TREATMENT OF CANCER WITH TG02

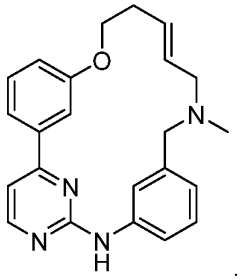
BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides therapeutic methods of treating a cancer patient with TG02 and a second therap eutic agent, e.g., TG02 and an immune checkpoint inhibitor, TG02 and a COX-2 inhibitor, and TG02 and an immune checkpoint inhibitor and a COX-2 inhibitor.

Background

[0002] TG02 is a pyrimidine-based multi-kinase inhibitor that inhibits CDKs 1, 2, 5, 7 and 9 together with JAK2 and FLT3. It dose-dependently inhibits signaling pathways downstream of CDKs, JAK2 and FLT3 in cancer cells with the main targets being CDKs. TG02 is anti-proliferative in a broad range of tumor cell lines, inducing G1 cell cycle arrest and apoptosis. Primary cultures of progenitor cells derived from acute myeloid leukemia (AML) and polycythemia vera patients are very sensitive to TG02. Comparison with reference inhibitors that block only one of the main targets of TG02 demonstrate the benefit of combined CDK and JAK2/FLT3 inhibition in cell lines as well as primary cells. *See* Goh *et al.*, *Leukemia 26*:236-43 (2012). TG02 is also known as SB1317 and by its chemical name: (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene. TG02 is disclosed as Compound 1 in US 8,143,255. US 9,120,815 discloses various salt, e.g., TG02 citrate, and crystalline forms of TG02. The chemical structure of TG02 is:



BRIEF SUMMARY OF THE INVENTION

[0003] In one aspect, the present disclosure provides therapeutic methods of treating a cancer patient, the methods comprising administering to the patient a therapeutically effective amount of TG02. In another aspect, the patient's cancer is characterized as overexpressing of MYC, MCL1, or both.

[0004] In another aspect, the present disclosure provides therapeutic methods of treating a cancer patient, the methods comprising administering to the patient therapeutically effective amounts of TG02 and an immune checkpoint inhibitor, e.g., a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, or a cd47 inhibitor.

[0005] In another aspect, the present disclosure provides therapeutic methods of treating a cancer patient, the methods comprising administering to the patient therapeutically effective amounts of TG02 and a COX inhibitor, e.g., apricoxib or 6-bromo-8-(methyl-D3)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid.

[0006] In another aspect, the present disclosure provides therapeutic methods of treating a cancer patient, the methods comprising administering to the patient therapeutically effective amounts of TG02, an immune checkpoint inhibitor, and a COX-2 inhibitor.

[0007] In another aspect, present disclosure provides therapeutic methods of treating a cancer patient who has tumors that overexpress MYC, MCL1, or both.

[0008] In another aspect, the present disclosure provides kits comprising TG02, TG02 and an immune checkpoint inhibitor, TG02 and a COX-2 inhibitor, and TG02 and an immune checkpoint inhibitor and a COX-2 inhibitor.

[0009] In another aspect, the present disclosure provides a pharmaceutical composition comprising TG02, a COX-2 inhibitor, e.g., apricoxib or 6-bromo-8-(methyl-D3)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF DRAWINGS

[0010] Fig. 1 is a bar graph showing the *in vitro* activity of TG02, TMZ (temozolomide), and TG02 + TMZ in GSC923 cells.

[0011] Fig. 2 is a bar graph showing the *in vitro* activity of TG02, TMZ, and TG02 + TMZ in LN18 cells.

[0012] Fig. 3 is a bar graph showing the *in vitro* activity of TG02, TMZ, and TG02 + TMZ in T98G cells.

[0013] Fig. 4 is a bar graph showing the *in vitro* activity of TG02, TMZ, and TG02 + TMZ in U251 cells.

[0014] Fig. 5 is a bar graph showing the *in vitro* activity of TG02, TMZ, and TG02 + TMZ in U87 cells.

[0015] Fig. 6 is a bar graph showing the *in vitro* activity of TG02, TMZ, and TG02 + TMZ in LN299 cells.

[0016] Fig. 7 is a bar graph showing the *in vitro* activity of TG02, TMZ, and TG02 + TMZ in GSC827 cells

[0017] Fig. 8 is a bar graph showing the *in vitro* cytotoxicity of TG02, TMZ, and TG02 + TMZ (T+T) in GSC923 cells.

[0018] Fig. 9 is a bar graph showing the *in vitro* cytotoxicity of TG02, TMZ, and TG02 + TMZ (T+T) in U251 cells.

[0019] Fig. 10 is a bar graph showing a lack of *in vitro* activity of TG02, TMZ, and TG02 + TMZ (T+T) in human pulmonary arterial endothelial cells.

[0020] Fig. 11 is a bar graph showing a lack of *in vitro* activity of TG02, TMZ, and TG02 + TMZ (T+T) in human astrocytes.

[0021] Fig. 12 is a dose response curve showing the *in vitro* activity of TG02 and TG02 + TMZ in GSC923 cells.

[0022] Fig. 13 is a dose response curve showing the *in vitro* activity of TMZ and TG02 + TMZ in GSC923 cells.

[0023] Fig. 14 is a dose response curve showing the *in vitro* activity of TG02 and TG02 + TMZ in U251 cells.

[0024] Fig. 15 is a dose response curve showing the *in vitro* activity of TMZ and TG02 + TMZ in U251 cells.

[0025] Fig. 16 is a schematic illustration of TG02 and TMZ administration in a mouse glioma GL261 cell allograft model.

[0026] Fig. 17 is a line graph showing percent survival following TG02, TMZ, and TG02 + TMZ administration in a mouse glioma GL261 cell allograft model.

[0027] Fig. 18 is a line graph showing the tumor burden following TG02, TMZ, and TG02 + TMZ administration in a mouse glioma GL261 cell allograft model.

[0028] Fig. 19 is an illustration showing the effect of TG02 on MYC protein levels in hepatocellular carcinoma (HCC) cells.

[0029] Fig. 20 is a dose response curve showing the effect of TG02 on MYC protein levels in HCC cells.

[0030] Fig. 21 is is an illustration showing showing the effect of TG02 on MYC protein levels in HCC tumor cells.

[0031] Fig. 22 is a line graph showing the *in vivo* activity of TG02 and TG02 + sorafenib in an orthotopic model of HepG2 HCC xenografts.

[0032] Fig. 23 is a bar graph showing PD-L1 expression following treatment with TG02 in a transgenic mouse model of MYC-induced T cell acute lymphoblastic leukemia.

[0033] Fig. 24 is a bar graph showing CD47 expression following treatment with TG02 in a transgenic mouse model of MYC-induced T cell acute lymphoblastic leukemia.

[0034] Fig. 25 is a bar graph showing BCL-xL expression following treatment with TG02 in a transgenic mouse model of MYC-induced T cell acute lymphoblastic leukemia.

[0035] Fig. 26 is a bar graph showing MYC expression following treatment with TG02 in a transgenic mouse model of MYC-induced T cell acute lymphoblastic leukemia.

[0036] Fig. 27 is a line graph showing the efficacy of TG02 in combination with anti-PD-1 in a mouse syngeneic GL261 orthotopic glioblastoma model.

[0037] Fig. 28 is an illustration showing that BT245 tumor cells exposed to TG02 show inhibition of MYC and MCL-1 expression.

[0038] Fig. 29 is a bar graph showing the area under the curve (AUC) for TG02 induced inhibition in glioblastoma (GBM) cells.

[0039] Fig. 30 is a scatter graph showing that high MYC expression correlates with low AUC in GBM cells.

[0040] Fig. 31 is a series of six line graphs showing the activity of TG02 in combination with radiation in glioblastoma cell lines.

[0041] Fig. 32 is a bar graph showing the activity of TG02 on 26 patient-derived GBM stem cell lines.

[0042] Fig. 33 is an illustration showing the expression level of CDK9, MYC, and Mcl-1 in patient-derived GBM stem cell lines following treatment with TG02.

DETAILED DESCRIPTION OF THE INVENTION

[0043] In one embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amount of TG02, wherein one or more of the genes listed in Table 1, see below, is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status. In another embodiment, MYC overexpression is differentially present in a sample taken from the patient. In another embodiment, MCL1 overexpression is differentially present in a sample taken from the patient.

[0044] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amounts of TG02 and an immune checkpoint inhibitor, wherein one or more of the genes listed in Table 1, see below, is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status. In another embodiment, MYC overexpression is differentially present in a sample taken from the patient. In another embodiment, MCL1 overexpression is differentially present in a sample taken from the patient. In another embodiment, TG02 is administered to the patient before the immune checkpoint inhibitor. In another embodiment, TG02 is administered to the patient after the immune checkpoint inhibitor. In another embodiment, TG02 is administered to the patient at the same time as an immune checkpoint inhibitor.

[0045] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amounts of TG02, an immune checkpoint inhibitor, and a COX-2 inhibitor wherein one or more of the genes listed in Table 1, see below, is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status. In another embodiment, MYC overexpression is differentially present in a sample taken from the patient. In another embodiment, MCL1 overexpression is differentially present in a sample taken from the patient. In another embodiment, TG02 is administered to the patient before the COX-2 inhibitor. In another embodiment, TG02 is administered to the

patient after the COX-2 inhibitor. In another embodiment, TG02 is administered to the patient at the same time as the COX-2 inhibitor.

[0046] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and an immune checkpoint inhibitor. In another embodiment, TG02 is administered to the patient before the immune checkpoint inhibitor. In another embodiment, TG02 is administered to the patient after the immune checkpoint inhibitor. In another embodiment, TG02 is administered to the patient at the same time as an immune checkpoint inhibitor.

[0047] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02, an immune checkpoint inhibitor, and a COX-2 inhibitor. In another embodiment, TG02 is administered to the patient before the COX-2 inhibitor. In another embodiment, TG02 is administered to the patient after the COX-2 inhibitor. In another embodiment, TG02 is administered to the patient at the same time as the COX-2 inhibitor.

[0048] In another embodiment, the present disclosure provides kits comprising TG02 and an immune checkpoint inhibitor, and instructions for administering TG02 and the immune checkpoint inhibitor to a patient having cancer. In another embodiment, the kit further comprises a COX-2 inhibitor.

[0049] In another embodiment, the present disclosure provides kits comprising TG02 and a COX-2 inhibitor, and instructions for administering TG02 and the COX-2 inhibitor to a patient having cancer.

[0050] In another embodiment, the kit is packaged in a manner that facilitates its use to practice methods of the present disclosure.

[0051] In another embodiment, the kit includes TG02 (or a composition comprising TG02) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of TG02 or composition to practice the method of the disclosure. In one embodiment, TG02 is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

[0052] The disclosure provides various therapeutic methods, kits, and compositions relating to the treatment of cancer. In one embodiment, the cancer is a solid tumor. In another embodiment, the cancer is a hematological malignancy. In another embodiment, the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma,

lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0053] In another embodiment, the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck, adenocarcinoma squamous cell carcinoma of the esophagus, adenocarcinoma of the stomach, adenocarcinoma of the colon, hepatocellular carcinoma, cholangiocarcinoma of the biliary system, adenocarcinoma of gall bladder, adenocarcinoma of the pancreas, ductal carcinoma in situ of the breast,

adenocarcinoma of the breast, adenocarcinoma of the lungs, squamous cell carcinoma of the lungs, transitional cell carcinoma of the bladder, squamous cell carcinoma of the bladder, squamous cell carcinoma of the cervix, adenocarcinoma of the cervix, endometrial carcinoma, penile squamous cell carcinoma, and squamous cell carcinoma of the skin.

[0054] In another embodiment, a precancerous tumor is selected from the group consisting of leukoplakia of the head and neck, Barrett's esophagus, metaplasia of the stomach, adenoma of the colon, chronic hepatitis, bile duct hyperplasia, pancreatic intraepithelial neoplasia, atypical adenomatous hyperplasia of the lungs, dysplasia of the bladder, cervical initraepithelial neoplasia, penile intraepithelial neoplasia, and actinic keratosis of the skin.

[0055] In another embodiment, the patient has tumors that overexpress MYC, MCL1, or both. The tumors may be determined to overexpress MYC, MCL1, or both, by methods known in the art.

[0056] In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0057] In another embodiment, the cancer is selected from the group consisting of glioblastoma, hepatocellular carcinoma, non-small cell and small-cell lung cancer, head and neck cancer, colorectal carcinoma, and triple-negative breast cancer.

[0058] In another embodiment, the cancer has become resistant to conventional cancer treatments. The term "conventional cancer treatments" as used herein refers to any cancer drugs or biologics, or combination of cancer drugs and/or biologics that have been tested and/or approved for therapeutic use in humans by the U.S. Food and Drug Administration, European Medicines Agency, or similar regulatory agency.

[0059] In another embodiment, the patient has been treated previously with an immune checkpoint inhibitor without TG02. For example, the previous immune checkpoint therapy may be an anti-PD-1 therapy.

[0060] In another embodiment, the patient has been treated previously with a COX-2 inhibitor without TG02.

[0061] In another embodiment, the present disclosure provides a pharmaceutical composition comprising TG02, a COX-2 inhibitor, and a pharmaceutically acceptable excipient.

[0062] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amount of TG02, wherein the phenotypic status of the patient is overexpression of MYC, overexpression of MCL1, or overexpression of MYC and MCL1. In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0063] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and a second therapeutic agent, wherein the second therapeutic agent is neither an immune checkpoint inhibitor nor a COX-2 inhibitor.

[0064] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, comprising administering to the patient therapeutically effective amounts of TG02, an immune checkpoint inhibitor, and a third therapeutic agent, wherein the third therapeutic agent is not a COX-2 inhibitor.

[0065] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, comprising administering to the patient therapeutically effective amounts of TG02, a COX-2 inhibitor, and a third therapeutic agent, wherein the third therapeutic agent is not an immune checkpoint inhibitor.

[0066] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, comprising administering to the patient therapeutically effective amounts of TG02, an immune checkpoint inhibitor, a COX-2 inhibitor, and a fourth therapeutic agent, wherein the fourth therapeutic agent is neither an immune checkpoint inhibitor nor a COX-2 inhibitor.

[0067] In another embodiment, the present disclosure provides personalized medicine for cancer patients, and encompasses the selection of treatment options with the highest likelihood of successful outcome for individual cancer patients. In another aspect, the

disclosure relates to the use of an assay(s) to predict the treatment outcome, *e.g.*, the likelihood of favorable responses or treatment success, in patients having cancer.

[0068] In another embodiment, the present disclosure provides methods of selecting a patient, *e.g.*, a human subject for treatment of cancer with TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor, comprising obtaining a biological sample, *e.g.*, blood cells, from the patient, testing a biological sample from the patient for the presence of a biomarker, *e.g.*, overexpression of MYC, overexpression of MCL1, or both, and selecting the patient for treatment if the biological sample contains that biomarker. In another embodiment, the methods further comprise administering a therapeutically effective amount of TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor, to the patient if the biological sample contains the biomarker. Examples of cancer biomarkers are provided in Table 1. In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer is a hematological malignancy. In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0069] In another embodiment, the present disclosure provides methods of predicting treatment outcomes in a patient having cancer, comprising obtaining a biological sample, from the patient, testing the biological sample from the patient for the presence of a biomarker, e.g., overexpression of MYC, overexpression of MCL1, or both, wherein the detection of the biomarker indicates the patient will respond favorably to administration of a therapeutically effective amount of TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor. Favorable responses include, but are not limited to, a decrease in tumor size and an increase in progression-free or overall survival.

[0070] In another embodiment, the present disclosure provides methods of treating cancer, comprising administering a therapeutically effective amount of TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor, to a patient, *e.g.*, a human subject, with cancer in whom the patient's cells contain a biomarker. In another embodiment, the patient is selected for treatment with TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor, after the patient's cells have been determined to contain an overexpression of MYC. In another embodiment, the patient is selected for treatment with TG02 and, optionally, an immune checkpoint inhibitor and/or

a COX-2 inhibitor, after the patient's cells have been determined to contain an overexpression of MCL1. In another embodiment, the patient is selected for treatment with TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor, after the patient's cells have been determined to contain an overexpression of MYC and an overexpression of MCL1.

[0071] In another embodiment, the method of treating a patient having cancer comprises obtaining a biological sample from the patient, determining whether the biological sample contains a biomarker, *e.g.,* overexpression of MYC, overexpression of MCL1, or both, and administering to the patient a therapeutically effective amount of TG02 and, optionally, an immune checkpoint inhibitor and/or a COX-2 inhibitor, if the biological sample contains the biomarker. In another embodiment, the methods provided herein comprise determining whether the patient's cells contain an overexpression of MYC. In another embodiment, the methods provided herein comprise determining whether the patient's cells contain an overexpression of MCL1. In another embodiment, the methods provided herein comprise determining whether the patient's cells contain an overexpression of MYC and MCL1.

[0072] In another embodiment, the disclosure provides a method of treating a subject having cancer, the method comprising obtaining a biological sample from the subject, determining the expression level of MYC, MCL1, or both in the biological sample; and administering a therapeutically effective amount of TG02 and a second therapeutic agent, e.g., temozolomide, carfilzomib, sorafenib, bortezomib, doxorubicin, cisplatin, lenalidomide, dexamethasone, or Ara-C, to the subject if the biological sample shows overexpression of MYC, MCL1, or both.

[0073] In another embodiment, the patient has been treated previously with immune checkpoint inhibitor alone. For example, the previous immune checkpoint therapy may be an anti-PD-1 therapy.

[0074] In another embodiment, the patient has been treated previously with COX-2 inhibitor alone.

I. Immune checkpoint inhibitors

[0075] Immune checkpoint inhibitors are therapies that blockade immune system inhibitor checkpoints. Immune checkpoints can be stimulatory or inhibitory. Blockade of inhibitory immune checkpoint activates immune system function and can be used for

cancer immunotherapy. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012). Tumor cells turn off activated T cells when they attach to specific T-cell receptors. Immune checkpoint inhibitors prevent tumor cells from attaching to T cells, which results in T cells remaining activated. In effect, the coordinated action by cellular and soluble components combats pathogens and injuries by cancers. The modulation of immune system pathways may involve changing the expression or the functional activity of at least one component of the pathway to then modulate the response by the immune system. U.S. 2015/0250853. Examples of immune checkpoint inhibitors include PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, LAG3 inhibitors, TIM3 inhibitors, cd47 inhibitors, and B7-H1 inhibitors. Thus, in one embodiment, the immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, and a cd47 inhibitor.

[0076] In another embodiment, the immune checkpoint inhibitor is a programmed cell death (PD-1) inhibitor. PD-1 is a T-cell coinhibitory receptor that plays a pivotal role in the ability of tumor cells to evade the host's immune system. Blockage of interactions between PD-1 and PD-L1, a ligand of PD-1, enhances immune function and mediates antitumor activity. Examples of PD-1 inhibitors include antibodies that specifically bind to PD-1. Particular anti-PD-1 antibodies include, but are not limited to nivolumab, pembrolizumab, STI-1014, and pidilzumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies of anti-PD-1 antibodies, see U.S. 2013/0309250, U.S. 6,808,710, U.S. 7,595,048, U.S. 8,008,449, U.S. 8,728,474, U.S. 8,779,105, U.S. 8,952,136, U.S. 8,900,587, U.S. 9,073,994, U.S. 9,084,776, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0077] In another embodiment, the immune checkpoint inhibitor is a PD-L1 (also known as B7-H1 or CD274) inhibitor. Examples of PD-L1 inhibitors include antibodies that specifically bind to PD-L1. Particular anti-PD-L1 antibodies include, but are not limited to, avelumab, atezolizumab, durvalumab, and BMS-936559. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 8,217,149, U.S. 2014/0341917, U.S. 2013/0071403, WO 2015036499, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0078] In another embodiment, the immune checkpoint inhibitor is a CTLA-4 inhibitor. CTLA-4, also known as cytotoxic T-lymphocyte antigen 4, is a protein receptor that

downregulates the immune system. CTLA-4 is characterized as a "brake" that binds costimulatory molecules on antigen-presenting cells, which prevents interaction with CD28 on T cells and also generates an overtly inhibitory signal that constrains T cell activation. Examples of CTLA-4 inhibitors include antibodies that specifically bind to CTLA-4. Particular anti-CTLA-4 antibodies include, but are not limited to, ipilimumab and tremelimumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 6,984,720, U.S. 6,207,156, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0079] In another embodiment, the immune checkpoint inhibitor is a LAG3 inhibitor. LAG3, Lymphocyte Activation Gene 3, is a negative co-simulatory receptor that modulates T cell homeostatis, proliferation, and activation. In addition, LAG3 has been reported to participate in regulatory T cells (Tregs) suppressive function. A large proportion of LAG3 molecules are retained in the cell close to the microtubule-organizing center, and only induced following antigen specific T cell activation. U.S. 2014/0286935. Examples of LAG3 inhibitors include antibodies that specifically bind to LAG3. Particular anti-LAG3 antibodies include, but are not limited to, GSK2831781. For a general discussion of the availability, methods of production, mechanism of action, and studies, see, U.S. 2011/0150892, U.S. 2014/0093511, U.S. 20150259420, and Huang *et al.*, *Immunity* 21:503-13 (2004).

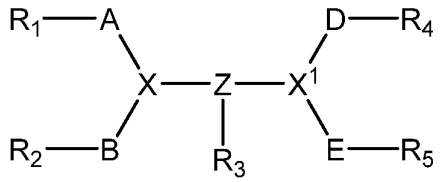
[0080] In another embodiment, the immune checkpoint inhibitor is a TIM3 inhibitor. TIM3, T-cell immunoglobulin and mucin domain 3, is an immune checkpoint receptor that functions to limit the duration and magnitude of T_H1 and T_C1 T-cell responses. The TIM3 pathway is considered a target for anticancer immunotherapy due to its expression on dysfunctional $CD8^+$ T cells and Tregs, which are two reported immune cell populations that constitute immunosuppression in tumor tissue. Anderson, *Cancer Immunology Research 2:*393-98 (2014). Examples of TIM3 inhibitors include antibodies that specifically bind to TIM3. For a general discussion of the availability, methods of production, mechanism of action, and studies of TIM3 inhibitors, see U.S. 20150225457, U.S. 20130022623, U.S. 8,522,156, Ngiow *et al.*, *Cancer Res 71:* 6567-71 (2011), Ngiow, *et al.*, *Cancer Res 71:*3540-51 (2011), and *Anderson*, *Cancer Immunology Res* 2:393-98 (2014).

[0081] In another embodiment, the immune checkpoint inhibitor is a cd47 inhibitor. *See* Unanue, E.R., *PNAS* 110:10886-87 (2013).

[0082] The term "antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity. In another embodiment, "antibody" is meant to include soluble receptors that do not possess the Fc portion of the antibody. In one embodiment, the antibodies are humanized monoclonal antibodies and fragments thereof made by means of recombinant genetic engineering.

[0083] Another class of immune checkpoint inhibitors include polypeptides that bind to and block PD-1 receptors on T-cells without triggering inhibitor signal transduction. Such peptides include B7-DC polypeptides, B7-H1 polypeptides, B7-1 polypeptides and B7-2 polypeptides, and soluble fragments thereof, as disclosed in U.S. Pat. 8,114,845.

[0084] Another class of immune checkpoint inhibitors include compounds with peptide moieties that inhibit PD-1 signaling. Examples of such compounds are disclosed in U.S. Pat. 8,907,053 and have the structure:



or a pharmaceutically acceptable salt thereof, wherein the compound comprises at least 5 amino acids useful as therapeutic agents capable of inhibiting the PD-1 signaling pathway.

