolefin), or metal alloy (such as stainless steel or hastelloy). In some instances, the container holds the formulation and the label on, or associated with, the container may indicate directions for use. The article of manufacture or kit may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use. In some instances, the article of manufacture further includes one or more of another agent (e.g., an additional chemotherapeutic agent or anti-neoplastic agent). Suitable containers for the one or more agents include, for example, bottles, vials, bags, and syringes.

Any of the articles of manufacture or kits may include instructions to administer a PD-1 axis binding antagonist and/or a VEGF antagonist, or another anti-cancer therapy, to a patient in accordance with any of the methods described herein, e.g., any of the methods set forth in Section III above.

EXAMPLES

Example 1: Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade

This Example describes integrated multi-omics analyses that led to identification of robust molecular subtypes in 823 tumors from patients with advanced renal cell carcinoma (RCC), including 134 tumors with sarcomatoid features, from a randomized, global Phase III trial (IMmotion151). These molecular subgroups were associated with differential clinical outcomes of the combination of an anti-angiogenesis agent (i.e., bevacizumab, anti-VEGF) and a checkpoint inhibitor (CPI; i.e., atezolizumab, anti-PD-L1) versus a VEGF receptor tyrosine kinase inhibitor (TKI; i.e., sunitinib). The biological and clinical insights gained from this study inform biomarker strategies for personalized treatment and guide future therapeutic development in RCC and other cancers.

A. Study Design

IMmotion151 (NCT02420821) was a multicenter, open-label, Phase 3, randomized controlled trial of atezolizumab plus bevacizumab (n=454) versus sunitinib (n=461) in patients with previously untreated advanced RCC (Rini et al. *Lancet*. 393: 2404-2415 (2019)). The study design, methods, and primary clinical findings from IMmotion151 have been reported previously (Rini et al. *Lancet*. 393: 2404-2415 (2019)).

Briefly, previously untreated patients with unresectable locally advanced or metastatic renal cell carcinoma with any component of clear-cell or sarcomatoid histology were randomized to receive atezolizumab 1200 mg + bevacizumab 15 mg/kg (atezolizumab+bevacizumab) once every 3 weeks (n=454) or sunitinib 50 mg once daily (n=461; 4 weeks on, 2 weeks off). The co-primary endpoints were investigator-assessed progression-free survival (PFS) in patients with ≥ 1% expressing PD-L1 on immune

cells (IC, PD-L1+) and overall survival (OS) in the intent-to-treat (ITT) population. Patients with PD-L1+ tumors who received atezolizumab+bevacizumab showed improved PFS vs. sunitinib (Hazard ratio, HR 0.74, 95% CI: 0.57-0.96; p=0.0217, median PFS (mPFS) 11.2 vs 7.7 months; Rini et al. *Lancet*. 393: 2404-2415 (2019)).

In the present study, pre-treatment tumors from 823/915 (90%) patients were transcriptionally profiled by RNA-seq. This subset comprised of 198 metastatic and 625 primary tumors, all of which were collected no longer than 2 years prior to enrollment in this study. In this biomarker evaluable tumor collection, 688 tumors were of clear cell histology without a sarcomatoid component, 110 tumors were of clear cell histology with any sarcomatoid component, 1 tumor was of clear cell histology with unknown sarcomatoid component, and 24 tumors were of non-clear cell histology with any sarcomatoid component. Pre-treatment tumors from 715 patients were assessed for somatic mutations and alterations using the FOUNDATIONONE® assay (Foundation Medicine, MA). Overall, tumors from 702 patients were profiled both by RNA-seq and the FOUNDATIONONE® assay, representing the largest genomic biomarker dataset to date in a randomized trial in untreated advanced RCC. Validation of molecular classification was conducted in tumors collected from patients in the randomized Phase II trial, IMmotion150.

B. Materials and Methods

i. Patients

IMmotion151 (NCT02420821) was a multicenter, open-label, Phase 3, randomized controlled trial of atezolizumab plus bevacizumab (n=454) vs. sunitinib (n=461) in patients with previously untreated advanced renal cell carcinoma (Rini et al. *Lancet*. 393: 2404-2415 (2019)).

ii. PD-L1 Immunohistochemistry and Scoring

PD-L1 expression was assessed by immunohistochemistry using the SP142 assay (Ventana, AZ). Tumors were characterized as PD-L1+ if PD-L1 staining of any intensity on immune cells covered ≥1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma.

iii. RNA Processing

Formalin-fixed paraffin-embedded (FFPE) tissue was macro-dissected for tumor area using hematoxylin and eosin (H&E) staining as a guide. RNA was extracted using the High Pure FFPET RNA Isolation Kit (Roche) and assessed by QUBIT™ (Thermo Fisher Scientific) and Agilent Bioanalyzer for quantity and quality. First-strand cDNA synthesis was primed from total RNA using random primers, followed by the generation of second strand cDNA with dUTP in place of dTTP in the master mix to facilitate preservation of strand information. Libraries were enriched for the mRNA fraction by positive selection using a cocktail of biotinylated oligos corresponding to coding regions of the genome. Libraries were sequenced using the Illumina sequencing method.

iv. RNA-seq Data Generation and Processing

Whole-transcriptome profiles were generated using TruSeq RNA Access technology (Illumina). RNA-seq reads were first aligned to ribosomal RNA sequences to remove ribosomal reads. The remaining reads were aligned to the human reference genome (NCBI Build 38) using GSNAP (Wu and Nacu. *Bioinformatics*. 26(7): 873-881 (2010); Wu et al. *Methods Mol Biol*. 1418: 283-334 (2016)) version 2013-10-10, allowing a maximum of two mismatches per 75 base sequence (parameters: '-M 2 -n 10 -B 2 -i 1 -N 1 -w 200000 -E 1-pairmax-rna = 200000 –clip-overlap). To quantify gene expression levels, the number of reads mapped to the exons of each RefSeq gene was calculated using the functionality provided by the R/Bioconductor package GenomicAlignments. Raw counts were adjusted for gene length using transcript-per-million (TPM) normalization, and subsequently log2-transformed.

v. DNA Mutation and Copy-Number Profiling by FOUNDATIONONE® Assay

Comprehensive genomic profiling (CGP) was carried out using the FOUNDATIONONE® T7 assay (Foundation Medicine Inc., Cambridge, MA) in a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited laboratory. Hybrid capture was carried out for all coding exons from up to 395 cancer-related genes plus select introns from up to 31 genes frequently rearranged in cancer. All classes of genomic alterations (GA) were assessed, including short variant (missense, stop, nonstart, splice site point mutations as well as short indels), biallelic deletions, amplifications and rearrangement alterations, as previously described (Frampton et al. *Nat Biotechnol*. 31: 1023-1031 (2013)). Shallow copy-number loss (CN=1) was called using similar methodology to arm-level calling. Normalized coverage data for exonic, intronic, and SNP targets accounting for stromal admixture were plotted on a logarithmic scale and minor allele SNP frequencies were concordantly plotted. Custom circular binary segmentation further clustered targets and minor allele SNPs to define upper and lower bounds of genomic segments. Signal-to-noise ratios for each segment were used to determine whether the segment was gained or lost. The sum of those segment sizes determined the fraction of each segment gained or lost. For gene alteration analyses described herein, position-level information was leveraged to define per-gene alteration profiles, and every gene's mutational profile was dichotomized as altered (including copy-number loss or gain) or non-altered.

vi. Fusion Detection

Paired trimmed/clipped and de-duplicated RNA-seq reads were used to identify gene fusion events. Reads were aligned using STAR v2.7.2b with default parameters to the GRCh38 genome. This aligned output was used as input to STAR-Fusion v1.9.1 (Haas et al. *Genome Biol*. 20: 213 (2019)) using the developer-supplied gencode v33 CTAT library from April 6, 2020. Each fusion gene was required to be supported by at least two reads.

vii. T-effector and Angiogenesis Gene Signature Threshold Definition and Validation

RNA-seq data from the randomized Phase II trial IMmotion150 were processed as described above. Transcriptional signature scores were derived from T-effector and angiogenesis signatures

(McDermott et al. *Nat Med.* 24: 749-757 (2018)) for each sample, and hazard ratios were calculated at various gene expression scores. Gene expression score cutoffs of 2.93 (40% prevalence) and 5.82 (50% prevalence) were defined for the T-effector and angiogenesis signatures in IMmotion150 based on a combination of prevalence and hazard ratio plateauing. These absolute thresholds were prospectively applied to the IMmotion151 data to classify tumors with high and low T-effector and angiogenesis signatures. Cox-proportional hazard regression models were fit to compare PFS in atezolizumab+bevacizumab or sunitinib-treated patients in gene expression high and low subsets.

viii. Non-negative Matrix Factorization (NMF)

Using Median Absolute Deviation (MAD) analysis, 3072 genes (top 10%) were selected with the highest variability across patients. Subclasses were then computed by reducing the dimensionality of the expression data from thousands of genes to a few metagenes using consensus NMF clustering (CRAN. R package version 0.22.0, Brunet et al. *Proc Natl Acad Sci U S A.* 101: 4164-4169 (2004)). This method computes multiple k-factor factorization decompositions of the expression matrix and evaluates the stability of the solutions using a cophenetic coefficient. The most robust consensus NMF clustering of 823 patient samples using the 3072 most variable genes selected and testing k=2 to k=8 was identified as k=7.

ix. Validation of NMF Clustering in IMmotion150

To validate molecular subtypes derived in IMmotion151, the random forest machine learning algorithm (R package *randomForest*) was used to derive a classifier and then predict the NMF clusters in an independent data set (IMmotion150). A random forest classifier involves learning a large number of binary decision trees from random subsets of a training set. These trees in the classifier can then be used in a predication algorithm to identify the similarity of a given sample to a given class in the training set. Before learning the random forest classifier, the data was preprocessed to generate the training set. First, the gene expression matrix in the test and training set was limited to the top 10% most variable genes in IMmotion151 (n = 3,072), from which the initial NMF classification was derived. The gene expression values were normalized (z-score transformed) in each set to ensure that the test and training set were on the same scale. Finally, the random forest classifier was learned on the IMmotion151-derived trained data and then the classifier was utilized to predict the NMF classes in IMmotion150. Subsequently, the expression of gene expression signatures assessed in IMmotion151 was evaluated (**Fig. 1C**) in the NMF clusters identified in IMmotion150 (**Figs. 2A-2D**).

x. Quantitative Set Analysis for Gene Expression (QuSAGE)

To understand biological pathways underlying NMF clustering, QuSAGE analysis (R/Bionconductor qusage v2.18.0) was conducted to compare each cluster to all others, leveraging MSigDb hallmark gene sets to identify enriched pathways within each cluster. Enrichment scores were represented as a heatmap (**Fig. 1B**).

xi. Gene Signatures and Scores

Gene signatures were defined as follows: Angiogenesis: VEGFA, KDR, ESM1, PECAM1, ANGPTL4, CD34; T-effector: CD8A, EOMES, PRF1, IFNG, and CD274; Fatty Acid Oxidation /AMP-activated protein kinase (FAO/AMPK): CPT2, PPARA, CPT1A, PRKAA2, PDK2, PRKAB1; Cell cycle: CDK2, CDK4, CDK6, BUB1B, CCNE1, POLQ, AURKA, MKI67, CCNB2; Fatty Acid Synthesis (FAS)/Pentose Phosphate: FASN, PARP1, ACACA, G6PD, TKT, TALDO1, PGD; Stroma: FAP, FN1, COL5A1, COL5A2, POSTN, COL1A1, COL1A2, MMP2; Myeloid Inflammation: CXCL1, CXCL2, CXCL3, CXCL8, IL6, PTGS2; Complement Cascade: F2, C1S, C1R, CFB, C3; Omega Oxidation: CYP4F3, CYP8B1, NNMT, MGST1, MAOA, CYP4F11, CYP4F2, CYP4F12; snoRNA: SNORD38A, SNORD104, SNORD32A, SNORD68, SNORD66, SNORD100. Signature scores were calculated as the median z-score of genes included in each signature for each sample. When summarized by patient group, as in **Fig. 1D**, log2-transformed expression data were first aggregated by patient group using the mean, and subsequently converted to a group z-score.

xii. Quantification and Statistical Analysis

All analyses were conducted using Rv3.6.1. Unless otherwise stated, all comparisons for continuous variables use the two-sided Mann-Whitney test (R function wilcox.test) for two groups and the Kruskal-Wallis test (R function kruskal.test) for more than two groups. Dunn's post-hoc test was applied with Benjamini-Hochberg multiple testing correction for pairwise comparisons. For categorical variables, Pearson's Chi-squared test with continuity correction was used (R function chisq.test). Unless otherwise stated, false discovery rate (FDR)-adjusted p-values are reported. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. Survival analyses were conducted using Cox-proportional hazard models using the R survival package (v3.1.7). Log-rank p-values were reported for survival analyses including more than two groups. For all boxplots, the horizontal line represents the median. The lower and upper hinges correspond to the first and third quartiles. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge.

C. Results

i. Patient Cohorts, Biomarker Collection and Validation of Initial Biomarker Findings

The study design and primary clinical findings from IMmotion151 were reported previously (Rini et al. *Lancet*. 393: 2404-2415 (2019)). Here, integrated RNA-seq and targeted somatic variant analysis using pre-treatment tumor samples from this study are reported. Baseline tumors from 823/915 (90%) patients were available for biomarker evaluation (**Table 4**). This subset comprised 625 primary and 198 metastatic tumors, all of which were collected no longer than two years prior to enrollment in the study. Of these, 688 tumors were of clear cell histology without a sarcomatoid component, 110 tumors were of clear cell histology with any sarcomatoid component, 1 tumor was of clear cell histology with unknown sarcomatoid component, and 24 tumors were of non-clear cell histology with any sarcomatoid component. In these exploratory analyses, biomarker associations with objective response (OR) and progression free

survival (PFS) were evaluated, as these clinical outcomes capture the immediate effect of therapeutic intervention and are less affected than OS by subsequent treatments.

Table 4. Patient Characteristics

Variable	ITT n (%)	RNAseq BEP n (%)	RNAseq/FMI BEP n (%)	p-value
All Patients	915	823	702	N/A
Age				
Median age (years, range)	61 (18-88)	61 (18-88)	61 (18-84)	N/A
Sex				
Male	669 (73)	594 (72)	513 (73)	>0.05
Female	246 (27)	229 (28)	189 (27)	
Race				
White	660 (72)	596 (72)	516 (73)	>0.05
Black	5 (1)	5 (1)	4 (1)	
Asian	171 (19)	157 (19)	128 (18)	
Other	79 (8)	65 (8)	54 (8)	
Liver Metastasis				
Yes	169 (18)	154 (19)	131 (19)	>0.05
No	746 (82)	669 (81)	571 (81)	
MSKCC Risk Score				
Favorable	179 (19)	156 (19)	134 (19)	>0.05
Intermediate	629 (69)	573 (70)	498 (71)	
Poor	107 (12)	94 (11)	70 (10)	
IMDC Risk Score				
Favorable	202 (22)	176 (21)	151 (22)	>0.05
Intermediate	560 (61)	513 (62)	444 (63)	
Poor	153 (17)	134 (17)	107 (15)	
Sarcomatoid component				
Yes	142 (16)	134 (16)	120 (17)	>0.05
No	772 (84)	688 (84)	581 (83)	

ITT, intent to treat; BEP, biomarker evaluable population; N/A, not applicable; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Previous reports describe the associations between Angiogenesis and T-effector gene expression signatures and clinical outcome to treatment with atezolizumab+bevacizumab or sunitinib in the randomized Phase II trial IMmotion150 (McDermott et al. *Nat Med.* 24: 749-757 (2018)). The association of these signatures with clinical outcomes in IMmotion151 were evaluated by pre-determining transcriptional cutoffs for both signatures in IMmotion150 and retrospectively applying them in

IMmotion151 to define high and low expression patient subsets (**Fig. 3A**). Supporting observations in IMmotion150, high expression of the Angiogenesis signature was associated with improved PFS in the sunitinib treatment arm (HR=0.59, 95% CI 0.47, 0.75, **Fig. 3B**). When compared across treatment arms, no difference in PFS was observed in the Angiogenesis^{high} or T-effector^{low} tumors. Atezolizumab+bevacizumab improved PFS vs. sunitinib in T-effector^{high} (HR=0.76, 95% CI 0.59-0.99) and in Angiogenesis^{low} (HR=0.68, 95% CI 0.52-0.88) tumors (**Fig. 3C**). These findings underscore the relevance of immune and angiogenesis biology as reproducible biomarkers of differential clinical outcomes to checkpoint and angiogenesis blockade in independent advanced RCC cohorts.

ii. Identification and Characterization of Seven Molecular Subtypes of Clear Cell Renal Cell Carcinoma (ccRCC) Tumors

To expand the understanding of the biology of RCC, the large IMmotion151 RNA-seq data set was leveraged to further identify and refine transcriptionally-defined subgroups of patients in an unbiased manner by utilizing non-negative matrix factorization (NMF). NMF is an unsupervised clustering algorithm that iteratively selects the most robust clustering pattern within a given dataset (Brunet et al. *Proc Natl Acad Sci U S A.* 101: 4164-4169 (2004)). Here, NMF identified seven clusters of patients based on the top 10% (3074) most variable genes in the IMmotion151 cohort (**Figs. 1A and 4A**).

To understand the main biological features driving these clusters, the clusters were compared individually to all others using quantitative set analysis for gene expression (QuSAGE) (Yaari et al. *Nucleic Acids Res.* 41: e170 (2013)), leveraging hallmark gene sets from the Molecular Signatures Database (MSigDb) (Liberzon et al. *Cell Syst.* 1: 417-425 (2015)) combined with the previously described angiogenesis, T-effector, and myeloid inflammation signatures (McDermott et al. *Nat Med.* 24: 749-757 (2018)) (**Fig. 1B**). This analysis was complemented with differential gene expression (DGE) analysis, again contrasting each cluster to all others, and conducting pathway enrichment analysis using gene sets from the Reactome database (Fabregat et al. *Nucleic Acids Res.* 46: D649-D655 (2018)). To summarize these pathway-level analyses and further refine discriminatory transcriptomic profiles, simplified signatures were derived consisting of representative genes associated with cell cycle, stroma, the complement cascade, small nucleolar RNAs (snoRNAs), and metabolism-related pathways including fatty acid oxidation (FAO)/AMPK signaling, fatty acid synthesis (FAS)/pentose phosphate and biological oxidation pathways that complemented the initial T-effector, angiogenesis and myeloid inflammation signatures. These transcriptional programs were summarized across patient clusters both at the gene- (**Fig. 1C**) and signature-levels (**Figs. 1D and 4B**). In addition, xCell (Aran et al. *Genome Biol.* 18: 220 (2017)) was applied to infer relative frequency of immune and stromal cell types across the tumor transcriptomes (**Fig. 4C**).

Patient tumors in NMF-derived clusters 1 (n=98, 12%) and 2 (n=245, 30%) were primarily characterized as highly angiogenic, with enrichment of vascular and VEGF pathway-related genes (**Figs. 1B-1D**) as well as inferred endothelial cell presence (**Fig. 4C**). These clusters also exhibited high expression of TGF-β, WNT, hedgehog and NOTCH signaling modules (**Fig. 1B**). Cluster 1 differentiated from cluster 2 by higher stroma-specific expression (**Figs. 1C, 1D, and 4C**), exemplified by high degree of

fibroblast-derived gene expression (**Fig. 4C**), and elevated expression of collagens and activated stroma-associated genes (*FAP*, *FN1*, *POSTN*, *MMP2*). Cluster 2 additionally showed moderate T-effector gene signature expression, low cell cycle-associated genes, and higher expression of genes associated with catabolic metabolism, including those in fatty acid oxidation (*CPT2*, *PPARA*, *CPT1A*) and AMPK (*PRKAA2*, *PDK2*, *PRKAB1*) pathways. Thus, cluster 1 was labeled as Angiogenic/Stromal, and cluster 2 was labeled as Angiogenic.

Tumors in cluster 3 (n=156, 19%) were characterized by relatively lower expression of both angiogenesis and immune genes and moderate expression of cell cycle genes. These tumors showed elevated expression of genes associated with the complement cascade (*C3*, *C1S*, *C1R*), which has been associated with poor prognosis in the ccRCC TCGA cohort (Roumenina et al. *Nat Rev Cancer.* 19: 698-715 (2019)), as well as genes associated with the cytochrome P450 family, which is involved in omega oxidation. This cluster was labeled as the Complement/Ω-oxidation cluster.

Tumors in clusters 4 (n=116, 14%), 5 (n=74, 9%), and 6 (n=106, 13%) were characterized by enrichment of cell cycle transcriptional programs (G2M, E2F targets, MYC targets), and lower expression of angiogenesis-related genes. Mutual exclusion was observed between the angiogenesis signature enriched in clusters 1 and 2 and the cell cycle signature (including the cyclin-dependent kinases *CDK2*, *CDK4*, *CDK6*) enriched in clusters 4, 5 and 6 (**Figs. 1C and 1D**), which was confirmed by correlation analysis ($R = -0.50$, $p<0.001$; **Fig. 4E**). Clusters 4, 5, and 6 also exhibited an anabolic metabolism transcriptomic profile, with higher expression of genes associated with FAS (*FASN*, *PARP1*, *ACACA*) and the pentose phosphate pathway (*TKT*, *TALDO1*, *PGD*), which may be related to the proliferative nature of these tumors. Tumors in cluster 4 were additionally characterized as highly immunogenic, exhibiting strong enrichment in T-effector, JAK/STAT, and interferon-α and -γ gene expression modules (**Figs. 1B and 1C**). These tumors also showed the highest expression of PD-L1 by IHC (**Fig. 1E**) and highest infiltration of both adaptive and innate immune cell subsets, including $CD8^+$, $CD4^+$, and regulatory T cells, B cells, macrophages, and dendritic cells (**Fig. 4C**). In contrast, while tumors in clusters 5 and 6 showed enrichment of the myeloid gene signature and innate immune cell presence as inferred from xCell, they exhibited lower expression of T-effector gene signature and inferred T cell presence (**Fig. 4C**). The expression of FAS/Pentose phosphate pathway-associated genes was highest in cluster 5. Moreover, Cluster 5 included 15 tumors that contained *TFE*-fusions (12 tumors with *TFE3* fusions and 3 tumors with *TFEB* fusions, **Fig. 4F**), which have been implicated in mTORC1 signaling, upregulation of cyclin proteins, dysregulation of metabolic pathways, and increased tumor aggressiveness (Brady et al. *Elife.* 7 (2018); Kauffman et al. *Nat Rev Urol.* 11: 465-475 (2014)). Cluster 6 showed high expression of the epithelial-mesenchymal transition (EMT) transcriptional module and enrichment of collagen- and fibroblast-associated stromal genes. Cluster 4 was termed as T-effector/Proliferative, cluster 5 as Proliferative, and cluster 6 as Stromal/Proliferative.

Finally, cluster 7 (n=28, 3%) was characterized by enrichment of expression of snoRNA, especially, C/D box snoRNAs (SNORDs). SNORDs have been implicated in alterations of epigenetic and translation programs and have been linked to carcinogenesis (Gong et al. *Cell Rep.* 21: 1968-1981 (2017)). For example, SNORD66, which was upregulated in this cluster, has been reported to be

associated with lung cancer tumorigenesis (Braicu et al. *Cancers (Basel)*. 11 (2019)). The precise role of the overexpressed SNORDs in RCC tumors remains to be characterized. This small cluster was labeled as the snoRNA cluster.

Overall, molecular stratification of 823 RCC tumors identified seven groups of patients with biologically distinct transcriptomes. Given that the tumors in IMmotion151 included both primary and metastatic collections, the prevalence of each was evaluated across the seven NMF subsets. As shown in **Fig. 4D**, metastatic tumors were distributed across all clusters, suggesting that the transcriptional stratification scheme is not primarily driven by the primary or metastatic origin of tumors.

To validate these molecular subgroups in an independent cohort, a random forest classifier was trained from the RNA-seq data in IMmotion151 and was used to predict the NMF class of tumors from patients in the IMmotion150 randomized Phase II trial. The observed distribution of the NMF clusters and the transcriptional expression profile of these clusters in IMmotion150 were highly concordant with those in IMmotion151 (**Figs. 5A and 5B**), confirming the robustness of these molecular subtypes.

iii. RCC Molecular Subtypes Associate with Prognostic Risk Categories and Differential Clinical Outcomes to Atezolizumab+Bevacizumab and Sunitinib

The Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) models are frequently applied in advanced RCC for patient prognostication (Heng et al. *J Clin Oncol.* 27: 5794-5799 (2009); Motzer et al. *J Clin Oncol.* 17, 2530-2540 (1999)). These models utilize clinical and laboratory parameters to stratify patients into favorable, intermediate, and poor risk categories. However, the molecular features of tumors associated with these risk categories are incompletely understood. The distribution of the NMF molecular clusters across MSKCC and IMDC risk categories was evaluated, and enrichment of the Angiogenic/Stromal (#1) and Angiogenic (#2) clusters in the favorable risk groups in both classifications was observed. Conversely, the T-effector/Proliferative (#4), Proliferative (#5) and Stromal/Proliferative (#6) clusters were enriched in the poor risk groups (**Fig. 6A**).

Subsequently, clinical outcomes to atezolizumab+bevacizumab and sunitinib treatment in each cluster were evaluated. Patients in the Angiogenic/Stromal (#1) and Angiogenic (#2) clusters demonstrated longer PFS in both treatment arms, suggesting better outcome regardless of treatment, while those in the Stromal/Proliferative cluster (#5) had relatively shorter PFS (atezolizumab+bevacizumab mPFS: 6.8 months; sunitinib mPFS: 5.2 months), suggesting poor prognostic association of proliferative/stromal biology with clinical outcomes (**Fig. 6B**).

When evaluated across treatment arms, no apparent difference in clinical outcomes was observed between atezolizumab+bevacizumab and sunitinib arms in the Angiogenic/Stromal (#1), Angiogenic (#2) and Complement/Ω-oxidation (#3) clusters (**Figs. 6C and 6D**). Atezolizumab+bevacizumab demonstrated improved objective response rate (ORR, 52.0% vs 19.4%, p <0.001) and PFS (hazard ratio(HR) 0.52, 95% CI 0.33-0.82) vs. sunitinib (**Figs. 6C and 6D**) in the T-effector/Proliferative cluster (#4), confirming the contribution of pre-existing intratumoral adaptive immune presence in determining benefit to immunotherapy containing regimens. In addition,

atezolizumab+bevacizumab showed improved ORR (26.2% vs 3.1%, p <0.001, **Fig. 6C**) and PFS (HR 0.47, 95% CI 0.27-0.82, **Fig. 6D**) in the Proliferative cluster (#5), including in tumors that harbored *TFE*-fusions (**Fig. 4G**), implicating the relevance of PD-L1 blockade in this low angiogenesis, but high proliferative subgroup. Atezolizumab+bevacizumab also showed improved PFS (HR 0.1, 95% CI 0.01−0.77) in the snoRNA cluster (#7); however, the biological basis of this effect in this small cluster of patients remains to be elucidated.

Subsequently, the HRs obtained above using cox proportional hazard model that only tests treatment arm in each NMF subgroup were compared against a model that included treatment arm, PD-L1 IHC, and MSKCC clinical risk score. These multivariate analyses confirmed that the differential clinical benefit observed in these NMF clusters is independent of PD-L1 expression and MSKCC prognostic risk (**Table 5**).