[0085] Another class of immune checkpoint inhibitors include inhibitors of certain metabolic enzymes, such as indoleamine 2,3 dioxygenase (IDO), which is expressed by infiltrating myeloid cells and tumor cells. The IDO enzyme inhibits immune responses by depleting amino acids that are necessary for anabolic functions in T cells or through the synthesis of particular natural ligands for cytosolic receptors that are able to alter lymphocyte functions. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012); Löb, *Cancer Immunol Immunother 58:*153-57 (2009). Particular IDO blocking agents include, but are not limited to levo-1-methyl typtophan (L-1MT) and 1-methyl-tryptophan (1MT). Qian *et al., Cancer Res 69:*5498-504 (2009); and Löb *et al., Cancer Immunol Immunother 58:*153-7 (2009).

[0086] In one embodiment, the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, STI-1110, avelumab, atezolizumab, durvalumab, STI-1014, ipilimumab, tremelimumab, GSK2831781, BMS-936559 or MED14736.

II. COX-2 Inhibitors

[0087] Cyclooxygenase-2 (COX-2) is an enzyme that promotes inflammation and plays a role in tumor progression. COX-2 inhibitors include non-selective inhibitors such as aspirin, ibuprofen, sulindac sulphone, sulindac sulphide, diclofenac, nabumetone, naproxen, indomethacine, and piroxicam, selective inhibitors such as celecoxib, rofecoxib, valdecoxib, ANS-398, Cay10404, SC-236, and DUP697, and preferential inhibitors such as meloxicam and nimesulide. Other COX-2 inhibitors include apricoxib, tilmacoxib, and cimicoxib. Any COX-2 inhibitor is contemplated for use in the therapeutic methods of this disclosure. *See* Sobolewski *et al.*, "The Role of Cyclooxygenase-2 in Cell Proliferation and Cell Death in Human Malignancies," *International Journal of Cell Biology*, vol. 2010, Article ID 215158, 21 pages, 2010. doi:10.1155/2010/215158.

[0088] In another embodiment, the COX-2 inhibitor is apricoxib. *See* Kirane *et* al., *Clin. Cancer Res. 18*:5031-5042 (2012).

[0089] In another embodiment, the COX-2 inhibitor is selected from the group consisting of:

8-(ethyl-D5)-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

6-chloro-8-(methyl-D3)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

6-bromo-8-(methyl-D3)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

8-chloro-6-(methyl-D3)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

6,8-dibromo-5,7-(dimethyl-D6)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

8-(1-methylhexyl-D15)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

6-chloro-8-(1-methylhexyl-D15)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

8-(hexyl-D13)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid;

7,8-(dimethyl-D6)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid; and

6-chloro-8-(hexyl-D13)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid.

See US 2015/0133538.

[0090] In another embodiment, the COX-2 inhibitor is 6-bromo-8-(methyl-D3)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid.

III. Optional Therapeutic agents

[0091] In certain therapeutic methods of the disclosure, a second therapeutic agent is administered to a cancer patient in combination with TG02, a third therapeutic agent is administered to a cancer patient in combination with TG02 and an immune checkpoint inhibitor or in combination with TG02 and a COX-2 inhibitor, or a fourth therapeutic agent is administered to a cancer patient in combination with TG02, an immune checkpoint inhibitor, and a COX-2 inhibitor. The second, third and fourth therapeutic agents used in the therapeutic methods of the present disclosure are referred to as "optional therapeutic agents." Such optional therapeutic agents useful in the treatment of cancer patients are known in the art. In one embodiment, the optional therapeutic agent combined with TG02 is an anticancer agent that is neither an immune checkpoint inhibitor nor a COX-2 inhibitor.

[0092] Optional therapeutic agents are administered in an amount to provide their desired therapeutic effect. The effective dosage range for each optional therapeutic agent is known in the art, and the optional therapeutic agent is administered to an individual in need thereof within such established ranges.

[0093] TG02, the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent can be administered together as a single-unit dose or separately as multi-unit doses, and in any order, e.g., wherein TG02 is administered before the immune checkpoint inhibitor, COX-2 inhibitor, and/or the optional therapeutic agent, or vice versa. One or more doses of TG02, the immune checkpoint inhibitor, the COX-2 inhibitor and/or the optional therapeutic agent can be administered to the patient.

[0094] In one embodiment, the optional therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat.

[0095] In another embodiment, the optional therapeutic agent is a chemotherapeutic agent or other anti-proliferative agent that can be administered in combination with TG02, or a pharmaceutically acceptable salt thereof, to treat cancer. Examples of therapies and anticancer agents that can be used in combination with TG02, or a pharmaceutically acceptable salt thereof, include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved chemotherapeutic drug.

[0096] Nonlimiting exemplary antiproliferative compounds include an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent, e.g., temozolomide; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; a heparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0097] Nonlimiting exemplary aromatase inhibitors include steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[0098] Nonlimiting anti-estrogens include tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[0099] Nonlimiting exemplary topoisomerase I inhibitors include topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular

camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[0100] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtubulin polymerization inhibitors including, but not limited to, taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine, vinblastine sulfate, vincristine, and vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof.

[0101] Nonlimiting exemplary alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[0102] Nonlimiting exemplary matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[0103] Nonlimiting exemplary mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0104] Nonlimiting exemplary antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[0105] Nonlimiting exemplary platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[0106] Nonlimiting exemplary methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0107] Nonlimiting exemplary bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0108] Nonlimiting exemplary heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[0109] Nonlimiting exemplary compounds which target, decrease, or inhibit the oncogenic activity of Ras include farnesyl transferase inhibitors, such as L-744832, DK8G557, tipifarnib, and lonafarnib.

[0110] Nonlimiting exemplary telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0111] Nonlimiting exemplary proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomib. In some embodiments, the proteasome inhibitor is carfilzomib.

[0112] Nonlimiting exemplary FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R) include interferon, I-β-D-arabinofuransylcytosine (ara-c), and bisulfan; and ALK inhibitors, which are compounds which target, decrease, or inhibit anaplastic lymphoma kinase.

[0113] Nonlimiting exemplary Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[0114] Nonlimiting exemplary HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0115] Nonlimiting exemplary protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, include a) a compound targeting, decreasing, or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, such as an N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUlOl, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as a compound that targets, decreases, or inhibits the activity of IGF-IR; d) a compound targeting, decreasing,

or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; f) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase; g) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521 ; LY333531/LY379196; a isochinoline compound; a farnesyl transferase inhibitor; PD184352 or QAN697, or AT7519; k) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); 1) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, OSI-774, Cl-1033, EKB-569, GW-2016, antibodies El.l, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; and m) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[0116] Nonlimiting exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0117] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[0118] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with TG02, or a pharmaceutically acceptable salt thereof, include: avastin, daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin, anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610, bevacizumab, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[0119] A number of suitable optional therapeutic, e.g., anticancer, agents are contemplated for use in the therapeutic methods provided herein. Indeed, the methods provided herein can include, but are not limited to, administration of numerous optional therapeutic agents such as: agents that induce apoptosis; polynucleotides (*e.g.*, anti-sense, ribozymes, siRNA); polypeptides (*e.g.*, enzymes and antibodies); biological mimetics (*e.g.*, gossypol or BH3 mimetics); agents that bind (*e.g.*, oligomerize or complex) with a Bcl-2 family protein such as Bax; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal or polyclonal antibodies (*e.g.*, antibodies conjugated with anticancer drugs, toxins, defensins), toxins; radionuclides; biological response modifiers (*e.g.*, interferons (*e.g.*, IFN-α) and

interleukins (*e.g.*, IL-2)); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (*e.g.*, all-trans-retinoic acid); gene therapy reagents (*e.g.*, antisense therapy reagents and nucleotides); tumor vaccines; angiogenesis inhibitors; proteosome inhibitors: NF-KB modulators; anti-CDK compounds; HDAC inhibitors; and the like. Numerous other examples of optional therapeutic agents such as chemotherapeutic compounds and anticancer therapies suitable for co-administration with the disclosed compounds are known to those skilled in the art.

[0120] In certain embodiments, anticancer agents comprise agents that induce or stimulate apoptosis. Agents that induce or stimulate apoptosis include, for example, agents that interact with or modify DNA, such as by intercalating, cross-linking, alkylating, or otherwise damaging or chemically modifying DNA. Agents that induce apoptosis include, but are not limited to, radiation (*e.g.*, X-rays, gamma rays, UV); tumor necrosis factor (TNF)-related factors (*e.g.*, TNF family receptor proteins, TNF family ligands, TRAIL, antibodies to TRAIL-R1 or TRAIL-R2); kinase inhibitors (*e.g.*, epidermal growth factor receptor (EGFR) kinase inhibitor. Additional anticancer agents include: vascular growth factor receptor (VGFR) kinase inhibitor, fibroblast growth factor receptor (FGFR) kinase inhibitor, platelet-derived growth factor receptor (PDGFR) kinase inhibitor, and Bcr-Abl kinase inhibitors (such as GLEEVEC)); antisense molecules; antibodies (*e.g.*, HERCEPTIN, RITUXAN, ZEVALIN, and AVASTIN); anti-estrogens (*e.g.*, raloxifene and tamoxifen); anti-androgens (*e.g.*, flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids); cyclooxygenase 2 (COX-2) inhibitors (*e.g.*, celecoxib, meloxicam, NS-398, and non-steroidal anti-inflammatory drugs (NSAIDs)); anti-inflammatory drugs (*e.g.*, butazolidin, DECADRON, DELTASONE, dexamethasone, dexamethasone intensol, DEXONE, HEXADROL, hydroxychloroquine, METICORTEN, ORADEXON, ORASONE, oxyphenbutazone, PEDIAPRED, phenylbutazone, PLAQUENIL, prednisolone, prednisone, PRELONE, and TANDEARIL); and cancer chemotherapeutic drugs (*e.g.*, irinotecan (CAMPTOSAR), CPT-11, fludarabine (FLUDARA), dacarbazine (DTIC), dexamethasone, mitoxantrone, MYLOTARG, VP-16, cisplatin, carboplatin, oxaliplatin, 5-FU, doxorubicin, gemcitabine, bortezomib, gefitinib, bevacizumab, TAXOTERE or TAXOL); cellular signaling molecules; ceramides and cytokines; staurosporine, and the like.

[0121] In still other embodiments, the therapeutic methods provided herein include administering to a cancer patient a therapeutically effective amount of TG02 and at least one additional anti-hyperproliferative or antineoplastic agent selected from alkylating agents, antimetabolites, and natural products (*e.g.*, herbs and other plant and/or animal derived compounds).

[0122] Alkylating agents suitable for use in the present methods include, but are not limited to: 1) nitrogen mustards (*e.g.*, mechlorethamine, cyclophosphamide, ifosfamide, melphalan (L-sarcolysin); and chlorambucil); 2) ethylenimines and methylmelamines (*e.g.*, hexamethylmelamine and thiotepa); 3) alkyl sulfonates (*e.g.*, busulfan); 4) nitrosoureas (*e.g.*, carmustine (BCNU); lomustine (CCNU); semustine (methyl-CCNU); and streptozocin (streptozotocin)); and 5) triazenes (*e.g.*, dacarbazine (DTIC; dimethyltriazenoimid-azolecarboxamide).

[0123] In some embodiments, antimetabolites suitable for use in the present methods include, but are not limited to: 1) folic acid analogs (*e.g.*, methotrexate (amethopterin)); 2) pyrimidine analogs (*e.g.*, fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorode-oxyuridine; FudR), and cytarabine (cytosine arabinoside)); and 3) purine analogs (*e.g.*, mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG), and pentostatin (2'-deoxycoformycin)).

[0124] In still further embodiments, chemotherapeutic agents suitable for use in the methods of the present disclosure include, but are not limited to: 1) vinca alkaloids (*e.g.*, vinblastine (VLB), vincristine); 2) epipodophyllotoxins (*e.g.*, etoposide and teniposide); 3) antibiotics (*e.g.*, dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin), and mitomycin (mitomycin C)); 4) enzymes (*e.g.*, L-asparaginase); 5) biological response modifiers (*e.g.*, interferon-alfa); 6) platinum coordinating complexes (*e.g.*, cisplatin (cis-DDP) and carboplatin); 7) anthracenediones (*e.g.*, mitoxantrone); 8) substituted ureas (*e.g.*, hydroxyurea); 9) methylhydrazine derivatives (*e.g.*, procarbazine (N-methylhydrazine; MIH)); 10) adrenocortical suppressants (*e.g.*, mitotane (o,p'–DDD) and aminoglutethimide); 11) adrenocorticosteroids (*e.g.*, prednisone); 12) progestins (*e.g.*, hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate); 13) estrogens (*e.g.*, diethylstilbestrol and ethinyl estradiol); 14) antiestrogens (*e.g.*, tamoxifen); 15) androgens (*e.g.*, testosterone propionate and fluoxymesterone); 16)

antiandrogens (*e.g.*, flutamide): and 17) gonadotropin-releasing hormone analogs (*e.g.*, leuprolide).

[0125] Any oncolytic agent that is routinely used in a cancer therapy context finds use in the therapeutic methods of the present disclosure. For example, the U.S. Food and Drug Administration (FDA) maintains a formulary of oncolytic agents approved for use in the United States. International counterpart agencies to the FDA maintain similar formularies. Those skilled in the art will appreciate that the "product labels" required on all U.S. approved chemotherapeutics describe approved indications, dosing information, toxicity data, and the like, for the exemplary agents.

[0126] Anticancer agents further include compounds which have been identified to have anticancer activity. Examples include, but are not limited to, 3-AP, 12-O-tetradecanoylphorbol-13-acetate, 17AAG, 852A, ABI-007, ABR-217620, ABT-751, ADI-PEG 20, AE-941, AG-013736, AGRO100, alanosine, AMG 706, antibody G250, antineoplastons, AP23573, apaziquone, APC8015, atiprimod, ATN-161, atrasenten, azacitidine, BB-10901, BCX-1777, bevacizumab, BG00001, bicalutamide, BMS 247550, bortezomib, bryostatin-1, buserelin, calcitriol, CCI-779, CDB-2914, cefixime, cetuximab, CG0070, cilengitide, clofarabine, combretastatin A4 phosphate, CP-675,206, CP-724,714, CpG 7909, curcumin, decitabine, DENSPM, doxercalciferol, E7070, E7389, ecteinascidin 743, efaproxiral, eflornithine, EKB-569, enzastaurin, erlotinib, exisulind, fenretinide, flavopiridol, fludarabine, flutamide, fotemustine, FR901228, G17DT, galiximab, gefitinib, genistein, glufosfamide, GTI-2040, histrelin, HKI-272, homoharringtonine, HSPPC-96, hu14.18-interleukin-2 fusion protein, HuMax-CD4, iloprost, imiquimod, infliximab, interleukin-12, IPI-504, irofulven, ixabepilone, lapatinib, lenalidomide, lestaurtinib, leuprolide, LMB-9 immunotoxin, lonafarnib, luniliximab, mafosfamide, MB07133, MDX-010, MLN2704, monoclonal antibody 3F8, monoclonal antibody J591, motexafin, MS-275, MVA-MUC1-IL2, nilutamide, nitrocamptothecin, nolatrexed dihydrochloride, nolvadex, NS-9, O6-benzylguanine, oblimersen sodium, ONYX-015, oregovomab, OSI-774, panitumumab, paraplatin, PD-0325901, pemetrexed, PHY906, pioglitazone, pirfenidone, pixantrone, PS-341, PSC 833, PXD101, pyrazoloacridine, R115777, RAD001, ranpirnase, rebeccamycin analogue, rhuAngiostatin protein, rhuMab 2C4, rosiglitazone, rubitecan, S-1, S-8184, satraplatin, SB-, 15992, SGN-0010, SGN-40, sorafenib, SR31747A, ST1571, SU011248, suberoylanilide

hydroxamic acid, suramin, talabostat, talampanel, tariquidar, temsirolimus, TGFa-PE38 immunotoxin, thalidomide, thymalfasin, tipifarnib, tirapazamine, TLK286, trabectedin, trimetrexate glucuronate, TroVax, UCN-1, valproic acid, vinflunine, VNP40101M, volociximab, vorinostat, VX-680, ZD1839, ZD6474, zileuton, and zosuquidar trihydrochloride.

[0127] For a more detailed description of anticancer agents and other optional therapeutic agents, those skilled in the art are referred to any number of instructive manuals including, but not limited to, the Physician's Desk Reference and to Goodman and Gilman's "Pharmaceutical Basis of Therapeutics" tenth edition, Eds. Hardman *et al.*, 2002.

[0128] In some embodiments, methods provided herein comprise administering TG02 to a cancer patient in combination with radiation therapy. The methods provided herein are not limited by the types, amounts, or delivery and administration systems used to deliver the therapeutic dose of radiation to a patient. For example, the patient may receive photon radiotherapy, particle beam radiation therapy, other types of radiotherapies, and combinations thereof. In some embodiments, the radiation is delivered to the patient using a linear accelerator. In still other embodiments, the radiation is delivered using a gamma knife.

[0129] The source of radiation can be external or internal to the patient. External radiation therapy is most common and involves directing a beam of high-energy radiation to a tumor site through the skin using, for instance, a linear accelerator. While the beam of radiation is localized to the tumor site, it is nearly impossible to avoid exposure of normal, healthy tissue. However, external radiation is usually well tolerated by patients. Internal radiation therapy involves implanting a radiation-emitting source, such as beads, wires, pellets, capsules, particles, and the like, inside the body at or near the tumor site including the use of delivery systems that specifically target cancer cells (*e.g.*, using particles attached to cancer cell binding ligands). Such implants can be removed following treatment, or left in the body inactive. Types of internal radiation therapy include, but are not limited to, brachytherapy, interstitial irradiation, intracavity irradiation, radioimmunotherapy, and the like.

[0130] The patient may optionally receive radiosensitizers (*e.g.*, metronidazole, misonidazole, intra-arterial Budr, intravenous iododeoxyuridine (IudR), nitroimidazole,

5-substituted-4-nitroimidazoles, 2H-isoindolediones, [[(2-bromoethyl)-amino]methyl]-nitro-1H-imidazole-1-ethanol, nitroaniline derivatives, DNA-affinic hypoxia selective cytotoxins, halogenated DNA ligand, 1,2,4 benzotriazine oxides, 2-nitroimidazole derivatives, fluorine-containing nitroazole derivatives, benzamide, nicotinamide, acridine-intercalator, 5-thiotretrazole derivative, 3-nitro-1,2,4-triazole, 4,5-dinitroimidazole derivative, hydroxylated texaphrins, cisplatin, mitomycin, tiripazamine, nitrosourea, mercaptopurine, methotrexate, fluorouracil, bleomycin, vincristine, carboplatin, epirubicin, doxorubicin, cyclophosphamide, vindesine, etoposide, paclitaxel, heat (hyperthermia), and the like), radioprotectors (*e.g.*, cysteamine, aminoalkyl dihydrogen phosphorothioates, amifostine (WR 2721), IL-1, IL-6, and the like). Radiosensitizers enhance the killing of tumor cells. Radioprotectors protect healthy tissue from the harmful effects of radiation.

[0131] Any type of radiation can be administered to an patient, so long as the dose of radiation is tolerated by the patient without unacceptable negative side-effects. Suitable types of radiotherapy include, for example, ionizing (electromagnetic) radiotherapy (*e.g.*, X-rays or gamma rays) or particle beam radiation therapy (*e.g.*, high linear energy radiation). Ionizing radiation is defined as radiation comprising particles or photons that have sufficient energy to produce ionization, *i.e.*, gain or loss of electrons (as described in, for example, U.S. 5,770,581 incorporated herein by reference in its entirety). The effects of radiation can be at least partially controlled by the clinician. In one embodiment, the dose of radiation is fractionated for maximal target cell exposure and reduced toxicity.

[0132] In one embodiment, the total dose of radiation administered to a patient is about .01 Gray (Gy) to about 100 Gy. In another embodiment, about 10 Gy to about 65 Gy (*e.g.*, about 15 Gy, 20 Gy, 25 Gy, 30 Gy, 35 Gy, 40 Gy, 45 Gy, 50 Gy, 55 Gy, or 60 Gy) are administered over the course of treatment. While in some embodiments a complete dose of radiation can be administered over the course of one day, the total dose is ideally fractionated and administered over several days. Desirably, radiotherapy is administered over the course of at least about 3 days, *e.g.*, at least 5, 7, 10, 14, 17, 21, 25, 28, 32, 35, 38, 42, 46, 52, or 56 days (about 1-8 weeks). Accordingly, a daily dose of radiation will comprise approximately 1-5 Gy (*e.g.*, about 1 Gy, 1.5 Gy, 1.8 Gy, 2 Gy, 2.5 Gy, 2.8 Gy, 3 Gy, 3.2 Gy, 3.5 Gy, 3.8 Gy, 4 Gy, 4.2 Gy, or 4.5 Gy), or 1-2 Gy (*e.g.*, 1.5-2 Gy). The

daily dose of radiation should be sufficient to induce destruction of the targeted cells. If stretched over a period, in one embodiment, radiation is not administered every day, thereby allowing the animal to rest and the effects of the therapy to be realized. For example, radiation desirably is administered on 5 consecutive days, and not administered on 2 days, for each week of treatment, thereby allowing 2 days of rest per week. However, radiation can be administered 1 day/week, 2 days/week, 3 days/week, 4 days/week, 5 days/week, 6 days/week, or all 7 days/week, depending on the animal's responsiveness and any potential side effects. Radiation therapy can be initiated at any time in the therapeutic period. In one embodiment, radiation is initiated in week 1 or week 2, and is administered for the remaining duration of the therapeutic period. For example, radiation is administered in weeks 1-6 or in weeks 2-6 of a therapeutic period comprising 6 weeks for treating, for instance, a solid tumor. Alternatively, radiation is administered in weeks 1-5 or weeks 2-5 of a therapeutic period comprising 5 weeks. These exemplary radiotherapy administration schedules are not intended, however, to limit the methods provided herein.

IV. Therapeutic methods

[0133] In the therapeutic methods provided herein, TG02, the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic, e.g., anticancer, agent may be administered to a cancer patient under one or more of the following conditions: at different periodicities, at different durations, at different concentrations, by different administration routes, *etc.*

[0134] In some embodiments, TG02 is administered prior to the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent, *e.g.*, 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks prior to the administration of the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent.

[0135] In some embodiments, TG02 is administered after the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent, *e.g.*, 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks after the administration of the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent.

[0136] In some embodiments, TG02, the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent are administered concurrently but on different schedules, *e.g.*, TG02 is administered daily while the immune checkpoint inhibitor is administered once a week, once every two weeks, once every three weeks, or once every four weeks. In other embodiments, TG02 is administered once a day while the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent is administered once a week, once every two weeks, once every three weeks, or once every four weeks.

[0137] The therapeutic methods provided herein comprise administering TG02 to a cancer patient in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, TG02 may be administered in an amount from about 1 mg/kg to about 500 mg/kg, about 1 mg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, 30-600 mg/day. Particular doses include 50, 100, 200, 250, 300, 400, 500, and 600 mg/day. In one embodiment, TG02 is administed once a day on 3-7 consecutive days prior to the administration of the immune checkpoint inhibitor. In another embodiment, 250 mg/day of TG02 is administered. In another embodiment, 250 mg/day of TG02 is administered twice weekly. In another embodiment, TG02 administration continues on the day of the immune checkpoint inhibitor and continues for additional days until disease progression or until TG02 administration is no longer beneficial. These dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0138] The unit oral dose of TG02 may comprise from about 0.01 to about 1000 mg, e.g., about 10 to about 500 mg of TG02. In one embodiment, the unit oral dose of TG02 is 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg. The

unit dose may be administered one or more times daily, e.g., as one or more tablets or capsules.

[0139] In addition to administering TG02 as a raw chemical, it may be administered as part of a pharmaceutical preparation or composition. In some embodiments, the pharmaceutical preparation or composition can include one or more pharmaceutically acceptable carriers, excipients, and/or auxiliaries. In some embodiments, the one or more carriers, excipients, and auxiliaries facilitate processing of TG02 into a preparation or composition which can be used pharmaceutically. The preparations, particularly those preparations which can be administered orally or topically and which can be used for one type of administration, such as tablets, dragees, slow release lozenges and capsules, mouth rinses and mouth washes, gels, liquid suspensions, hair rinses, hair gels, shampoos and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by intravenous infusion, injection, topically or orally, contain from about 0.01 to 99 percent, in one embodiment from about 0.25 to 75 percent of active compound(s), together with the one or more carriers, excipients, and/or auxiliaries.

[0140] The pharmaceutical compositions of provided herein may be administered to any patient which may experience the beneficial effects of TG02. Foremost among such patients are mammals, *e.g.*, humans, although the methods and compositions provided herein are not intended to be so limited. Other patients include veterinary animals (cows, sheep, pigs, horses, dogs, cats and the like).

[0141] The pharmaceutical preparations provided herein are manufactured by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0142] Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium

carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries can be suitable flow-regulating agents and lubricants. Suitable auxiliaries include, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0143] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are in one embodiment dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

[0144] Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

[0145] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty

oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[0146] The present disclosure encompasses the use of solvates of TG02. Solvates typically do not significantly alter the physiological activity or toxicity of a compound, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of TG02 with a solvent molecule such as, *e.g.* a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to TG02 is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. TG02 can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of TG02. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate involves dissolving TG02 in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

[0147] Therapeutically effective amounts of TG02 and/or the immune checkpoint inhibitor, and/or the COX-2 inhibitor, and/or the optional therapeutic agent formulated in

accordance with standard pharmaceutical practices, are administered to a human patient in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[0148] TG02, the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[0149] Pharmaceutical compositions include those wherein TG02, the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent are administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of TG02, immune checkpoint inhibitor, COX-2 inhibitor, and/or optional therapeutic agent that is sufficient to maintain therapeutic effects.

[0150] Toxicity and therapeutic efficacy of TG02, the immune checkpoint inhibitor, the COX-2 inhibitor, and/or the optional therapeutic agent can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in a patient. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0151] A therapeutically effective amount of TG02, immune checkpoint inhibitor, COX-2 inhibitor, and/or optional therapeutic agent required for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the patient, and ultimately is determined by the attendant physician. For example, dosage amounts and intervals can be adjusted individually to provide plasma levels of TG02 and immune checkpoint inhibitor that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. Multiple doses often are desired, or required. For example, TG02 and immune checkpoint inhibitor can be administered at a frequency of: one dose per day; four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[0152] The immune checkpoint inhibitor is administered in therapeutically effective amounts. When the immune checkpoint inhibitor is a monoclonal antibody, 1-20 mg/kg is administered as an intravenous infusion every 2-4 weeks. For example, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg and 2000 mg of the antibody may be administered.

[0153] For example, when the immune checkpoint inhibitor is the anti-PD-1 antibody nivolumab, 3 mg/kg may be administered by intravenous infusion over 60 minutes every two weeks. When the immune checkpoint inhibitor is the anti-PD-1 antibody pembrolizumab, 2 mg/kg may be administered by intravenous infusion over 30 minutes every two or three weeks. When the immune checkpoint inhibitor is the anti-PD-L1 antibody avelumab, 10 mg/kg may be administered by intravenous infusion as frequently as every 2 weeks. Disis *et al.*, *J. Clin Oncol. 33* (2015) (suppl; abstr 5509). When the immune checkpoint inhibitor is the anti-PD-L1 antibody MPDL3280A, 20 mg/kg may be administered by intravenous infusion every 3 weeks. Herbst *et al.*, *Nature 515:*563-80 (2014). When the immune checkpoint inhibitor is the anti-CTLA-4 antibody ipilumumab, 3 mg/kg may be administered by intravenous infusion over 90 minutes every 3 weeks.

When the immune checkpoint inhibitor is the anti-CTLA-4 antibody tremelimumab, 15 mg/kg may be administered by intravenous infusion every 12 weeks. Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014); *Drugs R D*, *10:*123-32 (2010). When the immune checkpoint inhibitor is the anti-LAG3 antibody GSK2831781, 1.5 to 5 mg/kg may be administered by intravenous infusion over 120 minutes every 2-4 weeks. When the immune checkpoint inhibitor is an anti-TIM3 antibody, 1-5 mg/kg may be administered by intravenous infusion over 30-90 minutes every 2-4 weeks. When an inhibitor of indoleamine 2,3-dioxygenase (IDO) pathway is inhibitor indoximod in combination with temozolomide, 18.5 mg/kg/dose BID with an escalation to 27.7 mg/kg/dose BID of indoximod with 200 mg/m^2 every 5 days of temozolomide.

[0154] The COX-2 inhibitor is also administered in therapeutically effective amounts, e.g., from about 1 mg/kg to about 500 mg/kg, about 1 mg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The unit oral dose of the COX-2 inhibitor may comprise from about 0.01 to about 1000 mg, e.g., about 1 to about 250 mg of the COX-2 inhibitor. In one embodiment, the unit oral dose of the COX-2 inhibitor is 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, or 250 mg. The unit dose may be administered one or more times daily, e.g., as one or more tablets or capsules.

[0155] In one embodiment, the immune checkpoint inhibitor is an antibody and 1-20 mg/kg is administered by intravenous infusion every 2-4 weeks. In another embodiment, 50-2000 mg of the antibody is administered by intravenous infusion every 2-4 weeks. In another embodiment, TG02 is administered prior to administration of the antibody. In another embodiment, TG02 is administered 3-7 days prior to the day of administration of the antibody. In another embodiment, TG02 is also administered the day the antibody is administered and on consecutive days thereafter until disease progression or until TG02 administration is no longer beneficial.

[0156] In one embodiment, the cancer patient has tumors with a biomarker, e.g., overexpression of MYC and/or MCL1, and receives 2 mg/kg pembrolizumab administered by intravenous infusion every three weeks and 30-600 mg of TG02 administered for 3-7 days prior to pembrolizumab administration, on the day of

pembrolizumab administration, and thereafter until disease progression or until there is no therapeutic benefit.

[0157] In another embodiment, the cancer patient has tumors with a biomarker, e.g., overexpression of MYC and/or MCL1, and receives 3 mg/kg nivolumab administered by intravenous infusion every 2 weeks and 30-600 mg TG02 administered orally for 3-7 days prior to nivolumab administration, on the day of nivolumab administration, and thereafter until disease progression or until there is no therapeutic benefit.

[0158] In another embodiment, the cancer patient has tumors with a biomarker, e.g., overexpression of MYC and/or MCL1, and receives 3 mg/kg nivolumab administered by intravenous infusion every 2 weeks and 30-600 mg TG02 administered orally twice weekly prior to nivolumab administration, on the day of nivolumab administration, and thereafter until disease progression or until there is no therapeutic benefit.

[0159] In another embodiment, the treatment of the cancer patient with an immune checkpoint inhibitor and TG02 induces anti-proliferative response faster than when the immune checkpoint inhibitor is administered alone.

[0160] In another embodiment, the treatment of the cancer patient with a COX-2 inhibitor and TG02 induces anti-proliferative response faster than when the COX-2 inhibitor is administered alone.

V. Biomarkers

[0161] The term "biomarker" as used herein refers to any biological compound, such as a gene, a protein, a fragment of a protein, a peptide, a polypeptide, a nucleic acid, etc., that can be detected and/or quantified in a cancer patient *in vivo* or in a biological sample obtained from a cancer patient. A biomarker can be the entire intact molecule, or it can be a portion or fragment thereof. In one embodiment, the expression level of the biomarker is measured. The expression level of the biomarker can be measured, for example, by detecting the protein or RNA, e.g., mRNA, level of the biomarker. In some embodiments, portions or fragments of biomarkers can be detected or measured, for example, by an antibody or other specific binding agent. In some embodiments, a measurable aspect of the biomarker is associated with a given state of the patient, such as a particular stage of cancer. For biomarkers that are detected at the protein or RNA level,

such measurable aspects may include, for example, the presence, absence, or concentration, i.e., expression level, of the biomarker in a cancer patient, or biological sample obtained from the cancer patient. For biomarkers that are detected at the nucleic acid level, such measurable aspects may include, for example, allelic versions of the biomarker or type, rate, and/or degree of mutation of the biomarker, also referred to herein as mutation status.

[0162] For biomarkers that are detected based on expression level of protein or RNA, expression level measured between different phenotypic statuses can be considered different, for example, if the mean or median expression level of the biomarker in the different groups is calculated to be statistically significant. Common tests for statistical significance include, among others, t-test, ANOVA, Kruskal-Wallis, Wilcoxon, Mann-Whitney, Significance Analysis of Microarrays, odds ratio, etc. Biomarkers, alone or in combination, provide measures of relative likelihood that a subject belongs to one phenotypic status or another. Therefore, they are useful, inter alia, as markers for disease and as indicators that particular therapeutic treatment regimens will likely result in beneficial patient outcomes.

[0163] Biomarkers include, but are not limited, the genes listed in Table 1. In one embodiment, the measurable aspect of the biomarker is its expression status. In one embodiment, the measurable aspect of the biomarker is its mutation status.

Table 1

Gene	Gene synonym	Gene description
A2M	CPAMD5, FWP007, S863-7	Alpha-2-macroglobulin
ABCB1	ABC20, CD243, CLCS, GP170, MDR1, P-gp, PGY1	ATP-binding cassette, sub-family B (MDR/TAP), member 1
ABCC1	GS-X, MRP, MRP1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1
ABCC2	CMOAT, cMRP, DJS, MRP2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2
ABCC3	cMOAT2, EST90757, MLP2, MOAT-D, MRP3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3
ABCC5	EST277145, MOAT-C, MRP5, SMRP	ATP-binding cassette, sub-family C (CFTR/MRP), member 5
ABCC6	ARA, EST349056, MLP1, MRP6, PXE, URG7	ATP-binding cassette, sub-family C (CFTR/MRP), member 6
ABCG2	ABCP, BCRP, CD338, EST157481, MXR	ATP-binding cassette, sub-family G (WHITE), member 2 (Junior blood group)
ABL1	ABL, c-ABL, JTK7, p150	ABL proto-oncogene 1, non-receptor tyrosine kinase

ABL2	ABLL, ARG	ABL proto-oncogene 2, non-receptor tyrosine kinase
ACAP1	CENTB1, KIAA0050	ArfGAP with coiled-coil, ankyrin repeat and PH domains 1
ACLY	ACL, ATPCL, CLATP	ATP citrate lyase
ACPP	ACP-3, ACP3	Acid phosphatase, prostate
ACVR1B	ActRIB, ACVRLK4, ALK4, SKR2	Activin A receptor, type IB
ACVR2A	ACTRII, ACVR2	Activin A receptor, type IIA
ACVR2B	ActR-IIB	Activin A receptor, type IIB
ADAM9	CORD9, KIAA0021, MCMP, MDC9, Mltng	ADAM metallopeptidase domain 9
ADAMTS1	C3-C5, KIAA1346, METH1	ADAM metallopeptidase with thrombospondin type 1 motif, 1
ADAMTS14		ADAM metallopeptidase with thrombospondin type 1 motif, 14
ADAMTS18	ADAMTS21	ADAM metallopeptidase with thrombospondin type 1 motif, 18
ADAMTS20	GON-1	ADAM metallopeptidase with thrombospondin type 1 motif, 20
ADAMTS3	ADAMTS-4, KIAA0366	ADAM metallopeptidase with thrombospondin type 1 motif, 3
ADAMTS4	ADAMTS-2, ADMP-1, KIAA0688	ADAM metallopeptidase with thrombospondin type 1 motif, 4
ADAMTS5	ADAMTS11, ADMP-2	ADAM metallopeptidase with thrombospondin type 1 motif, 5
ADAMTS6	ADAM-TS6	ADAM metallopeptidase with thrombospondin type 1 motif, 6
ADAMTS8	ADAM-TS8, FLJ41712, METH2	ADAM metallopeptidase with thrombospondin type 1 motif, 8
ADAMTS9	KIAA1312	ADAM metallopeptidase with thrombospondin type 1 motif, 9
ADM	AM	Adrenomedullin
ADRA1B		Adrenoceptor alpha 1B
AFP	FETA, HPAFP	Alpha-fetoprotein
AGER	RAGE	Advanced glycosylation end product-specific receptor
AHR	bHLHe76	Aryl hydrocarbon receptor
AHSG	A2HS, FETUA, HSGA	Alpha-2-HS-glycoprotein
AKAP12	AKAP250, SSeCKS	A kinase (PRKA) anchor protein 12
AKR1B1	ALDR1, AR	Aldo-keto reductase family 1, member B1 (aldose reductase)
AKT1	AKT, PKB, PRKBA, RAC	V-akt murine thymoma viral oncogene homolog 1
AKT2		V-akt murine thymoma viral oncogene homolog 2
AKT3	PKBG, PRKBG, RAC-	V-akt murine thymoma viral oncogene homolog

	gamma	3
ALB		Albumin
ALCAM	CD166, MEMD	Activated leukocyte cell adhesion molecule
ALDOA		Aldolase A, fructose-bisphosphate
ALDOB		Aldolase B, fructose-bisphosphate
ALDOC		Aldolase C, fructose-bisphosphate
ALPL	HOPS, TNSALP	Alkaline phosphatase, liver/bone/kidney
ALPP		Alkaline phosphatase, placental
ANG	RNASE5	Angiogenin, ribonuclease, RNase A family, 5
ANGPT1	Ang1, KIAA0003	Angiopoietin 1
ANGPT2	Ang2	Angiopoietin 2
ANXA1	ANX1, LPC1	Annexin A1
ANXA11	ANX11	Annexin A11
ANXA2	ANX2, ANX2L4, CAL1H, LIP2, LPC2D	Annexin A2
ANXA4	ANX4	Annexin A4
ANXA7	ANX7	Annexin A7
AOC3	HPAO, VAP-1, VAP1	Amine oxidase, copper containing 3
AP2B1	ADTB2, CLAPB1	Adaptor-related protein complex 2, beta 1 subunit
APAF1	APAF-1, CED4	Apoptotic peptidase activating factor 1
APEX1	APE, APE-1, APEN, APEX, APX, HAP1, REF-1, REF1	APEX nuclease (multifunctional DNA repair enzyme) 1
APOA1		Apolipoprotein A-I
APOA2		Apolipoprotein A-II
APOC1		Apolipoprotein C-I
APOC3		Apolipoprotein C-III
APOD		Apolipoprotein D
APOE	AD2	Apolipoprotein E
APPBP2	Hs.84084, KIAA0228, PAT1	Amyloid beta precursor protein (cytoplasmic tail) binding protein 2
AR	AIS, DHTR, HUMARA, NR3C4, SBMA, SMAX1	Androgen receptor
AREG	AREGB, SDGF	Amphiregulin
ARG2		Arginase 2
ARNT	bHLHe2, HIF-1beta	Aryl hydrocarbon receptor nuclear translocator
ASPH	BAH, CASQ2BP1, HAAH, JCTN	Aspartate beta-hydroxylase
ATM	ATA, ATC, ATD, ATDC, TEL1, TELO1	ATM serine/threonine kinase
ATOH1	bHLHa14, HATH1, MATH-1, Math1	Atonal homolog 1 (Drosophila)
ATP7B	WND	ATPase, Cu++ transporting, beta polypeptide
AURKA	AIK, ARK1, AurA, BTAK, PPP1R47, STK15, STK6, STK7	Aurora kinase A
AURKB	Aik2, AIM-1, ARK2, AurB,	Aurora kinase B

	IPL1, PPP1R48, STK12, STK5	
AZGP1	ZA2G, ZAG	Alpha-2-glycoprotein 1, zinc-binding
B2M		Beta-2-microglobulin
BAD	BBC2, BCL2L8	BCL2-associated agonist of cell death
BAG1		BCL2-associated athanogene
BAI1		Brain-specific angiogenesis inhibitor 1
BAX	BCL2L4	BCL2-associated X protein
BCL11A	BCL11A-L, BCL11A-S, BCL11A-XL, CTIP1, EVI9, HBFQTL5, ZNF856	B-cell CLL/lymphoma 11A (zinc finger protein)
BCL2	Bcl-2, PPP1R50	B-cell CLL/lymphoma 2
BCL2A1	ACC-1, ACC-2, BCL2L5, BFL1, GRS, HBPA1	BCL2-related protein A1
BCL2L1	Bcl-X, bcl-xL, bcl-xS, BCL2L, BCLX, PPP1R52	BCL2-like 1
BCL2L2	BCL-W, KIAA0271, PPP1R51	BCL2-like 2
BCL2L2-PABPN1		BCL2L2-PABPN1 readthrough
BCL3	BCL4, D19S37	B-cell CLL/lymphoma 3
BCL6	BCL5, BCL6A, LAZ3, ZBTB27, ZNF51	B-cell CLL/lymphoma 6
BDNF		Brain-derived neurotrophic factor
BIRC2	API1, c-IAP1, cIAP1, hiap-2, MIHB, RNF48	Baculoviral IAP repeat containing 2
BIRC3	API2, c-IAP2, cIAP2, hiap-1, MALT2, MIHC, RNF49	Baculoviral IAP repeat containing 3
BIRC5	API4, EPR-1, survivin	Baculoviral IAP repeat containing 5
BIRC6	BRUCE	Baculoviral IAP repeat containing 6
BLK	MGC10442	BLK proto-oncogene, Src family tyrosine kinase
BLMH	BH	Bleomycin hydrolase
BMI1	PCGF4, RNF51	BMI1 proto-oncogene, polycomb ring finger
BMP2	BMP2A	Bone morphogenetic protein 2
BMP4	BMP2B	Bone morphogenetic protein 4
BNIP3	Nip3	BCL2/adenovirus E1B 19kDa interacting protein 3
BNIP3L	BNIP3a, Nix	BCL2/adenovirus E1B 19kDa interacting protein 3-like
BRCA1	BRCC1, PPP1R53, RNF53	Breast cancer 1, early onset
BRCA2	BRCC2, FACD, FAD, FAD1, FANCD, FANCD1	Breast cancer 2, early onset
BRMS1	DKFZP564A063	Breast cancer metastasis suppressor 1
BTG2	MGC126063, MGC126064, PC3, TIS21	BTG family, member 2
C18orf8	HsT2591, MIC-1, MIC1	Chromosome 18 open reading frame 8

C1QBP	gC1Q-R, gC1qR, HABP1, p32, SF2p32	Complement component 1, q subcomponent binding protein
C6		Complement component 6
C7		Complement component 7
CA8	CALS, CARP	Carbonic anhydrase VIII
CALCA	CALC1	Calcitonin-related polypeptide alpha
CALM1	CALML2, CAMI, DD132, PHKD	Calmodulin 1 (phosphorylase kinase, delta)
CALM2	CAMII, PHKD	Calmodulin 2 (phosphorylase kinase, delta)
CALM3	PHKD	Calmodulin 3 (phosphorylase kinase, delta)
CALR	cC1qR, CRT, FLJ26680, RO, SSA	Calreticulin
CANX	CNX, IP90, P90	Calnexin
CAPN6	CalpM, CANPX, CAPNX	Calpain 6
CASC3	BTZ, MLN51	Cancer susceptibility candidate 3
CASP1	ICE, IL1BC	Caspase 1, apoptosis-related cysteine peptidase
CASP10	MCH4	Caspase 10, apoptosis-related cysteine peptidase
CASP2	ICH1, MGC2181, NEDD2, PPP1R57	Caspase 2, apoptosis-related cysteine peptidase
CASP3	apopain, CPP32, CPP32B, Yama	Caspase 3, apoptosis-related cysteine peptidase
CASP4	ICE(rel)II, ICH-2, TX	Caspase 4, apoptosis-related cysteine peptidase
CASP5	ICE(rel)III	Caspase 5, apoptosis-related cysteine peptidase
CASP6	MCH2	Caspase 6, apoptosis-related cysteine peptidase
CASP7	CMH-1, ICE-LAP3, MCH3	Caspase 7, apoptosis-related cysteine peptidase
CASP8	Casp-8, FLICE, MACH, MCH5	Caspase 8, apoptosis-related cysteine peptidase
CASP9	APAF-3, ICE-LAP6, MCH6, PPP1R56	Caspase 9, apoptosis-related cysteine peptidase
CAT		Catalase
CAV1	CAV	Caveolin 1, caveolae protein, 22kDa
CBL	c-Cbl, CBL2, RNF55	Cbl proto-oncogene, E3 ubiquitin protein ligase
CCKBR		Cholecystokinin B receptor
CCL11	eotaxin, MGC22554, SCYA11	Chemokine (C-C motif) ligand 11
CCL13	CKb10, MCP-4, MGC17134, NCC-1, SCYA13, SCYL1	Chemokine (C-C motif) ligand 13
CCL14	CKb1, HCC-1, HCC-3, MCIF, NCC-2, SCYA14, SCYL2	Chemokine (C-C motif) ligand 14
CCL16	CKb12, HCC-4, LCC-1, LEC, LMC, Mtn-1, NCC-4, SCYA16, SCYL4	Chemokine (C-C motif) ligand 16
CCL18	AMAC-1, CKb7, DC-CK1, DCCK1, MIP-4, PARC, SCYA18	Chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)

CCL19	CKb11, ELC, exodus-3, MIP-3b, SCYA19	Chemokine (C-C motif) ligand 19
CCL2	GDCF-2, HC11, MCAF, MCP-1, MCP1, MGC9434, SCYA2, SMC-CF	Chemokine (C-C motif) ligand 2
CCL21	6Ckine, CKb9, ECL, exodus-2, SCYA21, SLC, TCA4	Chemokine (C-C motif) ligand 21
CCL23	Ckb-8, CKb8, MIP-3, MPIF-1, SCYA23	Chemokine (C-C motif) ligand 23
CCL3	G0S19-1, LD78ALPHA, MIP-1-alpha, SCYA3	Chemokine (C-C motif) ligand 3
CCL4	Act-2, AT744.1, LAG1, MIP-1-beta, SCYA4	Chemokine (C-C motif) ligand 4
CCL5	D17S136E, MGC17164, RANTES, SCYA5, SISd, TCP228	Chemokine (C-C motif) ligand 5
CCL7	FIC, MARC, MCP-3, MCP3, NC28, SCYA6, SCYA7	Chemokine (C-C motif) ligand 7
CCL8	HC14, MCP-2, SCYA8	Chemokine (C-C motif) ligand 8
CCNA1	CT146	Cyclin A1
CCNA2	CCN1, CCNA	Cyclin A2
CCNB1	CCNB	Cyclin B1
CCNB2	HsT17299	Cyclin B2
CCND1	BCL1, D11S287E, PRAD1, U21B31	Cyclin D1
CCND2		Cyclin D2
CCNE1	CCNE	Cyclin E1
CCNE2	CYCE2	Cyclin E2
CCNG1	CCNG	Cyclin G1
CCNG2		Cyclin G2
CCNH	CycH, p34, p37	Cyclin H
CCR10	GPR2	Chemokine (C-C motif) receptor 10
CCR7	BLR2, CD197, CDw197, CMKBR7, EBI1	Chemokine (C-C motif) receptor 7
CD14		CD14 molecule
CD27	S152, TNFRSF7, Tp55	CD27 molecule
CD36	FAT, GP3B, GP4, GPIV, SCARB3	CD36 molecule (thrombospondin receptor)
CD38		CD38 molecule
CD40	Bp50, p50, TNFRSF5	CD40 molecule, TNF receptor superfamily member 5
CD40LG	CD154, CD40L, gp39, hCD40L, HIGM1, IMD3, TNFSF5, TRAP	CD40 ligand
CD44	CD44R, CSPG8, HCELL,	CD44 molecule (Indian blood group)