Table 5. Univariate vs. Multivariate PFS Hazard Ratios (HR) Comparing Atezolizumab+Bevacizumab vs. Sunitinib in NMF Clusters

	Univariate Treatment arm		**Multivariate Treatment arm + PD-L1 + MSKCC**	
	PFS HR	**p-value**	**PFS HR**	**p-value**
Stromal/Angiogenic (Cluster 1)	1.110	0.708	1.174	0.562
Angiogenic (Cluster 2)	1.160	0.397	1.092	0.613
Complement/Ω-oxidation (Cluster 3)	0.920	0.666	0.894	0.558
T-effector/Proliferative (Cluster 4)	0.520	0.005	0.515	0.005
Proliferative (Cluster 5)	0.470	0.007	0.467	0.007
Stromal/Proliferative (Cluster 6)	0.810	0.331	0.847	0.457
snoRNA (Cluster 7)	0.100	0.028	0.088	0.025

Finally, differentially expressed genes between responders (complete or partial objective response, CR/PR) and non-responders (progressive disease, PD) within and across treatment arms were additionally evaluated. In sunitinib-treated patients, linear modeling complemented with MSigDb hallmark gene set enrichment analysis revealed higher expression of genes associated with VEGF pathway in tumors from responders and higher expression of cell cycle-associated pathways in tumors from non-responders (**Figs. 2A and 2B**). Comparison of gene expression in responders with non-responders treated with atezolizumab+bevacizumab did not identify any significantly differentially expressed genes (FDR < 0.05). Within responders across treatment arms, genes associated with proliferation and immune pathways were enriched in patients responding to atezolizumab+bevacizumab, while genes associated with VEGF signaling (hypoxia) were enriched in patients responding to sunitinib (**Figs. 2C and 2D**). No differentially expressed genes (FDR<0.05) were observed in non-responders treated with atezolizumab+bevacizumab vs. sunitinib. These data confirm and support the findings from the unbiased NMF classification.

iv. Somatic Alterations Associate with Tumor Intrinsic and Extrinsic Transcriptional Profiles

Transcriptional profiling was complemented with evaluation of somatic alterations in tumors from 715 patients. The pattern and prevalence of somatic alterations in this cohort were broadly in alignment with prior reports of recurrent gene alterations in RCC tumors (**Figs. 7A and 8A**) (Cancer Genome Atlas Research. *Nature*. 499: 43-49 (2013); Chen et al. *Cell Rep*. 14: 2476-2489 (2016); Ricketts et al. *Cell Rep*. 23: 3698 (2018)).

Previous studies have reported differences in genomic alteration profiles between primary and metastatic tumors, including enrichment of loss of chromosome 9p21.3 in metastatic lesions compared to primary tumors (Turajlic et al. *Cell*. 173: 581-594, e512 (2018)). In the IMmotion151 cohort, while no genes were exclusively expressed in metastatic tumors, the frequency of genomic alterations in 12 genes, including *CDKN2A/B* (23.8% vs 14.6%, p=0.011), *BRCA2* (15.7% vs 9.2%, p=0.034), *ZNF216* (12.2% vs 6.3%, p=0.025) and *NF2* (10.9% vs 5.6%, p=0.036) was increased in metastatic tumors compared to primary tumors (**Table 6**).

Table 6. Genomic Alterations in Primary vs. Metastatic Tumors

Gene	Primary non-altered (n)	Primary altered (n)	Primary %	Metastasis non-altered (n)	Metastasis altered (n)	Metastasis %	chi-square statistic	chi-square p-value
CDKN2A/B	474	81	14.59	112	35	23.81	6.5	0.011
EGFR	544	11	1.98	138	9	6.12	5.78	0.016
NTRK2	548	7	1.26	140	7	4.76	5.61	0.018
TIPARP	553	2	0.36	143	4	2.72	5.11	0.024
ZNF217	520	35	6.31	129	18	12.24	5.05	0.025
STAT4	551	4	0.72	142	5	3.40	4.65	0.031
MAP2K4	551	4	0.72	142	5	3.40	4.65	0.031
MEN1	549	6	1.08	141	6	4.08	4.57	0.033
BRCA2	504	51	9.19	124	23	15.65	4.48	0.034
NF2	524	31	5.59	131	16	10.88	4.41	0.036
ZNRF3	542	13	2.34	138	9	6.12	4.3	0.038
ERCC4	544	11	1.98	139	8	5.44	4.05	0.044

Alterations that showed statistically different prevalence (Chi square test, p<0.05) are shown.

Co-occurrence analysis showed >50% overlap of *SETD2*, *KDM5C,* or *PTEN* alterations with *PBRM1* mutations (**Fig. 8B**). Conversely, mutations in *PBRM1*, *BAP1*, and *CDKN2A/B* were largely non-overlapping (<25% overlap, hypergeometric p=9.5e-09, **Figs. 8B-8D**), supporting models of distinct tumor lineages associated with *PBRM1* vs. *BAP1* mutations (Kapur et al. *Lancet Oncol.* 14: 159-167 (2013); Pena-Llopis et al. *Nat Genet*. 44: 751-759 (2012)) and further suggesting evolutionary distinctions

between tumors harboring 3p associated aberrations only versus those that also have 9p arm level or focal copy number alterations (Turajlic et al. *Cell.* 173, 595-610, e511 (2018)). Additionally, *CDKN2A/B* alterations were non-overlapping with *TP53* mutations (<20% overlap, **Figs. 8B and 8C**).

The prevalence of the top altered genes in each NMF cluster was further characterized, and the observations showed lower prevalence of *PBRM1* mutations ($p<0.001$) and enrichment of *CDKN2A/B* alterations ($p<0.001$) in the T-effector/Proliferative (#4), Proliferative (#5) and Stromal/Proliferative (#6) clusters (**Fig. 7B**). The prevalence of *TP53* mutations was highest in the Proliferative (#5) and Stromal/Proliferative (#6) clusters ($p<0.001$) and that of *BAP1* mutations was highest in the T-effector/Proliferative cluster (#4) ($p<0.01$) (**Fig. 7B**). When analyzing cluster distribution by mutation status, the Angiogenic cluster (#2) was enriched in *PBRM1* and *KDM5C* mutants, while the Proliferative (#5) and Stromal/Proliferative (#6) clusters were enriched in *CDKN2A/B* mutants (**Fig. 7C**).

Subsequently, evaluations were conducted on the association of somatic alterations present in at least 10% of the tumors with transcriptomic signatures discussed above (**Fig. 7D**). Compared to non-mutants, tumors with mutations in *PBRM1* or *KDM5C* exhibited higher expression of angiogenesis (*PBRM1* p=3.46e-20; *KDM5C* p=0.001) and FAO/AMPK (*PBRM1* p=4.59e-17; *KDM5C* p=3.79e-05) associated gene signatures, and reduced expression of the cell cycle gene signature (*PBRM1* p=7.74e-12; *KDM5C* p=1.09e-04). In contrast, tumors harboring *TP53*, *CDKN2A/B*, and *PTEN* alterations showed upregulation of cell cycle (*TP53* p=1.22e-13; *CDKN2A/B* p=5.00e-18; *PTEN* p=3.71e-04), FAS/pentose phosphate pathway (*TP53* p=2.52e-09; *CDKN2A/B* p=1.97e-14), and stromal gene expression (*TP53* p=4.69e-04; *CDKN2A/B* p=8.35e-06; *PTEN* p=2.46e-07). *KMT2C* mutations also showed higher expression of cell cycle genes (p=0.022). *PTEN* alterations were associated with higher myeloid inflammation (p=0.03). *BAP1* mutations showed elevated expression of cell cycle (p=0.0028) and T-effector (p=8.64e-04) gene signatures, the latter supporting previously described association of *BAP1* mutations with IFN-γ signaling (Clark et al. *Cell.* 179: 964-983, e931 (2019); Wang et al. *Cancer Discov.* 8: 1142-1155 (2018)).

Overall, somatic alteration profiles suggest a genetic basis for the distinct transcriptomic profiles in advanced RCC. Functional depletion of *PBRM1* and/or *KDM5C* associate with a subtype typified by angiogenic features, whereas functional depletions of tumor suppressor genes including *CDKN2A/B* and *TP53*, associate with high proliferation, anabolic metabolism, and stromal biology (**Fig. 7D**).

v. Associations Between Somatic Alterations and Clinical Outcome

Evaluation of clinical outcomes in somatic alteration subgroups showed that *PBRM1* mutations conferred overall better prognosis, regardless of treatment arm (**Figs. 8E, 9A, and 9C**). Sunitinib-treated patients whose tumors harbored *PBRM1* mutations showed longer PFS compared to those with non-mutant *PBRM1* (HR = 0.67; 95% CI: 0.51, 0.87; mPFS: 11.2 months vs. 6.9 months). This trend of longer PFS in *PBRM1* mutant tumors was also observed in atezolizumab+bevacizumab-treated patients, but did not reach statistical significance. When compared across treatment arms, there was no difference in PFS or ORR in *PBRM1* mutated tumors. In patients with *PBRM1* non-mutant tumors, atezolizumab+bevacizumab improved PFS (HR = 0.74; 95% CI: 0.58-0.94; mPFS

atezolizumab+bevacizumab: 9.9 months; mPFS sunitinib: 6.9 months) (**Figs. 8E and 9A**) and ORR (40% vs. 27%, p=0.036) (**Fig. 9B**) vs. sunitinib.

Conversely, *CDKN2A/B* alterations conferred worse prognosis when compared to non-altered tumors (**Figs. 9A and 9C**). When compared across treatment arms, patients whose tumors had *CDKN2A/B* alterations showed longer PFS (HR = 0.63; 95% CI: 0.41-0.96, mPFS: 8.3 months vs. 4.1 months) (**Fig. 9A**) and higher ORR (42% vs. 20%, p=0.045) (**Fig. 9B**), including complete responses (11% vs. 0%) when treated with atezolizumab+bevacizumab vs. sunitinib. Patients with *TP53* mutant tumors, which were largely non-overlapping with *CDKN2A/B* altered tumors (**Figs. 10C and 10D**), also showed a statistically non-significant trend toward improved clinical benefit with atezolizumab+bevacizumab vs. sunitinib (**Figs. 9A and 9B**).

Finally, this analysis revealed that patients with tumors harboring loss-of-function mutations in *ARID1A* and/or *KMT2C* had significantly better PFS when treated with atezolizumab+bevacizumab vs. sunitinib (*ARID1A* HR = 0.50; 95% CI: 0.26-0.96; mPFS: 20.7 vs. 6.8 months; *KMT2C* HR = 0.47; 95% CI: 0.27-0.83; mPFS: 13.8 months vs. 7.0 months) (**Figs. 8E, 9A, and 9B**).

Overall, five genes were identified with frequent loss-of-function alterations that associate with distinct clinical outcomes to atezolizumab+bevacizumab vs. sunitinib, suggesting that targeted somatic mutation profiling in advanced RCC could help guide treatment selection.

vi. Molecular Characterization of Sarcomatoid RCC Tumors

RCC tumors that include a sarcomatoid component (sRCC) associate with poor prognosis and show limited response to standard-of-care treatment with VEGF pathway inhibitors (Golshayan et al. *J Clin Oncol.* 27: 235-241 (2009)). Therefore, the molecular characteristics of sRCC tumors that distinguish it from non-sarcomatoid RCC (non-sRCC) tumors were subsequently examined.

DGE analysis (FDR<0.05) identified 2917 overexpressed and 6309 under expressed genes in sRCC compared to non-sRCC tumors (**Fig. 11A**). Gene set enrichment analysis demonstrated enrichment of transcriptional pathways involved in cell cycle/proliferation (E2F targets, G2M checkpoints, MYC targets, EMT and immune response (Allograft rejection, Interferon gamma response, Inflammatory response) and lower expression of genes involved in the VEGF pathway (Angiogenesis, Hypoxia) (**Fig. 11B**) in sRCC. The distribution of sRCC and non-sRCC tumors in the transcriptomic NMF clusters were further compared, and it was observed that sRCC tumors were enriched in the T-effector/Proliferative (#4), Proliferative (#5) and Stromal/Proliferative (#6) clusters, and were less prevalent in the Angiogenic/Stromal (#1) and Angiogenic (#2) clusters (**Fig. 11C**). Moreover, evaluation of gene expression signatures confirmed lower expression of angiogenesis and FAO/AMPK signatures and higher expression of cell cycle, stromal, T-effector, and myeloid signatures in sRCC tumors compared to non-sRCC tumors (**Fig. 11D**).

PD-L1 protein prevalence was significantly higher in sRCC vs. non-sRCC (63% vs 39%, p<0.001, **Fig. 11E**), confirming the increased presence of IFN-γ response observed by gene expression analysis, and reflective of adaptive upregulation of PD-L1 by IFN-γ in sRCC.

Somatic alteration analysis revealed lower prevalence of *PBRM1* (29% vs 50%, p=3.33e-05)

mutations in sRCC, which suggests a genomic basis for the observed lower angiogenesis gene expression in these tumors. Conversely, the prevalence of *CDKN2A/B* (26% vs 15%, p=0.004), and *PTEN* (20% vs 11%, p=0.009) alterations was significantly higher in sRCC, suggesting that somatic loss-of-function in these genes may contribute to the aggressive phenotype of sarcomatoid tumors (**Fig. 11F**).

Given the differences in etiology between ccRCC and non-ccRCC, molecular features between ccRCC non-sarcomatoid (ccRCC-NonSarc), ccRCC-Sarc, and non-ccRCC-Sarc tumors were compared. ccRCC-Sarc tumors showed enrichment of pathways associated with cell cycle/proliferation and immune response, and lower expression of genes associated with angiogenesis and hypoxia compared to ccRCC-NonSarc tumors (**Figs. 10A and 10B**). This is noteworthy, as it confirms that the downregulation of angiogenesis pathways in the overall sarcomatoid subset (sRCC) is independent of non-ccRCC-Sarc tumors.

DGE analysis (FDR<0.05) comparing the two subsets of sarcomatoid tumors (ccRCC-Sarc vs. non-ccRCC-Sarc) (**Figs. 10C and 10D**) showed upregulation of VEGF pathway-associated genes (hypoxia) in ccRCC-Sarc tumors and higher expression of cell cycle/proliferation pathways (G2M, E2F targets, EMT, MYC targets) in non-ccRCC-Sarc tumors. Compared with ccRCC-NonSarc tumors, PD-L1 expression was enriched in both ccRCC-Sarc and non-ccRCC-Sarc tumors (**Fig. 10E**).

Comparison of the distribution of NMF clusters in the histological subtypes showed that ccRCC-Sarc tumors were enriched in T-effector/Proliferative (#4) and Stromal/Proliferative (#5) clusters, and non-ccRCC-Sarc tumors were enriched in Proliferative (#5) and Stromal/Proliferative (#6) clusters (**Fig. 10F**).

Evaluation of somatic alterations across the three histological subtypes (**Table 7**) confirmed higher prevalence of *VHL* mutations in ccRCC subtypes reported in previous studies. The prevalence of *PBRM1* mutations was lower and that of *CDKN2A/2B* and *PTEN* alterations was higher in ccRCC-Sarc and non-ccRCC-Sarc tumors compared to ccRCC-NonSarc tumors. Prevalence of *BAP1* mutations was highest in ccRCC-Sarc, whereas non-ccRCC-Sarc showed enrichment in *TP53* and *RB1* alterations.

Table 7. Genomic Alterations in Sarcomatoid Subsets

	ccRCC-NonSarc			ccRCC-Sarc			Non-ccRCC-Sarc			p-value	p-value	
Gene	Non-altered (n)	Altered (n)	% Altered	Non-altered (n)	Altered (n)	% Altered	Non-altered (n)	Altered (n)	% Altered	ccRCC_nonSarc vs. ccRCC_Sarc	ccRCC_Sarc vs. non-ccRCC_Sarc	all p-value
VHL	124	457	78.7%	29	70	70.7%	18	3	14.3%	1.05E-01	4.99E-06	6.11E-11
PBRM1	288	293	50.4%	65	34	34.3%	20	1	4.8%	4.34E-03	1.45E-02	5.70E-06
BAP1	461	120	20.7%	58	41	41.4%	20	1	4.8%	1.28E-05	3.21E-03	4.51E-06
CDKN2A/2B	496	85	14.6%	73	26	26.3%	16	5	23.8%	6.00E-03	1.00E+00	1.05E-02
TP53	500	81	13.9%	84	15	15.2%	10	11	52.4%	8.70E-01	5.21E-04	9.38E-06
FAT3	517	64	11.0%	87	12	12.1%	15	6	28.6%	8.81E-01	1.14E-01	4.81E-02
PTEN	518	63	10.8%	80	19	19.2%	16	5	23.8%	2.85E-02	8.57E-01	1.82E-02
SPTA1	529	52	9.0%	82	17	17.2%	17	4	19.0%	2.01E-02	1.00E+00	1.97E-02
TERT	533	48	8.3%	87	12	12.1%	15	6	28.6%	2.89E-01	1.14E-01	4.53E-03
MAP3K1	539	42	7.2%	85	14	14.1%	17	4	19.0%	3.44E-02	8.14E-01	1.65E-02
RANBP2	549	32	5.5%	93	6	6.1%	17	4	19.0%	1.00E+00	1.28E-01	3.69E-02

TRRAP	549	32	5.5%	98	1	1.0%	18	3	14.3%	9.45E-02	1.60E-02	2.69E-02
NF2	550	31	5.3%	86	13	13.1%	19	2	9.5%	7.07E-03	9.28E-01	1.29E-02
ASXL1	558	23	4.0%	92	7	7.1%	18	3	14.3%	2.59E-01	5.14E-01	4.39E-02
SH2B3	563	18	3.1%	97	2	2.0%	18	3	14.3%	7.91E-01	5.07E-02	1.38E-02
FANCF	564	17	2.9%	89	10	10.1%	21	0	0.0%	1.93E-03	2.77E-01	1.81E-03
RPTOR	566	15	2.6%	97	2	2.0%	17	4	19.0%	1.00E+00	6.92E-03	6.49E-05
CDH20	567	14	2.4%	98	1	1.0%	18	3	14.3%	6.13E-01	1.60E-02	1.89E-03
RB1	574	7	1.2%	98	1	1.0%	15	6	28.6%	1.00E+00	1.17E-05	1.08E-17
CDH2	574	7	1.2%	97	2	2.0%	18	3	14.3%	8.57E-01	5.07E-02	3.24E-05

ccRCC-NonSarc = clear cell RCC, non-sarcomatoid tumors; ccRCC-Sarc = clear cell RCC, sarcomatoid tumors; Non-ccRCC-Sarc = non-clear cell RCC, sarcomatoid tumors. Genes with at least 10% alterations in either of the three subsets are included in this table.

Overall, these analyses show that sRCC tumors exhibit a highly proliferative molecular phenotype, characterized by relatively low angiogenesis, and accompanied with high immune presence and PD-L1 expression, which may explain the increased sensitivity of sarcomatoid tumors to therapeutic intervention with atezolizumab+bevacizumab vs. sunitinib (**Figs. 11G and 11H**; Rini et al. *Lancet.* 393: 2404-2415 (2019)).

vii. Discussion

This Example presents comprehensive molecular analyses of 823 tumors from advanced RCC patients treated with atezolizumab+bevacizumab or sunitinib, representing the largest set of integrated multi-omics characterization of advanced RCC in a randomized global Phase III clinical trial. The findings provide important new insights into key biological pathways underlying RCC progression, validate for the first time the prognostic and predictive capability of transcriptional signatures identified in a Phase II cohort in a randomized Phase III trial, describe distinct molecular subtypes that associate with differential overall outcome to antiangiogenics alone or combined with checkpoint blockade, and identify additional targets for future therapeutic development.

The unsupervised transcriptomic analysis identified seven robust tumor subsets (summarized in **Fig. 12**). This subtyping scheme corroborates and significantly expands on recent reports on gene expression-based subgrouping in smaller RCC data sets (Beuselinck et al. *Clin Cancer Res.* 21, 1329-1339, 2015; Brannon et al. *Genes Cancer.* 1, 152-163, 2010; Clark et al. *Cell.* 179, 964-983 e931, 2019; Hakimi et al. *Cancer Discov.* 9, 510-525, 2019). The substantially larger number of samples in the present data set resulted in increased resolution and detection of additional transcriptomic features associated with these subsets, such as differential metabolic profiles. Importantly, the clustering scheme was validated using an independent transcriptomic data set from IMmotion150 (McDermott et al. *Nat Med.* 24, 749-757, 2018), which also enrolled patients with untreated advanced RCC. Overall, the concordance of molecular subtypes across these different studies strengthens the case for a unified molecular classification in advanced RCC and its utility in understanding differential prognosis and sensitivity to therapeutics, including antiangiogenics, CPIs, and their combinations, which are now standards of care in untreated advanced RCC.

Indeed, RCC molecular subgroups could be reproducibly associated with differential clinical

responses to anti-angiogenics and a CPI. Patients in angiogenesis enriched clusters 1 and 2 demonstrated superior prognosis in both atezolizumab+bevacizumab and sunitinib-treated patients, with no significant difference in PFS between the two treatment arms, likely as a result of both treatment arms containing an angiogenesis inhibitor. In contrast, sunitinib showed worse clinical outcomes in the angiogenesis poor, but immune rich, and cell cycle enriched clusters 4 and 5, and atezolizumab+bevacizumab significantly improved ORR and PFS vs sunitinib in these subsets, consistent with the inclusion of an immunotherapeutic in the combination regimen.

The dual CPI combination of nivolumab plus ipilimumab showed improved OS and ORR in patients with intermediate and poor prognostic risk as assessed by the IMDC score, whereas patients with favorable risk showed numerically superior results for OS, PFS, and ORR with sunitinib (Motzer et al. *N Engl J Med.* 378, 1277-1290, 2018). In contrast, combined VEGF and checkpoint inhibition by atezolizumab+bevacizumab, avelumab+axitinib, and pembrolizumab+axitinib (Motzer et al. *N Engl J Med.* 378, 1277-1290 (2019); Rini et al. *N Engl J Med.* 380, 1116-1127 (2019); Rini et al. *Lancet.* 393, 2404-2415 (2019)) showed PFS benefit across clinical risk groups, including in patients with favorable prognostic risk. In this study, tumors from favorable risk patients were enriched in the Angiogenic/Stromal (#1) and the Angiogenic (#2) clusters, which exhibited higher expression of genes associated with the VEGF pathway. These findings provide a molecular explanation for improved clinical outcomes to combined CPI+VEGF inhibition vs. CPI only therapy across clinical risk categories and support treatment of favorable risk patients with therapeutic regimens that include VEGF pathway inhibitors. Moving forward, treatment of patients based on transcriptomic profiling of tumors, and independent of IMDC risk categorization, if prospectively validated, could allow for a more personalized, biology-based approach to treatment selection.

Integration of gene expression profiles with somatic alterations provided further insights into the molecular underpinnings of the transcriptomic subgroups. *PBRM1* mutant tumors associated with higher expression of the angiogenesis gene signature, and in agreement with previous clinical findings (Carlo et al. *Kidney Cancer.* 1, 49-56, 2017; Hakimi et al. *Cancer Discov.* 9, 510-525, 2019; McDermott et al. *Nat Med.* 24, 749-757, 2018; Voss et al. *Lancet Oncol.* 19, 1688-1698, 2018), showed improved clinical outcomes to sunitinib vs. *PBRM1* non-mutants. Recent preclinical studies have shown that *PBRM1* loss in VHL deficient cell lines and mouse models induced amplification of HIF-1A/HIF-2A mediated hypoxia response (Gao et al. *Proc Natl Acad Sci U S A.* 114: 1027-1032 (2017); Nargund et al. *Cell Rep.* 18: 2893-2906 (2017)). Thus, evaluation of clinical activity of novel agents targeting hypoxia and angiogenesis, such as HIF-2A inhibitors (Jonasch et al. *Ann Oncol.* 30(suppl_5): v356-v402 (2019)), is especially warranted in *PBRM1* mutant tumors.

Tumors harboring *CDKN2A/2B* alterations were more prevalent in T-effector/Proliferative (#4), Proliferative (#5), and Stromal/Proliferative (#6) clusters; and *TP53* mutations were more prevalent in Proliferative (#5), and Stromal/Proliferative (#6) clusters. Atezolizumab+bevacizumab improved clinical outcomes vs. sunitinib in these highly proliferative and aggressive tumors. Importantly, patients whose tumors harbored *CDKN2A/B* loss and/or *TP53* mutations showed overall worse prognosis and may additionally benefit from therapeutic approaches that target these specific aberrations, such as stromal

disruptors, cytotoxic agents, or CDK4/6 inhibitors. Preclinical studies have demonstrated immunomodulatory effects of CDK4/6 inhibition in tumor models, such as increase in antigen presentation by tumor cells, upregulation of PD-L1 expression, reduction in intratumoral regulatory T cells, and activation of $CD8^+$ T cells, as well as enhancement of anti-tumor efficacy in combination with PD-L1 blockade (Deng et al. *Cancer Discov.* 8: 216-233 (2018); Goel et al. *Nature.* 548: 471-475 (2017); Schaer et al. *Cell Rep.* 22: 2978-2994 (2018)). Collectively, these data support clinical investigation of CDK4/6 inhibitors in combination with CPI in RCC.

Intriguingly, loss-of-function mutations in *ARID1A* and *KMT2C* associated with improved PFS in atezolizumab+bevacizumab vs. sunitinib-treated patients, in the absence of clear associations with transcriptional signatures. Alterations in *ARID1A*, a component of the chromatin remodeling SWI/SNF complex, and *KMT2C*, a histone methyl transferase, have been implicated in epigenetic dysregulation and DNA damage repair deficiency (Rampias et al. *EMBO Rep.* 20(3): e46821 (2019); Shen et al. *Nat Med.* 24: 556-562 (2018)). While the mechanistic basis for the differential clinical outcome in patients with either mutation remains to be elucidated in RCC, these observations support combining epigenetic regulators with CPI in subsets of patients with RCC.

Sarcomatoid dedifferentiation in RCC has been historically associated with poor outcomes to VEGF inhibition (Golshayan et al. *J Clin Oncol.* 27: 235-241 (2009)). In contrast, atezolizumab+bevacizumab, as well as other CPI-based therapies, have demonstrated substantial efficacy, including complete responses, in patients whose tumors include a sarcomatoid component (Choueiri et al. *Ann Oncol.* 30(Supp. 5): v361 (2019); McDermott et al. *J Clin Oncol.* 37(15_suppl): 4513 (2019); Rini et al. *J Clin Oncol.* 37(15_suppl): 4500 (2019); Rini et al. *Lancet.* 393: 2404-2415 (2019)). The distinct genomic features of sarcomatoid tumors identified in this study suggest a molecular basis for the aggressive phenotype of sarcomatoid tumors, and provide a biological rationale for prioritizing checkpoint blockade-based therapy in patients with sarcomatoid RCC.

Overall, findings from this randomized Phase III study expand our understanding of RCC biology and provide a molecular basis for differential clinical outcomes and resistance mechanisms associated with angiogenesis blockade, checkpoint inhibition and their combinations in patients with untreated advanced RCC. Given that these combinations are under clinical evaluation and have shown promising activity in additional indications, such as hepatocellular carcinoma, non-small cell lung cancer, and endometrial cancer, the findings from this study may be applicable in interpreting clinical outcomes and developing personalized therapies across many cancers.