	IN, MC56, MDU2, MDU3, MIC4, Pgp1	
CD46	MCP, MGC26544, MIC10, TLX, TRA2.10	CD46 molecule, complement regulatory protein
CD52	CDW52	CD52 molecule
CD59	16.3A5, EJ16, EJ30, EL32, G344, MIC11, MIN1, MIN2, MIN3, MSK21, p18-20	CD59 molecule, complement regulatory protein
CD70	CD27L, CD27LG, TNFSF7	CD70 molecule
CD74	DHLAG	CD74 molecule, major histocompatibility complex, class II invariant chain
CD82	IA4, KAI1, R2, ST6, TSPAN27	CD82 molecule
CD9	BA2, MIC3, MRP-1, P24, TSPAN29	CD9 molecule
CDC16	ANAPC6, APC6, CUT9	Cell division cycle 16
CDC20	CDC20A, p55CDC	Cell division cycle 20
CDC25A		Cell division cycle 25A
CDC25B		Cell division cycle 25B
CDC25C	CDC25, PPP1R60	Cell division cycle 25C
CDC34	E2-CDC34, UBC3, UBE2R1	Cell division cycle 34
CDC37	P50CDC37	Cell division cycle 37
CDC6	CDC18L	Cell division cycle 6
CDH1	CD324, UVO, uvomorulin	Cadherin 1, type 1, E-cadherin (epithelial)
CDH17	cadherin, HPT-1	Cadherin 17, LI cadherin (liver-intestine)
CDH5	7B4, CD144	Cadherin 5, type 2 (vascular endothelium)
CDK1	CDC2, CDC28A	Cyclin-dependent kinase 1
CDK2		Cyclin-dependent kinase 2
CDK4	PSK-J3	Cyclin-dependent kinase 4
CDK6	PLSTIRE	Cyclin-dependent kinase 6
CDK7	CAK, CAK1, CDKN7, MO15, STK1	Cyclin-dependent kinase 7
CDKN1A	CAP20, CDKN1, CIP1, P21, p21CIP1, p21Cip1/Waf1, SDI1, WAF1	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)
CDKN1C	BWCR, BWS, KIP2, P57	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)
CDKN2A	ARF, CDK4I, CDKN2, CMM2, INK4, INK4a, MLM, MTS1, p14, p14ARF, p16, p16INK4a, p19, p19Arf	Cyclin-dependent kinase inhibitor 2A
CEACAM5	CD66e, CEA	Carcinoembryonic antigen-related cell adhesion molecule 5

CEACAM6	CD66c, NCA	Carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)
CENPF	hcp-1	Centromere protein F, 350/400kDa
CFHR1	CFHL, CFHL1, CFHL1P, CFHR1P, FHR1, H36-1, H36-2, HFL1, HFL2	Complement factor H-related 1
CFLAR	c-FLIP, CASH, CASP8AP1, Casper, CLARP, FLAME, FLIP, I-FLICE, MRIT	CASP8 and FADD-like apoptosis regulator
CFTR	ABC35, ABCC7, CF, CFTR/MRP, dJ760C5.1, MRP7, TNR-CFTR	Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)
CGA	FSHA, GPHa, GPHA1, HCG, LHA, TSHA	Glycoprotein hormones, alpha polypeptide
CGB	CGB3	Chorionic gonadotropin, beta polypeptide
CGB5	HCG	Chorionic gonadotropin, beta polypeptide 5
CGB7	CG-beta-a	Chorionic gonadotropin, beta polypeptide 7
CGB8		Chorionic gonadotropin, beta polypeptide 8
CHD7	CRG, FLJ20357, FLJ20361, KIAA1416	Chromodomain helicase DNA binding protein 7
CHEK1	CHK1	Checkpoint kinase 1
CHEK2	bA444G7, CDS1, CHK2, HuCds1, PP1425, RAD53	Checkpoint kinase 2
CHFR	FLJ10796, RNF196	Checkpoint with forkhead and ring finger domains, E3 ubiquitin protein ligase
CHGA		Chromogranin A (parathyroid secretory protein 1)
CHI3L1	GP39, YKL40	Chitinase 3-like 1 (cartilage glycoprotein-39)
CHP2		Calcineurin-like EF-hand protein 2
CIB2	DFNB48, KIP2, USH1J	Calcium and integrin binding family member 2
CKB	CKBB	Creatine kinase, brain
CKS1B	CKS1, ckshs1	CDC28 protein kinase regulatory subunit 1B
CKS2		CDC28 protein kinase regulatory subunit 2
CLDN3	C7orf1, CPE-R2, CPETR2, HRVP1, RVP1	Claudin 3
CLDN4	CPE-R, CPETR, CPETR1, hCPE-R, WBSCR8	Claudin 4
CLDN7	CEPTRL2, CPETRL2, Hs.84359	Claudin 7
CLEC3B	TN, TNA	C-type lectin domain family 3, member B
CLIC1	NCC27, p64CLCP	Chloride intracellular channel 1
CLIP1	CLIP, CLIP-170, CLIP170, CYLN1, RSN	CAP-GLY domain containing linker protein 1
CLSTN1	CDHR12, CSTN1, KIAA0911	Calsyntenin 1
CLU	APOJ, CLI, CLU1, CLU2, KUB1, SGP-2, SP-40,	Clusterin

	TRPM-2	
CNN1	Sm-Calp, SMCC	Calponin 1, basic, smooth muscle
CNTF	HCNTF	Ciliary neurotrophic factor
COL11A1	CO11A1, COLL6, STL2	Collagen, type XI, alpha 1
COL17A1	BP180, BPAG2	Collagen, type XVII, alpha 1
COL18A1	KNO, KNO1, KS	Collagen, type XVIII, alpha 1
COL1A1	OI4	Collagen, type I, alpha 1
COL1A2	OI4	Collagen, type I, alpha 2
COL4A2	DKFZp686I14213, FLJ22259	Collagen, type IV, alpha 2
COL4A3		Collagen, type IV, alpha 3 (Goodpasture antigen)
COL4A4	CA44	Collagen, type IV, alpha 4
COL4A5	ASLN, ATS	Collagen, type IV, alpha 5
COL6A1		Collagen, type VI, alpha 1
COX17		COX17 cytochrome c oxidase copper chaperone
CP		Ceruloplasmin (ferroxidase)
CRABP1	CRABP, CRABP-I, CRABPI, RBP5	Cellular retinoic acid binding protein 1
CRADD	RAIDD	CASP2 and RIPK1 domain containing adaptor with death domain
CREBBP	CBP, KAT3A, RSTS, RTS	CREB binding protein
CRP	PTX1	C-reactive protein, pentraxin-related
CRYAB	CRYA2, HSPB5	Crystallin, alpha B
CSE1L	CAS, CSE1, XPO2	CSE1 chromosome segregation 1-like (yeast)
CSF1	M-CSF, MCSF, MGC31930	Colony stimulating factor 1 (macrophage)
CSF1R	C-FMS, CD115, CSFR, FMS	Colony stimulating factor 1 receptor
CSF2	GM-CSF, GMCSF	Colony stimulating factor 2 (granulocyte-macrophage)
CSF2RA	CD116, CSF2R	Colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
CSF3	C17orf33, G-CSF, GCSF, MGC45931	Colony stimulating factor 3 (granulocyte)
CSN1S1	CASA, CSN1	Casein alpha s1
CSNK1E	CKIE, CKIepsilon, HCKIE	Casein kinase 1, epsilon
CSNK2A1		Casein kinase 2, alpha 1 polypeptide
CSNK2A2	CSNK2A1	Casein kinase 2, alpha prime polypeptide
CSNK2B		Casein kinase 2, beta polypeptide
CST3		Cystatin C
CST6		Cystatin E/M
CSTA	STF1, STFA	Cystatin A (stefin A)
CSTB	CST6, EPM1, PME, STFB	Cystatin B (stefin B)
CTAG1A	ESO1, LAGE2A	Cancer/testis antigen 1A
CTAG1B	CT6.1, CTAG, CTAG1, ESO1, LAGE2A, LAGE2B, NY-ESO-1	Cancer/testis antigen 1B

CTAG2	CAMEL, CT6.2a, CT6.2b, ESO2, LAGE-1, LAGE-1a, LAGE-1b, LAGE1, MGC138724, MGC3803	Cancer/testis antigen 2
CTGF	CCN2, IGFBP8	Connective tissue growth factor
CTNNB1	armadillo, beta-catenin, CTNNB	Catenin (cadherin-associated protein), beta 1, 88kDa
CTNNBL1	C20orf33, FLJ21108, NAP, NYD-SP19, P14, P14L	Catenin, beta like 1
CTSB		Cathepsin B
CTSD	CLN10, CPSD	Cathepsin D
CTSH	ACC-4, ACC-5, CPSB	Cathepsin H
CTSL	CTSL1, FLJ31037	Cathepsin L
CUL2		Cullin 2
CUL5	VACM-1	Cullin 5
CXCL1	FSP, GRO1, GROa, MGSA, MGSA-a, NAP-3, SCYB1	Chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)
CXCL10	C7, crg-2, gIP-10, IFI10, INP10, IP-10, mob-1, SCYB10	Chemokine (C-X-C motif) ligand 10
CXCL13	ANGIE, ANGIE2, BCA-1, BLC, BLR1L, SCYB13	Chemokine (C-X-C motif) ligand 13
CXCL2	CINC-2a, GRO2, GROb, MGSA-b, MIP-2a, SCYB2	Chemokine (C-X-C motif) ligand 2
CXCL5	ENA-78, SCYB5	Chemokine (C-X-C motif) ligand 5
CXCL8	3-10C, AMCF-I, b-ENAP, GCP-1, GCP1, IL-8, IL8, K60, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1, SCYB8, TSG-1	Chemokine (C-X-C motif) ligand 8
CXCL9	CMK, crg-10, Humig, MIG, SCYB9	Chemokine (C-X-C motif) ligand 9
CXCR1	CD181, CDw128a, CKR-1, CMKAR1, IL8RA	Chemokine (C-X-C motif) receptor 1
CXCR2	CD182, CMKAR2, IL8RB	Chemokine (C-X-C motif) receptor 2
CXCR4	CD184, D2S201E, fusin, HM89, HSY3RR, LESTR, NPY3R, NPYR, NPYY3R	Chemokine (C-X-C motif) receptor 4
CYB5R3	DIA1	Cytochrome b5 reductase 3
CYP19A1	ARO, ARO1, aromatase, CPV1, CYAR, CYP19, P-450AROM	Cytochrome P450, family 19, subfamily A, polypeptide 1
CYP1A2	CP12, P3-450	Cytochrome P450, family 1, subfamily A, polypeptide 2
CYP2C19	CPCJ, CYP2C, P450IIC19	Cytochrome P450, family 2, subfamily C, polypeptide 19
CYP2E1	CYP2E	Cytochrome P450, family 2, subfamily E,

		polypeptide 1
CYP3A4	CYP3A3	Cytochrome P450, family 3, subfamily A, polypeptide 4
CYP3A5	CP35, P450PCN3, PCN3	Cytochrome P450, family 3, subfamily A, polypeptide 5
DAD1	OST2	Defender against cell death 1
DAPK1	DAPK	Death-associated protein kinase 1
DAXX	DAP6	Death-domain associated protein
DBI	ACBD1, ACBP	Diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)
DCC	IGDCC1, NTN1R1	DCC netrin 1 receptor
DCDC1		Doublecortin domain containing 1
DCN	DSPG2, SLRR1B	Decorin
DDB2	DDBB, FLJ34321, UV-DDB2	Damage-specific DNA binding protein 2, 48kDa
DDIT3	CHOP, CHOP10, GADD153	DNA-damage-inducible transcript 3
DEFA1	DEF1, DEFA2, HNP-1, MRS	Defensin, alpha 1
DEFA1B		Defensin, alpha 1B
DEFA3	DEF3, HNP-3	Defensin, alpha 3, neutrophil-specific
DEK	D6S231E	DEK proto-oncogene
DES	CMD1I, CSM1, CSM2	Desmin
DHFR		Dihydrofolate reductase
DIAPH3	AN, AUNA1, DRF3, FLJ34705, NSDAN	Diaphanous-related formin 3
DLC1	ARHGAP7, DLC-1, HP, p122-RhoGAP, STARD12	DLC1 Rho GTPase activating protein
DNAJC2	MPHOSPH11, MPP11, ZRF1, ZUO1, zuotin	DnaJ (Hsp40) homolog, subfamily C, member 2
DST	BP240, BPA, BPAG1, CATX-15, FLJ13425, FLJ21489, FLJ30627, FLJ32235, KIAA0728, MACF2	Dystonin
DUSP1	CL100, HVH1, MKP-1, PTPN10	Dual specificity phosphatase 1
DUSP14	MKP-L, MKP6	Dual specificity phosphatase 14
DUSP4	HVH2, MKP-2, TYP	Dual specificity phosphatase 4
DVL3	KIAA0208	Dishevelled segment polarity protein 3
DYNLL1	DLC1, DLC8, DNCL1, hdlc1, LC8, PIN	Dynein, light chain, LC8-type 1
DYRK2		Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2
E2F1	RBBP3, RBP3	E2F transcription factor 1
E2F3		E2F transcription factor 3
E2F5		E2F transcription factor 5, p130-binding

EBAG9	EB9, RCAS1	Estrogen receptor binding site associated, antigen, 9
EDN1	ET1	Endothelin 1
EEF2	EEF-2, EF2	Eukaryotic translation elongation factor 2
EFNA1	ECKLG, EPLG1, LERK1, TNFAIP4	Ephrin-A1
EFNA2	ELF-1, EPLG6, LERK6	Ephrin-A2
EFNA5	AF1, EPLG7, LERK7	Ephrin-A5
EFNB1	CFNS, Elk-L, EPLG2, LERK2	Ephrin-B1
EFNB2	EPLG5, Htk-L, HTKL, LERK5, MGC126226, MGC126227, MGC126228	Ephrin-B2
EFNB3	EPLG8, LERK-8	Ephrin-B3
EGF		Epidermal growth factor
EGFR	ERBB, ERBB1	Epidermal growth factor receptor
EGR1	AT225, G0S30, KROX-24, NGFI-A, TIS8, ZIF-268, ZNF225	Early growth response 1
EI24	EPG4, PIG8, TP53I8	Etoposide induced 2.4
EIF3H	eIF3-gamma, eIF3-p40, eIF3h, EIF3S3	Eukaryotic translation initiation factor 3, subunit H
EIF4E	EIF4E1, EIF4EL1, EIF4F	Eukaryotic translation initiation factor 4E
EIF4EBP1	4E-BP1, PHAS-I	Eukaryotic translation initiation factor 4E binding protein 1
EIF4G1	EIF4F, EIF4G, p220, PARK18	Eukaryotic translation initiation factor 4 gamma, 1
EIF4H	KIAA0038, WBSCR1, WSCR1	Eukaryotic translation initiation factor 4H
EIF5A	EIF-5A, EIF5A1, MGC104255, MGC99547	Eukaryotic translation initiation factor 5A
ELANE	ELA2, HLE, HNE, NE	Elastase, neutrophil expressed
ELK3	ERP, NET, SAP2	ELK3, ETS-domain protein (SRF accessory protein 2)
ENC1	ENC-1, KLHL37, NRPB, PIG10, TP53I10	Ectodermal-neural cortex 1 (with BTB domain)
ENG	CD105, END, HHT1, ORW, ORW1	Endoglin
ENO1	ENO1L1, MBP-1, MPB1, PPH	Enolase 1, (alpha)
ENO2		Enolase 2 (gamma, neuronal)
ENPP2	ATX, PD-IALPHA, PDNP2	Ectonucleotide pyrophosphatase/phosphodiesterase 2
EPAS1	bHLHe73, HIF2A, HLF, MOP2, PASD2	Endothelial PAS domain protein 1
EPCAM	17-1A, 323/A3, CD326, CO-17A, EGP-2, EGP34,	Epithelial cell adhesion molecule

	EGP40, Ep-CAM, ESA, GA733-2, HEA125, KS1/4, KSA, Ly74, M4S1, MH99, MIC18, MK-1, MOC31, TACST-1, TACSTD1, TROP1	
EPHA1	EPH, EPHT, EPHT1	EPH receptor A1
EPHA2	ECK	EPH receptor A2
EPHA3	ETK, ETK1, HEK, HEK4, TYRO4	EPH receptor A3
EPHA4	Hek8, TYRO1	EPH receptor A4
EPHA7	Hek11	EPH receptor A7
EPHA8	EEK, Hek3	EPH receptor A8
EPHB2	DRT, EPHT3, ERK, Hek5, Tyro5	EPH receptor B2
EPHB3	ETK2, Hek2, Tyro6	EPH receptor B3
EPHB4	HTK, Tyro11	EPH receptor B4
EPHX1	EPHX	Epoxide hydrolase 1, microsomal (xenobiotic)
EPO	EP	Erythropoietin
EPOR		Erythropoietin receptor
ERBB2	CD340, HER-2, HER2, NEU, NGL	V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2
ERBB3	HER3, LCCS2	V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3
ERBB4	ALS19	V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4
ERCC1	RAD10	Excision repair cross-complementation group 1
ERCC2	EM9, MAG, MGC102762, MGC126218, MGC126219, TFIIH, XPD	Excision repair cross-complementation group 2
ERCC3	BTF2, GTF2H, RAD25, TFIIH, XPB	Excision repair cross-complementation group 3
ERCC4	FANCQ, RAD1, XPF	Excision repair cross-complementation group 4
ERCC5	ERCM2, XPGC	Excision repair cross-complementation group 5
ERCC6	ARMD5, CKN2, CSB, RAD26	Excision repair cross-complementation group 6
ESR1	Era, ESR, NR3A1	Estrogen receptor 1
ESR2	Erb, NR3A2	Estrogen receptor 2 (ER beta)
ETHE1	HSCO, YF13H12	Ethylmalonic encephalopathy 1
ETV4	E1A-F, E1AF, PEA3	Ets variant 4
ETV5	ERM	Ets variant 5
EXT1	LGCR, LGS, ttv	Exostosin glycosyltransferase 1
EZH2	ENX-1, EZH1, KMT6, KMT6A	Enhancer of zeste 2 polycomb repressive complex 2 subunit
EZR	VIL2	Ezrin
F13A1	F13A	Coagulation factor XIII, A1 polypeptide
F13B	FXIIIB	Coagulation factor XIII, B polypeptide

F2		Coagulation factor II (thrombin)
F3	CD142	Coagulation factor III (thromboplastin, tissue factor)
FABP1	L-FABP	Fatty acid binding protein 1, liver
FABP2	I-FABP	Fatty acid binding protein 2, intestinal
FABP4	A-FABP, aP2	Fatty acid binding protein 4, adipocyte
FABP5	E-FABP, KFABP, PA-FABP	Fatty acid binding protein 5 (psoriasis-associated)
FADD	GIG3, MORT1	Fas (TNFRSF6)-associated via death domain
FAF1	CGI-03, hFAF1, HFAF1s, UBXD12, UBXN3A	Fas (TNFRSF6) associated factor 1
FAM129A	C1orf24, GIG39, NIBAN	Family with sequence similarity 129, member A
FAP	DPPIV	Fibroblast activation protein, alpha
FAS	APO-1, APT1, CD95, FAS1, TNFRSF6	Fas cell surface death receptor
FASLG	APT1LG1, CD178, FasL, TNFSF6	Fas ligand (TNF superfamily, member 6)
FASN	FAS, SDR27X1	Fatty acid synthase
FBXO6	FBG2, FBS2, FBX6, Fbx6b	F-box protein 6
FCER2	CD23, CD23A, CLEC4J, FCE2	Fc fragment of IgE, low affinity II, receptor for (CD23)
FEN1	FEN-1, MF1, RAD2	Flap structure-specific endonuclease 1
FES	FPS	FES proto-oncogene, tyrosine kinase
FGA		Fibrinogen alpha chain
FGB		Fibrinogen beta chain
FGF1	AFGF, ECGF, ECGF-beta, ECGFA, ECGFB, FGF-alpha, FGFA, GLIO703, HBGF1	Fibroblast growth factor 1 (acidic)
FGF17	FGF-13	Fibroblast growth factor 17
FGF18	FGF-18, ZFGF5	Fibroblast growth factor 18
FGF19		Fibroblast growth factor 19
FGF2	FGFB	Fibroblast growth factor 2 (basic)
FGF23		Fibroblast growth factor 23
FGF3	HBGF-3, INT2	Fibroblast growth factor 3
FGF4	HBGF-4, HST, HST-1, HSTF1, K-FGF, KFGF	Fibroblast growth factor 4
FGF6		Fibroblast growth factor 6
FGF7	KGF	Fibroblast growth factor 7
FGF8	AIGF	Fibroblast growth factor 8 (androgen-induced)
FGF9		Fibroblast growth factor 9
FGFR1	BFGFR, CD331, CEK, FLG, FLT2, H2, H3, H4, H5, KAL2, N-SAM	Fibroblast growth factor receptor 1
FGFR2	BEK, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25	Fibroblast growth factor receptor 2

FGFR3	ACH, CD333, CEK2, JTK4	Fibroblast growth factor receptor 3
FGFR4	CD334, JTK2	Fibroblast growth factor receptor 4
FGG		Fibrinogen gamma chain
FHIT	AP3Aase, FRA3B	Fragile histidine triad
FIGF	VEGF-D, VEGFD	C-fos induced growth factor (vascular endothelial growth factor D)
FKBP5	FKBP51, FKBP54, P54, PPIase, Ptg-10	FK506 binding protein 5
FKBP8	FKBP38, FKBPr38	FK506 binding protein 8, 38kDa
FLT1	FLT, VEGFR1	Fms-related tyrosine kinase 1
FLT4	PCL, VEGFR3	Fms-related tyrosine kinase 4
FMO5		Flavin containing monooxygenase 5
FN1	CIG, FINC, GFND2, LETS, MSF	Fibronectin 1
FOLH1	FOLH, GCP2, GCPII, NAALAD1, NAALAdase, PSM, PSMA	Folate hydrolase (prostate-specific membrane antigen) 1
FOS	AP-1, c-fos	FBJ murine osteosarcoma viral oncogene homolog
FOSL1	fra-1	FOS-like antigen 1
FOXJ1	FKHL13, HFH-4, HFH4	Forkhead box J1
FOXM1	FKHL16, HFH-11, HNF-3, INS-1, MPHOSPH2, MPP2, TGT3, trident	Forkhead box M1
FOXO1	FKH1, FKHR, FOXO1A	Forkhead box O1
FOXO3	AF6q21, FKHRL1, FOXO2, FOXO3A	Forkhead box O3
FOXQ1	HFH1	Forkhead box Q1
FSCN1	FLJ38511, p55, SNL	Fascin actin-bundling protein 1
FSHB		Follicle stimulating hormone, beta polypeptide
FST	FS	Follistatin
FTH1	FHC, FTH, FTHL6, PIG15, PLIF	Ferritin, heavy polypeptide 1
FTL	MGC71996, NBIA3	Ferritin, light polypeptide
FZD1	DKFZp564G072	Frizzled class receptor 1
FZD2		Frizzled class receptor 2
G6PD	G6PD1	Glucose-6-phosphate dehydrogenase
GADD45A	DDIT1, GADD45	Growth arrest and DNA-damage-inducible, alpha
GADD45G	CR6, DDIT2, GADD45gamma, GRP17	Growth arrest and DNA-damage-inducible, gamma
GAS1		Growth arrest-specific 1
GAST	GAS	Gastrin
GATA3	HDR	GATA binding protein 3
GCLM	GLCLR	Glutamate-cysteine ligase, modifier subunit
GDF15	MIC-1, MIC1, NAG-1, PDF, PLAB, PTGFB	Growth differentiation factor 15

GDNF	ATF1, ATF2, HFB1-GDNF	Glial cell derived neurotrophic factor
GH1	GH, GH-N, GHN, hGH-N	Growth hormone 1
GH2	GH-V , GH2, GHL, GHV, hGH-V	Growth hormone 2
GJA1	CX43, GJAL, ODD, ODDD, ODOD, SDTY3	Gap junction protein, alpha 1, 43kDa
GJB5	CX31.1	Gap junction protein, beta 5, 31.1kDa
GLO1	GLOD1	Glyoxalase I
GMNN	Gem	Geminin, DNA replication inhibitor
GNAS	GNAS1, GNASXL, GPSA, NESP, NESP55, SCG6	GNAS complex locus
GPA33	A33	Glycoprotein A33 (transmembrane)
GPC3	DGSX, OCI-5, SDYS, SGB, SGBS, SGBS1	Glypican 3
GPI	AMF, NLK	Glucose-6-phosphate isomerase
GPX1		Glutathione peroxidase 1
GPX2	GSHPX-GI	Glutathione peroxidase 2 (gastrointestinal)
GRB10		Growth factor receptor-bound protein 10
GRB2	NCKAP2	Growth factor receptor-bound protein 2
GRB7		Growth factor receptor-bound protein 7
GSK3A		Glycogen synthase kinase 3 alpha
GSN	DKFZp313L0718	Gelsolin
GSR		Glutathione reductase
GSTM1	GST1, H-B, MU	Glutathione S-transferase mu 1
GSTM3	GST5	Glutathione S-transferase mu 3 (brain)
GSTP1	FAEES3, GST3, GSTP	Glutathione S-transferase pi 1
HDAC10	DKFZP761B039	Histone deacetylase 10
HDAC2	RPD3, YAF1	Histone deacetylase 2
HDAC5	FLJ90614, KIAA0600, NY-CO-9	Histone deacetylase 5
HGF	DFNB39, F-TCF, HGFB, HPTA, SF	Hepatocyte growth factor (hepapoietin A; scatter factor)
HGFAC	HGFA, HGFAP	HGF activator
HIF1A	bHLHe78, HIF-1alpha, HIF1, MOP1, PASD8	Hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)
HIP1R	FLJ14000, HIP12, HIP3, ILWEQ, KIAA0655	Huntingtin interacting protein 1 related
HIST1H2AC	H2AFL	Histone cluster 1, H2ac
HK1		Hexokinase 1
HK2		Hexokinase 2
HLA-G		Major histocompatibility complex, class I, G
HMGA1	HMGIY	High mobility group AT-hook 1
HMGA2	BABL, HMGIC, LIPO	High mobility group AT-hook 2
HMOX1	bK286B10, HO-1	Heme oxygenase (decycling) 1
HOXA5	HOX1, HOX1C	Homeobox A5
HOXA9	HOX1, HOX1G	Homeobox A9
HP		Haptoglobin

HPGD	SDR36C1	Hydroxyprostaglandin dehydrogenase 15-(NAD)
HPN	TMPRSS1	Hepsin
HRAS	HRAS1	Harvey rat sarcoma viral oncogene homolog
HSF1	HSTF1	Heat shock transcription factor 1
HSP90AA1	FLJ31884, Hsp89, Hsp90, HSP90N, HSPC1, HSPCA	Heat shock protein 90kDa alpha (cytosolic), class A member 1
HSP90AB1	HSPC2, HSPCB	Heat shock protein 90kDa alpha (cytosolic), class B member 1
HSP90B1	GP96, GRP94, TRA1	Heat shock protein 90kDa beta (Grp94), member 1
HSPA1A	HSP70-1, HSPA1	Heat shock 70kDa protein 1A
HSPA1B	HSP70-2	Heat shock 70kDa protein 1B
HSPA1L	HSP70-HOM, hum70t	Heat shock 70kDa protein 1-like
HSPA2		Heat shock 70kDa protein 2
HSPA4	HS24/P52, HSPH2	Heat shock 70kDa protein 4
HSPA8	HSC70, HSC71, HSP73, HSPA10	Heat shock 70kDa protein 8
HSPB1	Hs.76067, Hsp25, HSP27, HSP28	Heat shock 27kDa protein 1
HSPD1	GROEL, HSP60, SPG13	Heat shock 60kDa protein 1 (chaperonin)
HSPE1	CPN10, GROES	Heat shock 10kDa protein 1
HSPH1	HSP105A, HSP105B, KIAA0201, NY-CO-25	Heat shock 105kDa/110kDa protein 1
IBSP	BSP, BSP-II, SP-II	Integrin-binding sialoprotein
ICAM1	BB2, CD54	Intercellular adhesion molecule 1
ID1	bHLHb24, dJ857M17.1.2	Inhibitor of DNA binding 1, dominant negative helix-loop-helix protein
ID2	bHLHb26, GIG8	Inhibitor of DNA binding 2, dominant negative helix-loop-helix protein
ID3	bHLHb25, HEIR-1	Inhibitor of DNA binding 3, dominant negative helix-loop-helix protein
IDO1	IDO, INDO	Indoleamine 2,3-dioxygenase 1
IFNA1	IFL, IFN, IFN-ALPHA, IFN-alphaD, IFNA13, IFNA@	Interferon, alpha 1
IFNA13		Interferon, alpha 13
IFNAR1	IFNAR, IFRC	Interferon (alpha, beta and omega) receptor 1
IFNAR2	IFNABR	Interferon (alpha, beta and omega) receptor 2
IFNB1	IFB, IFF, IFNB	Interferon, beta 1, fibroblast
IFNG		Interferon, gamma
IGF1	IGF-I, IGF1A, IGFI	Insulin-like growth factor 1 (somatomedin C)
IGF1R	CD221, IGFIR, IGFR, JTK13, MGC18216	Insulin-like growth factor 1 receptor
IGF2	C11orf43, FLJ44734, IGF-II	Insulin-like growth factor 2
IGF2R	CD222, CIMPR, M6P-R, MPR1, MPRI	Insulin-like growth factor 2 receptor

IGFBP2	IBP2	Insulin-like growth factor binding protein 2, 36kDa
IGFBP3	BP-53, IBP3	Insulin-like growth factor binding protein 3
IL10	CSIF, IL-10, IL10A, TGIF	Interleukin 10
IL11	AGIF, IL-11	Interleukin 11
IL12A	CLMF, IL-12A, NFSK, NKSF1, p35	Interleukin 12A
IL13	ALRH, BHR1, IL-13, MGC116786, MGC116788, MGC116789, P600	Interleukin 13
IL13RA2	CD213a2, CT19, IL-13R, IL13BP	Interleukin 13 receptor, alpha 2
IL15	IL-15, MGC9721	Interleukin 15
IL16	FLJ16806, FLJ42735, HsT19289, IL-16, LCF, prIL-16	Interleukin 16
IL17A	CTLA8, IL-17, IL-17A, IL17	Interleukin 17A
IL17B	IL-17B, IL-20, MGC138900, MGC138901, NIRF, ZCYTO7	Interleukin 17B
IL18	IGIF, IL-18, IL-1g, IL1F4	Interleukin 18
IL1A	IL-1A, IL1, IL1-ALPHA, IL1F1	Interleukin 1, alpha
IL1B	IL-1B, IL1-BETA, IL1F2	Interleukin 1, beta
IL1R1	CD121A, D2S1473, IL1R, IL1RA	Interleukin 1 receptor, type I
IL1R2	CD121b, IL1RB	Interleukin 1 receptor, type II
IL1RN	ICIL-1RA, IL-1RN, IL1F3, IL1RA, IRAP, MGC10430	Interleukin 1 receptor antagonist
IL2	IL-2, TCGF	Interleukin 2
IL24	C49A, FISP, IL-24, IL10B, mda-7, Mob-5, ST16	Interleukin 24
IL2RA	CD25, IDDM10, IL2R	Interleukin 2 receptor, alpha
IL2RB	CD122, IL15RB	Interleukin 2 receptor, beta
IL2RG	CD132, CIDX, IMD4, SCIDX1	Interleukin 2 receptor, gamma
IL4	BCGF-1, BCGF1, BSF1, IL-4, MGC79402	Interleukin 4
IL4R	CD124	Interleukin 4 receptor
IL5	EDF, IL-5, TRF	Interleukin 5
IL6	BSF2, HGF, HSF, IFNB2, IL-6	Interleukin 6
IL6R	CD126	Interleukin 6 receptor
IL6ST	CD130, GP130	Interleukin 6 signal transducer
IL7	IL-7	Interleukin 7
IL9	HP40, IL-9, P40	Interleukin 9

ILF3	DRBP76, MPHOSPH4, MPP4, NF90, NFAR-1	Interleukin enhancer binding factor 3, 90kDa
ILK		Integrin-linked kinase
INHBA		Inhibin, beta A
INHBB		Inhibin, beta B
INS	IDDM1, IDDM2	Insulin
IRF1	MAR	Interferon regulatory factor 1
IRF4	LSIRF, MUM1	Interferon regulatory factor 4
ITGA1	CD49a, VLA1	Integrin, alpha 1
ITGA2	CD49B	Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)
ITGA2B	CD41, CD41B, GP2B, PPP1R93	Integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41)
ITGA3	CD49c, GAP-B3, MSK18, VCA-2, VLA3a	Integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)
ITGA4	CD49D	Integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
ITGA5	CD49e, FNRA	Integrin, alpha 5 (fibronectin receptor, alpha polypeptide)
ITGA6	CD49f	Integrin, alpha 6
ITGAM	CD11B, CR3A, MAC-1	Integrin, alpha M (complement component 3 receptor 3 subunit)
ITGAV	CD51, MSK8, VNRA, VTNR	Integrin, alpha V
ITGB1	CD29, FNRB, GPIIA, MDF2, MSK12	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)
ITGB3	CD61, GP3A, GPIIIa	Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)
ITGB4	CD104	Integrin, beta 4
ITGB5		Integrin, beta 5
ITGB6		Integrin, beta 6
ITGB8		Integrin, beta 8
ITIH4	H4P, IHRP, ITIHL1	Inter-alpha-trypsin inhibitor heavy chain family, member 4
JKAMP	C14orf100, CDA06, HSPC213, HSPC327, JAMP	JNK1/MAPK8-associated membrane protein
JTB	hJT	Jumping translocation breakpoint
JUN	AP-1, c-Jun	Jun proto-oncogene
JUND	AP-1	Jun D proto-oncogene
JUP	CTNNG, DP3, DPIII, PDGB, PKGB	Junction plakoglobin
KAT2B	GCN5, GCN5L, P/CAF, PCAF	K(lysine) acetyltransferase 2B
KDR	CD309, FLK1, VEGFR, VEGFR2	Kinase insert domain receptor (a type III receptor tyrosine kinase)
KIF2A	HK2, KIF2	Kinesin heavy chain member 2A

KIF2C	CT139, KNSL6, MCAK	Kinesin family member 2C
KISS1		KiSS-1 metastasis-suppressor
KIT	C-Kit, CD117, PBT, SCFR	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KITLG	FPH2, Kitl, KL-1, MGF, SCF, SF	KIT ligand
KLF4	EZF, GKLF	Kruppel-like factor 4 (gut)
KLF5	BTEB2, CKLF, IKLF	Kruppel-like factor 5 (intestinal)
KLK10	NES1, PRSSL1	Kallikrein-related peptidase 10
KLK11	PRSS20, TLSP	Kallikrein-related peptidase 11
KLK13	KLK-L4	Kallikrein-related peptidase 13
KLK14	KLK-L6	Kallikrein-related peptidase 14
KLK15	ACO, HSRNASPH, prostinogen	Kallikrein-related peptidase 15
KLK2		Kallikrein-related peptidase 2
KLK3	APS, PSA	Kallikrein-related peptidase 3
KLK4	EMSP, EMSP1, KLK-L1, PRSS17, PSTS	Kallikrein-related peptidase 4
KLK5	KLK-L2, SCTE	Kallikrein-related peptidase 5
KLK6	Bssp, Klk7, neurosin, PRSS18, PRSS9	Kallikrein-related peptidase 6
KLK7	PRSS6, SCCE	Kallikrein-related peptidase 7
KLK8	HNP, neuropsin, ovasin, PRSS19, TADG14	Kallikrein-related peptidase 8
KLRK1	CD314, D12S2489E, KLR, NKG2-D, NKG2D	Killer cell lectin-like receptor subfamily K, member 1
KRAS	KRAS1, KRAS2	Kirsten rat sarcoma viral oncogene homolog
KRT13	CK13, K13, MGC161462, MGC3781	Keratin 13
KRT14	EBS3, EBS4	Keratin 14
KRT15	CK15, K15, K1CO	Keratin 15
KRT17	PCHC1	Keratin 17
KRT18		Keratin 18
KRT19	CK19, K19, K1CS, MGC15366	Keratin 19
KRT4	CK4, CYK4, K4	Keratin 4
KRT8	CARD2, CK8, CYK8, K2C8, K8, KO	Keratin 8
LALBA	LYZL7	Lactalbumin, alpha-
LAMB1	CLM	Laminin, beta 1
LAMC1	LAMB2	Laminin, gamma 1 (formerly LAMB2)
LCN1	MGC71975, PMFA, TLC, TP, VEGP	Lipocalin 1
LDHA		Lactate dehydrogenase A
LEP	OB, OBS	Leptin
LGALS3	GALIG, LGALS2, MAC-2	Lectin, galactoside-binding, soluble, 3
LGALS3BP	90K, BTBD17B, CyCAP,	Lectin, galactoside-binding, soluble, 3 binding

	gp90, M2BP, MAC-2-BP, TANGO10B	protein
LGALS4	GAL4	Lectin, galactoside-binding, soluble, 4
LGI1	EPITEMPIN, EPT, ETL1, IB1099	Leucine-rich, glioma inactivated 1
LGMN	LGMN1, PRSC1	Legumain
LHB	CGB4, hLHB, LSH-B	Luteinizing hormone beta polypeptide
LHX1	LIM-1, LIM1	LIM homeobox 1
LIF	CDF, DIA, HILDA	Leukemia inhibitory factor
LIG4		Ligase IV, DNA, ATP-dependent
LIMK1	LIMK	LIM domain kinase 1
LMNA	CMD1A, HGPS, LGMD1B, LMN1, LMNL1, PRO1	Lamin A/C
LRP1B	LRP-DIT, LRPDIT	Low density lipoprotein receptor-related protein 1B
LRP6	ADCAD2	Low density lipoprotein receptor-related protein 6
LTA	LT, TNFB, TNFSF1	Lymphotoxin alpha
LTA4H		Leukotriene A4 hydrolase
LTB	p33, TNFC, TNFSF3	Lymphotoxin beta (TNF superfamily, member 3)
LTBR	D12S370, TNF-R-III, TNFCR, TNFR-RP, TNFR2-RP, TNFRSF3	Lymphotoxin beta receptor (TNFR superfamily, member 3)
LTF	HLF2	Lactotransferrin
MAD2L1	HSMAD2, MAD2	MAD2 mitotic arrest deficient-like 1 (yeast)
MAD2L2	MAD2B, POLZ2, REV7	MAD2 mitotic arrest deficient-like 2 (yeast)
MAGEA3	CT1.3, HIP8, HYPD, MAGE3, MGC14613	Melanoma antigen family A, 3
MAGEA4	CT1.4, MAGE-41, MAGE-X2, MAGE4, MAGE4A, MAGE4B, MGC21336	Melanoma antigen family A, 4
MAGEA6	CT1.6, MAGE6	Melanoma antigen family A, 6
MAGEB5	CT3.3, MAGE-B5	Melanoma antigen family B, 5
MAGEB6	CT3.4, FLJ40242, MAGE-B6, MAGEB6A	Melanoma antigen family B, 6
MAGEC1	CT7, CT7.1, MAGE-C1, MGC39366	Melanoma antigen family C, 1
MAGEC2	CT10, MAGE-C2, MAGEE1	Melanoma antigen family C, 2
MAGEC3	CT7.2, HCA2, MAGE-C3	Melanoma antigen family C, 3
MAGED1	DLXIN-1, NRAGE	Melanoma antigen family D, 1
MAGED2	11B6, BCG1, HCA10, JCL-1, MAGE-D2, MAGED, MGC8386	Melanoma antigen family D, 2
MAGI1	AIP3, BAIAP1, BAP1, MAGI-1, TNRC19, WWP3	Membrane associated guanylate kinase, WW and PDZ domain containing 1

MAP2K1	MAPKK1, MEK1, PRKMK1	Mitogen-activated protein kinase kinase 1
MAP2K2	MEK2, PRKMK2	Mitogen-activated protein kinase kinase 2
MAP2K4	JNKK1, MEK4, MKK4, PRKMK4, SERK1	Mitogen-activated protein kinase kinase 4
MAPK1	ERK, ERK2, MAPK2, p41mapk, PRKM1, PRKM2	Mitogen-activated protein kinase 1
MAPK14	CSBP1, CSBP2, CSPB1, Mxi2, p38, PRKM14, PRKM15	Mitogen-activated protein kinase 14
MAPK3	ERK1, p44erk1, p44mapk, PRKM3	Mitogen-activated protein kinase 3
MAPK7	BMK1, ERK5, PRKM7	Mitogen-activated protein kinase 7
MAPK8	JNK, JNK1, PRKM8, SAPK1	Mitogen-activated protein kinase 8
MAPKAPK2		Mitogen-activated protein kinase-activated protein kinase 2
MBD1	CXXC3, PCM1	Methyl-CpG binding domain protein 1
MBD2		Methyl-CpG binding domain protein 2
MBD4	MED1	Methyl-CpG binding domain protein 4
MCL1	BCL2L3, Mcl-1	Myeloid cell leukemia 1
MCM2	BM28, CCNL1, cdc19, CDCL1, D3S3194, KIAA0030	Minichromosome maintenance complex component 2
MCM3		Minichromosome maintenance complex component 3
MCM5	CDC46	Minichromosome maintenance complex component 5
MCM7	CDC47, MCM2, PPP1R104	Minichromosome maintenance complex component 7
MDH1		Malate dehydrogenase 1, NAD (soluble)
MDK	FLJ27379, MK, NEGF2	Midkine (neurite growth-promoting factor 2)
MDM2	HDM2, MGC5370	MDM2 proto-oncogene, E3 ubiquitin protein ligase
MECP2	MRX16, MRX79, RTT	Methyl CpG binding protein 2
MED1	CRSP1, CRSP200, DRIP230, PBP, PPARBP, PPARGBP, RB18A, TRAP220, TRIP2	Mediator complex subunit 1
MET	HGFR, RCCP2	MET proto-oncogene, receptor tyrosine kinase
MFGE8	BA46, EDIL1, hP47, HsT19888, MFG-E8, OAcGD3S, SED1, SPAG10	Milk fat globule-EGF factor 8 protein
MGMT		O-6-methylguanine-DNA methyltransferase
MIA	CD-RAP	Melanoma inhibitory activity
MIF	GIF, GLIF	Macrophage migration inhibitory factor (glycosylation-inhibiting factor)

MKI67	MIB-, PPP1R105	Marker of proliferation Ki-67
MLH1	COCA2, FCC2, HNPCC, HNPCC2	MutL homolog 1
MLLT11	AF1Q	Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11
MME	CALLA, CD10, NEP	Membrane metallo-endopeptidase
MMP1	CLG	Matrix metallopeptidase 1 (interstitial collagenase)
MMP10	STMY2	Matrix metallopeptidase 10 (stromelysin 2)
MMP11	STMY3	Matrix metallopeptidase 11 (stromelysin 3)
MMP12	HME	Matrix metallopeptidase 12 (macrophage elastase)
MMP13	CLG3	Matrix metallopeptidase 13 (collagenase 3)
MMP14	MT1-MMP	Matrix metallopeptidase 14 (membrane-inserted)
MMP15	MT2-MMP, MTMMP2, SMCP-2	Matrix metallopeptidase 15 (membrane-inserted)
MMP16	C8orf57, DKFZp761D112, MT3-MMP	Matrix metallopeptidase 16 (membrane-inserted)
MMP2	CLG4, CLG4A, TBE-1	Matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)
MMP3	STMY, STMY1	Matrix metallopeptidase 3 (stromelysin 1, progelatinase)
MMP7	MPSL1, PUMP-1	Matrix metallopeptidase 7 (matrilysin, uterine)
MMP8	CLG1	Matrix metallopeptidase 8 (neutrophil collagenase)
MMP9	CLG4B	Matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
MPO		Myeloperoxidase
MRE11A	ATLD, MRE11	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)
MSH6	GTBP	MutS homolog 6
MSLN	CAK1, MPF	Mesothelin
MSMB	IGBF, MSP, MSPB, PN44, PRPS, PSP, PSP-94, PSP57, PSP94	Microseminoprotein, beta-
MSR1	CD204, SCARA1	Macrophage scavenger receptor 1
MT1A	MT1, MT1S	Metallothionein 1A
MT1G	MT1, MT1K	Metallothionein 1G
MTA1		Metastasis associated 1
MUC1	ADMCKD, ADMCKD1, CD227, MCD, MCKD, MCKD1, PEM, PUM	Mucin 1, cell surface associated
MUTYH	MYH	MutY homolog
MVP	LRP, VAULT1	Major vault protein
MXI1	bHLHc11, MAD2, MXD2,	MAX interactor 1, dimerization protein

	MXI	
MYBL2	B-MYB, BMYB	V-myb avian myeloblastosis viral oncogene homolog-like 2
MYC	bHLHe39, c-Myc, MYCC	V-myc avian myelocytomatosis viral oncogene homolog
MYOCD	MYCD	Myocardin
MYOD1	bHLHc1, MYF3, MYOD, PUM	Myogenic differentiation 1
MYOG	bHLHc3, MYF4	Myogenin (myogenic factor 4)
NAGA	D22S674	N-acetylgalactosaminidase, alpha-
NAIP	BIRC1, NLRB1	NLR family, apoptosis inhibitory protein
NAMPT	PBEF, PBEF1	Nicotinamide phosphoribosyltransferase
NAT2	AAC2	N-acetyltransferase 2 (arylamine N-acetyltransferase)
NCAM1	CD56, NCAM	Neural cell adhesion molecule 1
NCOA3	ACTR, AIB1, bHLHe42, CAGH16, KAT13B, p/CIP, RAC3, SRC-3, SRC3, TNRC16, TRAM-1	Nuclear receptor coactivator 3
NDRG1	CAP43, DRG1, NDR1, RTP, TDD5	N-myc downstream regulated 1
NEDD8	Nedd-8	Neural precursor cell expressed, developmentally down-regulated 8
NEO1	HsT17534, IGDCC2, NGN, NTN1R2	Neogenin 1
NFKB1	KBF1, NF-kappaB, NF-kB1, NFkappaB, NFKB-p50, p105, p50	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1
NFKB2	LYT-10, NF-kB2, p105, p52	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)
NFKBIA	IkappaBalpha, IKBA, MAD-3, NFKBI	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
NFKBIE	IKBE	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon
NGF	NGFB	Nerve growth factor (beta polypeptide)
NGFR	CD271, p75NTR, TNFRSF16	Nerve growth factor receptor
NKX3-1	BAPX2, NKX3.1, NKX3A	NK3 homeobox 1
NME1	NDPKA, NM23, NM23-H1	NME/NM23 nucleoside diphosphate kinase 1
NME2	NDPKB, NM23-H2	NME/NM23 nucleoside diphosphate kinase 2
NOS1	nNOS, NOS	Nitric oxide synthase 1 (neuronal)
NOS2	HEP-NOS, iNOS, NOS, NOS2A	Nitric oxide synthase 2, inducible
NOS3	ECNOS, eNOS	Nitric oxide synthase 3 (endothelial cell)
NOTCH1	TAN1	Notch 1
NOTCH2		Notch 2
NOTCH3	CADASIL, CASIL	Notch 3