Example 2: Evaluation of IMmotion151 Molecular Subtypes in JAVELIN 101 Data Set

This Example describes a study that validated the IMmotion151 molecular subtypes identified in Example 1 using an independent data set obtained from the JAVELIN 101 study. Briefly, the IMmotion151 gene set was used as a training set to develop a transcriptional classifier model. The model was then applied to predict NMF clusters in the JAVELIN 101 data set (n=724). Comparisons of the transcriptional signatures from the IMmotion151 and JAVELIN 101 data sets indicated that the biological pathways and distribution of the NMF subtypes among patients was similar. In addition, NMF subtypes

were associated with similar prognostic and predictive clinical effects in the IMmotion151 and JAVELIN 101 data. In summary, these findings demonstrate the identification and reproducibility of the first transcriptomic classifier in advanced RCC across multiple data sets.

A. Study Design

JAVELIN 101 (NCT02684006) was a multicenter, randomized, open-label, Phase 3 trial comparing avelumab in combination with axitinib versus sunitinib monotherapy in the first-line treatment of patients with advanced RCC. The study design, methods, and primary clinical findings from JAVELIN 101 have been reported previously (Motzer et al. *N Engl J Med.* 380: 1103-1115 (2019)).

Key inclusion criteria of patients for entry into the JAVELIN 101 study:

- Previously untreated advanced RCC with a clear cell component
- At least one measurable lesion as defined by RECIST, version 1.1
- Tumor tissue available for PD-L1 staining
- Eastern Cooperative Oncology Group performance-status score (ECOG PS) of 0 or 1

Randomization in a 1:1 ratio was stratified according to ECOG PS (0 vs. 1) and geographic region (United States vs. Canada and Western Europe vs. rest of the world).

Patients were randomly assigned in a 1:1 ratio to receive avelumab (10 mg per kg of body weight) intravenously every 2 weeks plus axitinib (5 mg) orally twice daily or sunitinib (50 mg) orally once daily for 4 weeks of a 6-week cycle (4 weeks on, 2 weeks off). The two independent primary efficacy endpoints were PFS and OS among patients with PD-L1-positive tumors (≥1% of immune cells staining positive within the tumor area of the tested tissue sample). A key secondary efficacy endpoint was PFS in the overall population; other endpoints included objective response rate and tumor-tissue biomarkers.

B. Materials and Methods

Method details are described in the *Validation of NMF Clustering in IMmotion150* section in Example 1. Similar to Example 1, a classifier was developed using the random forest machine learning algorithm (R package *randomForest*). The random forest classifier was learned on the IMmotion151-derived training gene set and then the classifier was used to predict the NMF classes in the JAVELIN data set. Each gene was normalized by z-score, and downsampling was also performed.

C. Results

i. Similar Biological Pathways and Distribution of NMF Subtypes in IMmotion151 and JAVELIN 101 Data Sets

To validate the IMmotion151 molecular subtypes identified in Example 1, gene expression data from patient tumors (n=724) was obtained and a random forest model trained on the IMmotion151 data set was applied to predict the NMF subtypes in the JAVELIN 101 samples. A comparison of the IMmotion151 and JAVELIN 101 transcriptional signatures indicated that the biological pathways of the NMF clusters was similar between the two studies (Fig. 13A). Also similar between the IMmotion151 and JAVELIN 101 studies was the distribution of the NMF clusters among patients (Fig. 13B). These results

indicate that this transcriptomic classifier for advanced RCC molecular biology is highly reproducible across multiple, independent data sets.

ii. NMF Subtypes are Associated with Similar Prognostic and Predictive Clinical Outcomes in IMmotion151 and JAVELIN 101 Data Sets

To characterize the clinical outcomes in the IMmotion151 and JAVELIN 101 studies by NMF molecular subtypes, the PFS of the treatment groups was compared for each NMF cluster. The NMF clusters were associated with similar clinical outcomes in the IMmotion151 and JAVELIN 101 data sets (**Figs. 14A and 14B**). For the T-effector/Proliferative cluster (#4) in both the IMmotion151 and JAVELIN 101 data sets, the clinical benefit was significantly enriched in atezolizumab+bevacizumab versus sunitib and avelumab+axinitinib versus sunitinib, respectively. In contrast, for the Stromal/Proliferative cluster (#6), the clinical outcome was the lowest (as measured by lowest PFS) to atezolizumab+bevacizumab versus sunitinib and avelumab+axitinib versus sunitinib for IMmotion151 and JAVELIN 101, respectively. Angiogenesis-enriched subtypes (clusters #1 and 2) exhibited similar PFS outcomes to atezolizumab+bevacizumab, sunitinib, and avelumab+axitinib. Immune and/or proliferative subtypes (clusters #4, 5, and 6) show improved outcomes to atezolizumab+bevacizumab versus sunitinib and avelumab+axitinib versus sunitinib.

In summary, this analysis of the JAVELIN 101 data set provides confirmation of the prevalence, biology, and differential clinical outcomes associated with molecular subtypes identified in Example 1. These integrative biomarker analyses improve understanding of RCC biology and identify molecular bases for differential clinical outcomes to VEGF inhibition, checkpoint inhibitors, and combination therapies thereof in advanced RCC.

Other Embodiments

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention.

WHAT IS CLAIMED IS:

1. A method of classifying an inoperable, locally advanced, or metastatic renal cell carcinoma (RCC) in a human patient, wherein the inoperable, locally advanced, or metastatic RCC is previously untreated, the method comprising:

(a) assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and

(b) assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor:

(1) angiogenic/stromal;

(2) angiogenic;

(3) complement/Ω-oxidation;

(4) T-effector/proliferative;

(5) proliferative;

(6) stromal/proliferative; and

(7) snoRNA,

thereby classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient.

2. A method of treating an inoperable, locally advanced, or metastatic RCC in a human patient, the method comprising:

classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient according to the method of claim 1; and

administering an anti-cancer therapy to the patient based on the classification.

3. The method of claim 2, wherein the anti-cancer therapy comprises atezolizumab and bevacizumab.

4. The method of any one of claims 1-3, wherein assaying mRNA in the tumor sample from the patient comprises RNA sequencing (RNA-seq), reverse transcription-quantitative polymerase chain reaction (RT-qPCR), qPCR, multiplex qPCR or RT-qPCR, microarray analysis, serial analysis of gene expression (SAGE), MassARRAY technique, in situ hybridization (ISH), or a combination thereof.

5. The method of any one of claims 1-4, wherein assaying mRNA in the tumor sample from the patient comprises RNA-seq.

6. The method of any one of claims 1-5, wherein the seven clusters are identified by non-negative matrix factorization (NMF).

7. The method of claim 6, wherein the seven clusters identified by NMF are based on a set of genes representing the top 10% most variable genes in a population of patients having previously untreated inoperable, locally advanced, or metastatic RCC.

8. The method of claim 7, wherein the set of genes is set forth in Table 1.

9. The method of any one of claims 1-8, wherein the method further comprises determining the mRNA expression level of one or more of the following gene signatures in the tumor sample from the patient:

(a) a T-effector signature comprising CD8A, IFNG, EOMES, PRF1, and PD-L1;

(b) an angiogenesis signature comprising VEGFA, KDR, ESM1, CD34, PECAM1, and ANGPTL4;

(c) a fatty acid oxidation (FAO)/AMPK signature comprising CPT2, PPARA, CPT1A, PRKAA2, PDK2, and PRKAB1;

(d) a cell cycle signature comprising CDK2, CDK4, CDK6, BUB1, BUB1B, CCNE1, POLQ, AURKA, MKI67, and CCNB2;

(e) a fatty acid synthesis (FAS)/pentose phosphate signature comprising FASN, PARP1, ACACA, G6PD, TKT, TALDO1, and PGD;

(f) a stroma signature comprising FAP, FN1, COL5A1, COL5A2, POSTN, COL1A1, COL1A2, and MMP2;

(g) a myeloid inflammation signature comprising CXCL1, CXCL2, CXCL3, CXCL8, IL6, and PTGS2;

(h) a complement cascade signature comprising F2, C1S, C9, C1R, CFB, and C3;

(i) an Ω-oxidation signature comprising CYP4F3, CYP8B1, NNMT, MGST1, MAOA, CYP4F11, CYP4F2, CYP4F12; and/or

(j) a snoRNA signature comprising SNORD38A, SNORD104, SNORD32A, SNORD68, SNORD66, and SNORD100.

10. The method of claim 9, wherein the patient's tumor sample is assigned into the angiogenic/stromal cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the angiogenesis signature and the stroma signature,

optionally wherein the patient's tumor sample has decreased expression levels, relative to reference expression levels, of the T-effector signature, the cell cycle signature, and/or the FAS/pentose phosphate signature.

11. The method of claim 9, wherein the patient's tumor sample is assigned into the angiogenic cluster, and the patient's tumor sample has increased expression levels, relative to a reference expression levels, of the angiogenesis signature and the FAO/AMPK signature,

optionally wherein the patient's tumor has decreased expression levels, relative to reference expression levels, of the cell cycle signature, the FAS/pentose phosphate signature, the stroma signature, the myeloid inflammation signature, and/or the complement cascade signature.

12. The method of claim 9, wherein the patient's tumor sample is assigned into the complement/Ω-oxidation cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the complement cascade signature and the Ω-oxidation signature,

optionally wherein the patient's tumor sample has an increased expression level, relative to a reference expression level, of the myeloid inflammation signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature and/or the T-effector signature.

13. The method of claim 9, wherein the patient's tumor sample is assigned into the T-effector/proliferative cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the cell cycle signature and the T-effector signature,

optionally wherein the patient's tumor sample has increased expression levels, relative to reference expression levels, of the FAS/pentose phosphate signature, the myeloid inflammation signature, and/or the complement cascade signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature, the FAO/AMP signature, and/or the snoRNA signature.

14. The method of claim 9, wherein the patient's tumor sample is assigned into the proliferative cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the cell cycle signature and the FAS/pentose phosphate signature,

optionally wherein the patient's tumor sample has increased expression levels, relative to reference expression levels, of the myeloid inflammation signature and/or the FAO/AMPK signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature, the T-effector signature, the stroma signature, the complement cascade signature, the Ω-oxidation signature, and/or the snoRNA signature.

15. The method of claim 9, wherein the patient's tumor sample is assigned into the stromal/proliferative cluster, and the patient's tumor sample has increased expression levels, relative to reference expression levels, of the cell cycle signature and the stromal signature,

optionally wherein the patient's tumor sample has increased expression levels, relative to reference expression levels, of the FAS/pentose phosphate signature and/or the myeloid inflammation signature, and/or decreased expression levels, relative to reference expression levels, of the angiogenesis signature, the FAO/AMPK signature, the complement cascade signature, the Ω-oxidation signature, and/or the snoRNA signature.

16. The method of claim 9, wherein the patient's tumor sample is assigned into the snoRNA cluster, and the patient's tumor sample has an increased expression level, relative to a reference expression level, of the snoRNA signature,

optionally wherein the patient's tumor sample has decreased expression levels, relative to reference expression levels, of the FOA/AMPK signature, the cell cycle signature, and the FAS/pentose phosphate signature.

17. The method of any one of claims 10-16, wherein the reference expression level of a signature is the median Z-score of the signature in a population of patients having a previously untreated inoperable, locally advanced, or metastatic RCC.

18. The method of any one of claims 1-9, 13, 14, and 16, wherein assignment of the patient's tumor sample into one of the following clusters:

(4) T-effector/proliferative;

(5) proliferative; or

(7) snoRNA,

indicates that the patient is likely to have an increased clinical benefit from treatment with an anti-cancer therapy comprising atezolizumab and bevacizumab compared to treatment with sunitinib.

19. The method of claim 18, wherein increased clinical benefit comprises a relative increase in one or more of the following: objective response rate (ORR), overall survival (OS), progression-free survival (PFS), compete response (CR), partial response (PR), or a combination thereof.

20. The method of claim 19, wherein increased clinical benefit comprises a relative increase in ORR or PFS.

21. The method of any one of claims 1-9, 13, 14, 16, and 18-20, wherein the patient's tumor sample is assigned into one of the following clusters:

(4) T-effector/proliferative;

(5) proliferative; or

(7) snoRNA,

and the method further comprises treating the patient by administering an anti-cancer therapy comprising atezolizumab and bevacizumab to the patient.

22. The method of any one of claims 1-21, further comprising assaying for somatic alterations in the patient's genotype in the tumor sample obtained from the patient.

23. The method of claim 22, wherein the method comprises assaying for somatic alterations in *PBRM1, CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and/or *KMT2C*.

24. The method of claim 23, wherein (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1* indicates that the patient is likely to have an

increased clinical benefit from treatment with an anti-cancer therapy comprising atezolizumab and bevacizumab compared to treatment with sunitinib.

25. The method of any one of claims 22-24, wherein the patient's genotype is determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, and the method further comprises administering to the patient an anti-cancer therapy comprising atezolizumab and bevacizumab.

26. A method of treating a previously untreated inoperable, locally advanced, or metastatic RCC in a patient whose genotype has been determined to comprise (i) the presence of a somatic alteration in the patient's genotype in one or more of the following genes: *CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* or (ii) the absence of a somatic alteration in the patient's genotype in *PBRM1*, the method comprising administering to the patient an anti-cancer therapy comprising atezolizumab and bevacizumab.

27. The method of claim 23, wherein the presence of a somatic alteration in the patient's genotype in *PBRM1* indicates that the patient is likely to have an increased clinical benefit from treatment with sunitinib compared a patient whose genotype lacks a somatic alteration in *PBRM1*.

28. The method of claim 27, wherein the patient's genotype is determined to comprise a somatic alteration in *PBRM1*, and the method further comprises administering sunitinib to the patient.

29. The method of any one of claims 22-28, wherein the somatic alteration is a short variant, a loss, an amplification, a deletion, a duplication, a rearrangement, or a truncation.

30. The method of any one of claims 1-29, wherein the tumor sample is a formalin-fixed and paraffin-embedded (FFPE) sample, an archival sample, a fresh sample, or a frozen sample.

31. The method of any one of claims 1-30, wherein the tumor sample is a pre-treatment tumor sample.

32. The method of any one of claims 1-31, wherein the tumor sample from the patient has a clear cell histology.

33. The method of any one of claims 1-31, wherein the tumor sample from the patient has a non-clear cell histology.

34. The method of any one of claims 1-33, wherein the tumor sample from the patient has a sarcomatoid component.

35. The method of any one of claims 1-33, wherein the tumor sample lacks a sarcomatoid component.

36. The method of any one of claims 1-35, further comprising determining the patient's Memorial Sloan Kettering Cancer Center (MSKCC) risk score.

37. The method of any one of claims 2, 3, 21, 25, 26, and 28, further comprising administering an additional therapeutic agent to the patient.

38. The method of claim 37, wherein the additional therapeutic agent is an immunotherapy agent, a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent, or a combination thereof.

39. The method of claim 38, wherein the growth inhibitory agent is a CDK4/6 inhibitor.

40. The method of claim 39, wherein the CDK4/6 inhibitor is palbociclib, ribociclib, or abemaciclib.

41. The method of claim 38, wherein the anti-angiogenic agent is a VEGF antagonist or a HIF2A inhibitor.

42. The method of claim 38, wherein the stromal inhibitor is a TGF-β antagonist.

43. The method of claim 38, wherein the metabolism inhibitor is a PCSK9 inhibitor or a FAS inhibitor.

44. A kit for classifying an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the inoperable, locally advanced, or metastatic RCC is previously untreated, the kit comprising:

(a) reagents for assaying mRNA in a tumor sample from the patient to provide a transcriptional profile of the patient's tumor; and

(b) instructions for assigning the patient's tumor sample into one of the following seven clusters based on the transcriptional profile of the patient's tumor:

(1) angiogenic/stromal;

(2) angiogenic;

(3) complement/Ω-oxidation;

(4) T-effector/proliferative;

(5) proliferative;

(6) stromal/proliferative; and

(7) snoRNA,

thereby classifying the previously untreated inoperable, locally advanced, or metastatic RCC in the patient.

45. A kit for identifying a human patient suffering from an inoperable, locally advanced, or metastatic RCC who may benefit from treatment with an anti-cancer therapy comprising atezolizumab and bevacizumab, wherein the inoperable, locally advanced, or metastatic RCC is previously untreated, the kit comprising:

(a) reagents for determining the presence of a somatic alteration in one or more of the following genes: *PBRM1, CDKN2A*, *CDK2NB*, *TP53*, *ARID1A*, and *KMT2C* in a tumor sample obtained from the patient; and

(b) instructions for using the reagents to identify the patient as one who may benefit from a treatment with an anti-cancer therapy comprising atezolizumab and bevacizumab.

46. An anti-cancer therapy for use in treating an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the previously untreated inoperable, locally advanced, or metastatic RCC in the patient has been classified according to the method of any one of claims 1, 4-20, 22-24, 27, and 29-36.

47. The anti-cancer therapy for use of claim 46, wherein the anti-cancer therapy comprises atezolizumab and bevacizumab.

48. Use of an anti-cancer therapy in the preparation of a medicament for treating an inoperable, locally advanced, or metastatic RCC in a human patient, wherein the previously untreated inoperable, locally advanced, or metastatic RCC in the patient has been classified according to the method of any one of claims 1, 4-20, 22-24, 27, and 29-36.

49. The use of claim 48, wherein the anti-cancer therapy comprises atezolizumab and bevacizumab.

50. The anti-cancer therapy for use of claim 46 or 47, or the use of claim 48 or 49, wherein the anti-cancer therapy further comprises an additional therapeutic agent.

51. The anti-cancer therapy for use or the use of claim 50, wherein the additional therapeutic agent is an immunotherapy agent, a cytotoxic agent, a growth inhibitory agent, a stromal inhibitor, a metabolism inhibitor, a complement antagonist, a radiation therapy agent, an anti-angiogenic agent, or a combination thereof.

52. The anti-cancer therapy for use or the use of claim 51, wherein the growth inhibitory agent is a CDK4/6 inhibitor.

53. The anti-cancer therapy for use or the use of claim 52, wherein the CDK4/6 inhibitor is palbociclib, ribociclib, or abemaciclib.

54. The anti-cancer therapy for use or the use of claim 51, wherein the anti-angiogenic agent is a VEGF antagonist or a HIF2A inhibitor.

55. The anti-cancer therapy for use or the use of claim 51, wherein the stromal inhibitor is a TGF-β antagonist.

56. The anti-cancer therapy for use or the use of claim 51, wherein the metabolism inhibitor is a PCSK9 inhibitor or a FAS inhibitor.

FIG. 1A

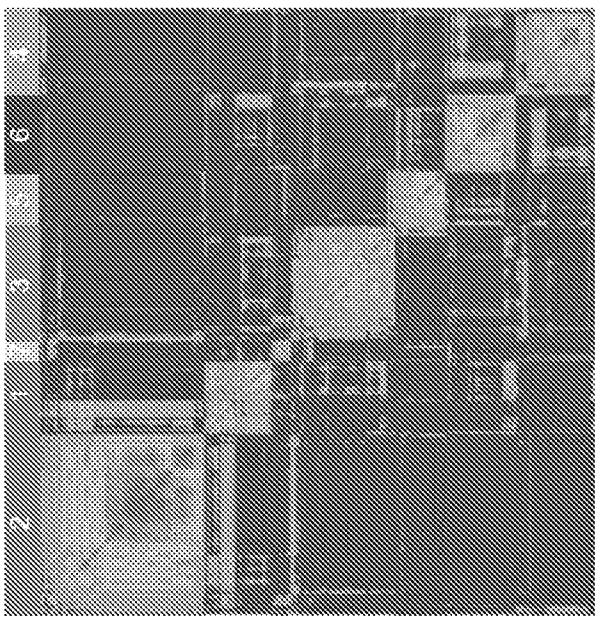

(245)
(98)
(28)
(156)
(74)
(106)
(116)
NMF cluster
Tumors from 823 patients

FIG. 1B

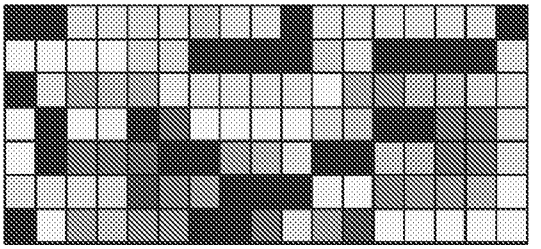

GNE MYELOID INFLAMMATION
EPITHELIAL MESENCHYMAL TRANSITION
G2M CHECKPOINT
E2F TARGETS
MYC TARGETS V1
MYC TARGETS V2
IL6 JAK STAT3 SIGNALING
INTERFERON GAMMA RESPONSE
INTERFERON ALPHA RESPONSE
GNE T-EFFECTOR
OXIDATIVE PHOSPHORYLATION
FATTY ACID METABOLISM
WNT BETA CATENIN SIGNALING
TGF BETA SIGNALING
HEDGEHOG SIGNALING
NOTCH SIGNALING
GNE ANGIOGENESIS
1 2 3 4 5 6 7
NMF cluster
Enrichment
0.4
0.2
0
−0.2
−0.4

FIG. 1C

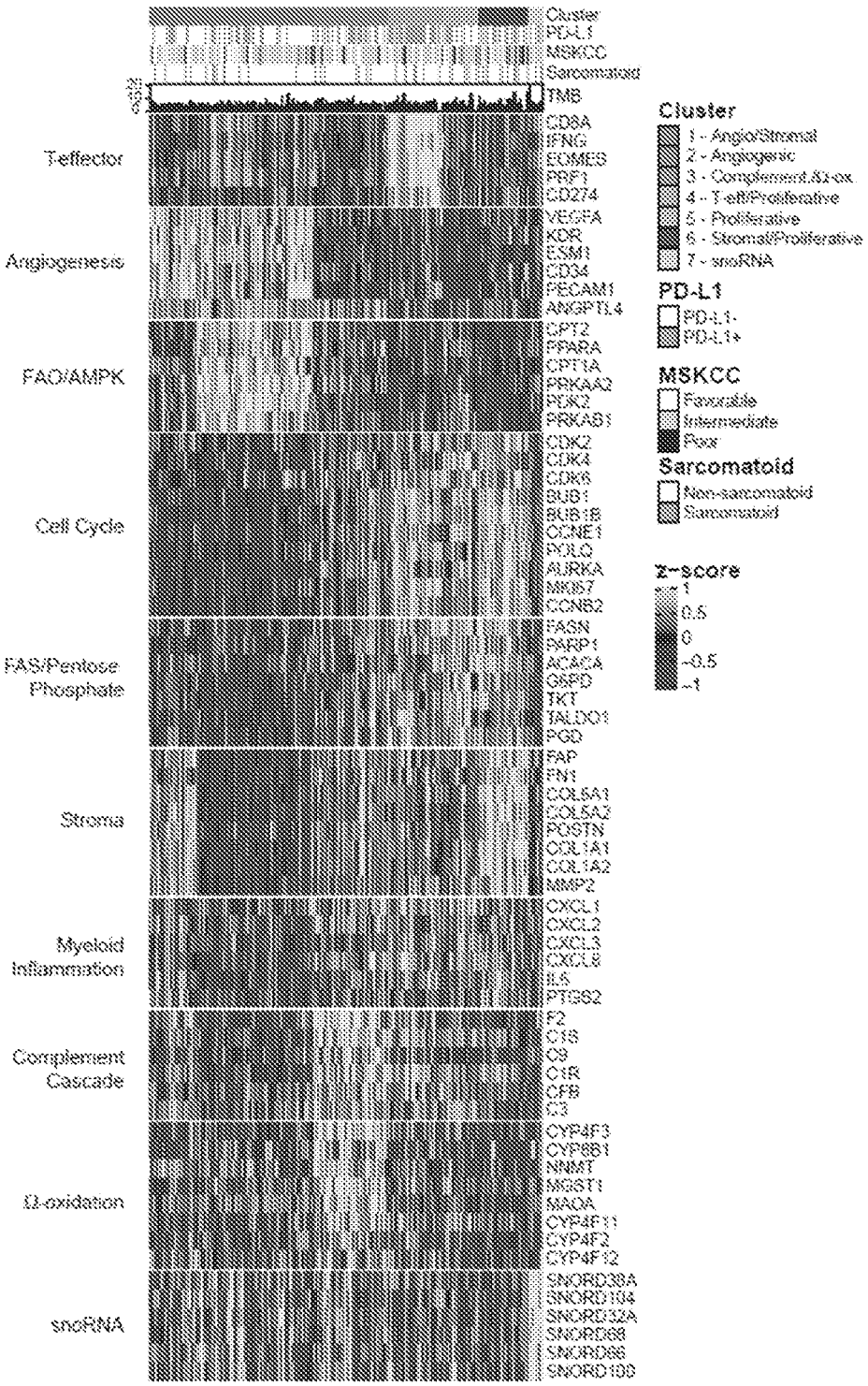

Cluster
PD-L1
MSKCC
Sarcomatoid
TMB
Teffector
CD8A
IFNG
EOMES
PRF1
CD274
Angiogenesis
VEGFA
KDR
ESM1
CD34
PECAM1
ANGPTL4
FAO/AMPK
CPT2
PPARA
CPT1A
PRKAA2
PDK2
PRKAB1
Cell Cycle
CDK2
CDK4
CDK6
BUB1
BUB1B
CCNE1
POLQ
AURKA
MKI67
CCNB2
FAS/Pentose Phosphate
FASN
PARP1
ACACA
G6PD
TKT
TALDO1
PGD
Stroma
FAP
FN1
COL5A1
COL5A2
POSTN
COL1A1
COL1A2
MMP2
Myeloid Inflammation
CXCL1
CXCL2
CXCL3
CXCL8
IL6
PTGS2
Complement Cascade
F2
C1S
C9
C1R
CFB
C3
ω-oxidation
CYP4F3
CYP4B1
NNMT
MGST1
MAOA
CYP4F11
CYP4F2
CYP4F12
snoRNA
SNORD38A
SNORD104
SNORD32A
SNORD88
SNORD96
SNORD100
Cluster
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Anox
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA
PD-L1
PD-L1-
PD-L1+
MSKCC
Favorable
Intermediate
Poor
Sarcomatoid
Non-sarcomatoid
Sarcomatoid
z-score
1
0.5
0
−0.5
−1

FIG. 1D

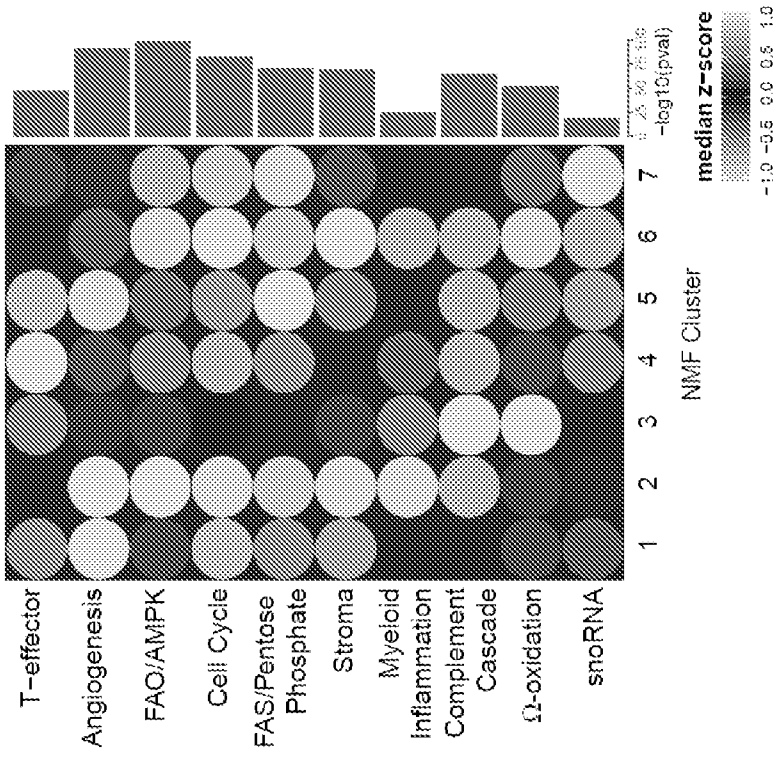

T−effector
Angiogenesis
FAO/AMPK
Cell Cycle
FAS/Pentose Phosphate
Stroma
Myeloid
Inflammation
Complement Cascade
Ω-oxidation
snoRNA
1 2 3 4 5 6 7
NMF Cluster
−log10(pval)
median z−score
−1.0 −0.5 0.0 0.5 1.0

FIG. 1E

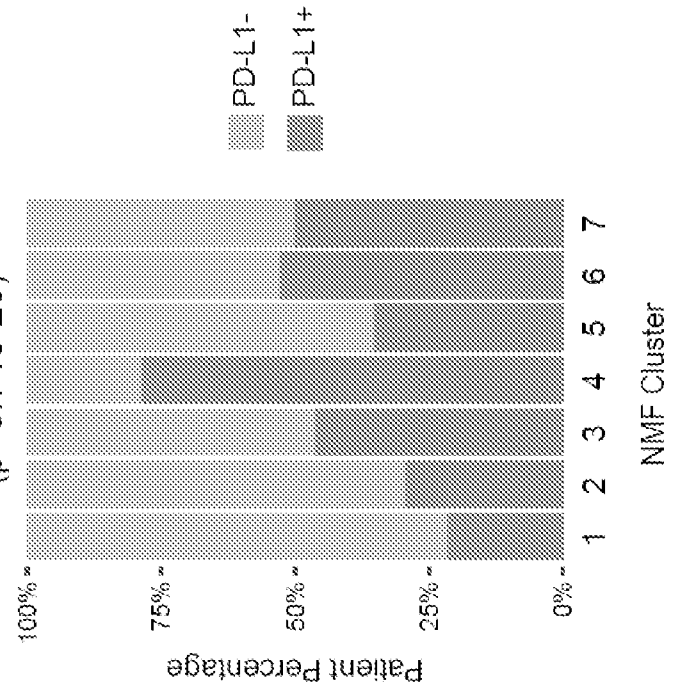

PD−L1 IHC Prevalence
(p=3.74e-20)
PD-L1-
PD-L1+
100%
75%
50%
25%
0%
Patient Percentage
1 2 3 4 5 6 7
NMF Cluster

FIG. 2A

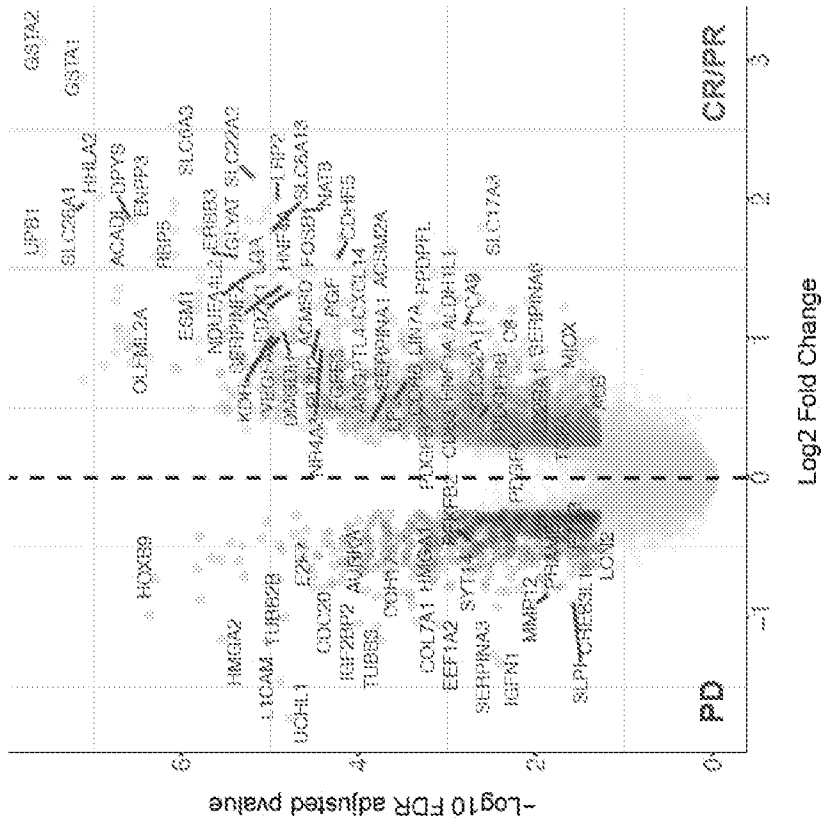

Sunitinib CR/PR vs. PD
-Log10 FDR adjusted pvalue
Log2 Fold Change
PD
CR/PR
HOXB9
HMGA2
UBE2B
UCHL1
COX20
IGF2BP2
TUBB5
COL7A1
EEF1A2
SERPINA3
IGFN1
SLPI
GSTA2
GSTA1
HLA2
ACADL
DPYS
ENPP3
OLFML2A
RBP5
ESM1
SLC6A3
ERBB3
GSTM1
SLC7A2
IRF2
SLC6A12
MAT3
CD4HS
FGF5
CXCL14
AQSM2A
PRDPPL
ALDH1L1
SLC17A3
C8
SERPINA6
MIC2
LOX

FIG. 2B

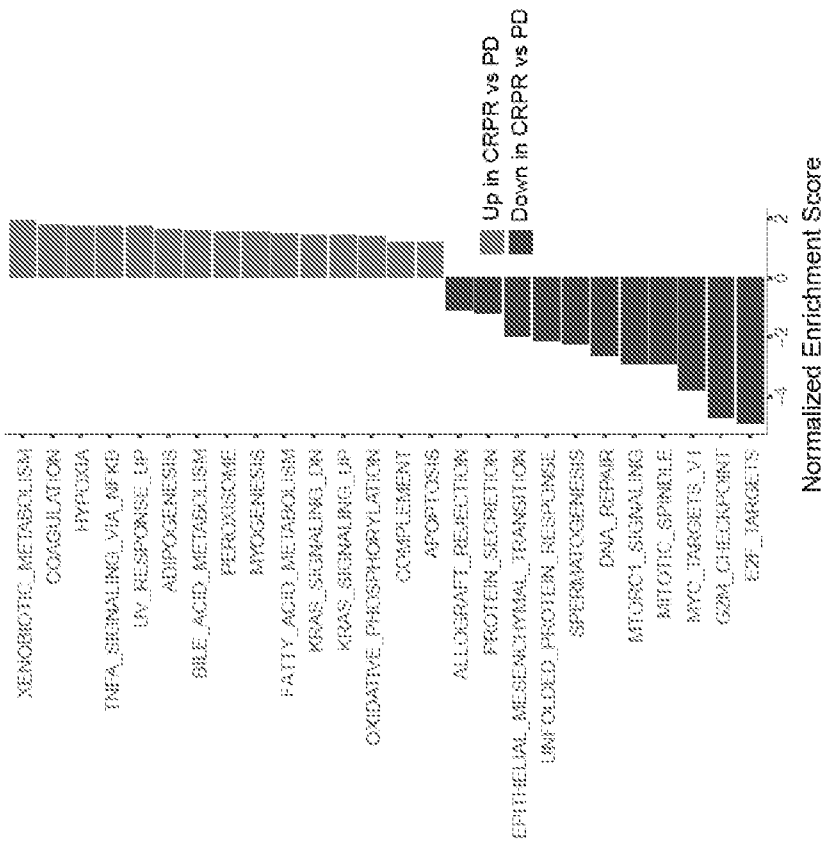

Sunitinib CR/PR vs. PD
XENOBIOTIC_METABOLISM
COAGULATION
HYPOXIA
TNFA_SIGNALING_VIA_NFKB
UV_RESPONSE_UP
ADIPOGENESIS
BILE_ACID_METABOLISM
PEROXISOME
MYOGENESIS
FATTY_ACID_METABOLISM
KRAS_SIGNALING_DN
KRAS_SIGNALING_UP
OXIDATIVE_PHOSPHORYLATION
COMPLEMENT
APOPTOSIS
ALLOGRAFT_REJECTION
PROTEIN_SECRETION
EPITHELIAL_MESENCHYMAL_TRANSITION
UNFOLDED_PROTEIN_RESPONSE
SPERMATOGENESIS
DNA_REPAIR
MTORC1_SIGNALING
MITOTIC_SPINDLE
MYC_TARGETS_V1
G2M_CHECKPOINT
E2F_TARGETS
Up in CRPR vs PD
Down in CRPR vs PD
Normalized Enrichment Score

FIG. 2C

CR/PR atezolizumab+bevacizumab vs. sunitinib

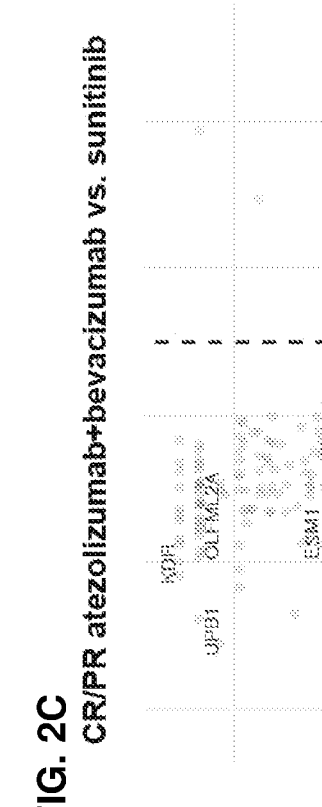


FIG. 2D

CR/PR atezolizumab+bevacizumab vs. sunitinib

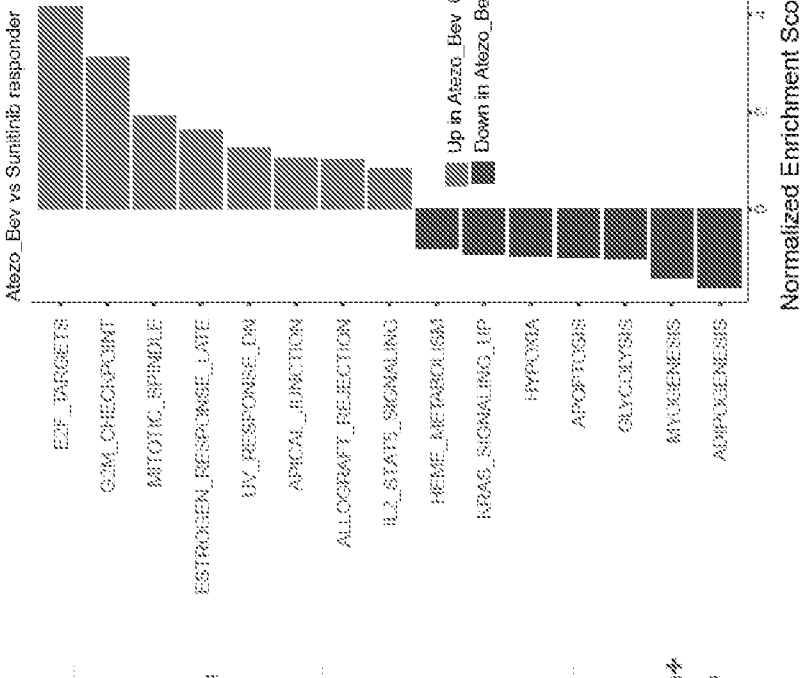


FIG. 3A

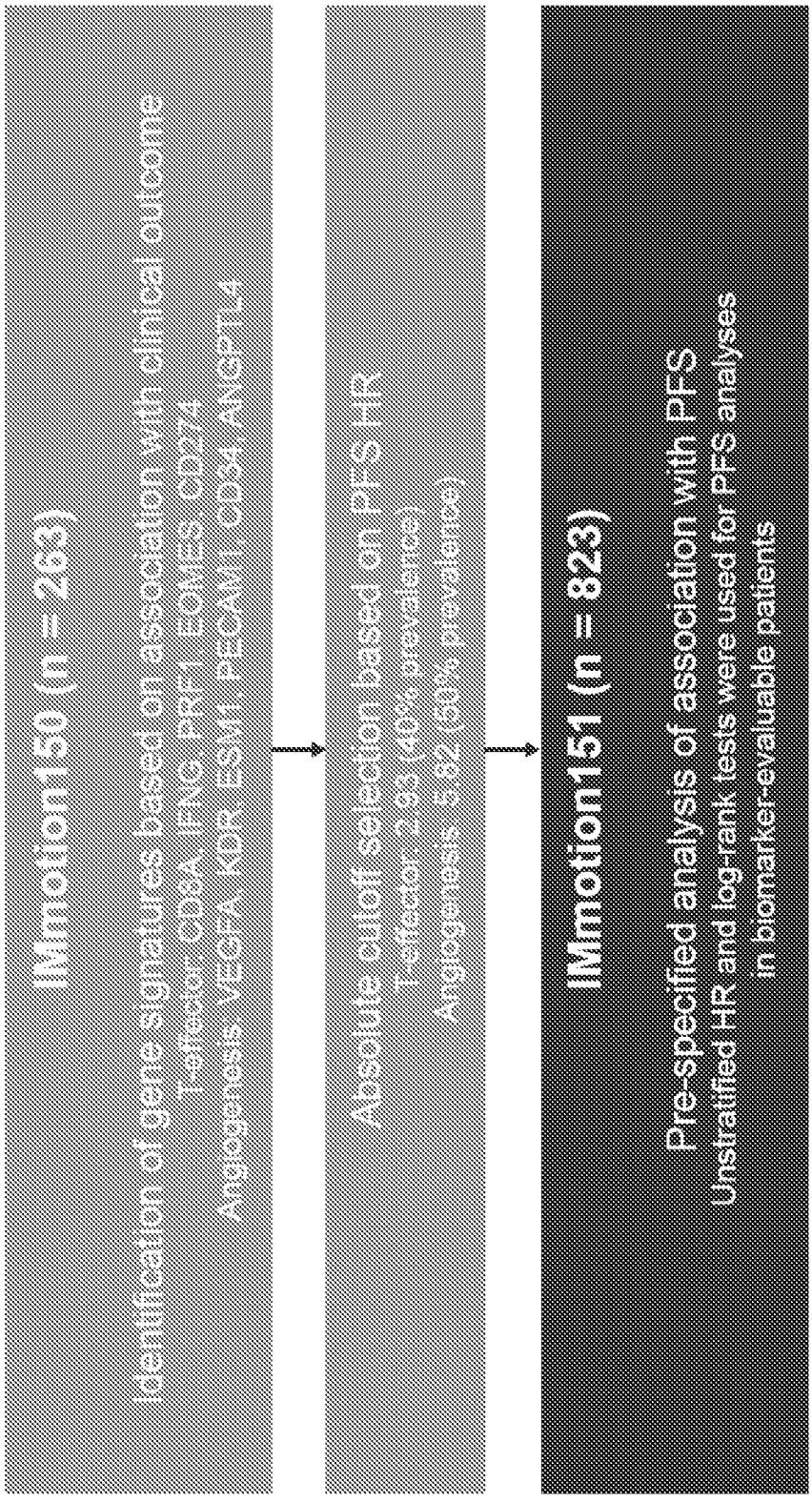

IMmotion150 (n = 263)
Identification of gene signatures based on association with clinical outcome
T-effector CD8A IFNG PRF1 EOMES CD274
Angiogenesis VEGFA KDR ESM1 PECAM1 CD34 ANGPTL4
Absolute cutoff selection based on PFS HR
T-effector 2.93 (40% prevalence)
Angiogenesis 5.92 (50% prevalence)
IMmotion151 (n = 823)
Pre-specified analysis of association with PFS
Unstratified HR and log-rank tests were used for PFS analyses
in biomarker-evaluable patients

FIG. 3B

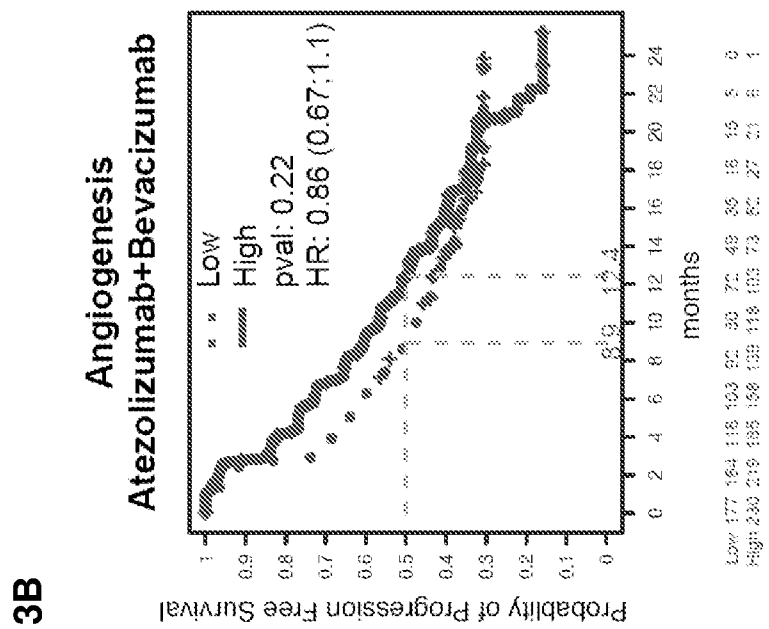
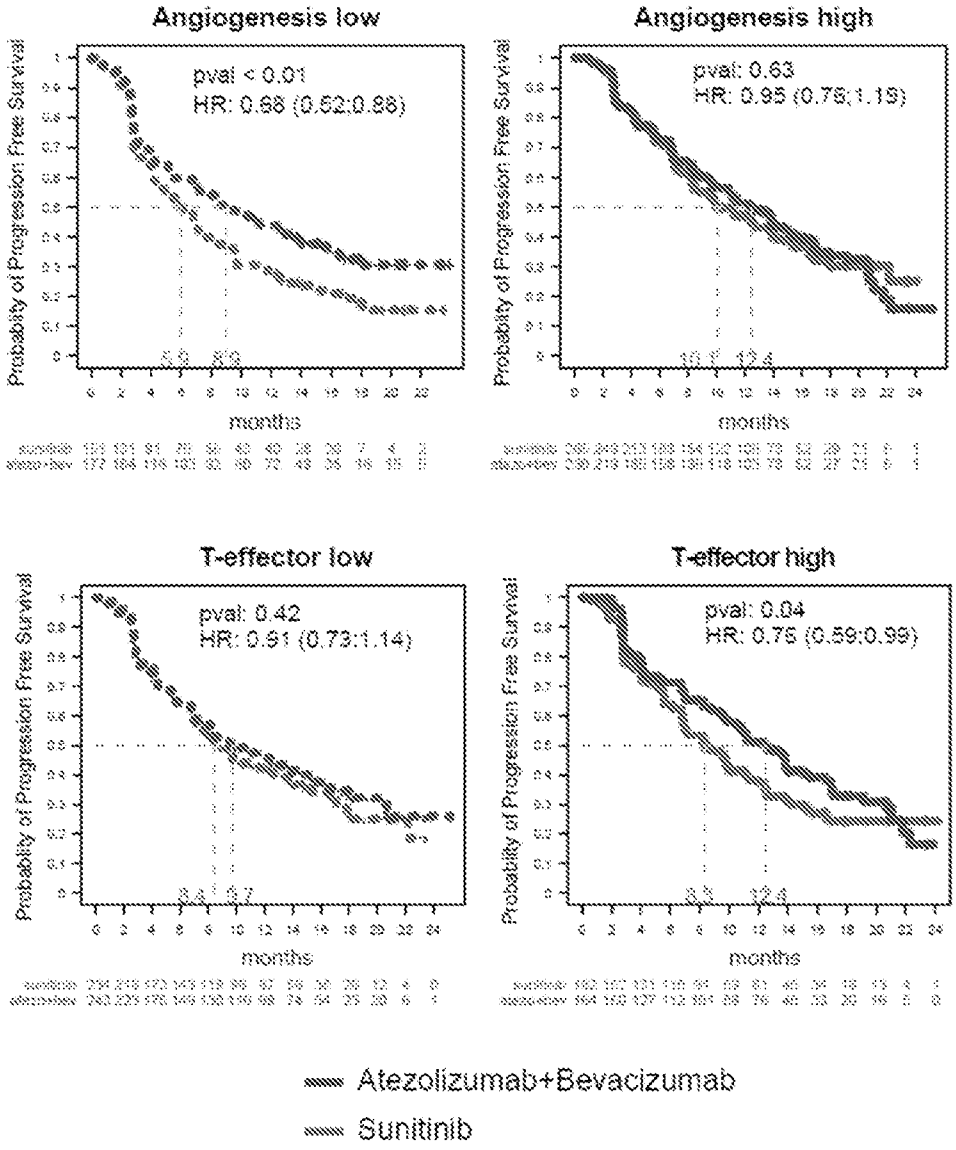

Angiogenesis
Atezolizumab+Bevacizumab
Low
High
pval: 0.22
HR: 0.86 (0.67;1.1)
Probability of Progression Free Survival
months
Angiogenesis
Sunitinib
Low
High
pval<0.01
HR: 0.59 (0.47;0.75)
Probability of Progression Free Survival
months

FIG. 3C


Angiogenesis low
pval < 0.01
HR: 0.68 (0.52:0.88)
Angiogenesis high
pval: 0.63
HR: 0.95 (0.78:1.15)
T-effector low
pval: 0.42
HR: 0.91 (0.73:1.14)
T-effector high
pval: 0.04
HR: 0.75 (0.59:0.99)
Probability of Progression Free Survival
months
Atezolizumab+Bevacizumab
Sunitinib

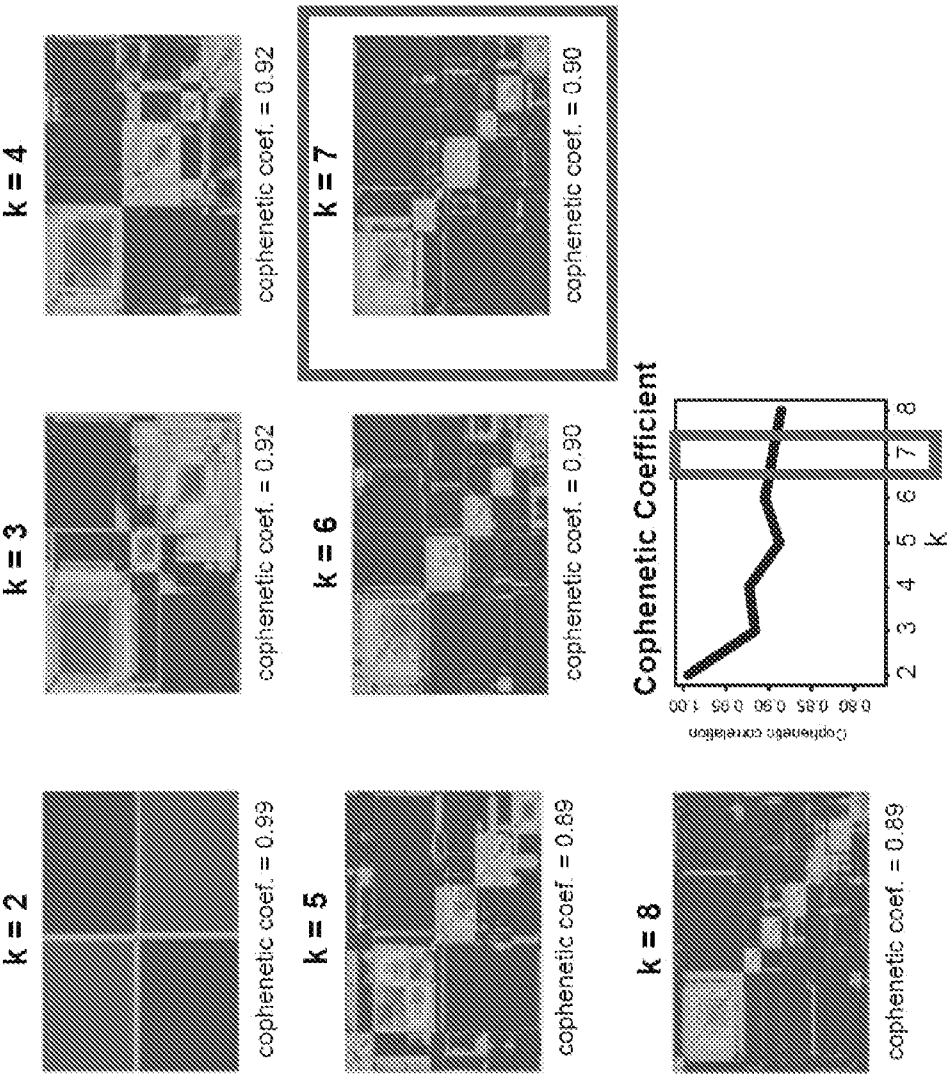

k = 2
cophenetic coef. = 0.99
k = 3
cophenetic coef. = 0.92
k = 4
cophenetic coef. = 0.92
k = 5
cophenetic coef. = 0.89
k = 6
cophenetic coef. = 0.90
k = 7
cophenetic coef. = 0.90
k = 8
cophenetic coef. = 0.89
Cophenetic Coefficient
Cophenetic correlation
1.00
0.95
0.90
0.85
0.80
2
3
4
5
6
7
8
k

FIG. 4A

FIG. 4B

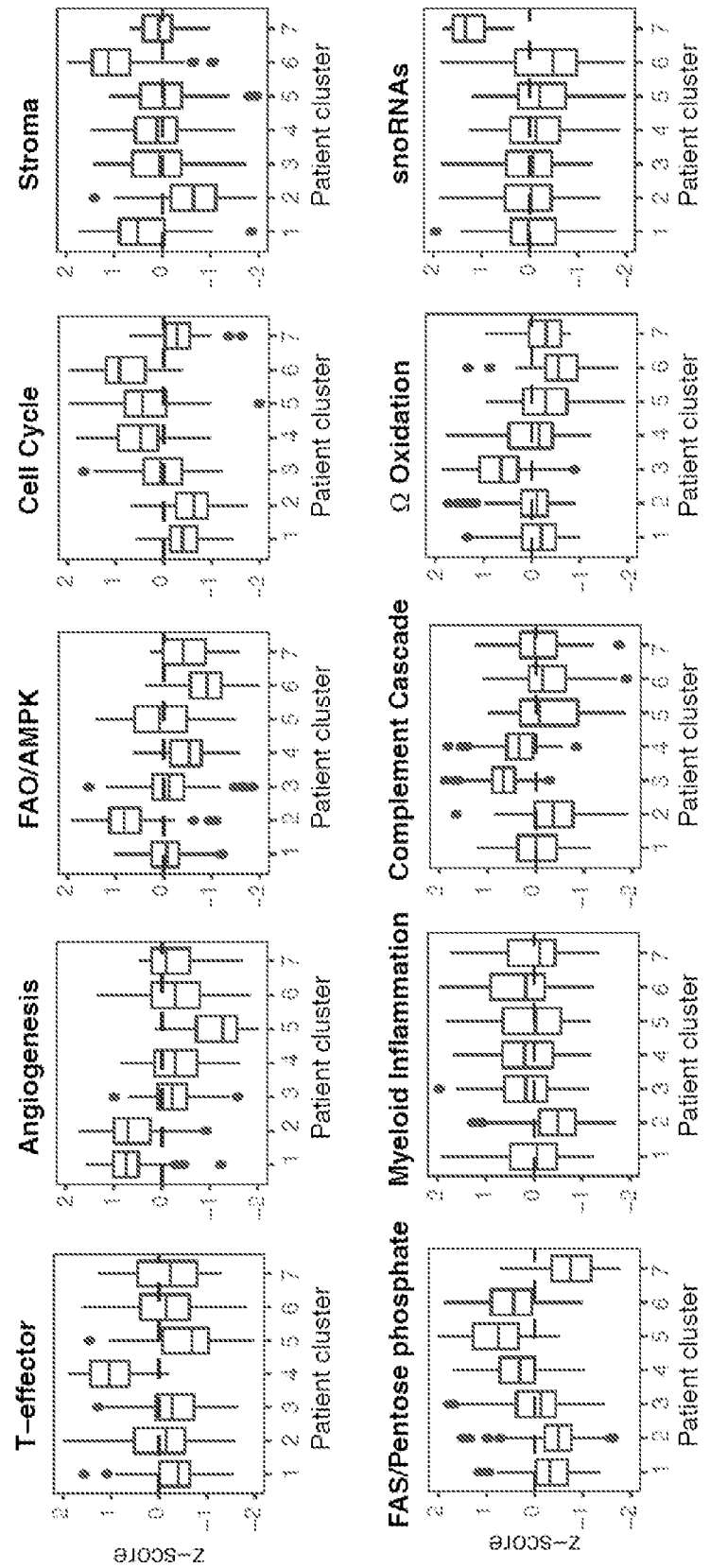

T-effector
Angiogenesis
FAO/AMPK
Cell Cycle
Stroma
FAS/Pentose phosphate
Myeloid Inflammation
Complement Cascade
Ω Oxidation
snoRNAs
Z-SCORE
Patient cluster
1 2 3 4 5 6 7
2
1
0
-1
-2