NQO1	DHQU, DIA4, DTD, NMOR1, QR1	NAD(P)H dehydrogenase, quinone 1
NR0B1	AHC, AHCH, DAX1, DSS, NR0B1	Nuclear receptor subfamily 0, group B, member 1
NRG1	GGF, HGL, HRG, NDF, NRG1-IT2	Neuregulin 1
NRG2	Don-1, HRG2, NTAK	Neuregulin 2
NRG3		Neuregulin 3
NRP1	CD304, NRP, VEGF165R	Neuropilin 1
NRP2	VEGF165R2	Neuropilin 2
NTF3	NGF2	Neurotrophin 3
NTF4	GLC1O, NT-4/5, NTF5	Neurotrophin 4
NTHL1	NTH1, OCTS3	Nth endonuclease III-like 1 (E. coli)
NTN1	NTN1L	Netrin 1
NTRK1	MTC, TRK, TRKA	Neurotrophic tyrosine kinase, receptor, type 1
NTRK2	TRKB	Neurotrophic tyrosine kinase, receptor, type 2
NTRK3	TRKC	Neurotrophic tyrosine kinase, receptor, type 3
NUDT1	MTH1	Nudix (nucleoside diphosphate linked moiety X)-type motif 1
NUMB	C14orf41	Numb homolog (Drosophila)
OGG1	HMMH, HOGG1, MUTM, OGH1	8-oxoguanine DNA glycosylase
OR51E2	PSGR	Olfactory receptor, family 51, subfamily E, member 2
ORM1		Orosomucoid 1
OSM	MGC20461	Oncostatin M
PAGE4	CT16.7, GAGEC1, PAGE-4	P antigen family, member 4 (prostate associated)
PAPPA	ASBABP2, DIPLA1, IGFBP-4ase, PAPA, PAPP-A, PAPPA1	Pregnancy-associated plasma protein A, pappalysin 1
PARP1	ADPRT, PARP, PPOL	Poly (ADP-ribose) polymerase 1
PARVB	CGI-56	Parvin, beta
PAX5	BSAP	Paired box 5
PAX8		Paired box 8
PCNA		Proliferating cell nuclear antigen
PDGFA	PDGF-A, PDGF1	Platelet-derived growth factor alpha polypeptide
PDGFB	SIS, SSV	Platelet-derived growth factor beta polypeptide
PDGFRA	CD140a, PDGFR2	Platelet-derived growth factor receptor, alpha polypeptide
PDGFRB	CD140b, JTK12, PDGFR, PDGFR1	Platelet-derived growth factor receptor, beta polypeptide
PDZD4	FLJ34125, KIAA1444, LU1, PDZK4, PDZRN4L	PDZ domain containing 4
PF4	CXCL4, SCYB4	Platelet factor 4
PGC		Progastricsin (pepsinogen C)
PGF	D12S1900, PGFL, PLGF,	Placental growth factor

	PlGF-2, SHGC-10760	
PGR	NR3C3, PR	Progesterone receptor
PHF20	C20orf104, dJ1121G12.1, TDRD20A	PHD finger protein 20
PIGR		Polymeric immunoglobulin receptor
PIK3CA	PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIK3R1	GRB1, p85, p85-ALPHA	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)
PIK3R2	p85, P85B	Phosphoinositide-3-kinase, regulatory subunit 2 (beta)
PIK3R3	p55	Phosphoinositide-3-kinase, regulatory subunit 3 (gamma)
PIM1	PIM	Pim-1 proto-oncogene, serine/threonine kinase
PIM2		Pim-2 proto-oncogene, serine/threonine kinase
PIM3		Pim-3 proto-oncogene, serine/threonine kinase
PIN1	dod	Peptidylprolyl cis/trans isomerase, NIMA-interacting 1
PIP4K2B	PIP5K2B, PIP5KIIB, PIP5KIIbeta	Phosphatidylinositol-5-phosphate 4-kinase, type II, beta
PKM	OIP3, PK3, PKM2, THBP1	Pyruvate kinase, muscle
PLAT		Plasminogen activator, tissue
PLAU	UPA, URK	Plasminogen activator, urokinase
PLAUR	CD87, UPAR, URKR	Plasminogen activator, urokinase receptor
PLG		Plasminogen
PLK1	PLK	Polo-like kinase 1
PLP1	GPM6C, PLP, SPG2	Proteolipid protein 1
PMEPA1	STAG1, TMEPAI	Prostate transmembrane protein, androgen induced 1
PML	MYL, RNF71, TRIM19	Promyelocytic leukemia
PMP22	GAS-3, HNPP, Sp110	Peripheral myelin protein 22
PNMT	PENT	Phenylethanolamine N-methyltransferase
POMC	ACTH, CLIP, LPH, MSH, NPP, POC	Proopiomelanocortin
PON1	ESA, PON	Paraoxonase 1
POSTN	OSF-2, periostin, PN	Periostin, osteoblast specific factor
POU2F2	OCT2, OTF2	POU class 2 homeobox 2
PPA2	FLJ20459	Pyrophosphatase (inorganic) 2
PPARG	NR1C3, PPARG1, PPARG2, PPARgamma	Peroxisome proliferator-activated receptor gamma
PPARGC1A	PGC1, PGC1A, PPARGC1	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
PPM1D	PP2C-DELTA, Wip1	Protein phosphatase, Mg2+/Mn2+ dependent, 1D
PPP1R15A	GADD34	Protein phosphatase 1, regulatory subunit 15A
PPY	PNP	Pancreatic polypeptide
PRDM13		PR domain containing 13

PRDM16	KIAA1675, MEL1, MGC166915, PFM13	PR domain containing 16
PRDX2	MGC4104, NKEFB, PRP, PRX2, PRXII, TDPX1, TSA	Peroxiredoxin 2
PRDX4	AOE37-2	Peroxiredoxin 4
PRKCA	PKCA	Protein kinase C, alpha
PRKCB	PKCB, PRKCB1, PRKCB2	Protein kinase C, beta
PRKCE		Protein kinase C, epsilon
PRKCH	PKC-L, PKCL, PRKCL	Protein kinase C, eta
PRKCI	DXS1179E, PKCI	Protein kinase C, iota
PRKCQ		Protein kinase C, theta
PRKDC	DNA-PKcs, DNAPK, DNPK1, HYRC, HYRC1, p350, XRCC7	Protein kinase, DNA-activated, catalytic polypeptide
PRL		Prolactin
PROC		Protein C (inactivator of coagulation factors Va and VIIIa)
PRSS1	TRY1	Protease, serine, 1 (trypsin 1)
PSCA		Prostate stem cell antigen
PSMD4	AF, AF-1, Rpn10, S5A	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 4
PTCH1	BCNS, NBCCS, PTCH	Patched 1
PTCH2		Patched 2
PTGS1	COX1, PGHS-1, PTGHS	Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)
PTGS2	COX2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)
PTH	PTH1	Parathyroid hormone
PTHLH	HHM, PLP, PTHR, PTHRP	Parathyroid hormone-like hormone
PTK2	FADK, FAK, FAK1, PPP1R71	Protein tyrosine kinase 2
PTN	HBGF8, HBNF, NEGF1	Pleiotrophin
PTPRO	GLEPP1, NPHS6, PTP-oc, PTP-U2, PTPU2	Protein tyrosine phosphatase, receptor type, O
PTTG1	EAP1, HPTTG, PTTG, securin, TUTR1	Pituitary tumor-transforming 1
PURA	PUR-ALPHA, PUR1, PURALPHA	Purine-rich element binding protein A
PZP	CPAMD6	Pregnancy-zone protein
RAB11FIP3	eferin, KIAA0665, Rab11-FIP3	RAB11 family interacting protein 3 (class II)
RAB18		RAB18, member RAS oncogene family
RAB25	CATX-8	RAB25, member RAS oncogene family
RAC1	p21-Rac1, Rac-1, TC-25	Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)

RAD23A	HHR23A, MGC111083	RAD23 homolog A (S. cerevisiae)
RAD23B	HHR23B, HR23B, P58	RAD23 homolog B (S. cerevisiae)
RAD51	BRCC5, HsRad51, HsT16930, RAD51A, RECA	RAD51 recombinase
RAD51D	HsTRAD, R51H3, RAD51L3, Trad	RAD51 paralog D
RAD52		RAD52 homolog (S. cerevisiae)
RAD54B	RDH54	RAD54 homolog B (S. cerevisiae)
RAF1	c-Raf, CRAF, Raf-1	Raf-1 proto-oncogene, serine/threonine kinase
RARA	NR1B1, RAR	Retinoic acid receptor, alpha
RARB	HAP, NR1B2, RRB2	Retinoic acid receptor, beta
RARG	NR1B3, RARC	Retinoic acid receptor, gamma
RASA1	CM-AVM, GAP, p120GAP, p120RASGAP, RASA	RAS p21 protein activator (GTPase activating protein) 1
RB1	OSRC, PPP1R130, RB	Retinoblastoma 1
RBBP4	lin-53, NURF55, RbAp48	Retinoblastoma binding protein 4
RBL1	cp107, p107, PRB1	Retinoblastoma-like 1
RBL2	p130, Rb2	Retinoblastoma-like 2
RBM6	3G2, DEF-3, DEF3, g16, NY-LU-12	RNA binding motif protein 6
RBP4		Retinol binding protein 4, plasma
REL	c-Rel, I-Rel	V-rel avian reticuloendotheliosis viral oncogene homolog
RELA	NFKB3, p65	V-rel avian reticuloendotheliosis viral oncogene homolog A
RELB	REL-B	V-rel avian reticuloendotheliosis viral oncogene homolog B
RET	CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET51	Ret proto-oncogene
RHOA	ARH12, ARHA, Rho12, RhoA, RHOH12	Ras homolog family member A
RHOB	ARH6, ARHB, MST081, RhoB, RHOH6	Ras homolog family member B
RHOC	ARH9, ARHC, RhoC	Ras homolog family member C
RPΛ2		Replication protein Λ2, 32kDa
RPL27	L27	Ribosomal protein L27
RPS3	FLJ26283, FLJ27450, MGC87870, S3	Ribosomal protein S3
RPS6KA1	HU-1, RSK, RSK1	Ribosomal protein S6 kinase, 90kDa, polypeptide 1
RPS6KA3	CLS, HU-3, MRX19, RSK, RSK2	Ribosomal protein S6 kinase, 90kDa, polypeptide 3
RXRA	NR2B1	Retinoid X receptor, alpha
RXRB	H-2RIIBP, NR2B2, RCoR-1	Retinoid X receptor, beta
RXRG	NR2B3	Retinoid X receptor, gamma

S100A1	S100-alpha, S100A	S100 calcium binding protein A1
S100A2	CAN19, S100L	S100 calcium binding protein A2
S100A4	18A2, 42A, CAPL, FSP1, MTS1, P9KA, PEL98	S100 calcium binding protein A4
S100A6	2A9, CABP, CACY, PRA	S100 calcium binding protein A6
S100A7	PSOR1, S100A7c	S100 calcium binding protein A7
S100A8	60B8AG, CAGA, CFAG, CGLA, MRP8, P8	S100 calcium binding protein A8
S100A9	60B8AG, CAGB, CFAG, CGLB, LIAG, MAC387, MIF, MRP14, NIF, P14	S100 calcium binding protein A9
S100B	S100beta	S100 calcium binding protein B
S1PR1	CD363, D1S3362, edg-1, EDG1	Sphingosine-1-phosphate receptor 1
SAA1	PIG4, SAA, TP53I4	Serum amyloid A1
SAA2		Serum amyloid A2
SART1	Ara1, SNRNP110, Snu66	Squamous cell carcinoma antigen recognized by T cells
SCGB1A1	CC10, CC16, CCSP, UGB	Secretoglobin, family 1A, member 1 (uteroglobin)
SCGB1D2	LIPB, LPHB	Secretoglobin, family 1D, member 2
SCGB2A1	LPHC, MGB2, MGC71973, UGB3	Secretoglobin, family 2A, member 1
SCGB2A2	MGB1, MGC71974, UGB2	Secretoglobin, family 2A, member 2
SDC1	CD138, SDC, SYND1, syndecan	Syndecan 1
SELE	CD62E, ELAM, ELAM1, ESEL	Selectin E
SELL	CD62L, hLHRc, LAM-1, LAM1, Leu-8, LNHR, LSEL, Lyam-1, LYAM1, PLNHR	Selectin L
SELP	CD62, CD62P, GMP140, GRMP, PADGEM, PSEL	Selectin P (granule membrane protein 140kDa, antigen CD62)
SEMA3B	LUCA-1, SemA, sema5, SEMAA, semaV	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3B
2-Sep	DIFF6, hNedd5, KIAA0158, NEDD5, Pnutl3	Septin 2
SERPINA1	A1A, A1AT, AAT, alpha-1-antitrypsin, alpha1AT, PI, PI1	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1
SERPINA3	AACT, ACT, alpha-1-antichymotrypsin	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3
SERPINA5	PAI3, PCI, PLANH3, PROCI	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5
SERPINB2	HsT1201, PAI2, PLANH2	Serpin peptidase inhibitor, clade B (ovalbumin), member 2

SERPINB3	HsT1196, SCC, SCCA1, T4-A	Serpin peptidase inhibitor, clade B (ovalbumin), member 3
SERPINB4	LEUPIN, PI11, SCCA-2, SCCA1, SCCA2	Serpin peptidase inhibitor, clade B (ovalbumin), member 4
SERPINE1	PAI, PAI1, PLANH1	Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1
SERPINF1	EPC-1, PEDF, PIG35	Serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 1
SFN	YWHAS	Stratifin
SHBG	ABP, MGC126834, MGC138391, TEBG	Sex hormone-binding globulin
SIRT2	SIR2L	Sirtuin 2
SKP2	FBL1, FBXL1, p45	S-phase kinase-associated protein 2, E3 ubiquitin protein ligase
SLC19A1	FOLT	Solute carrier family 19 (folate transporter), member 1
SLC2A1	DYT18, GLUT, GLUT1, HTLVR	Solute carrier family 2 (facilitated glucose transporter), member 1
SLC3A2	4F2, 4F2HC, 4T2HC, CD98, CD98HC, MDU1, NACAE	Solute carrier family 3 (amino acid transporter heavy chain), member 2
SLPI	ALK1, ALP, BLPI, HUSI, HUSI-I, WAP4, WFDC4	Secretory leukocyte peptidase inhibitor
SMAD1	JV4-1, MADH1, MADR1	SMAD family member 1
SMAD2	JV18-1, MADH2, MADR2	SMAD family member 2
SMAD3	HsT17436, JV15-2, MADH3	SMAD family member 3
SMAD4	DPC4, MADH4	SMAD family member 4
SMYD3	KMT3E, ZMYND1, ZNFN3A1	SET and MYND domain containing 3
SOD1	ALS, ALS1, IPOA	Superoxide dismutase 1, soluble
SOD2		Superoxide dismutase 2, mitochondrial
SOX1		SRY (sex determining region Y)-box 1
SOX9	CMD1, CMPD1, SRA1	SRY (sex determining region Y)-box 9
SP1		Sp1 transcription factor
SPARC	ON	Secreted protein, acidic, cysteine-rich (osteonectin)
SPARCL1	MAST9	SPARC-like 1 (hevin)
SPINK1	PCTT, PSTI, Spink3, TATI	Serine peptidase inhibitor, Kazal type 1
SPINT1	HAI, MANSC2	Serine peptidase inhibitor, Kunitz type 1
SPINT2	HAI-2, Kop	Serine peptidase inhibitor, Kunitz type, 2
SPP1	BNSP, BSPI, ETA-1, OPN	Secreted phosphoprotein 1
SPRR1B	GADD33, SPRR1	Small proline-rich protein 1B
SPRR3		Small proline-rich protein 3
SPRY1	hSPRY1	Sprouty homolog 1, antagonist of FGF signaling

		(Drosophila)
SRC	ASV, c-src, SRC1	SRC proto-oncogene, non-receptor tyrosine kinase
SRD5A1		Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)
SRD5A2		Steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)
SST	SMST	Somatostatin
SSX2	CT5.2a, HD21, HOM-MEL-40, MGC119055, MGC15364, MGC3884, SSX	Synovial sarcoma, X breakpoint 2
SSX2B	CT5.2b	Synovial sarcoma, X breakpoint 2B
ST14	HAI, MT-SP1, PRSS14, SNC19, TMPRSS14	Suppression of tumorigenicity 14 (colon carcinoma)
STARD3	es64, MLN64	StAR-related lipid transfer (START) domain containing 3
STAT4		Signal transducer and activator of transcription 4
STAT5A	MGF, STAT5	Signal transducer and activator of transcription 5A
STEAP1	PRSS24, STEAP	Six transmembrane epithelial antigen of the prostate 1
STMN1	C1orf215, FLJ32206, Lag, LAP18, OP18, PP17, PP19, PR22, SMN	Stathmin 1
STRAP	MAWD, pt-wd, UNRIP	Serine/threonine kinase receptor associated protein
STT3A	ITM1, MGC9042, STT3-A, TMC	STT3A, subunit of the oligosaccharyltransferase complex (catalytic)
SULT1E1	EST, STE	Sulfotransferase family 1E, estrogen-preferring, member 1
TAGLN	DKFZp686P11128, SM22, SMCC, TAGLN1, WS3-10	Transgelin
TDRD6	bA446F17.4, CT41.2, NY-CO-45, SPATA36	Tudor domain containing 6
TEK	CD202b, TIE-2, TIE2, VMCM, VMCM1	TEK tyrosine kinase, endothelial
TERT	EST2, hEST2, TCS1, TP2, TRT	Telomerase reverse transcriptase
TF	PRO1557, PRO2086	Transferrin
TFAP2B	AP2-B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)
TFDP1	Dp-1, DP1, DRTF1	Transcription factor Dp-1
TFDP2	Dp-2	Transcription factor Dp-2 (E2F dimerization partner 2)

TFF1	BCEI, D21S21, HP1.A, HPS2, pNR-2, pS2	Trefoil factor 1
TFF2	SML1	Trefoil factor 2
TFF3	HITF, ITF	Trefoil factor 3 (intestinal)
TFRC	CD71, p90, TFR1	Transferrin receptor
TG	AITD3, TGN	Thyroglobulin
TGFA		Transforming growth factor, alpha
TGFB1	CED, DPD1, TGFB, TGFbeta	Transforming growth factor, beta 1
TGFB2		Transforming growth factor, beta 2
TGFB3	ARVD, ARVD1	Transforming growth factor, beta 3
TGFBR3	betaglycan, BGCAN	Transforming growth factor, beta receptor III
TGM4	TGP	Transglutaminase 4
TGM7	TGMZ	Transglutaminase 7
THBS1	THBS, THBS-1, TSP, TSP-1, TSP1	Thrombospondin 1
THBS2	TSP2	Thrombospondin 2
THBS4		Thrombospondin 4
THPO	MGDF, MPLLG, TPO	Thrombopoietin
THRA	AR7, EAR-7.1/EAR-7.2, ERBA, ERBA1, NR1A1, THRA1, THRA2, THRA3	Thyroid hormone receptor, alpha
THRB	ERBA-BETA, ERBA2, GRTH, NR1A2, PRTH, THR1, THRB1, THRB2	Thyroid hormone receptor, beta
TIE1	JTK14, TIE	Tyrosine kinase with immunoglobulin-like and EGF-like domains 1
TIMP1	CLGI, EPO, TIMP	TIMP metallopeptidase inhibitor 1
TIMP2	CSC-21K	TIMP metallopeptidase inhibitor 2
TIMP3	SFD	TIMP metallopeptidase inhibitor 3
TK1		Thymidine kinase 1, soluble
TMF1	ARA160, TMF	TATA element modulatory factor 1
TMPRSS2	PRSS10	Transmembrane protease, serine 2
TMPRSS3	DFNB10, DFNB8	Transmembrane protease, serine 3
TNC	DFNA56, HXB, MGC167029, TN	Tenascin C
TNF	DIF, TNF-alpha, TNFA, TNFSF2	Tumor necrosis factor
TNFAIP2	B94, EXOC3L3	Tumor necrosis factor, alpha-induced protein 2
TNFAIP3	A20, OTUD7C	Tumor necrosis factor, alpha-induced protein 3
TNFRSF10A	Apo2, CD261, DR4, TRAILR-1	Tumor necrosis factor receptor superfamily, member 10a
TNFRSF10B	CD262, DR5, KILLER, TRAIL-R2, TRICK2A, TRICKB	Tumor necrosis factor receptor superfamily, member 10b
TNFRSF10C	CD263, DcR1, LIT, TRAILR3, TRID	Tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular

		domain
TNFRSF10D	CD264, DcR2, TRAILR4, TRUNDD	Tumor necrosis factor receptor superfamily, member 10d, decoy with truncated death domain
TNFRSF11B	OCIF, OPG, TR1	Tumor necrosis factor receptor superfamily, member 11b
TNFRSF12A	CD266, FN14, TweakR	Tumor necrosis factor receptor superfamily, member 12A
TNFRSF14	ATAR, CD270, HVEA, HVEM, LIGHTR, TR2	Tumor necrosis factor receptor superfamily, member 14
TNFRSF1A	CD120a, TNF-R, TNF-R-I, TNF-R55, TNFAR, TNFR1, TNFR60	Tumor necrosis factor receptor superfamily, member 1A
TNFRSF1B	CD120b, p75, TNF-R-II, TNF-R75, TNFBR, TNFR2, TNFR80	Tumor necrosis factor receptor superfamily, member 1B
TNFRSF4	ACT35, CD134, OX40, TXGP1L	Tumor necrosis factor receptor superfamily, member 4
TNFRSF8	CD30, D1S166E, KI-1	Tumor necrosis factor receptor superfamily, member 8
TNFRSF9	4-1BB, CD137, ILA	Tumor necrosis factor receptor superfamily, member 9
TNFSF10	Apo-2L, CD253, TL2, TRAIL	Tumor necrosis factor (ligand) superfamily, member 10
TNFSF11	CD254, ODF, OPGL, RANKL, TRANCE	Tumor necrosis factor (ligand) superfamily, member 11
TNFSF13	APRIL, CD256	Tumor necrosis factor (ligand) superfamily, member 13
TNFSF13B	BAFF, BLYS, CD257, TALL-1, TALL1, THANK, TNFSF20	Tumor necrosis factor (ligand) superfamily, member 13b
TNFSF4	CD252, gp34, OX-40L, TXGP1	Tumor necrosis factor (ligand) superfamily, member 4
TNFSF8	CD153, CD30LG	Tumor necrosis factor (ligand) superfamily, member 8
TNK2	ACK, ACK1, p21cdc42Hs	Tyrosine kinase, non-receptor, 2
TOP2A	TOP2	Topoisomerase (DNA) II alpha 170kDa
TP53	LFS1, p53	Tumor protein p53
TP53BP2	53BP2, ASPP2, PPP1R13A	Tumor protein p53 binding protein 2
TPD52	D52, hD52, N8L	Tumor protein D52
TPI1		Triosephosphate isomerase 1
TPM1	C15orf13, CMH3	Tropomyosin 1 (alpha)
TPM2	AMCD1, DA1, NEM4	Tropomyosin 2 (beta)
TPX2	C20orf1, C20orf2, DIL-2, p100	TPX2, microtubule-associated
TRAF1	EBI6	TNF receptor-associated factor 1
TRAF2	TRAP3	TNF receptor-associated factor 2