FIG. 4C

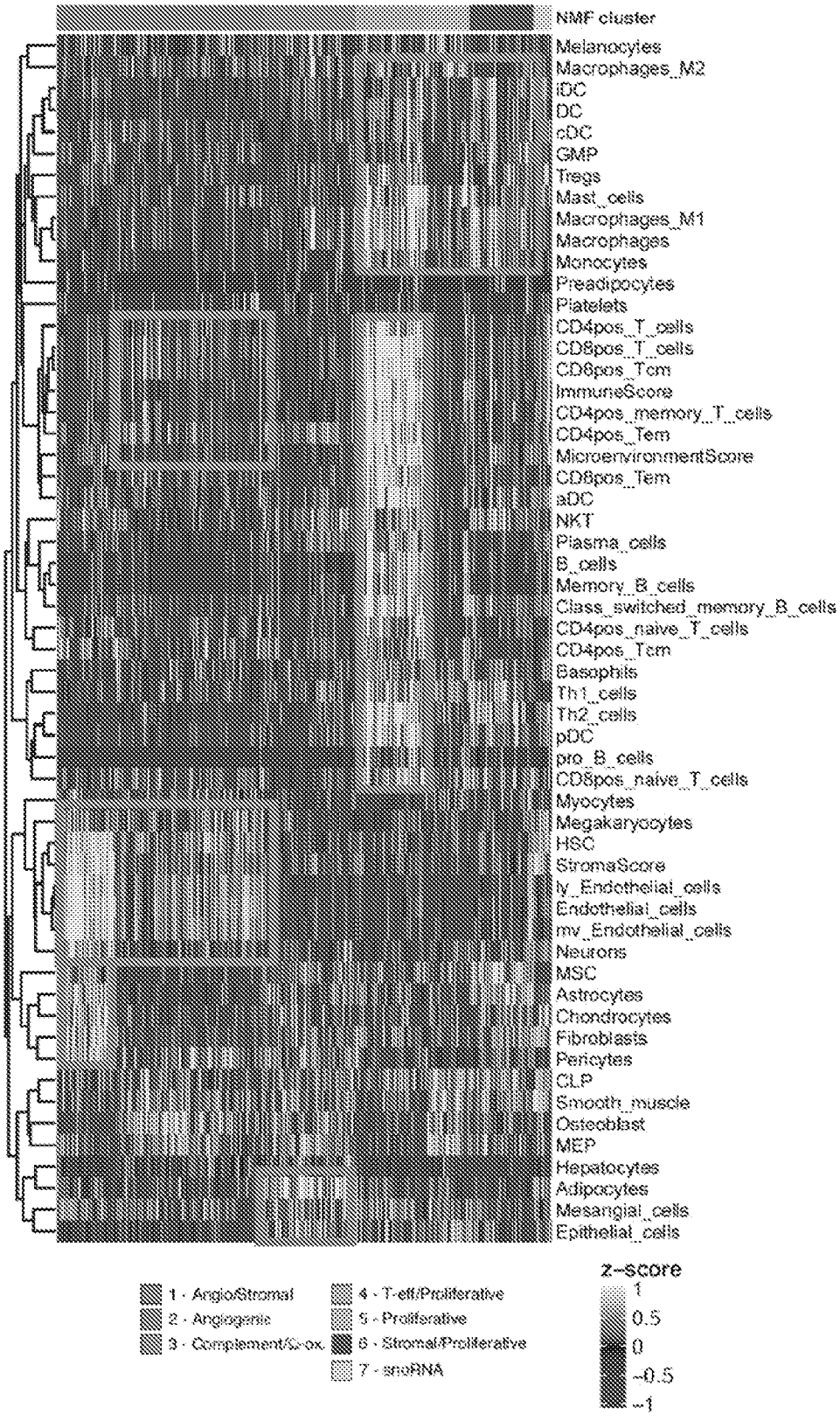

NMF cluster
Melanocytes
Macrophages_M2
iDC
DC
cDC
GMP
Tregs
Mast_cells
Macrophages_M1
Macrophages
Monocytes
Preadipocytes
Platelets
CD4pos_T_cells
CD8pos_T_cells
CD6pos_Tcm
ImmuneScore
CD4pos_memory_T_cells
CD4pos_Tem
MicroenvironmentScore
CD6pos_Tem
aDC
NKT
Plasma_cells
B_cells
Memory_B_cells
Class_switched_memory_B_cells
CD4pos_naive_T_cells
CD4pos_Tcm
Basophils
Th1_cells
Th2_cells
pDC
pro_B_cells
CD8pos_naive_T_cells
Myocytes
Megakaryocytes
HSC
StromaScore
ly_Endothelial_cells
Endothelial_cells
mv_Endothelial_cells
Neurons
MSC
Astrocytes
Chondrocytes
Fibroblasts
Pericytes
CLP
Smooth_muscle
Osteoblast
MEP
Hepatocytes
Adipocytes
Mesangial_cells
Epithelial_cells
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Cox
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA
z-score
1
0.5
0
-0.5
-1

FIG. 4E

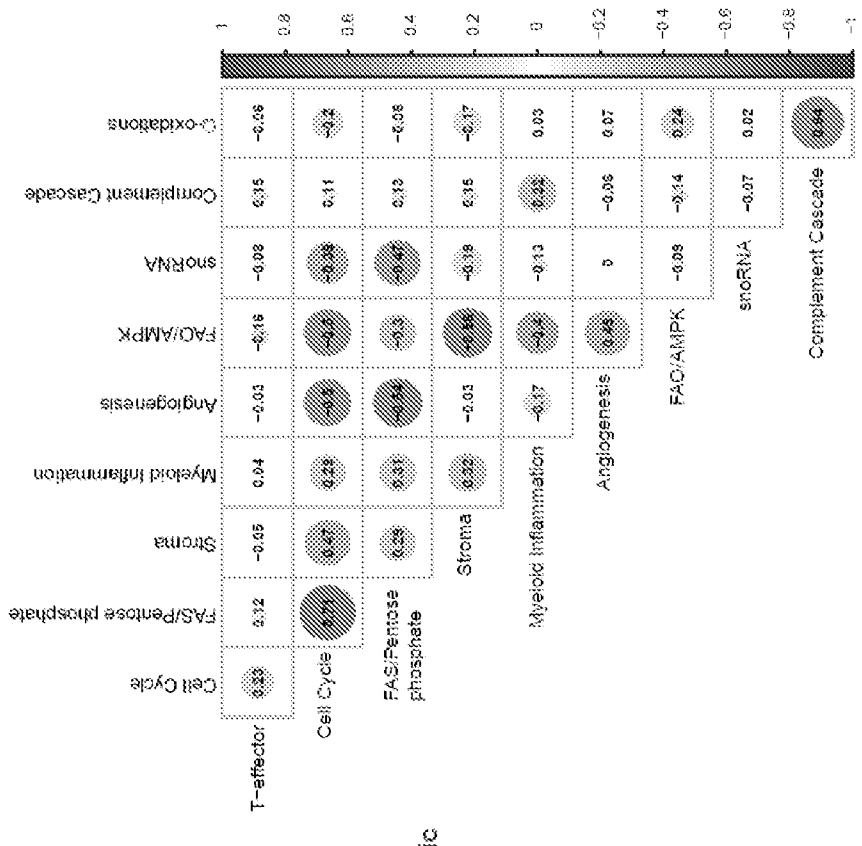

T-effector
Cell Cycle
FAS/Pentose phosphate
Stroma
Myeloid Inflammation
Angiogenesis
FAO/AMPK
snoRNA
snoRNA
Complement Cascade
Complement Cascade
C-oxidations
Cell Cycle
FAS/Pentose phosphate
Stroma
Myeloid Inflammation
Angiogenesis
FAO/AMPK
snoRNA
Complement Cascade
C-oxidations
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

FIG. 4D

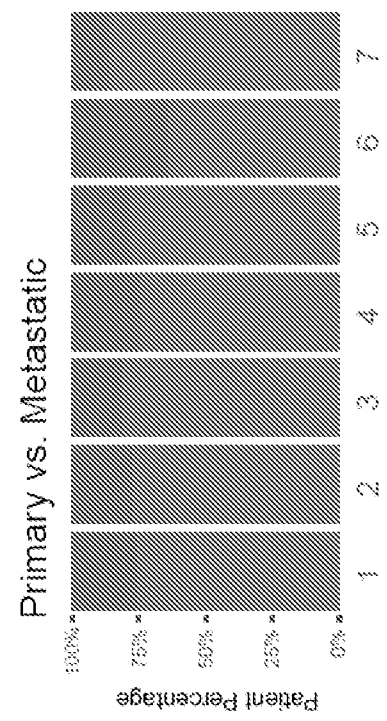

Primary vs. Metastatic
Patient Percentage
100%
75%
50%
25%
0%
1
2
3
4
5
6
7
Primary
Metastatic

FIG. 4F

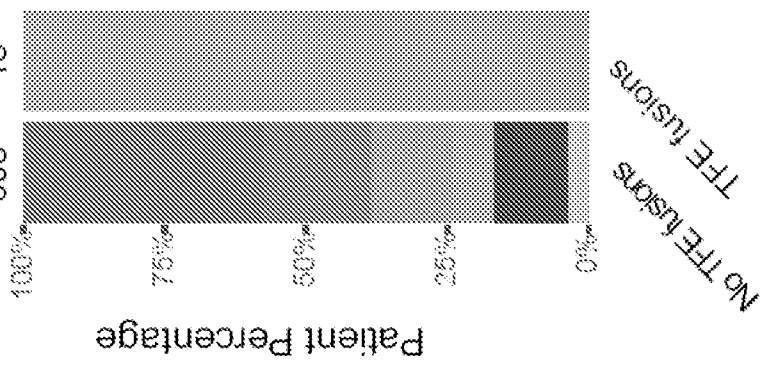
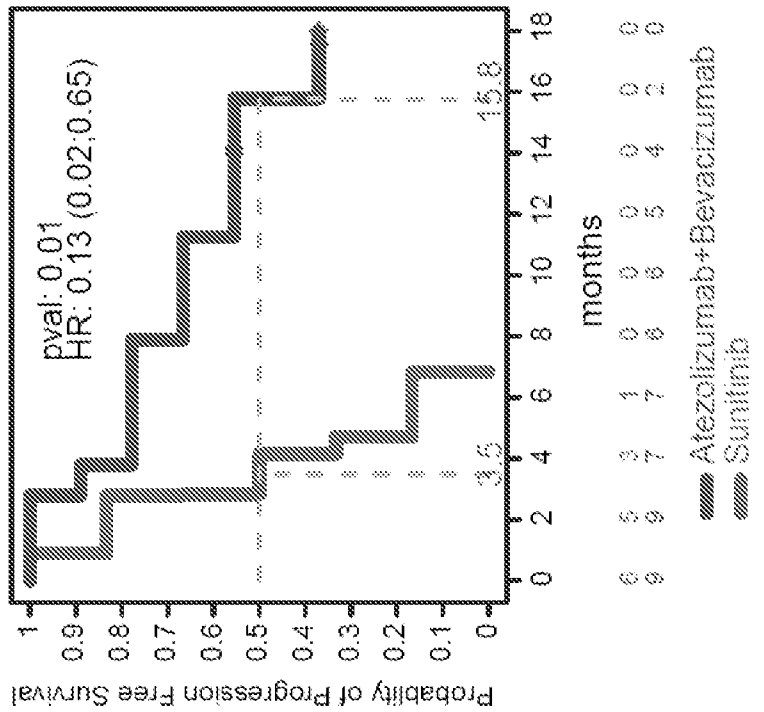

n= 808
n= 15
100%
75%
50%
25%
0%
Patient Percentage
No TFE fusions
TFE fusions
Cluster
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA

FIG. 4G


TFE fusions
pval: 0.01
HR: 0.13 (0.02;0.65)
Probability of Progression Free Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3.5
15.8
0 2 4 6 8 10 12 14 16 18
months
6 5 3 1 0 0 0 0 0 0
9 9 7 7 6 6 5 4 2 0
Atezolizumab+Bevacizumab
Sunitinib

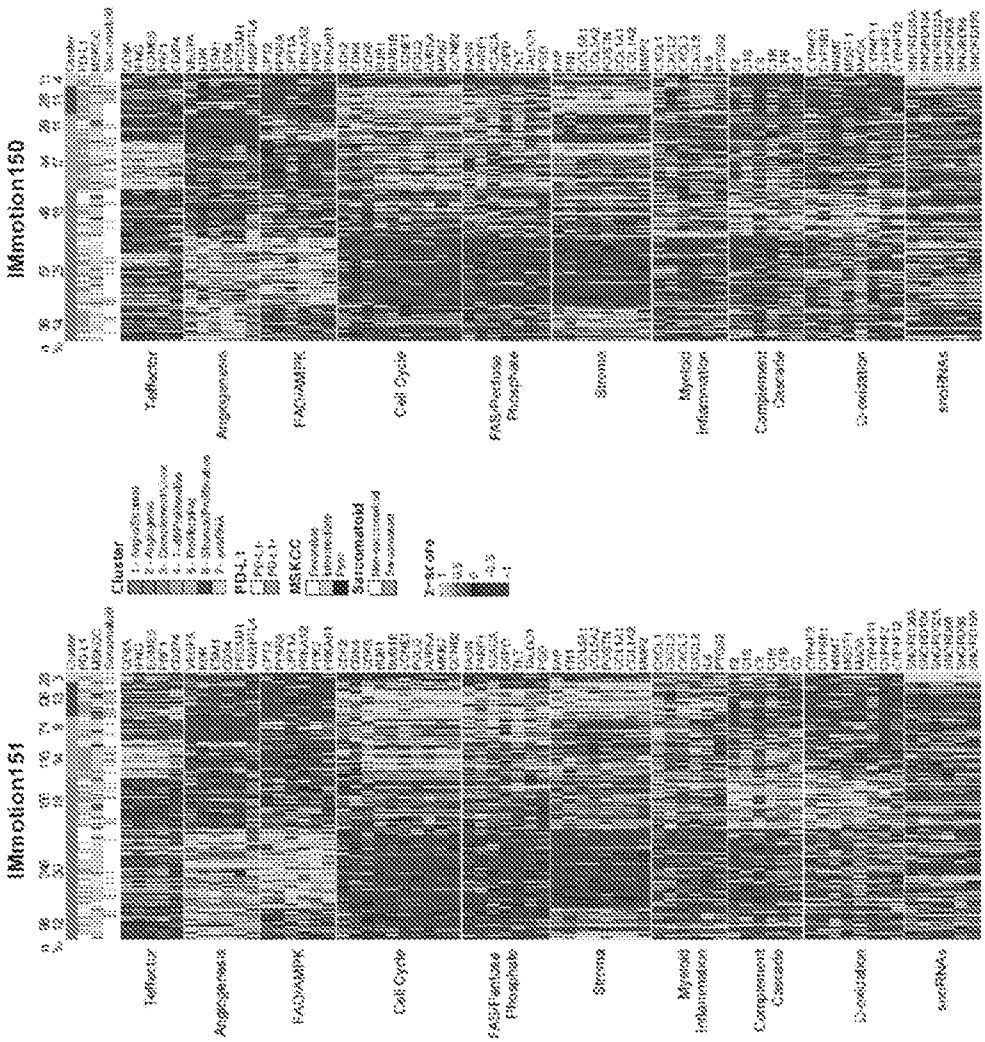
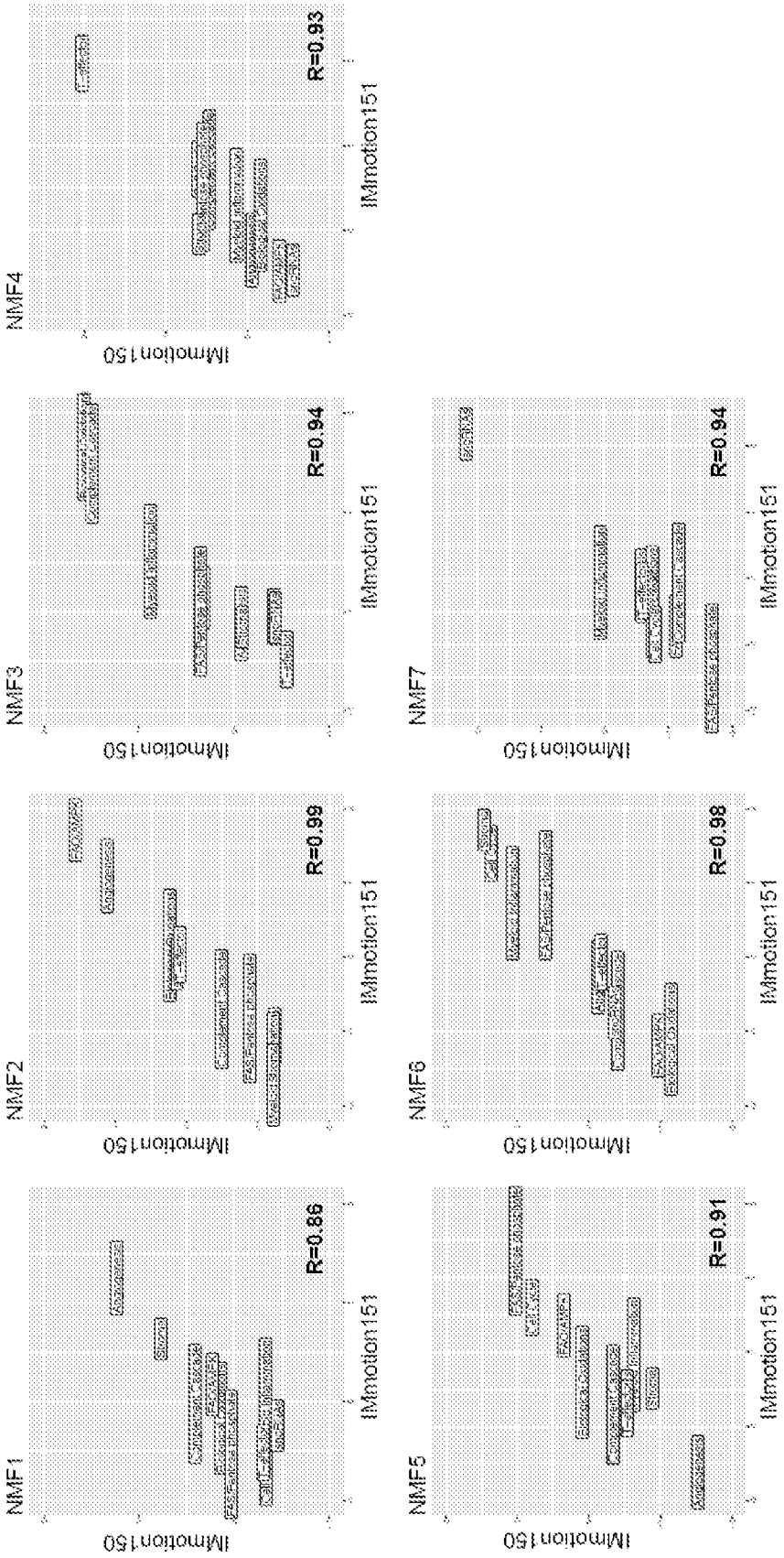

IMmotion151
IMmotion150
Cluster
PD-L1
MSKCC
Sarcomatoid
Response
Reflector
Angiogenesis
FAO/AMPK
Cell Cycle
FAS/Pentose Phosphate
Stroma
Myeloid Inflammation
Complement Cascade
Co-stimulation
snoRNAs

FIG. 5A

FIG. 5B


NMF1
R=0.86
NMF2
R=0.99
NMF3
R=0.94
NMF4
R=0.93
NMF5
R=0.91
NMF6
R=0.98
NMF7
R=0.94
IMmotion150
IMmotion151

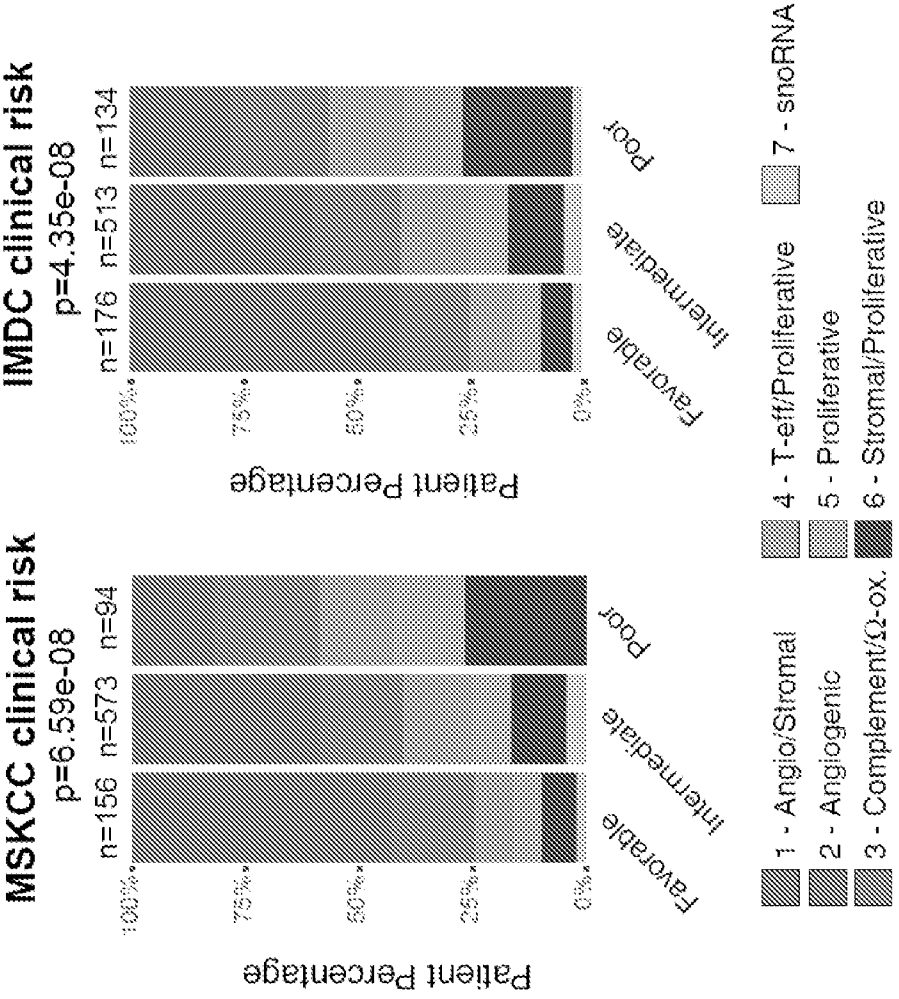
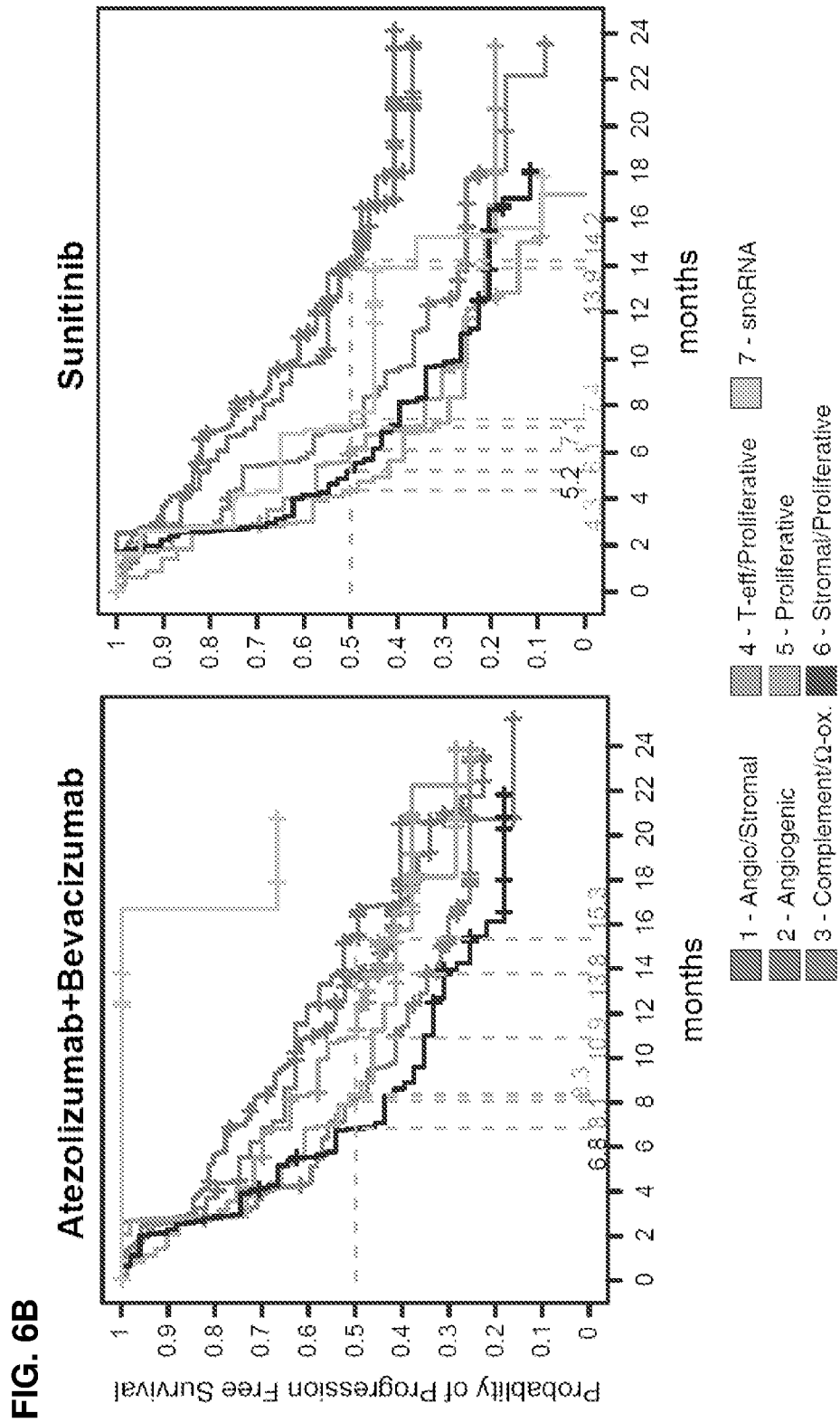

MSKCC clinical risk
p=6.59e-08
n=156 n=573 n=94
IMDC clinical risk
p=4.35e-08
n=176 n=513 n=134
Patient Percentage
100%
75%
50%
25%
0%
Favorable
Intermediate
Poor
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA

FIG. 6A

FIG. 6B


Atezolizumab+Bevacizumab
Sunitinib
Probability of Progression Free Survival
months
months
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA

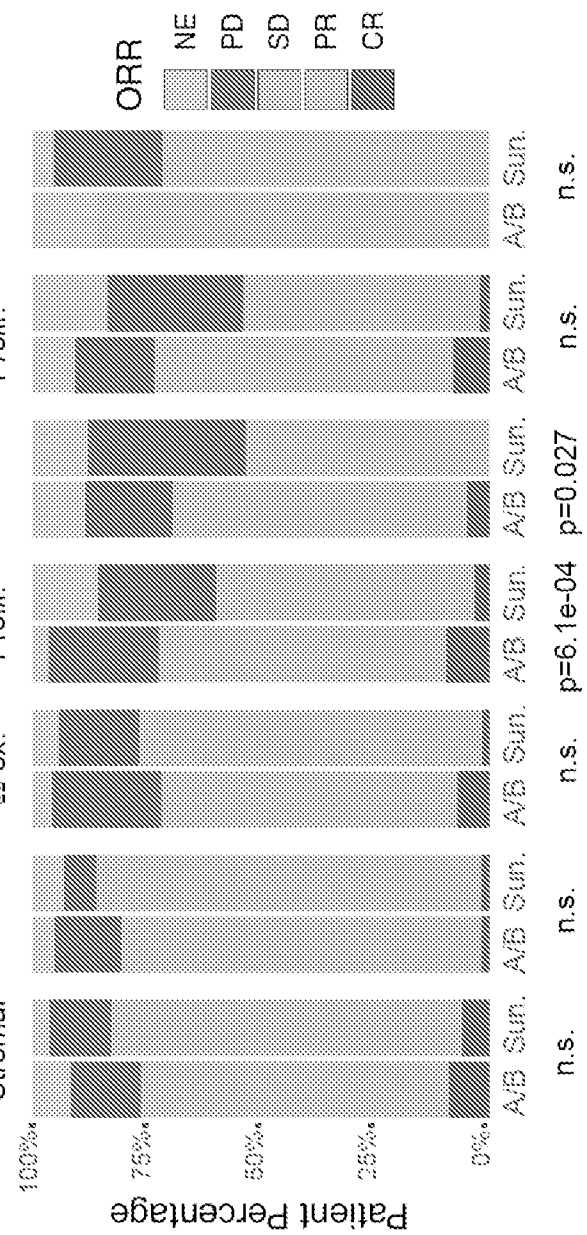

Cluster 1
Angio/
Stromal
Cluster 2
Angio
Cluster 3
Compl./
Ω-ox.
Cluster 4
Teff/
Prolif.
Cluster 5
Prolif.
Cluster 6
Stromal/
Prolif.
Cluster 7
snoRNA
ORR
NE
PD
SD
PR
CR
Patient Percentage
100%
75%
50%
25%
0%
A/B
Sum.
n.s.
n.s.
n.s.
p=6.1e-04
p=0.027
n.s.
n.s.