TRAF4	CART1, MLN62, RNF83	TNF receptor-associated factor 4
TRIM25	EFP, RNF147, ZNF147	Tripartite motif containing 25
TRIP4	HsT17391, ZC2HC5	Thyroid hormone receptor interactor 4
TRO	KIAA1114, MAGE-D3, MAGED3	Trophinin
TSG101	TSG10, VPS23	Tumor susceptibility 101
TSPAN8	CO-029, TM4SF3	Tetraspanin 8
TSPO	BZRP, DBI, IBP, MBR, mDRC, PBR, pk18, PKBS	Translocator protein (18kDa)
TTR	CTS, CTS1, HsT2651, PALB	Transthyretin
TUSC2	C3orf11, FUS1, PAP, PDAP2	Tumor suppressor candidate 2
TWIST1	ACS3, bHLHa38, BPES2, BPES3, CRS, CRS1, H-twist, SCS, TWIST	Twist family bHLH transcription factor 1
TXLNA	DKFZp451J0118	Taxilin alpha
TYMP	ECGF1, MNGIE	Thymidine phosphorylase
TYMS	HsT422, TMS, TS, Tsase	Thymidylate synthetase
TYRO3	Brt, Dtk, RSE, Sky, Tif	TYRO3 protein tyrosine kinase
UBA1	A1S9T, CFAP124, GXP1, POC20, UBE1, UBE1X	Ubiquitin-like modifier activating enzyme 1
UBE2C	UBCH10	Ubiquitin-conjugating enzyme E2C
UBE2I	UBC9	Ubiquitin-conjugating enzyme E2I
UBE2N	MGC8489, UBC13, UbcH-ben	Ubiquitin-conjugating enzyme E2N
UGT1A10	UGT1J	UDP glucuronosyltransferase 1 family, polypeptide A10
UGT1A3	UGT1C	UDP glucuronosyltransferase 1 family, polypeptide A3
UGT1A4	HUG-BR2, UGT1D	UDP glucuronosyltransferase 1 family, polypeptide A4
UGT1A8	UGT1H	UDP glucuronosyltransferase 1 family, polypeptide A8
UGT1A9	HLUGP4, LUGP4, UGT1AI	UDP glucuronosyltransferase 1 family, polypeptide A9
USH1C	AIE-75, DFNB18, harmonin, NY-CO-37, NY-CO-38, PDZ-73, PDZ73, PDZD7C	Usher syndrome 1C (autosomal recessive, severe)
VAMP3	CEB	Vesicle-associated membrane protein 3
VCAM1	CD106	Vascular cell adhesion molecule 1
VEGFA	VEGF, VEGF-A, VPF	Vascular endothelial growth factor A
VEGFB	VEGFL, VRF	Vascular endothelial growth factor B
VEGFC	VRP	Vascular endothelial growth factor C
VHL	VHL1	Von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase

VIL1	D2S1471, VIL	Villin 1
VIP		Vasoactive intestinal peptide
VTN	VN	Vitronectin
VWF	F8VWF	Von Willebrand factor
WEE1		WEE1 G2 checkpoint kinase
WFDC2	dJ461P17.6, EDDM4, HE4, WAP5	WAP four-disulfide core domain 2
WISP1	CCN4	WNT1 inducible signaling pathway protein 1
WNT1	INT1	Wingless-type MMTV integration site family, member 1
WNT2	INT1L1, IRP	Wingless-type MMTV integration site family member 2
WRN	RECQ3, RECQL2	Werner syndrome, RecQ helicase-like
WT1	AWT1, GUD, WAGR, WIT-2	Wilms tumor 1
XBP1	XBP2	X-box binding protein 1
XIAP	API3, BIRC4, hILP	X-linked inhibitor of apoptosis
XPA	XP1, XPAC	Xeroderma pigmentosum, complementation group A
XPC	RAD4, XPCC	Xeroderma pigmentosum, complementation group C
XRCC2		X-ray repair complementing defective repair in Chinese hamster cells 2
XRCC3		X-ray repair complementing defective repair in Chinese hamster cells 3
XRCC4		X-ray repair complementing defective repair in Chinese hamster cells 4
XRCC5	KARP-1, KU80, Ku86, KUB2	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining)
XRCC6	D22S671, D22S731, G22P1, KU70, ML8	X-ray repair complementing defective repair in Chinese hamster cells 6
YBX1	BP-8, CSDA2, CSDB, DBPB, MDR-NF1, NSEP-1, NSEP1, YB-1, YB1	Y box binding protein 1
YWHAB	YWHAA	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta
YWHAE	FLJ45465	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon
YWHAH	YWHA1	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta
ZBTB16	PLZF, ZNF145	Zinc finger and BTB domain containing 16
ZMAT3	FLJ12296, MGC10613, PAG608, WIG-1, WIG1	Zinc finger, matrin-type 3

[0164] In one embodiment, the biomarker is MYC. In one embodiment, the measurable aspect of MYC is its expression status. In one embodiment, the biomarker is overexpression of MYC.

[0165] Thus, in certain aspects of the disclosure, the biomarker is MYC which is differentially present in a subject of one phenotypic status, e.g., a patient having cancer, e.g., hepatocellular carcinoma (HCC), glioblastomas (GBM), lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, or colorectal cancer, as compared with another phenotypic status, e.g., a normal undiseased subject or a patient having cancer without overexpression MYC.

[0166] Biomarker standards can be predetermined, determined concurrently, or determined after a biological sample is obtained from the subject. Biomarker standards for use with the methods described herein can, for example, include data from samples from subjects without cancer; data from samples from subjects with cancer, e.g., GBM, that is not a progressive, recurrent, and/or metastatic cancer; and data from samples from subjects with cancer, e.g., GBM, that is a progressive, recurrent, and/or metastatic cancer. Comparisons can be made to establish predetermined threshold biomarker standards for differenct classes of subjects, e.g., diseased vs. non-diseased subjects. The standards can be run in the same assay or can be known standards from a previous assay.

[0167] In one embodiment, the biomarker is MCL1. In one embodiment, the measurable aspect of MCL1 is its expression status. In one embodiment, the biomarker is overexpression of MCL1.

[0168] A biomarker is differentially present between different phenotypic status groups if the mean or median expression or mutation levels of the biomarker is calculated to be different, i.e., higher or lower, between the groups. Thus, biomarkers provide an indication that a subject, e.g., a cancer patient, belongs to one phenotypic status or another.

[0169] Thus, in certain aspects of the disclosure, the biomarker is MCL1 which is differentially present, i.e., overexpressed, in a subject of one phenotypic status, e.g., a patient having cancer, e.g., hepatocellular carcinoma (HCC), glioblastomas (GBM), lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, colorectal cancer, medulloblastoma, or general brain tumors, as compared with another phenotypic status, e.g., an undiseased patient or a cancer patient without overexpression MCL1.

[0170] In addition to individual biological compounds, e.g., MYC or MCL1, the term "biomarker" as used herein is meant to include groups, sets, or arrays of multiple biological compounds. For example, the combination of MYC and MCL1 may comprise a biomarker. The term "biomarker" may comprise one, two, three, four, five, six, seven, eight, nine, ten, fifteen, twenty, twenty five, thirty, or more, biological compounds.

[0171] The determination of the expression level or mutation status of a biomarker in a patient can be performed using any of the many methods known in the art. Any method known in the art for quantitating specific proteins and/or detecting MYC and/or MCL1 expression, or the expression or mutation levels of any other biomarker in a patient or a biological sample may be used in the methods of the disclosure. Examples include, but are not limited to, PCR (polymerase chain reaction), or RT-PCR, Northern blot, Western blot, ELISA (enzyme linked immunosorbent assay), RIA (radioimmunoassay), gene chip analysis of RNA expression, immunohistochemistry or immunofluorescence. *See, e.g.*, Slagle et al. Cancer 83:1401 (1998). Certain embodiments of the disclosure include methods wherein biomarker RNA expression (transcription) is determined. Other embodiments of the disclosure include methods wherein protein expression in the biological sample is determined. See, for example, Harlow *et al.*, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, (1988) and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York 3rd Edition, (1995). For northern blot or RT-PCR analysis, RNA is isolated from the tumor tissue sample using RNAse free techniques. Such techniques are commonly known in the art.

[0172] In one embodiment of the disclosure, a biological sample is obtained from the patient and cells in the biopsy are assayed for determination of biomarker expression or mutation status.

[0173] In one embodiment of the disclosure, PET imaging is used to determine biomarker expression.

[0174] In another embodiment of the disclosure, Northern blot analysis of biomarker transcription in a tumor cell sample is performed. Northern analysis is a standard method for detection and/or quantitation of mRNA levels in a sample. Initially, RNA is isolated from a sample to be assayed using Northern blot analysis. In the analysis, the RNA samples are first separated by size via electrophoresis in an agarose gel under denaturing

conditions. The RNA is then transferred to a membrane, crosslinked and hybridized with a labeled probe. Typically, Northern hybridization involves polymerizing radiolabeled or nonisotopically labeled DNA, in vitro, or generation of oligonucleotides as hybridization probes. Typically, the membrane holding the RNA sample is prehybridized or blocked prior to probe hybridization to prevent the probe from coating the membrane and, thus, to reduce non-specific background signal. After hybridization, typically, unhybridized probe is removed by washing in several changes of buffer. Stringency of the wash and hybridization conditions can be designed, selected and implemented by any practitioner of ordinary skill in the art. Detection is accomplished using detectably labeled probes and a suitable detection method. Radiolabeled and non-radiolabled probes and their use are well known in the art. The presence and or relative levels of expression of the biomarker being assayed can be quantified using, for example, densitometry.

[0175] In another embodiment of the disclosure, biomarker expression and/or mutation status is determined using RT-PCR. RT-PCR allows detection of the progress of a PCR amplification of a target gene in real time. Design of the primers and probes required to detect expression and/or mutation status of a biomarker of the disclosure is within the skill of a practitioner of ordinary skill in the art. RT-PCR can be used to determine the level of RNA encoding a biomarker of the disclosure in a tumor tissue sample. In an embodiment of the disclosure, RNA from the biological sample is isolated, under RNAse free conditions, than converted to DNA by treatment with reverse transcriptase. Methods for reverse transcriptase conversion of RNA to DNA are well known in the art. A description of PCR is provided in the following references: Mullis et al., *Cold Spring Harbor Symp. Quant. Biol. 51*:263 (1986); EP 50,424; EP 84,796; EP 258,017; EP 237,362; EP 201,184; U.S. Patent Nos. 4,683,202; 4,582,788; 4,683,194.

[0176] RT-PCR probes depend on the 5'-3' nuclease activity of the DNA polymerase used for PCR to hydrolyze an oligonucleotide that is hybridized to the target amplicon (biomarker gene). RT-PCR probes are oligonucleotides that have a fluorescent reporter dye attached to the 5, end and a quencher moiety coupled to the 3' end (or vice versa). These probes are designed to hybridize to an internal region of a PCR product. In the unhybridized state, the proximity of the fluor and the quench molecules prevents the detection of fluorescent signal from the probe. During PCR amplification, when the polymerase replicates a template on which an RT-PCR probe is bound, the 5'-3' nuclease

activity of the polymerase cleaves the probe. This decouples the fluorescent and quenching dyes and FRET no longer occurs. Thus, fluorescence increases in each cycle, in a manner proportional to the amount of probe cleavage. Fluorescence signal emitted from the reaction can be measured or followed over time using equipment which is commercially available using routine and conventional techniques.

[0177] In another embodiment of the disclosure, expression of proteins encoded by biomarkers are detected by western blot analysis. A western blot (also known as an immunoblot) is a method for protein detection in a given sample of tissue homogenate or extract. It uses gel electrophoresis to separate denatured proteins by mass. The proteins are then transferred out of the gel and onto a membrane (*e.g.*, nitrocellulose or polyvinylidene fluoride (PVDF)), where they are detected using a primary antibodythat specifically bind to the protein. The bound antibody can then detected by a secondary antibody that is conjugated with a detectable label (*e.g.*, biotin, horseradish peroxidase or alkaline phosphatase). Detection of the secondary label signal indicates the presence of the protein.

[0178] In another embodiment of the disclosure, the expression of a protein encoded by a biomarker is detected by enzyme-linked immunosorbent assay (ELISA). In one embodiment of the disclosure, "sandwich ELISA" comprises coating a plate with a capture antibody; adding sample wherein any antigen present binds to the capture antibody; adding a detecting antibody which also binds the antigen; adding an enzyme-linked secondary antibody which binds to detecting antibody; and adding substrate which is converted by an enzyme on the secondary antibody to a detectable form. Detection of the signal from the secondary antibody indicates presence of the biomarker antigen protein.

[0179] In another embodiment of the disclosure, the expression of a biomarker is evaluated by use of a gene chip or microarray. Such techniques are within ordinary skill held in the art.

VI. Definitions

[0180] The disclosure provides various therapeutic methods, kits, and pharmaceutical compositions comprising TG02. The term "TG02" as used herein refers to (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene in any crystalline or amorphous form as a free

base or as a pharmaceutically acceptable salt or solvate. In one embodiment, TG02 refers to the free base of (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene. In another embodiment, TG02 refers to a pharmaceutically acceptable salt of (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene. A pharmaceutically acceptable salt of TG02 can be prepared during the final isolation and purification of TG02 or separately by reacting TG02 with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Nonlimiting examples of salts of TG02 include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts.

[0181] In another embodiment, TG02 refers to the citrate salt of (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene. This is refered to as TG02 citrate or (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene – citric acid.

[0182] The term "biological sample" as used herein refers any tissue or fluid from a patient that is suitable for detecting a biomarker, such as MYC and/or MCL1 expression status. Examples of useful biological samples include, but are not limited to, biopsied tissues and/or cells, *e.g.*, solid tumor, lymph gland, inflamed tissue, tissue and/or cells involved in a condition or disease, blood, plasma, serous fluid, cerebrospinal fluid, saliva, urine, lymph, cerebral spinal fluid, and the like. Other suitable biological samples will be familiar to those of ordinary skill in the relevant arts. A biological sample can be

analyzed for biomarker expression and/or mutation using any technique known in the art and can be obtained using techniques that are well within the scope of ordinary knowledge of a clinical practioner. In one embodiment of the disclosure, the biological sample comprises blood cells.

[0183] The terms "a", "an", "the", and similar referents in the context of describing the disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language, e.g., "such as," provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

[0184] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

[0185] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. However, in one embodiment, administration of TG02 and/or an immune checkpoint inhibitor and/or COX-2 inhibitor leads to complete remission of the cancer.

[0186] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to result in amelioration of one or more symptoms of a disorder, or prevent advancement of a disorder, or cause regression of the disorder. For example, with respect to the treatment of cancer, in one embodiment, a therapeutically effective amount will refer to the amount of a therapeutic agent that causes a therapeutic response, *e.g.*, normalization of blood counts, decrease in the rate of tumor growth, decrease in tumor mass, decrease in the number of metastases, increase in time to tumor progression, and/or increase patient survival time by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least

about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100%, or more.

[0187] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

[0188] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0189] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0190] "Concurrent administration," "administered in combination," "simultaneous administration," and similar phrases mean that two or more agents are administered concurrently to the subject being treated. By "concurrently," it is meant that each agent is administered either simultaneously or sequentially in any order at different points in time. However, if not administered simultaneously, it is meant that they are administered to an individual in a sequence and sufficiently close in time so as to provide the desired therapeutic effect and can act in concert. For example, TG02 can be administered at the same time or sequentially in any order at different points in time as the immune checkpoint inhibitor and/or the COX-2 inhibitor and/or the optional therapeutic agent. TG02 and the immune checkpoint inhibitor and/or the COX-2 inhibitor and/or the optional therapeutic agent can be administered separately, in any appropriate form and by any suitable route. When TG02 and the immune checkpoint inhibitor and/or the COX-2 inhibitor and/or the optional therapeutic agent are not administered concurrently, it is understood that they can be administered in any order to a patient in need thereof. For example, TG02 can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes,

45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the immune checkpoint inhibitor and/or COX-2 inhibitor, to an individual in need thereof. In various embodiments, TG02 and the immune checkpoint inhibitor and/or COX-2 inhibitor are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In one embodiment, the components of the combination therapies are administered at about 1 minute to about 24 hours apart. In one embodiument, TG02 is administered 3-7 days prior to the day the immune checkpoint inhibitor is administered. In another embodiment, TG02 is also administered on the day the immune checkpoint inhibitor is administered and continues to be administered until disease progression or TG02 therapy is no longer beneficial.

EXAMPLES

EXAMPLE 1

[0191] This study is being done to compare progression-free or overall survival using pembrolizumab (p) or nivolumab (n) to p or n in combination with TG02 for participants with cancer who are untreated or have progressed after prior therapy and who have been selected for overexpressed MYC and/or MCL1 status. Participants will be randomized to receive either standard anti-PD-1 therapy plus placebo or standard anti-PD-1 therapy plus TG02.

[0192] Primary Outcome Measures: Progression-free-survival (PFS) and/or Overall survival (OS)

[0193] Secondary Outcome Measures: Overall response rate (ORR) and/or Response Duration

Eligibility

[0194]	Ages Eligible for Study:	Generally – 18 Years and older
[0195]		For medulloblastoma patients – 6 months or older
[0196]	Genders Eligible for Study:	Both

Inclusion Criteria:

[0197] Histologically or cytologically confirmed diagnosis of cancer not amenable to local therapy

[0198] Must consent to allow correlative studies; must provide a newly obtained tissue/biopsy specimen (or specimen obtained within 60 days of consenting)

[0199] Radiographically measurable disease

[0200] Eastern Cooperative Oncology Group Performance Status of 0 or 1

[0201] Patient has disease with overexpressed MYC and/or MCL1

Exclusion criteria:

[0202] Chemotherapy, radiation therapy, or biological therapy within four weeks prior to the first dose of study drug, or not recovered from the AEs due to cancer therapies administered more than four weeks earlier

[0203] Participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of study drug

[0204] Expected to require any other form of systemic or localized antineoplastic therapy while on study

[0205] Chronic systemic steroid therapy within two weeks before the planned date for first dose randomized treatment or on any other form of immunosuppressive medication

[0206] Known history of any other than the current malignancy excepting adequately treated basal or squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, breast cancer, or other in situ cancers

[0207] Known active central nervous system (CNS) metastases and/or carcinomatous meningitis

[0208] Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents

[0209] Prior treatment with any other anti-programmed cell death (PD) agent

[0210] Active infection requiring systemic therapy

[0211] Known history of Human Immunodeficiency Virus (HIV)

[0212] Active Hepatitis B or Hepatitis C

[0213] Regular user (including recreational use of) illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol)

[0214] Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

Protocols:

[0215] A first group of patients receive 2-10 mg/kg pembrolizumab (or flat dose equivalent) administered by intravenous infusion every three weeks and TG02 administered orally at 100, 200 or 300 mg once daily until disease progression or is no longer beneficial. TG02 administration is started 3-7 days prior to initiating pembrolizumab therapy, continues on the day of pembrolizumab administration, and continues until disease progression or until TG02 therapy is no longer beneficial. The control patients receive 2-10 mg/kg pembrolizumab (or flat dose equivalent) administered by intravenous infusion every three weeks.

[0216] A second group of patients receive 3 mg/kg nivolumab administered over 60 minutes by intravenous infusion every 2 weeks and TG02 administered orally at 100, 200, or 300 mg once daily. TG02 administration is started 3-7 days prior to initiating nivolumab therapy, continues on the day of nivolumab administration, and continues until disease progression or until TG02 therapy is no longer beneficial. The control patients receive 3 mg/kg nivolumab administered over 60 minutes by intravenous infusion every 2 weeks.

Results:

[0217] TG02 in combination with pembrolizumab or nivolumab results in better antitumor clinical activity than the immune checkpoint inhibitors alone in patients whose tumors overexpress MYC and/or MCL1. Unexpected objective responses are obtained associated with lack of tumor progression and extension of long term survival compared to historical controls using (the antibody) alone. In one embodiment, patients receiving TG02 and the immune checkpoint inhibitor achieve an extension of time to progression (or progression-free survival) of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months. In another embodiment, at least

some of the patients receiving TG02 and the immune checkpoint inhibitor achieve an extension of duration of response of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months.

EXAMPLE 2

Open label Phase 2 study assessing the combination of checkpoint blockade immunotherapy and TG02 in patients relapsing from or refractory to standard anti-PD-1 therapy (p) or (n).

[0218] Primary endpoint: ORR

[0219] Secondary endpoints: PFS, OS, Duration of Response, Safety

Inclusion criteria:

[0220] Histologically confirmed diagnosis of cancer not amenable to local therapy

[0221] Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

[0222] At least one measurable lesion

[0223] Adequate organ function

[0224] Prior therapy with an anti-PD-1 or anti-PD-L1 antibody

[0225] Patient has disease with overexpressed MYC and/or MCL1

Exclusion criteria:

[0226] Chemotherapy, targeted small molecule therapy, radiotherapy, or biological cancer therapy (including monoclonal antibodies) within 4 weeks prior to the first dose of trial treatment, or not recovered (<= Grade 1 or baseline) from adverse events due to a previously administered agent.

[0227] Expected to require any other form of systemic or localized antineoplastic therapy while in study.

[0228] Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

[0229] Documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.

[0230] Receiving systemic steroid therapy or any other form of immunosuppressive therapy within 1 week prior to the first dose of study treatment.

[0231] Received a live vaccine within 4 weeks prior to the first dose of trial treatment.

[0232] History or evidence of active pneumonitis.

[0233] Human immunodeficiency virus (HIV)-positive.

[0234] Active Hepatitis B or C.

[0235] Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial treatment through 120 days after the last dose of study medication.

Dosing protocol:

Table 1 TG02 + CheckPoint Inhibitor Combination Dosing & Schedules

	Every 2 weeks	Every 3 weeks	Every 4 weeks
Pembrolizumab 2mg/kg	X	X	
Pembrolizumab 10mg/kg	X	X	
Pembrolizumab 200mg	X	X	
Pembrolizumab 300mg	X	X	
Nivolumab 3mg/kg	X	X	X
Nivolumab 1mg/kg	X	X	X
Pidilizumab 3mg/kg	X	X	X
Pidilizumab 1.5mg/kg	X	X	X
STI-110 2mg/kg	X	X	X
STI-110 2mg/kg	X	X	X
Durvalumab 10mg/kg	X	X	
Durvalumab 2mg/kg	X	X	
Durvalumab 15,g/kg		X	X
Avelumab 1200mg	X	X	X
Avelumab 10mg/kg	X	X	X
Avelumab 5mg/kg	X	X	X
Atezolizumab 1200mg		X	
STI-1014	X	X	X

10mg/kg			
STI-1014 15mg/kg	X	X	X

*TG02 is dosed weekly (50-400 mg) starting at least 5 days prior to initiating checkpoint inhibitor therapy and continuing until disease progression or investigator decision

Results

[0236] Combining TG02 with at least one checkpoint inhibitor in patients with overexpressed MYC and/or MCL1 tumors reverses immune evasion and induces clinically relevant responses in patients previously nonresponding to or failing checkpoint inhibitor therapy or *de novo* cancer patients. Unexpected objective responses are obtained associated with lack of tumor progression and extension of long term survival compared to historical controls using (the antibody) alone. In one embodiment, patients receiving TG02 and at least one immune checkpoint inhibitor achieve an extension of time to progression (or progression-free survival) of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months. In another embodiment, at least some of the patients receiving TG02 and at least one immune checkpoint inhibitor achieve an extension of duration of response of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months.