FIG. 6C

FIG. 6D

Cluster	PFS HR (95% CI)	p-value	A/B mPFS	Sunitinib mPFS
1 - Angio/stromal	1.11 (0.65−1.88)	0.708	15.3	13.9
2 - Angiogenic	1.16 (0.82−1.63)	0.397	13.8	14.2
3 - Complement/Ω-ox.	0.92 (0.63−1.34)	0.666	8.1	7.1
4 - T-eff/Proliferative	0.52 (0.33−0.82)	0.005	10.9	6.1
5 - Proliferative	0.47 (0.27−0.82)	0.007	8.3	4.3
6 - Stromal/Proliferative	0.81 (0.52−1.25)	0.331	6.8	5.2
7 - snoRNA	0.10 (0.01−0.77)	0.028	NR	7.4

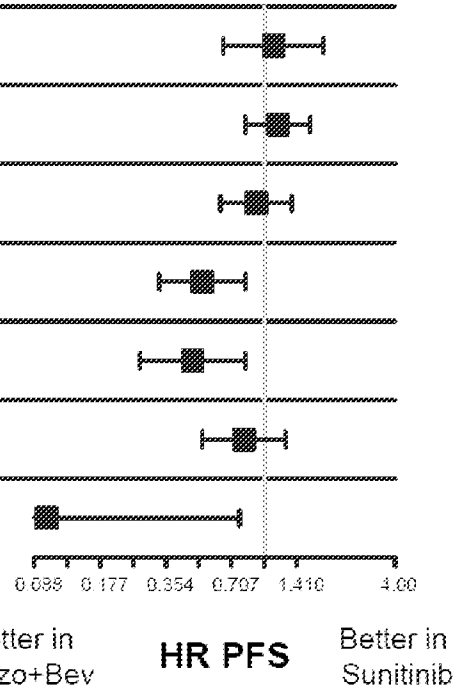


FIG. 7A

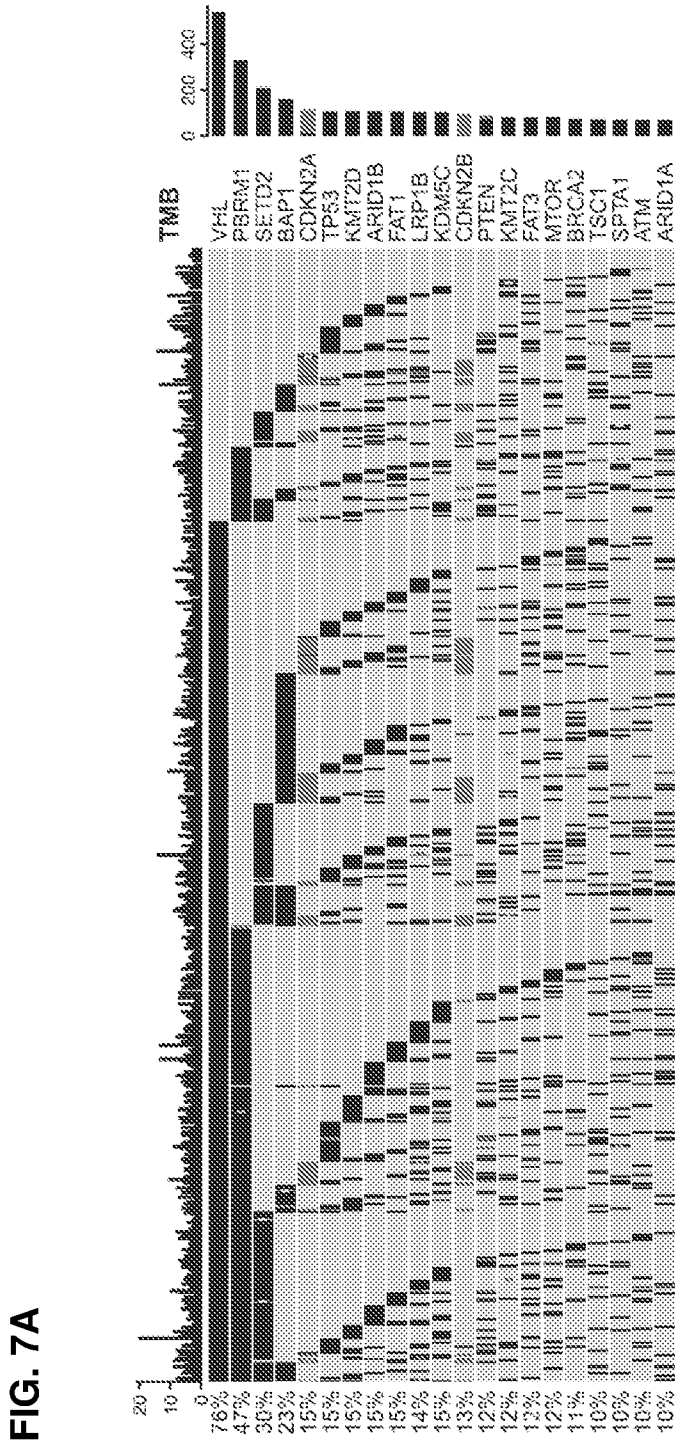
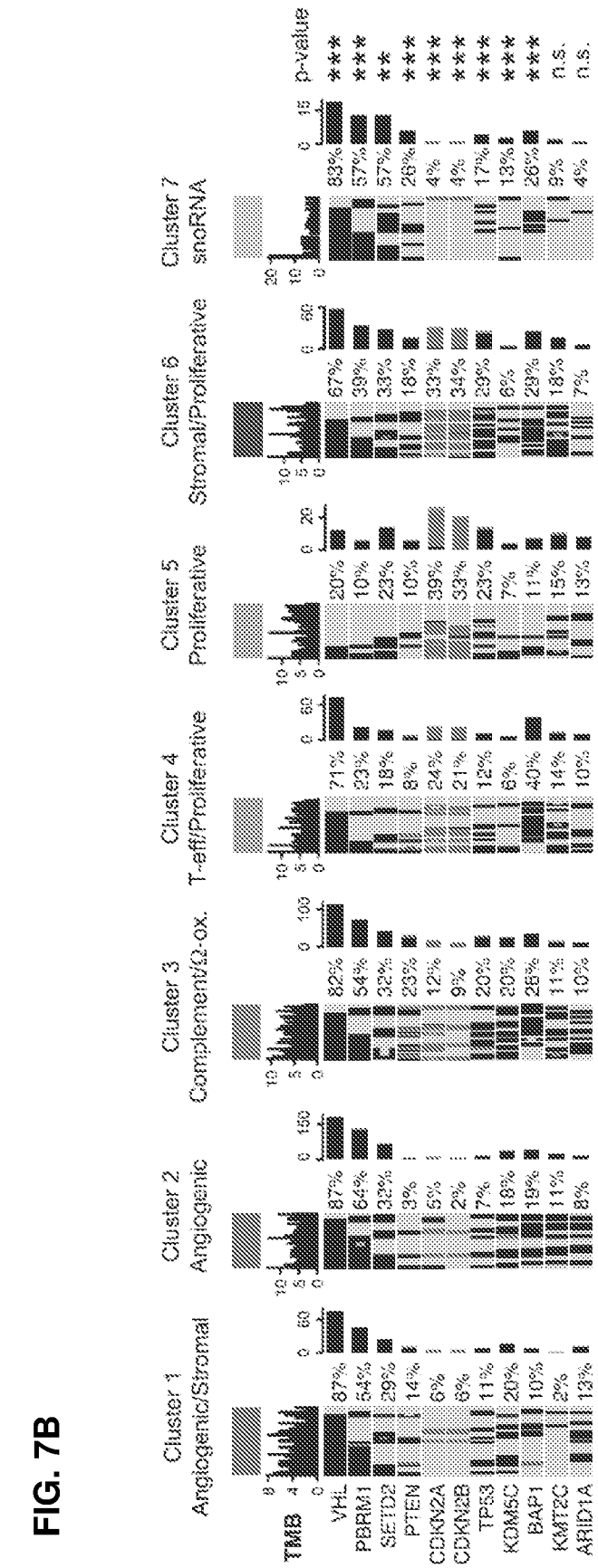

TMB
0
200
400
20
10
0
Alterations
short-variant
loss
amplification
deletion
rearrangement
truncation
VHL 76%
PBRM1 47%
SETD2 30%
BAP1 23%
CDKN2A 15%
TP53 15%
KMT2D 15%
ARID1B 15%
FAT1 14%
LRP1B 15%
KDM5C 13%
CDKN2B 12%
PTEN 12%
KMT2C 12%
FAT3 12%
MTOR 11%
BRCA2 10%
TSC1 10%
SPTA1 10%
ATM 10%
ARID1A 10%

FIG. 7B


Cluster 1
Angiogenic/Stromal
Cluster 2
Angiogenic
Cluster 3
Complement/Ω-ox.
Cluster 4
T-eff/Proliferative
Cluster 5
Proliferative
Cluster 6
Stromal/Proliferative
Cluster 7
snoRNA
TMB
VHL
PBRM1
SETD2
PTEN
CDKN2A
CDKN2B
TP53
KDM5C
BAP1
KMT2C
ARID1A
p-value
n.s.

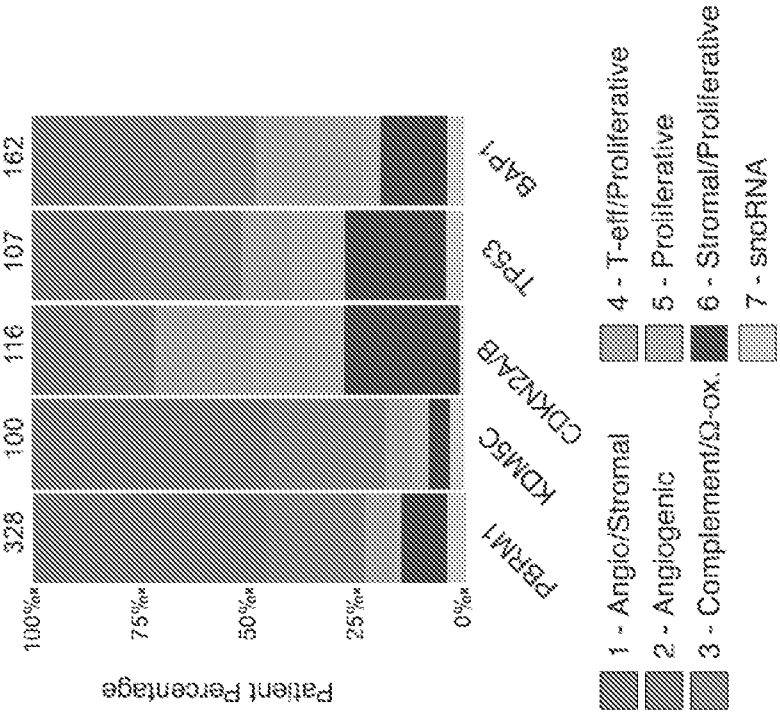

Patient Percentage
100%
75%
50%
25%
0%
n= 328
n= 100
n= 116
n= 107
n= 162
PBRM1
KDM6C
CDKN2AB
TP53
BAP1
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA

FIG. 7C

FIG. 7D

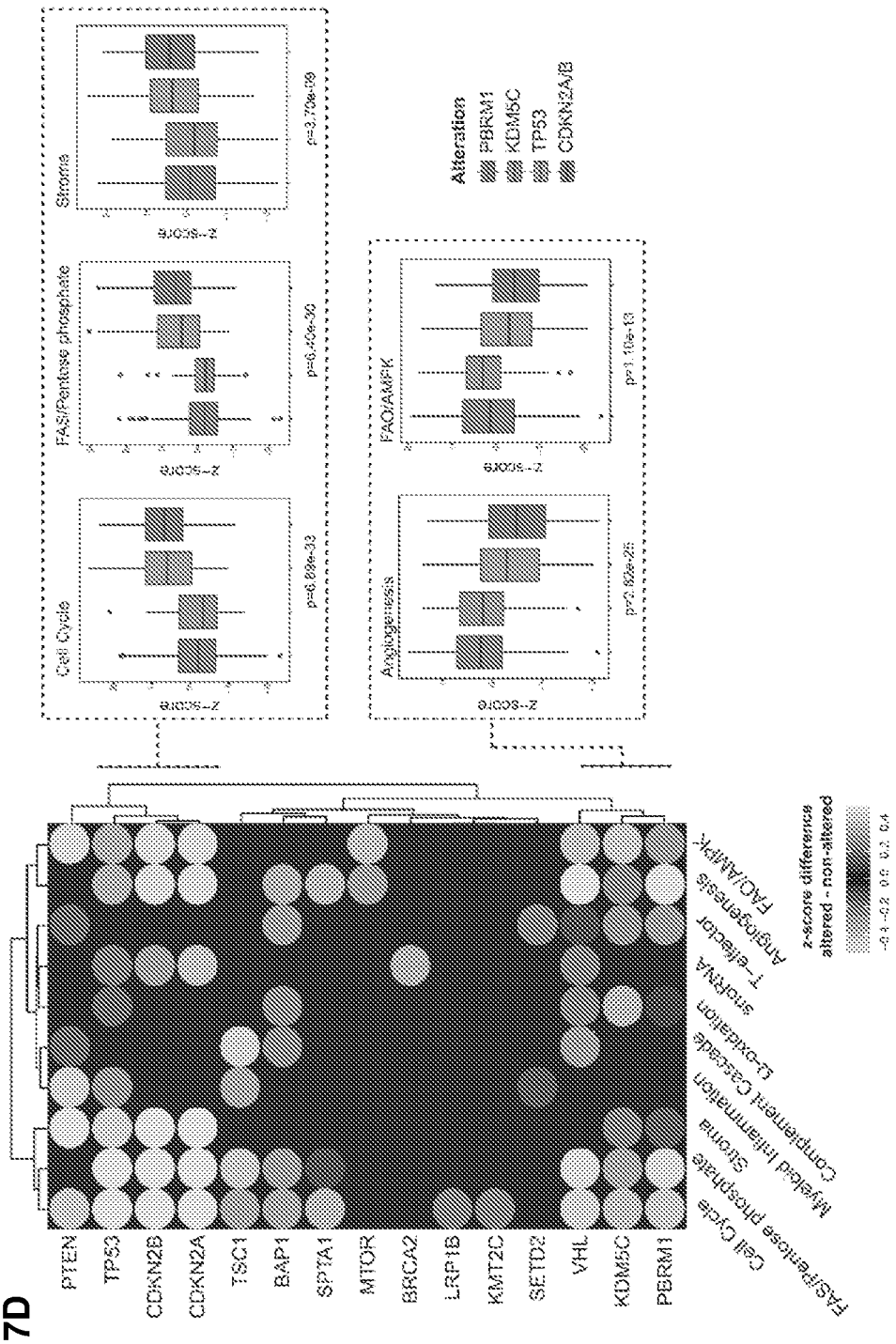

PTEN
TP53
CDKN2B
CDKN2A
TSC1
BAP1
SPTA1
MTOR
BRCA2
LRP1B
KMT2C
SETD2
VHL
KDM5C
PBRM1
Cell Cycle
FAS/Pentose phosphate
Myeloid Inflammation
Stroma
Complement Cascade
Up-Oxidation
snoRNA
T-elector
Angiogenesis
FAO/AMPK
z-score difference
altered - non-altered
Alteration
PBRM1
KDM5C
TP53
CDKN2A/B
Cell Cycle
FAS/Pentose phosphate
Stroma
Angiogenesis
FAO/AMPK
p=6.69e-33
p=6.40e-30
p=3.70e-09
p=2.62e-25
p=1.10e-13
z-score

FIG. 8A

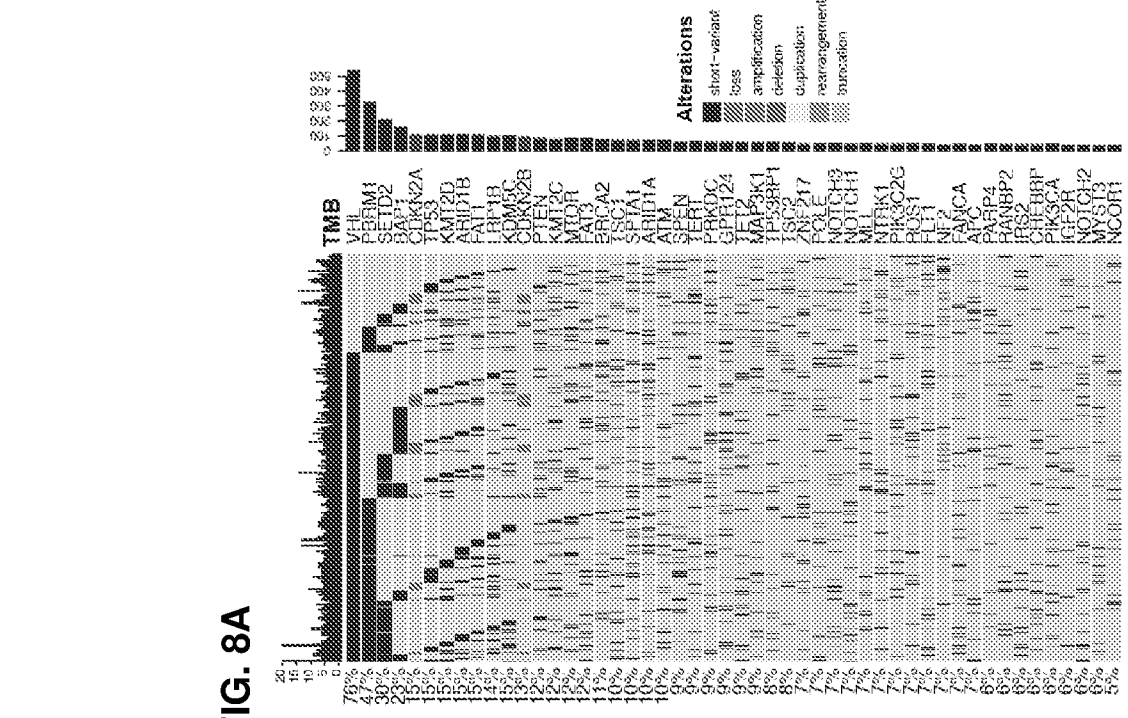

TMB
Alterations
short-variant
loss
amplification
deletion
duplication
rearrangement
truncation
VHL
PBRM1
SETD2
BAP1
CDKN2A
CDKN2B
TP53
KDM5C
PTEN
ARID1A
KMT2C

FIG. 8B

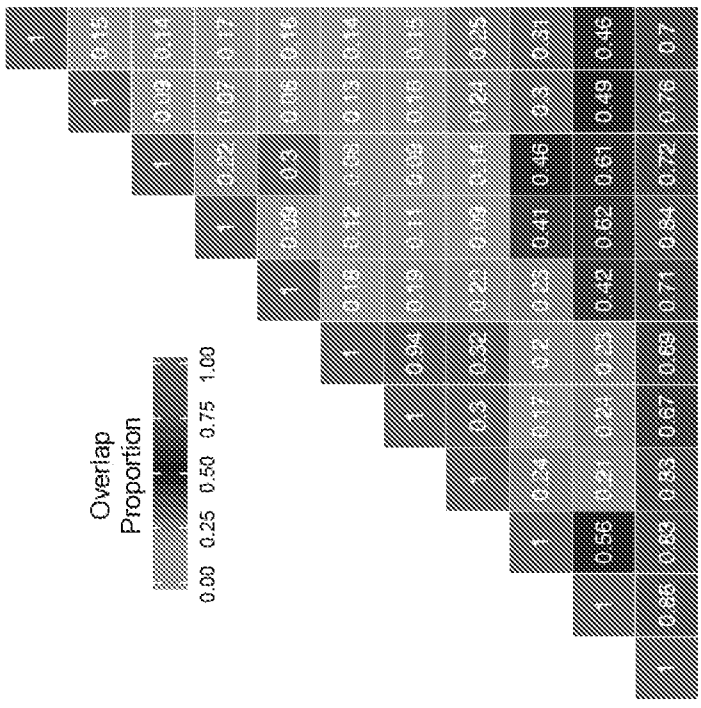

Overlap Proportion
0.00 0.25 0.50 0.75 1.00
KMT2C
ARID1A
PTEN
KDM5C
TP53
CDKN2B
CDKN2A
BAP1
SETD2
PBRM1
VHL

FIG. 8C

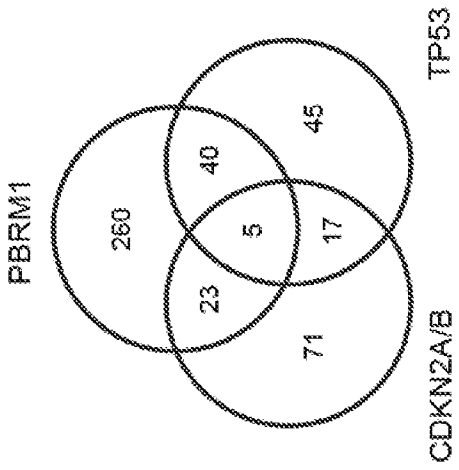

PBRM1
TP53
CDKN2A/B
260
40
45
5
23
17
71

FIG. 8D

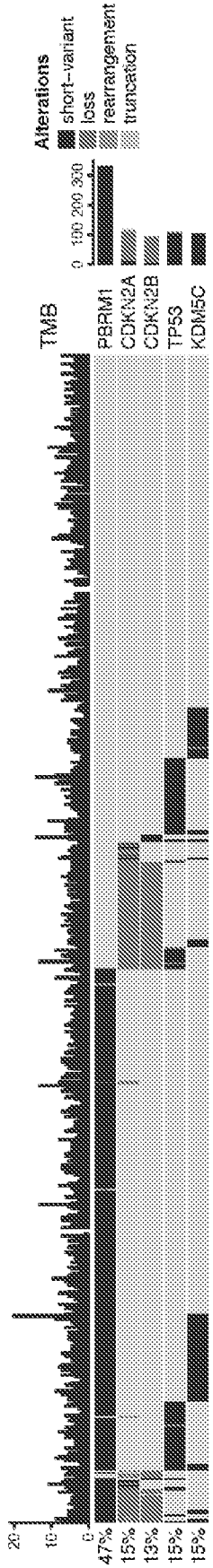

Alterations
short-variant
loss
rearrangement
truncation
TMB
0 100 200 300
PBRM1
CDKN2A
CDKN2B
TP53
KDM5C
47%
15%
13%
15%
15%