EXAMPLE 3

Placebo-controlled, randomized phase 2 study of pembrolizumab + TG02 vs. pembrolizumab + placebo in participants with previously-treated locally advanced unresectable or metastatic colorectal cancer exhibiting overexpressed MYC and/or MCL1 status.

[0237] Primary Endpoint: PFS

[0238] Secondary Endpoint: ORR, Duration of Response

Inclusion criteria:

[0239] Histologically-proven locally advanced unresectable or metastatic high colorectal carcinoma

[0240] Previously treated with at least two lines of approved standard therapies, which must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab

[0241] Eastern Cooperative Oncology Group performance status of 0 or 1

[0242] Patient has disease with overexpressed MYC and/or MCL1

[0243] Life expectancy of greater than 3 months

[0244] At least one measureable lesion

[0245] Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication

[0246] Male participants should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study medication

[0247] Adequate organ function

Exclusion criteria:

[0248] Currently participating in another study and receiving trial treatment, participated in a study of an investigational agent and received trial treatment within 4 weeks of the first dose of medication in this study, or used an investigational device within 4 weeks of the first dose of medication in this study

[0249] Active autoimmune disease that has required systemic treatment in past 2 years

[0250] Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication

[0251] Known active central nervous system (CNS) metastases and/or carcinomatous meningitis

[0252] Prior monoclonal antibody (mAb), chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or not recovered (i.e., $\leqslant$ Grade 1 or at baseline) from adverse events due to a previously administered agent

[0253] Prior therapy with an anti-programmed cell death (PD)-1, anti-PD-L1, or anti-PD-L2 agent, or participant has previously participated in Merck pembrolizumab (MK-3475) clinical trial

[0254] Known additional malignancy that is progressing or requires active treatment with the exception of basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer

[0255] Received a live vaccine within 30 days of planned start of study medication

[0256] Known history of human immunodeficiency virus (HIV)

[0257] Known active Hepatitis B or C

[0258] Known history or any evidence of interstitial lung disease or active, non-infectious pneumonitis

[0259] Active infection requiring systemic therapy

[0260] Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

[0261] Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial medication

Dosing protocol:

[0262] Patients receive 2-10 mg/kg pembrolizumab administered by intravenous infusion every three weeks and TG02 administered orally at 1, 2 or 3 mg/kg 3-7 days prior to pembrolizumab administration, on the day of pembrolizumab administration, and continuously thereafter until disease progression or until it is no longer beneficial. The control patients receive 2 mg/kg pembrolizumab administered by intravenous infusion every three weeks.

Results:

[0263] When used in patients with tumors overexpressing MYC and/or MCL1, TG02 combined with pembrolizumab provides superior clinical activity than pembrolizumab alone in the same patients. Unexpected objective responses are obtained in patients associated with lack of tumor progression and extension of long term survival compared to historical controls using (the antibody) alone. In one embodiment, patients receiving TG02 and pembrolizumab achieve an extension of time to progression (or progression-free survival) of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months. In another embodiment, at least some of the patients receiving TG02 and pembrolizumab achieve an extension of duration of response

of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months.

EXAMPLE 4

TG02 in Combination with Carfilzomib in Carfilzomib (CFZ) Refractory Multiple Myeloma (MM) Patients

Methods

[0264] An open-label Phase 1b study enrolled MM patients that previously received ≥2 lines of therapy. The primary objective was to determine the maximum tolerated dose (MTD) of TG02 in combination with carfilzomib (TG02/CFZ). Secondary objectives included anti-tumor activity and safety. TG02 was administered once daily on days 1, 4, 8, 11, 15, 18 of a 28-day schedule (BIW). The TG02 starting dose was 150 mg. TG02 dosing was escalated in 50 mg increments up to 300 mg. CFZ was dosed according to the Prescribing Information. Responses were assessed using standard criteria.

Results

[0265] Fourteen patients were enrolled for dose escalation and 10 patients were enrolled for the MTD cohort expansion. Patients were heavily pretreated: median 6 previous treatments [min 3; max 15] and 92% patients received CFZ in a prior regimen. The best response to previous therapy was progressive disease in 46% patients. The MTD was 250 mg TG02 combined with CFZ. Two dose-limiting toxicities were observed (including Grade (Gr) 4 sepsis and Gr 4 neutropenia), both on the 300 mg cohort. The most common drug-related adverse events (AEs) were diarrhea (Gr 1-2: 71% Gr 3: 17%), nausea (Gr 1-2: 79%), vomiting (Gr 1-2: 50%), fatigue (Gr 1-2: 38%, Gr 3: 4%), anorexia (Gr 1: 21%), anemia (Gr 1-2: 4%, Gr 3: 17%) and thrombocytopenia (Gr 3: 8%, Gr 4: 13%). Six patients (25%) discontinued treatment due to an AE. Serious AEs occurred in 50% patients; only acute renal failure and febrile neutropenia occurred in >1 pt (8% each). The severity of AEs was similar to single agent TG02. The incidence of diarrhea was increased in the TG02/CFZ administration (88% vs 67%) but the incidence of other AEs was similar to single agent TG02. Fourteen patients administered TG02 at the MTD were evaluable for response. The overall response rate (≥PR) was 27%; the clinical benefit rate (≥MR) was 45% (1 very good partial response, 2 partial response and 2

minimal response). All responders (MR or better) were CFZ-refractory in a previous treatment regimen. Durable stable disease was observed in 27% patients.

Conclusion

[0266] The safety profile of TG02 BIW/CFZ was similar to that of TG02 alone. The most common drug-related AEs were diarrhea, nausea, and vomiting; grade 4 AEs were infrequent. Objective responses were observed in CFZ-refractory patients.

EXAMPLE 5

TG02 Activity in Glioma Cells and Allograft Model

[0267] Several standard glioblastoma multiforme (GBM) cell lines and one stem cell line expressing O^6-methylguanine DNA methyltransferase (MGMT) were treated with TG02, temozolomiode (TMZ), or the combination of TG02 and TMZ in a 72-hour cell proliferation assay. *See* Figs. 1-3. TG02, TMZ, and the TG02 + TMZ combination was also tested in cell lines without MGMT expression. *See* Figs. 4-7. The cells were seeded onto 12-well plates and treated with 50 nM of TG02, 100 μM of TMZ or TG02 + TMZ for 72 hr. Cell viability was determined by cell counting.

[0268] The cytotoxic effect TG02, TMZ, and the combination of TG02 and TMZ was examined via the colony formation assay in GSC923 and U251 cells. *See* Figs. 8 and 9.

[0269] Pulmonary arterial endothelial cells and human astrocytes were tested with 50 nM of TG02, 100 μM of TMZ, or TG02 + TMZ for 72 hr. The cells were then changed to normal medium and cultured for another 7 days. Cell viability was determined by cell counting. *See* Figs. 10 and 11.

[0270] GSC923 (Figs. 12 and 13) and U251 (Figs. 14 and 15) cells were exposed to various concentrations of TG02, TMZ, and TG02+ TMZ for 72 hr, and cell viability was examined via cell counting. The synergistic effect of TG02 + TMZ was determined by Combination Index (CI). CI values were calculated by COMPUSYN software and shown Table 2 for GSC923 cells and Table 3 for U251 cells. CI < 1 is a synergistic, CI = 1 is an additive, and CI > 1 is an antagonistic effect of the two compounds combined.

Table 2

Fraction Affected (Fa)	CI value
0.25	0.077
0.5	0.136
0.75	0.242

0.90	0.430

Table 3

Fraction Affected (Fa)	CI value
0.25	0.029
0.5	0.104
0.75	0.376
0.90	1.333

[0271] Fig. 16 shows a schematic illustration of drug administration in an mouse glioma GL261 cell allograft model. Mouse glioma GL261 cells were injected stereotactically into the striatum of female C57BL/6 albino mice (n=5-7 per cohort) followed by vehicle, TG02, TMZ, and TG02 + TMZ combination treatment. A median overall survival of 24, 24.5, 27.5, and 32 days, respectively was observed. *See* Fig. 17. The result was analyzed using Logrank test for trend in GraphPad Prism software (Chi square= 9.063, df =1, P value =0.0026 **). The turmor burden was determined by bioluminescence imaging (BLI) taken using the PerkinElmer IVIS® Spectrum. The intensity of BLI was calculated and normalized to the initial intensity at day 5. *See* Fig. 18.

EXAMPLE 6

TG02 Activity in hepatocellular carcinoma (HCC) Cells and Xenograft Model

[0272] The effect of TG02 on MYC expression in HCC cell lines was investigated. Five HCC cell lines with varying levels of MYC expression were treated with 0.5 μM TG02 for 24 hours and MYC expression was evaluated by western blot. *See* Fig. 19. MYC expression levels were decreased by TG02 treatment in HepG2, SNU398 and HUH-1 cell lines but not in the JHH-5 line. Hep3B cells did not express MYC.

[0273] Eight HCC cell lines with either high or low MYC expression were then treated with TG02 *in vitro*. TG02 treatment resulted in inhibition of cell proliferation in all HCC cell lines tested. TG02 is selectively more potent in the cells lines with high levels of MYC expression as compared to those cells with low levels of MYC expression, with mean IC_{50} values of 84 nM and 524 nM, respectively. *See* Fig. 20.

[0274] Inhibition of MYC expression was also measured *in vivo*. HepG2 hepatocellular carcinoma xenografts was grown orthotopically in Balb/c nude mice. TG02 or vehicle was given orally at 50 mg/kg to 5 mice each; tumors were collected 8 hours post-

treatment and MYC protein expression levels were measured by western blot. MYC expression was observed in each of the control tumors. In the TG02 treatment group, MYC expression levels were decreased in 4 of 5 animals, with substantial MYC depletion in two animals and partial reduction in two other animals. *See* Fig. 21.

[0275] The therapeutic efficacy of TG02 as a single agent or in combination with sorafenib in the treatment of orthotopic HepG2 human liver cancer xenograft model was evaluated in BALB/c nude mice. On Day 19 post-inoculation, mice were randomized into treatment groups based on baseline serum AFP levels which trace tumor volume in the liver. TG02 was given orally twice weekly at 50 mg/kg and reduced to 40 mg/kg. Sorafenib was given orally daily at 15 mg/kg. TG02 as a single agent had a modest effect on tumor volume. TG02 combined with sorafenib led to significant anti-tumor activity. *See* Fig. 22.

EXAMPLE 7

TG02-mediated CDK9 inhibition

[0276] A Tet-off transgenic mouse model of MYC-induced T cell acute lymphoblastic leukemia (MYC T-ALL) which over-expresses and is dependent on MYC, was treated with TG02 at 100 or 500 μM.

[0277] MYC is a transcription factor that regulates the expression of a multitude of gene products involved in cell proliferation, growth, differentiation and apoptosis. The *MYC* gene is genetically activated and over-expressed in many human cancers and this over-expression has been causally linked to tumorigenesis, driving malignant growth and immune evasion. *See, e.g.*, Álvarez-Fernández *et al.*, Clin. Cancer Res. *Off. J. Am. Assoc. Cancer Res. 19*:2677-2687 (2013); Carter *et al., Blood 105*:4043-4050 (2005); Casey *et al.*, *Science 352*:227–231 (2016); Hannah, A.L., *Curr. Mol. Med. 5*:625–642 (2005); and Parcells *et al.*, *Stem Cells Dayt. Ohio 24*:1174–1184 (2006).

[0278] As shown in Figures 23-26, when MYC was turned "on," PD-L1 was expressed as detected by RT-PCR (t = 0 hr). But when MYC was turned "off", both CD47 and PD-L1 expression was significantly reduced in a time dependent manner. TG02 led to a time- and dose-dependent down-regulation of both PD-L1 and CD47 mRNA expression in MYC T-ALL cells (Figs. 23 and 24, respectively) and both BCL-xL and MYC expression were down-regulated (Figs. 25 and 26, respectively). Reduced expression of both CD47

and PD-L1 on tumor cells may result in reduced immune evasion and increased tumor cell death.

EXAMPLE 8

TG02 in Combination with Anti-PD-1

[0279] The combination of TG02 and PD-1 mAb (anti-PD-1) was tested in an orthotopic GL261 glioma model. GL261 allografts were established for 3 days and the mice were then randomized into 6 treatment cohorts (n=8) based on the bioluminescent tumor volumes.

[0280] Mice were treated with vehicle, TG02 alone (20 or 40 mg/kg), PD-1 mAb alone (500 ug), and the combination of TG02 and anti-PD-1. Median survival times of the mice were 27.5, 26.5, 33, 32, 78 and >95 days, respectively (Fig. 27).

[0281] There was a significant survival benefit in TG02 alone at 40 mg/kg (0.009), PD-1 mAb alone (0.003), TG02 20 mg/kg + PD-1 mAb (0.0001), and TG02 40 mg/kg + PD-1 mAb (0.0001) treated-mice compared with the vehicle group.

EXAMPLE 9

TG02 induces cell death and synergizes with radiation in MYC-driven glioblastoma

[0282] The relationship between TG02 antitumor activity and MYC expression was tested in a panel of patient-derived GBM cell lines (PDCLs). TG02 inhibited six out of twelve PDCLs at an IC_{50} of less than 0.2 μM. *See* Table 4.

Table 4

Patient-derived GBM lines	**TG02 IC_{50} (μM)**
BT245	0.066
BT360	0.073
BT145	0.052
BT224	0.109
BT187	0.176
BT164	0.178
BT228	0.267
BT286	0.371
BT182	0.416
BT359	0.624
BT139	57.88

BT181	~4828

[0283] Downregulation of MYC and Mcl-1 was observed in MYC-amplified BT245 cell line as early as 6 hours, while complete downregulation was seen at 24 hours, which coincided with a significant increase in apoptosis (Fig. 28). The AUC of TG02 induced inhibition of cell viability was calculated in this cell line panel to correlate with MYC expression levels (Fig. 29). TG02 was a more potent inhibitor of PDCLs exhibiting high MYC expression (Fig. 30). In vitro sensitivity (AUC) negatively correlated with MYC expression in GBM cells (P value = 0.02)

EXAMPLE 10

[0284] Radiation is an effective treatment for glioblastoma. But tumor resistance and recurrence develops in all patients.

[0285] A panel of GBM PDCLs, *see* Example 9, were chosen for evaluation of the combination of TG02 and radiation therapy for the treatment of glioblastoma (Fig. 31). Cells were treated first with TG02 at increasing concentrations. Within 30 minutes, cells were treated with increasing doses of radiation and cell proliferation was measured 72 hours post-treatment. TG02 alone had anti-proliferative activity in these cell lines. The addition of TG02 augmented the effects radiation in a synergistic manner. The combination of TG02 and radiation exceeds the Bliss predicted model (greater than a 10% change from the Bliss predicted model), demonstrating synergy between TG02 and radiation in multiple PDCLs.

EXAMPLE 11

TG02 Activity correlates with MYC expression in Glioblastoma Cell Lines

[0286] In a panel of 26 patient–derived GBM stem cell lines, the activity of TG02 on GBM stem cell proliferation was evaluated (Fig. 32). TG02 was potent in this panel with sixteen cell lines achieving an IC_{50} of less than 250 nM.

[0287] The expression level of CDK9 and downstream markers, including MYC and Mcl-1, were measured to explore whether a correlation exists between protein expression and IC_{50} values in this GBM panel. High MYC expression was found to correlate with greater sensitivity to TG02 treatment (Fig. 33).

[0288] Having now fully described the methods, compounds, and compositions herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A method of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amount of TG02, wherein one or more of the genes listed in Table 1 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

2. The method of claim 1, wherein MYC overexpression is differentially present in a sample taken from the patient.

3. The method of claims 1 or 2, wherein MCL1 overexpression is differentially present in a sample taken from the patient.

4. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of an immune checkpoint inhibitor.

5. The method of claim 4, wherein TG02 is administered to the patient before an immune checkpoint inhibitor.

6. The method of claim 4, wherein TG02 is administered to the patient after an immune checkpoint inhibitor.

7. The method of claim 4, wherein TG02 is administered to the patient at the same time as an immune checkpoint inhibitor.

8. The method of any one of claims 4-7, wherein the immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, and a cd47 inhibitor.

9. The method of claim 8, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

10. The method of claim 9, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

11. The method of claim 10, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab and STI-1110.

12. The method of claim 8, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

13. The method of claim 12, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

14. The method of claim 12, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-1014

15. The method of claim 8, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

16. The method of claim 15, wherein the CTLA-4 inhibitor is an anti-CTLA-4 antibody.

17. The method of claim 16, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

18. The method of claim 8, wherein immune checkpoint inhibitor is a LAG3 inhibitor.

19. The method of claim 18, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

20. The method of claim 19, wherein the anti-LAG3 antibody is GSK2831781.

21. The method of claim 20, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

22. The method of claim 21, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

23. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of an alkylating agent.

24. The method of claim 23, wherein TG02 is administered to the patient before the alkylating agent.

25. The method of claim 23, wherein TG02 is administered to the patient after the alkylating agent.

26. The method of claim 23, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the alkylating agent.

27. The method of any one of claims 23-26, wherein the alkylating agent is temozolimide.

28. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of a protein kinase inhibitor.

29. The method of claim 28, wherein TG02 is administered to the patient before the protein kinase inhibitor.

30. The method of claim 28, wherein TG02 is administered to the patient after the protein kinase inhibitor.

31. The method of claim 28, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the protein kinase inhibitor.

32. The method of any one of claims 28-31, wherein the protein kinase inhibitor is sorafenib.

33. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of a proteasome inhibitor.

34. The method of claim 33, wherein TG02 is administered to the patient before the proteasome inhibitor.

35. The method of claim 33, wherein TG02 is administered to the patient after the proteasome inhibitor.

36. The method of claim 33, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the proteasome inhibitor.

37. The method of any one of claims 33-36, wherein the proteasome inhibitor is bortezomib.

38. The method of any one of claims 33-36, wherein the proteasome inhibitor is carfilizomib.

39. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of a topoisomerase II inhibitor.

40. The method of claim 39, wherein TG02 is administered to the patient before the topoisomerase II inhibitor.

41. The method of claim 39, wherein TG02 is administered to the patient after the topoisomerase II inhibitor.

42. The method of claim 39, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the topoisomerase II inhibitor.

43. The method of any one of claims 39-42, wherein the topoisomerase II inhibitor is doxorubicin.

44. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of a platinum coordinating complex.

45. The method of claim 44, wherein TG02 is administered to the patient before the platinum coordinating complex.

46. The method of claim 44, wherein TG02 is administered to the patient after the platinum coordinating complex.

47. The method of claim 44, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the platinum coordinating complex.

48. The method of any one of claims 44-47, wherein the platinum coordinating complex is cisplatin.

49. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of lenalidomide.

50. The method of claim 49, wherein TG02 is administered to the patient before lenalidomide.

51. The method of claim 49, wherein TG02 is administered to the patient after lenalidomide.

52. The method of claim 49, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as lenalidomide.

53. The method of any one of claims 1-3 further comprising administering to the patient a therapeutically effective amount of radiotherapy.

54. The method of claim 53, wherein TG02 is administered to the patient before radiotherapy.

55. The method of claim 53, wherein TG02 is administered to the patient after radiotherapy.

56. The method of claim 53, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as radiotherapy.

57. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and an immune checkpoint inhibitor.

58. The method of claim 57, wherein TG02 is administered to the patient before the immune checkpoint inhibitor.

59. The method of claim 57, wherein TG02 is administered to the patient after the immune checkpoint inhibitor.

60. The method of claim 57, wherein TG02 is administered to the patient at the same time as the immune checkpoint inhibitor.

61. The method of any one of claims 57-60, wherein immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, and a TIM3 inhibitor.

62. The method of 61, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

63. The method of claim 62, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

64. The method of claim 63, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab and STI-1110.

65. The method of claim 61, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

66. The method of claim 65, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

67. The method of claim 66, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-1014

68. The method of claim 61, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

69. The method of claim 68, wherein the CTLA-4 inhibitor is an anti-CTLA-4 antibody.

70. The method of claim 69, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

71. The method of claim 61, wherein the immune checkpoint inhibitor is a LAG3 inhibitor.

72. The method of claim 71, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

73. The method of claim 72, wherein the anti-LAG3 antibody is GSK2831781.

74. The method of claim 61, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

75. The method of claim 74, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

76. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and an alkylating agent.

77. The method of claim 76, wherein TG02 is administered to the patient before the alkylating agent.

78. The method of claim 76, wherein TG02 is administered to the patient after the alkylating agent.

79. The method of claim 76, wherein TG02 is administered to the patient at the same time as the alkylating agent.

80. The method of any one of claims 76-79, wherein the alkylating agent is temozolimide.

81. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and a protein kinase inhibitor.

82. The method of claim 81, wherein TG02 is administered to the patient before the protein kinase inhibitor.

83. The method of claim 81, wherein TG02 is administered to the patient after the protein kinase inhibitor.

84. The method of claim 81, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the protein kinase inhibitor.

85. The method of any one of claims 77-80, wherein the protein kinase inhibitor is sorafenib.

86. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and a proteasome inhibitor.

87. The method of claim 86, wherein TG02 is administered to the patient before the proteasome inhibitor.

88. The method of claim 86, wherein TG02 is administered to the patient after the proteasome inhibitor.

89. The method of claim 86, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the proteasome inhibitor.

90. The method of any one of claims 86-89, wherein the proteasome inhibitor is bortezomib.

91. The method of any one of claims 86-89, wherein the proteasome inhibitor is carfilizomib.

92. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and a topoisomerase II inhibitor.

93. The method of claim 92, wherein TG02 is administered to the patient before the topoisomerase II inhibitor.

94. The method of claim 92, wherein TG02 is administered to the patient after the topoisomerase II inhibitor.

95. The method of claim 92, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the topoisomerase II inhibitor.

96. The method of any one of claims 92-95, wherein the topoisomerase II inhibitor is doxorubicin.

97. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and a platinum coordinating complex.

98. The method of claim 97, wherein TG02 is administered to the patient before the platinum coordinating complex.

99. The method of claim 97, wherein TG02 is administered to the patient after the platinum coordinating complex.

100. The method of claim 97, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as the platinum coordinating complex.

101. The method of any one of claims 97-100, wherein the platinum coordinating complex is cisplatin.

102. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and lenalidomide.

103. The method of claim 102, wherein TG02 is administered to the patient before lenalidomide.

104. The method of claim 102, wherein TG02 is administered to the patient after lenalidomide.

105. The method of claim 102, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as lenalidomide.

106. A method of treating a patient having cancer, the method comprising administering to the patient therapeutically effective amounts of TG02 and radiotherapy.

107. The method of claim 106, wherein TG02 is administered to the patient before radiotherapy.

108. The method of claim 106, wherein TG02 is administered to the patient after radiotherapy.

109. The method of claim 106, wherein a therapeutically effective amount of TG02 is administered to the patient at the same time as radiotherapy

110. The method of any one of claims 1-109, wherein the cancer is a solid tumor.

111. The method of any one of claims 1-109, wherein the cancer is a hematological malignancy.

112. The method of any one of claims 1-109, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell

lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

113. The method of claim 112, wherein the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

114. The method of claim 112, wherein the cancer is multiple myeloma.

115. The method of any one of claims 1-114, wherein the cancer has become resistant to conventional treatments.

116 The method of any one of claims 1-115, wherein TG02 is the citrate salt of (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene.

117. A kit comprising TG02 and an immune checkpoint inhibitor, an alkylating agent, a protein kinase inhibitor, a proteasome inhibitor, a topoisomerase II inhibitor, a platinum coordinating complex, or lenalidomide, and instructions for administering TG02 and the immune checkpoint inhibitor, alkylating agent, protein kinase inhibitor, proteasome inhibitor, topoisomerase II inhibitor, platinum coordinating complex, or lenalidomide, to a patient having cancer.