FIG. 8E

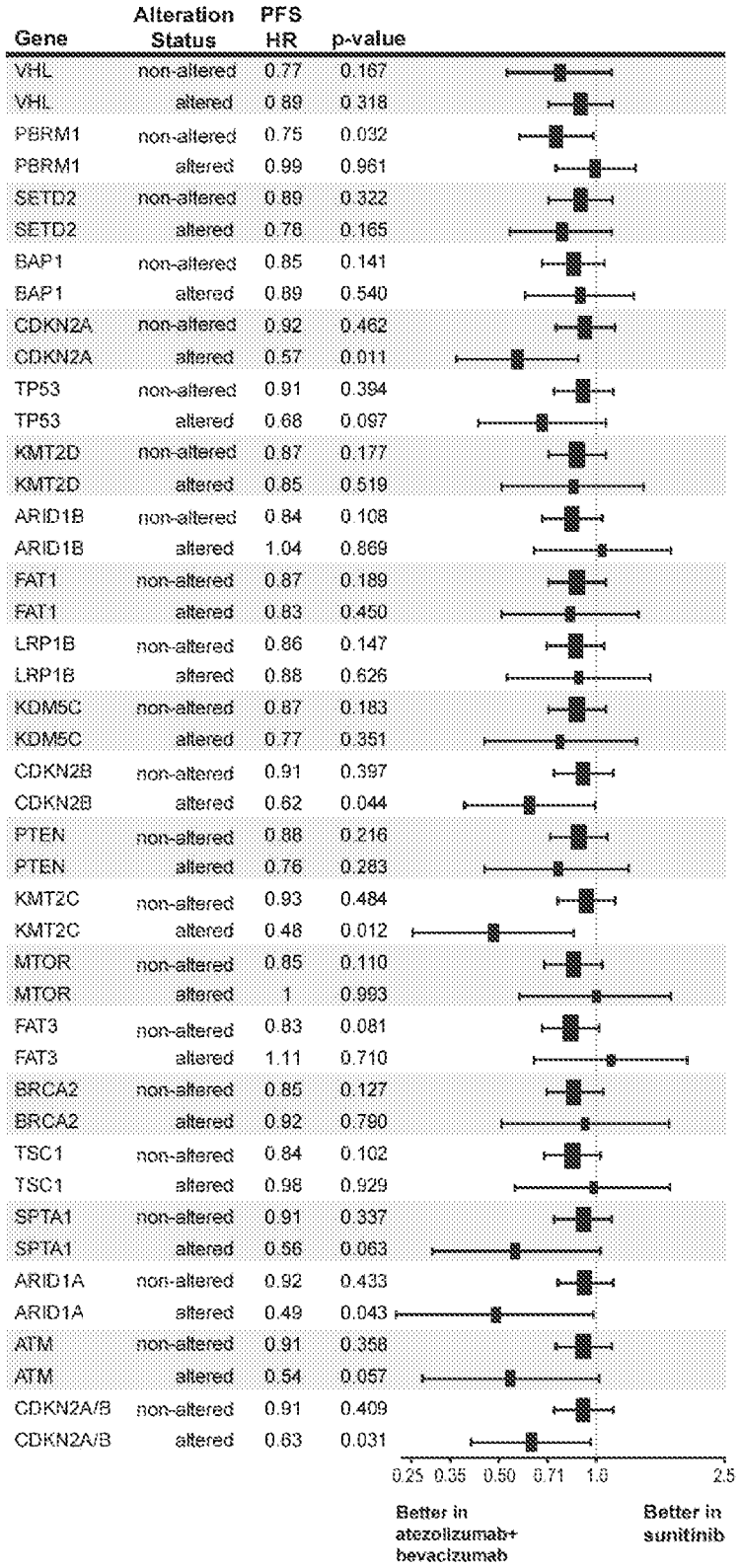

Gene
Alteration Status
PFS HR
p-value
VHL non-altered 0.77 0.167
VHL altered 0.89 0.318
PBRM1 non-altered 0.75 0.032
PBRM1 altered 0.99 0.961
SETD2 non-altered 0.89 0.322
SETD2 altered 0.76 0.165
BAP1 non-altered 0.85 0.141
BAP1 altered 0.89 0.540
CDKN2A non-altered 0.92 0.462
CDKN2A altered 0.57 0.011
TP53 non-altered 0.91 0.394
TP53 altered 0.68 0.097
KMT2D non-altered 0.87 0.177
KMT2D altered 0.85 0.519
ARID1B non-altered 0.84 0.108
ARID1B altered 1.04 0.869
FAT1 non-altered 0.87 0.189
FAT1 altered 0.83 0.450
LRP1B non-altered 0.86 0.147
LRP1B altered 0.88 0.626
KDM5C non-altered 0.87 0.183
KDM5C altered 0.77 0.351
CDKN2B non-altered 0.91 0.397
CDKN2B altered 0.62 0.044
PTEN non-altered 0.88 0.216
PTEN altered 0.76 0.283
KMT2C non-altered 0.93 0.484
KMT2C altered 0.48 0.012
MTOR non-altered 0.85 0.110
MTOR altered 1 0.993
FAT3 non-altered 0.83 0.081
FAT3 altered 1.11 0.710
BRCA2 non-altered 0.85 0.127
BRCA2 altered 0.92 0.790
TSC1 non-altered 0.84 0.102
TSC1 altered 0.98 0.929
SPTA1 non-altered 0.91 0.337
SPTA1 altered 0.56 0.063
ARID1A non-altered 0.92 0.433
ARID1A altered 0.49 0.043
ATM non-altered 0.91 0.358
ATM altered 0.54 0.057
CDKN2A/B non-altered 0.91 0.409
CDKN2A/B altered 0.63 0.031
0.25 0.35 0.50 0.71 1.0 2.5
Better in atezolizumab+ bevacizumab
Better in sunitinib

FIG. 9A

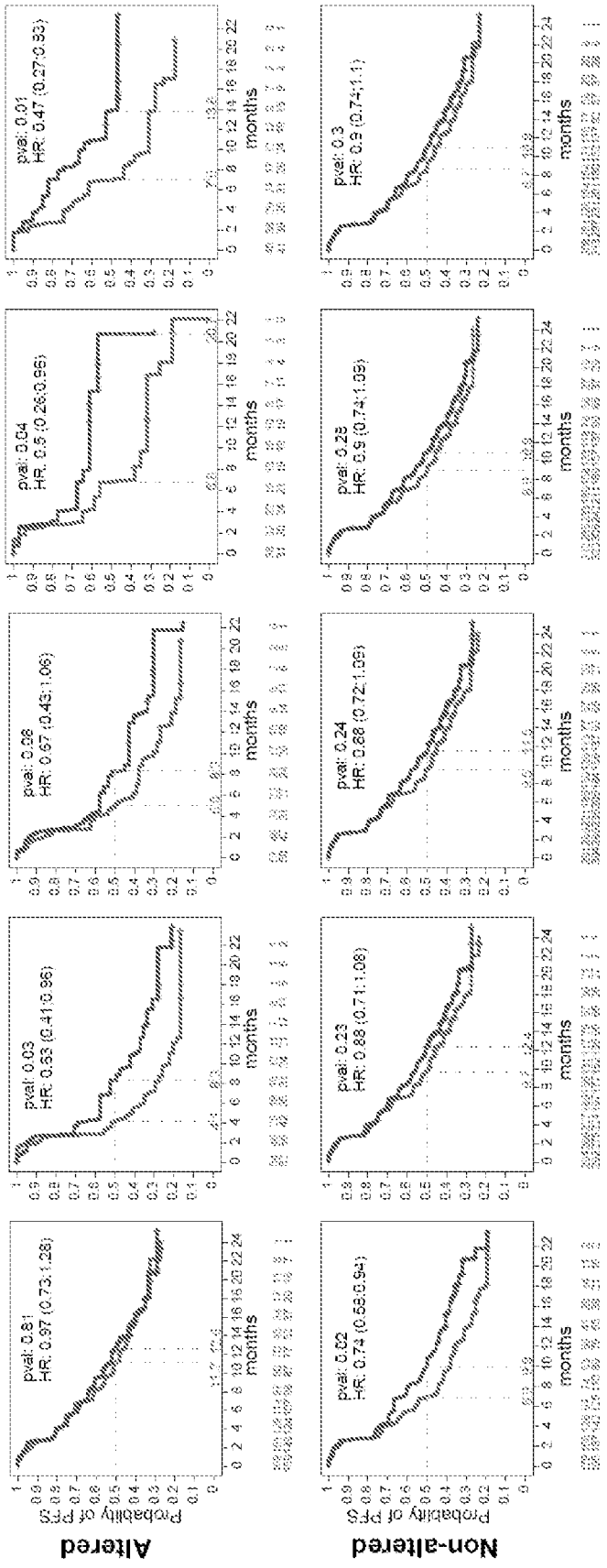

PBRM1
CDKN2A/B
TP53
ARID1A
KMT2C
Altered
Non-altered
Probability of PFS
months
pval: 0.81
HR: 0.97 (0.73;1.28)
pval: 0.03
HR: 0.63 (0.41;0.96)
pval: 0.26
HR: 0.87 (0.43;1.06)
pval: 0.04
HR: 0.5 (0.26;0.96)
pval: 0.01
HR: 0.47 (0.27;0.83)
pval: 0.02
HR: 0.74 (0.58;0.94)
pval: 0.23
HR: 0.88 (0.71;1.08)
pval: 0.24
HR: 0.88 (0.72;1.09)
pval: 0.23
HR: 0.9 (0.74;1.09)
pval: 0.3
HR: 0.9 (0.74;1.1)
Atezolizumab+Bevacizumab
Sunitinib

FIG. 9B

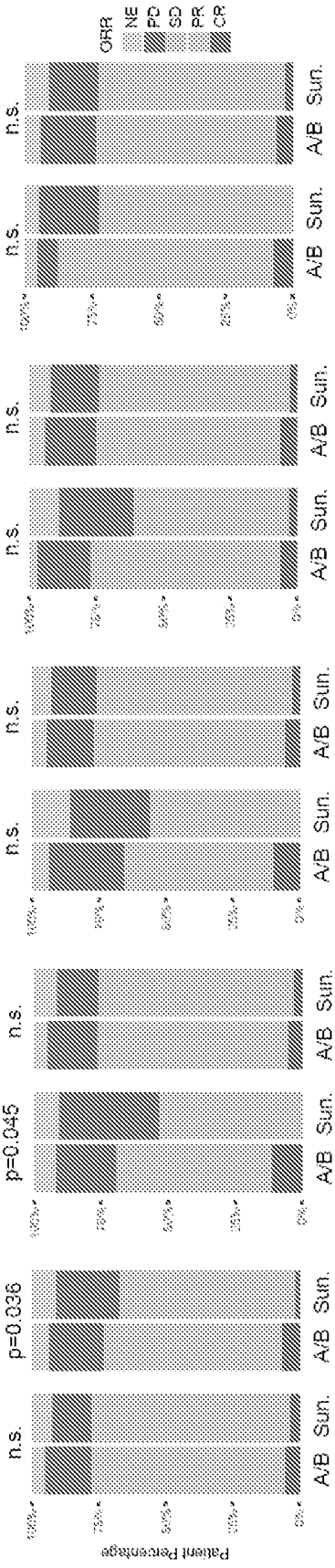

PBRM1
CDKN2A/B
TP53
ARID1A
KMT2C
Altered
n.s.
Non-altered
p=0.036
Altered
p=0.045
Non-altered
n.s.
A/B
Sun.
Patient Percentage
ORR
NE
PD
SD
PR
CR

FIG. 9C

Gene	Treatment Arm	PFS HR (95% CI)	p-value	mPFS Altered (n)	mPFS Non-altered (n)
PBRM1	Atezolizumab+Bevacizumab	0.88 (0.68–1.16)	0.367	12.6 (159)	9.9 (195)
PBRM1	Sunitinib	0.67 (0.51–0.87)	0.003	11.2 (169)	6.9 (179)
CDKN2A/B	Atezolizumab+Bevacizumab	1.35 (0.97–1.89)	0.077	8.3 (62)	12.4 (292)
CDKN2A/B	Sunitinib	2.04 (1.47–2.83)	<0.001	4.1 (54)	9.7 (294)
TP53	Atezolizumab+Bevacizumab	1.30 (0.90–1.87)	0.161	8.3 (50)	11.5 (304)
TP53	Sunitinib	1.79 (1.29–2.48)	0.001	5.1 (57)	9.5 (291)
ARID1A	Atezolizumab+Bevacizumab	0.62 (0.36–1.07)	0.083	20.7 (31)	10.9 (323)
ARID1A	Sunitinib	1.34 (0.89–2.02)	0.160	6.8 (36)	8.9 (312)
KMT2C	Atezolizumab+Bevacizumab	0.69 (0.44–1.10)	0.117	13.8 (41)	10.9 (313)
KMT2C	Sunitinib	1.28 (0.87–1.87)	0.213	7.0 (40)	8.7 (308)

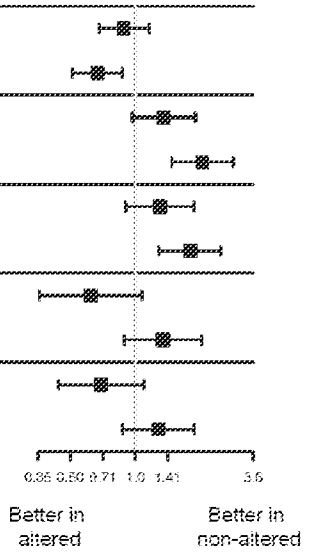


FIG. 10A

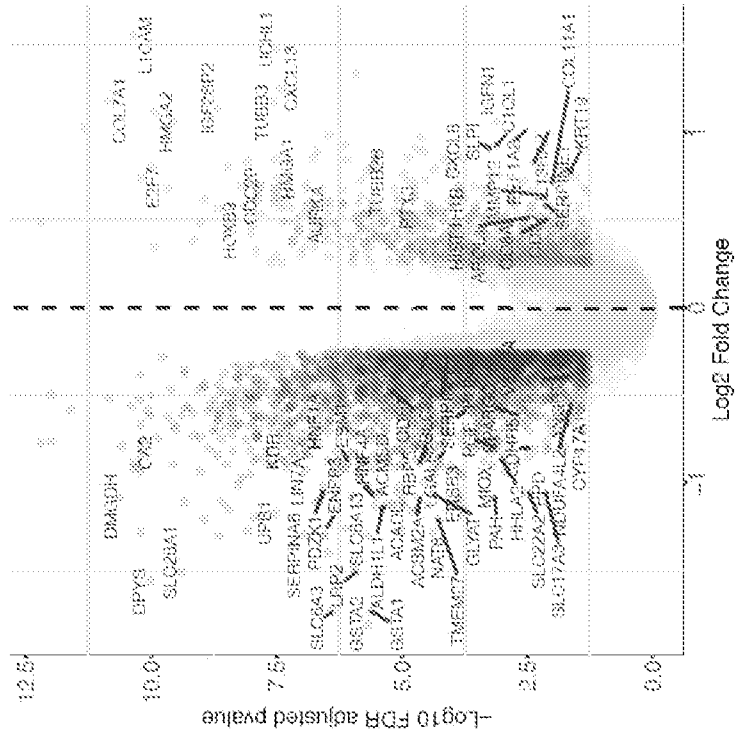


FIG. 10B

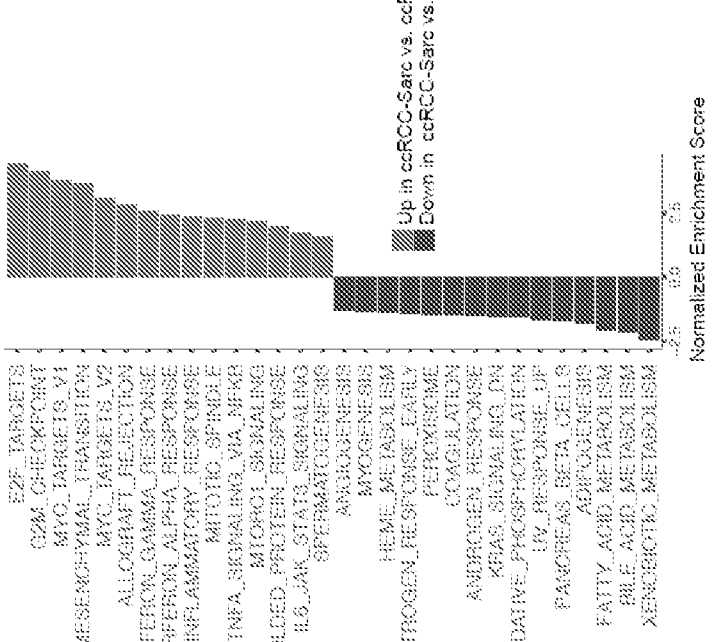


FIG. 10C

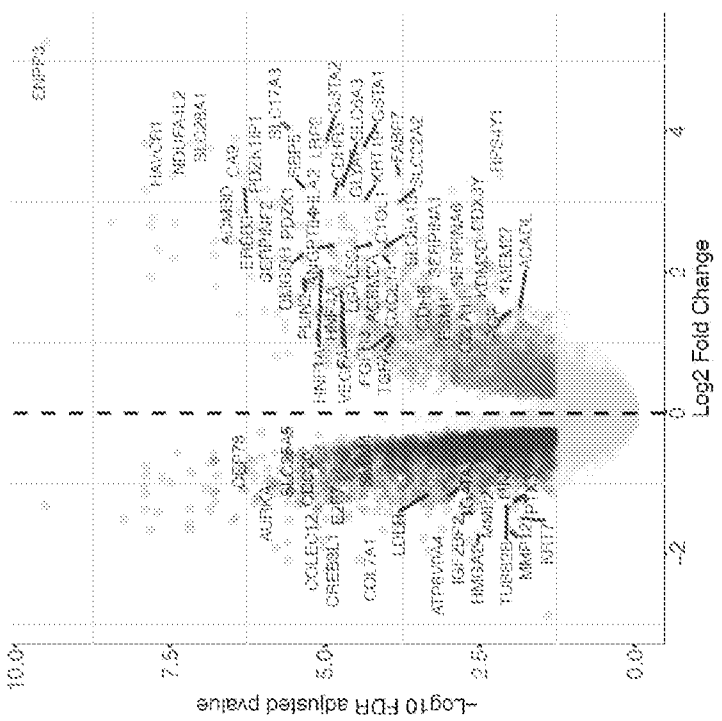


FIG. 10D

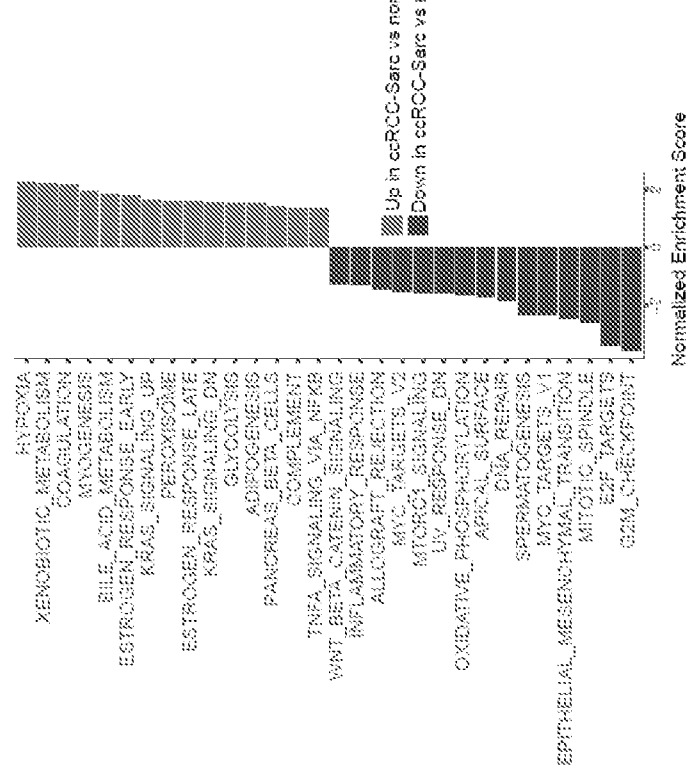


FIG. 10E

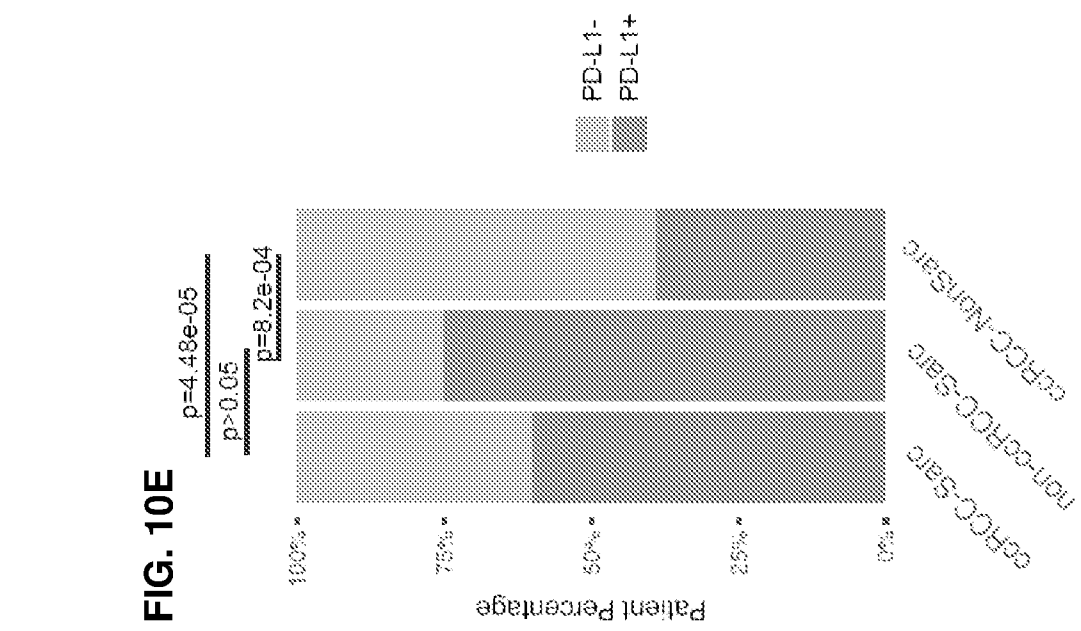


FIG. 10F

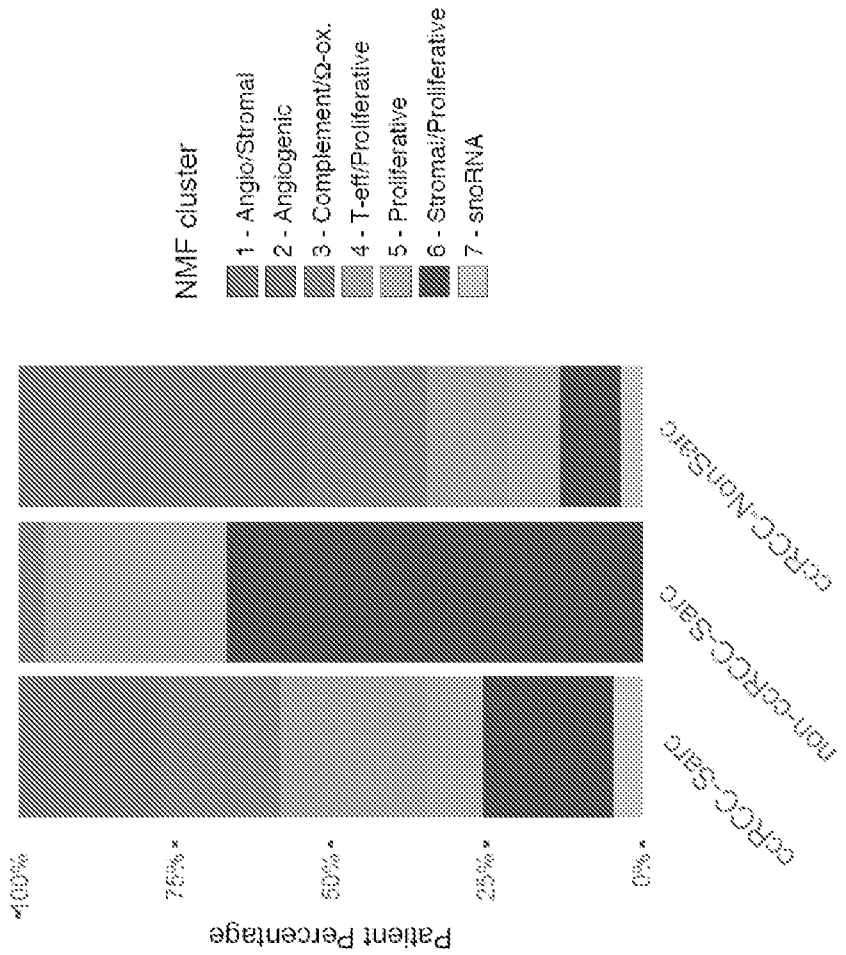


FIG. 11A

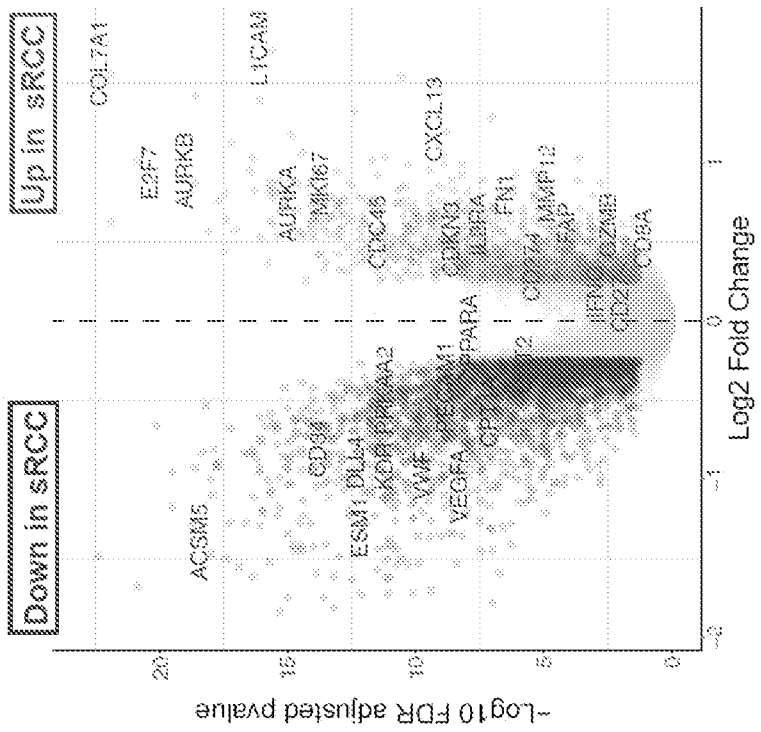
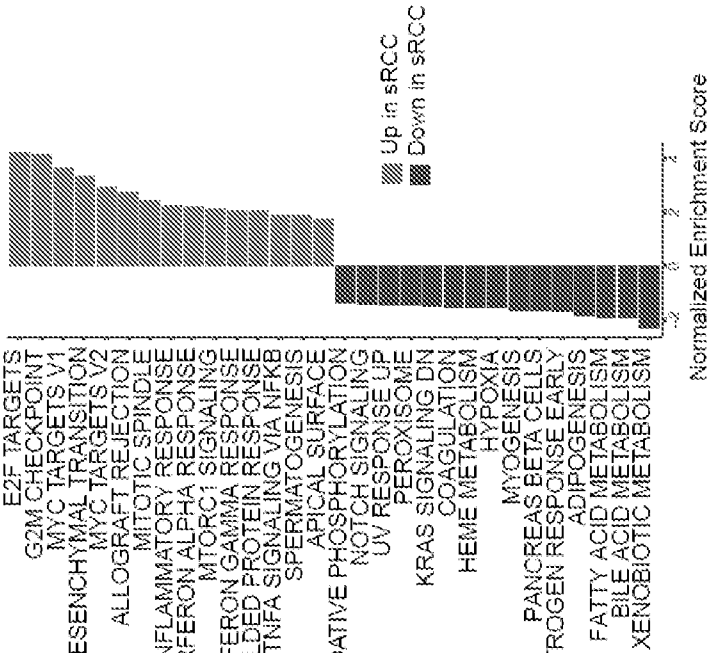


FIG. 11B



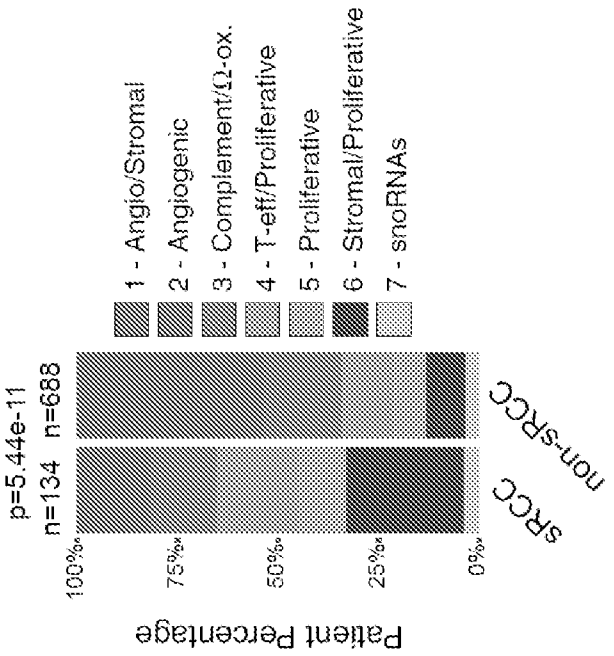

p=5.44e-11
n=134 n=688
100%
75%
50%
25%
0%
Patient Percentage
SRCC
non-SRCC
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNAs

FIG. 11C

FIG. 11D

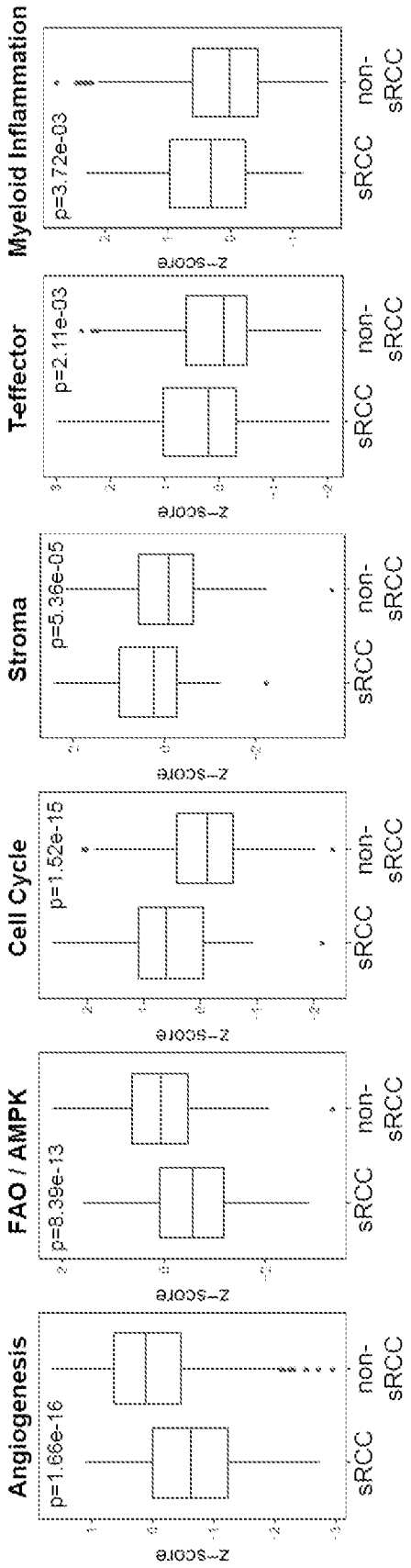

Angiogenesis
p=1.66e-16
FAO / AMPK
p=8.39e-13
Cell Cycle
p=1.52e-15
Stroma
p=5.36e-05
T-effector
p=2.11e-03
Myeloid Inflammation
p=3.72e-03
Z-score
sRCC
non-sRCC

FIG. 11E

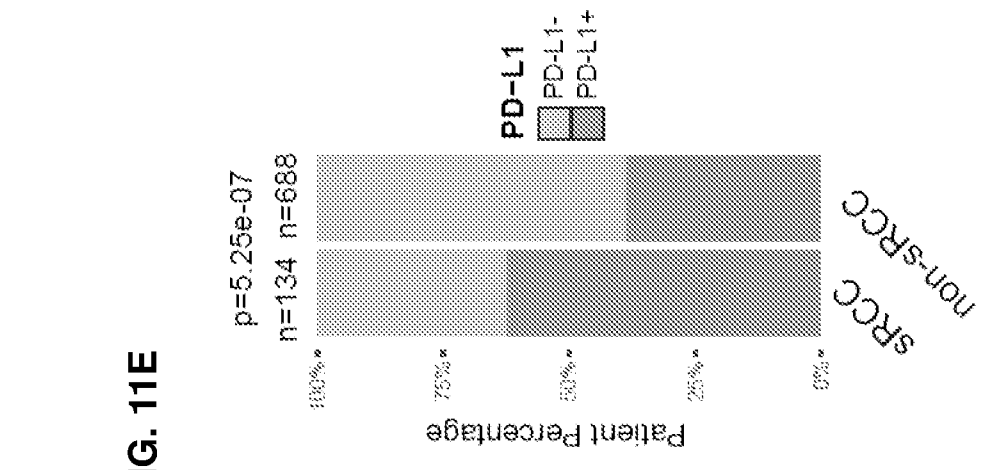


FIG. 11F

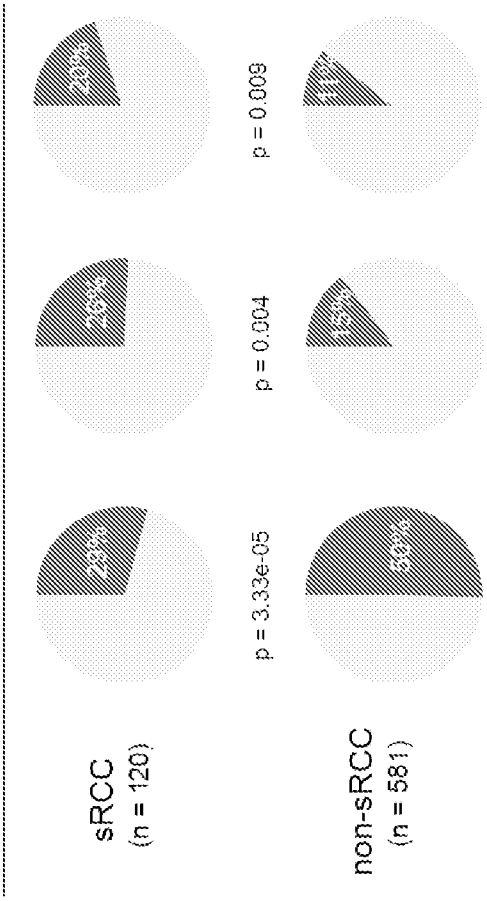


FIG. 11H

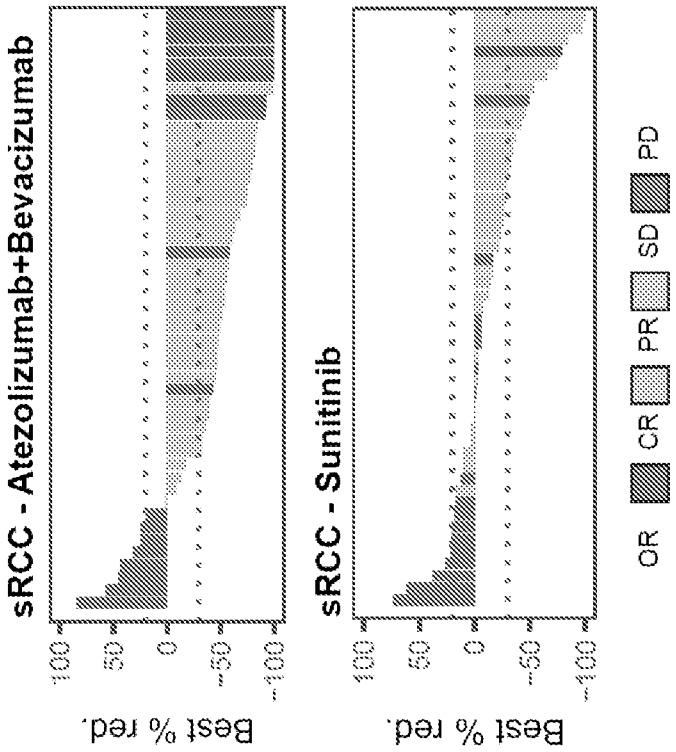
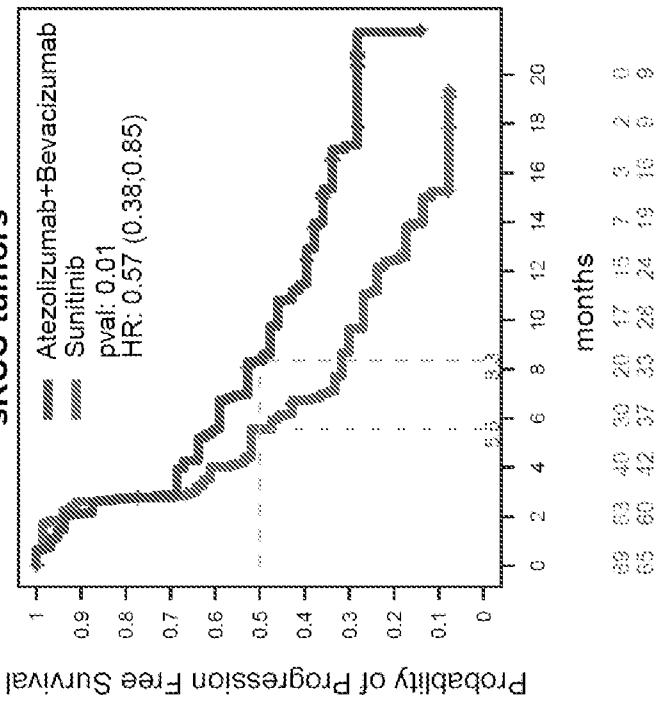


FIG. 11G



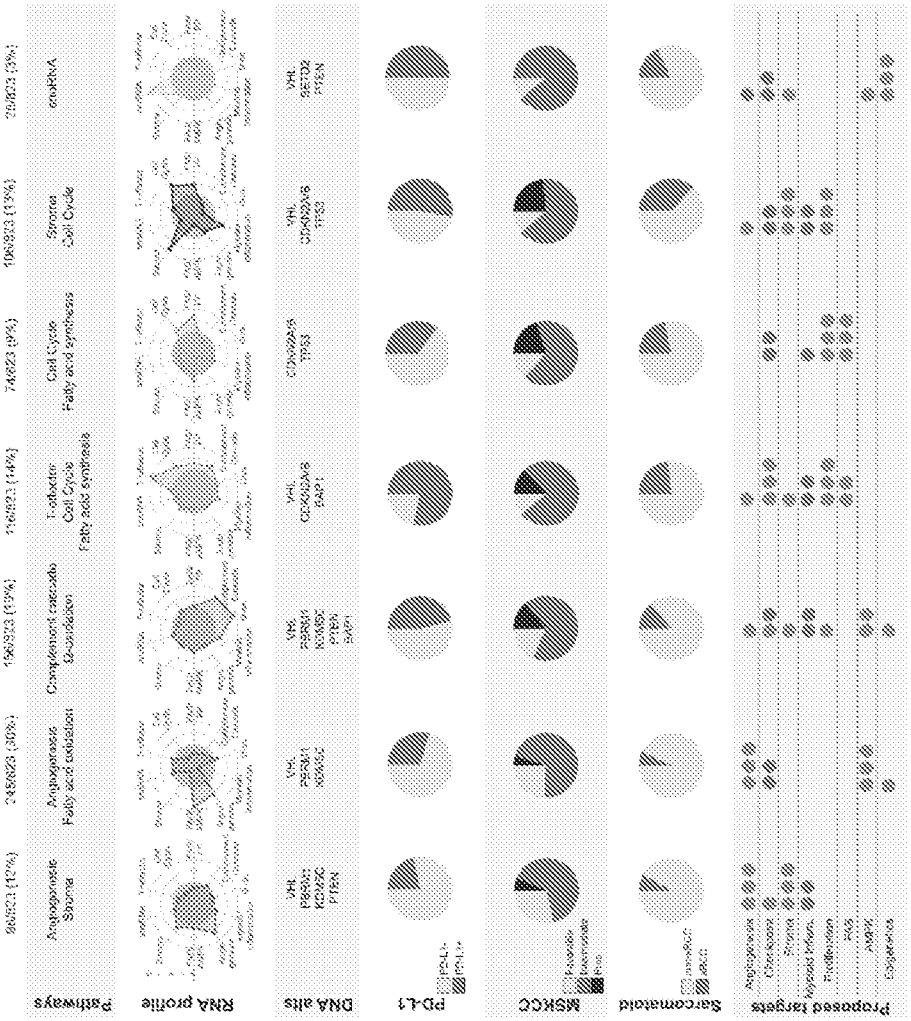

Cluster 1
Cluster 2
Cluster 3
Cluster 4
Cluster 5
Cluster 6
Cluster 7
Pathways
RNA profile
DNA alts
PD-L1
MSKCC
Sarcomatoid
Proposed targets

FIG. 12

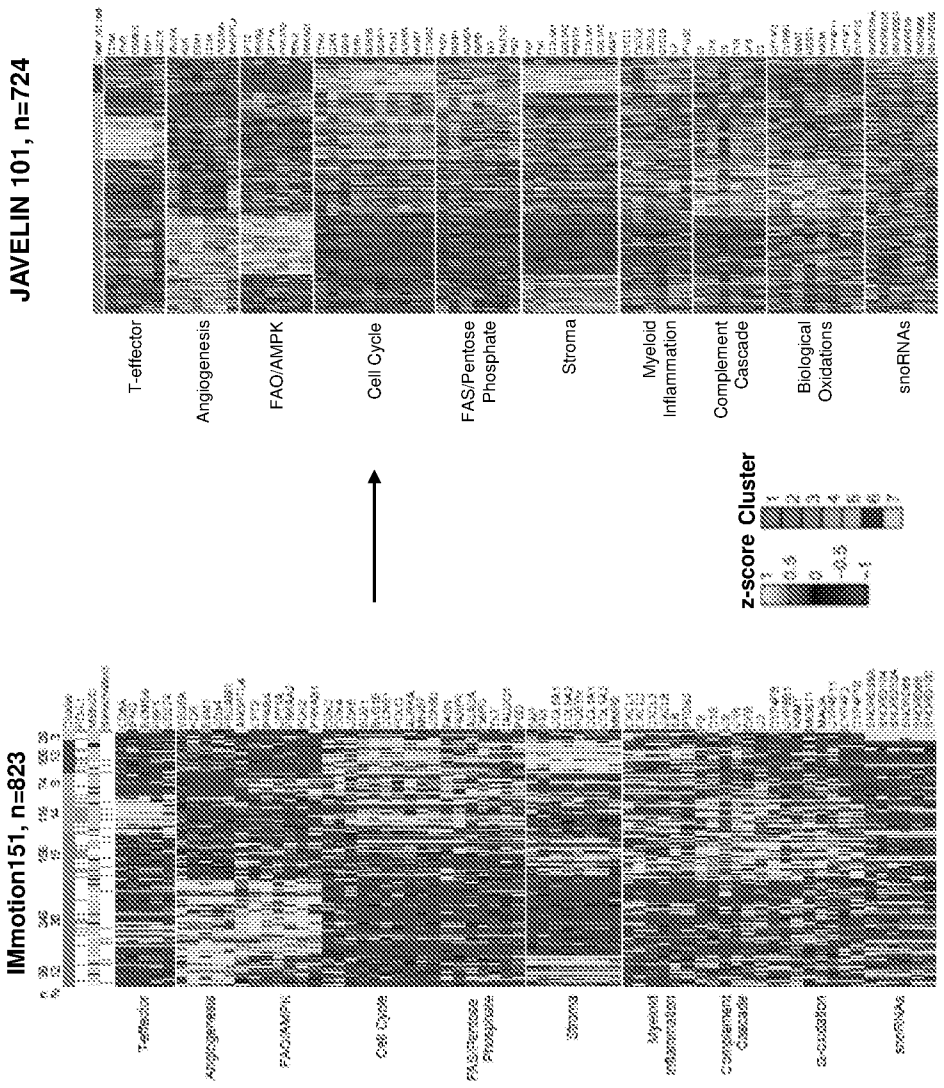

IMmotion151, n=823
JAVELIN 101, n=724
T-effector
Angiogenesis
FAO/AMPK
Cell Cycle
FAS/Pentose Phosphate
Stroma
Myeloid Inflammation
Complement Cascade
Biological Oxidations
snoRNAs
z-score
Cluster

FIG. 13A

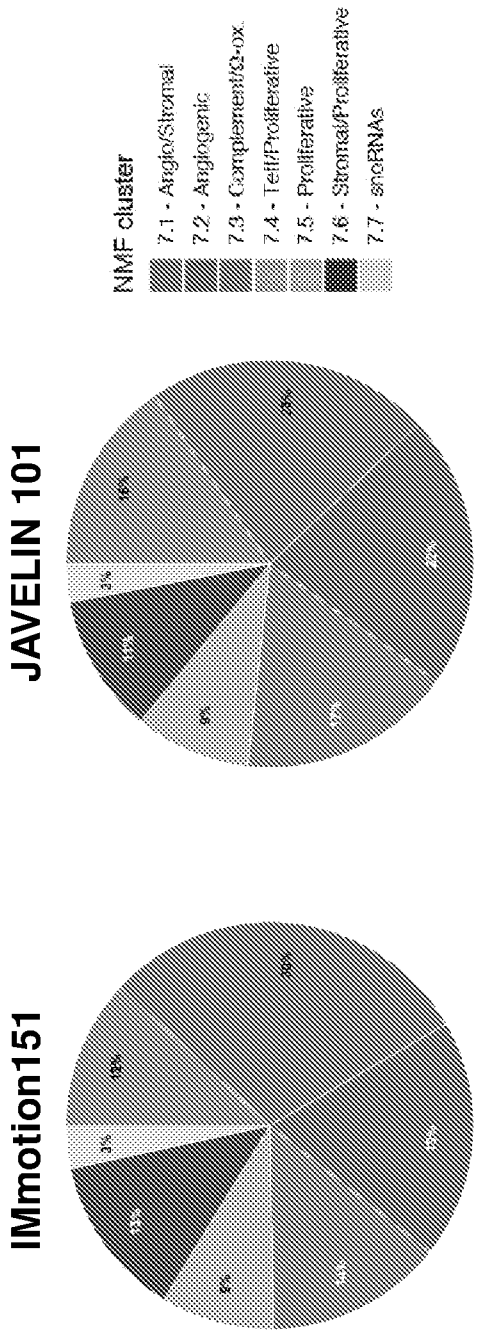

IMmotion151
JAVELIN 101
NMF cluster
7.1 - Angio/Stromal
7.2 - Angiogenic
7.3 - Complement/Cox
7.4 - Teff/Proliferative
7.5 - Proliferative
7.6 - Stromal/Proliferative
7.7 - smoRNAs

FIG. 13B

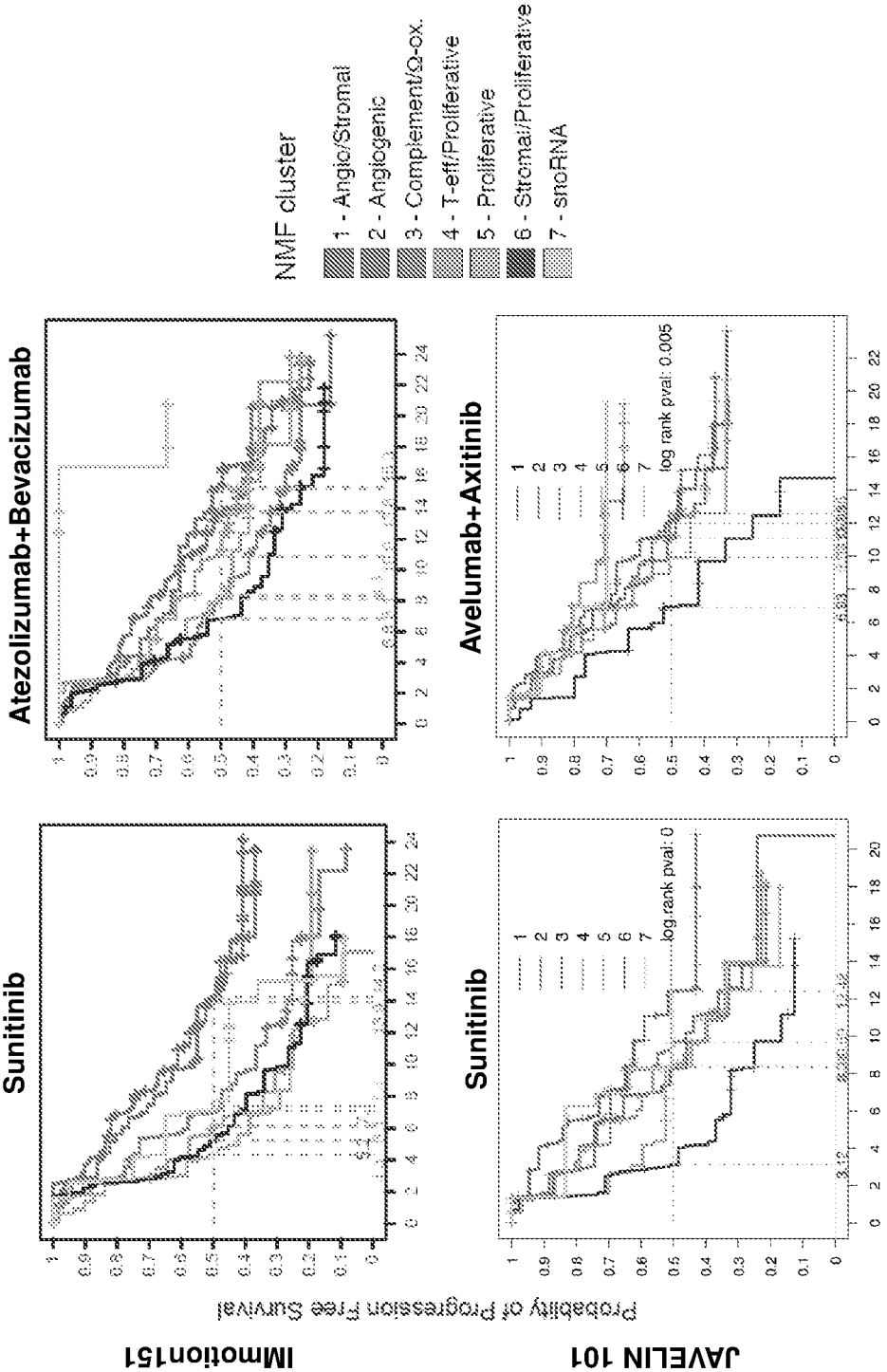
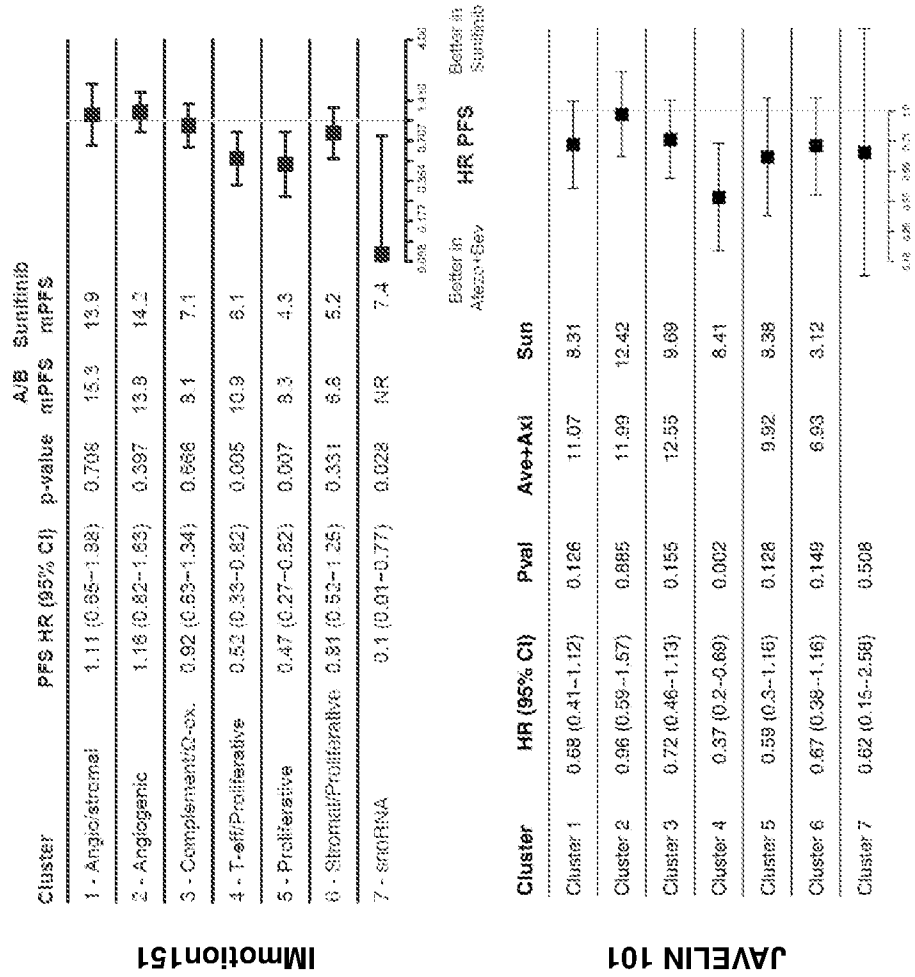

NMF cluster
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stroma/Proliferative
7 - snoRNA
Atezolizumab+Bevacizumab
Sunitinib
IMotion151
Avelumab+Axitinib
Sunitinib
JAVELIN 101
log rank pval: 0.005
log rank pval: 0
Probability of Progression Free Survival

FIG. 14A

FIG. 14B


IMotion151
Cluster
PFS HR (95% CI)
p-value
A/B mPFS
Sunitinib mPFS
1 - Angio/stromal
1.11 (0.85–1.38)
0.708
15.3
13.9
2 - Angiogenic
1.16 (0.82–1.63)
0.397
13.8
14.2
3 - Complement/Ox.
0.92 (0.63–1.34)
0.666
8.1
7.1
4 - T-eff/Proliferative
0.52 (0.33–0.82)
0.005
10.9
8.1
5 - Proliferative
0.47 (0.27–0.82)
0.007
8.3
4.3
6 - Stromal/Proliferative
0.81 (0.52–1.25)
0.331
6.6
5.2
7 - sroRNA
0.1 (0.01–0.77)
0.022
NR
7.4
Better in Ave+Axi
HR PFS
Better in Sunitinib
JAVELIN 101
Cluster
HR (95% CI)
Pval
Ave+Axi
Sun
Cluster 1
0.68 (0.41–1.12)
0.126
11.07
8.31
Cluster 2
0.96 (0.59–1.57)
0.885
11.99
12.42
Cluster 3
0.72 (0.46–1.13)
0.155
12.55
9.69
Cluster 4
0.37 (0.2–0.69)
0.002
8.41
Cluster 5
0.59 (0.3–1.16)
0.128
9.92
8.38
Cluster 6
0.67 (0.38–1.16)
0.149
8.93
3.12
Cluster 7
0.62 (0.15–2.58)
0.508

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/058362

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6886
ADD.

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)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOTZER ROBERT J ET AL: "Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade", CANCER CELL, CELL PRESS, US, vol. 38, no. 6, 5 November 2020 (2020-11-05), page 803, XP086409097, ISSN: 1535-6108, DOI: 10.1016/J.CCELL.2020.10.011 [retrieved on 2020-11-05] the whole document	1-56
X	WO 2020/081767 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]) 23 April 2020 (2020-04-23) the whole document	45

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[x] Further documents are listed in the continuation of Box C.

[x] 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2022	01/08/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Botz, Jürgen

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/058362

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/160841 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]) 7 September 2018 (2018-09-07) the whole document	45
A	WO 2011/085263 A2 (GENOMIC HEALTH INC [US]; COWENS WAYNE [US] ET AL.) 14 July 2011 (2011-07-14) the whole document	1-56
A	VUONG LYNDA ET AL: "Tumor Microenvironment Dynamics in Clear-Cell Renal Cell Carcinoma", CANCER DISCOVERY, vol. 9, no. 10, 1 October 2019 (2019-10-01), pages 1349-1357, XP055933177, US ISSN: 2159-8274, DOI: 10.1158/2159-8290.CD-19-0499 the whole document	1-56

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/058362

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/058362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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