

CLAIMS:

1. A method of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective combination of chemotherapy and an immune checkpoint inhibitor with a caloric restriction mimetic.
- 5 2. The method of claim 1, wherein the caloric restriction mimetic is selected from the group consisting of inhibitors of mitochondrial pyruvate carrier complex (MPC), inhibitors of mitochondrial carnitine palmitoytransferase-1 (CTP1), inhibitors of mitochondrial citrate carrier (CiC), inhibitors of ATP-citrate lyase (ACLY), EP300 acetyltransferase inhibitors, and inhibitors of acyl-CoA synthetase short-chain family member 2 (ACCS2).
- 10 3. The method according to claim 1 or 2, wherein the caloric restriction mimetic is selected from the group consisting of hydroxycitrate, lipoic acid, spermidine and mixtures thereof.
- 15 4. The method according to any one of claims 1 to 3, wherein the caloric restriction mimetic is hydroxycitrate.
5. The method according to any one of claims 1 to 3, wherein the caloric restriction mimetic is hydroxycitrate in association with lipoic acid.
- 20 6. The method according to any one of claims 1 to 5, wherein the chemotherapy consists in administering to the patient in administering to the patient a therapeutically effective amount of a chemotherapeutic agent selected from the group consisting of alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1);
- 25 eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as
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chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; 5 antibiotics such as the enediyne antibiotics (e.g. , calicheamicin, especially calicheamicin gammall and calicheamicin omegall ; dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, 10 carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxy doxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, 15 potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6- 20 azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanane, testolactone; anti-adrenals such as aminogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; 25 edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex); 30 razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine;

mercaptapurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP- 16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-1 1);
5 topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

7. The method according to any one of claims 1 to 5, wherein the chemotherapy consists in administering to the patient in administering to the patient a therapeutically effective
10 amount of a chemotherapeutic agent selected from cyclophosphamide, dolastatin, pancratistatin, mechlorethamine, bleomycins, dactinomycin, daunorubicin, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxy doxorubicin, epirubicin, idarubicin, 5-fluorouracil, trimetrexate, epothilones, lonidamine, maytansine, mitoxantrone, PSK polysaccharide complex,
15 verrucar A, vindesine, cytosine arabinoside, paclitaxel, nab-paclitaxel, docetaxel, 6-thioguanine, cisplatin, oxaliplatin, carboplatin, vinblastine, platinum, ansamitocins, vincristine, vinorelbine, novantrone (mitoxantrone), daunomycin, irinotecan, retinoic acid, bortezomib, digitoxin, digoxin, patupilone, hypericin, cetuximab, septacidin, hedamycin, CDDP, mitomycin C, temozolomide and pemetrexed

8. The method according to any one of claims 1 to 7, wherein the immune checkpoint inhibitor is selected from the group consisting of PD-1 antagonists, PD-L1 antagonists, PD-L2 antagonist CTLA-4 antagonists, VISTA antagonists, TIM-3 antagonists, LAG-3 antagonists, IDO antagonists, KIR2D antagonists, A2AR antagonists, B7-H3 antagonists, B7-H4 antagonists, and BTLA antagonists.

9. The method according to any one of claims 1 to 8, wherein the immune checkpoint inhibitor is a therapeutically effective combination of a PD-1 antagonist with a CTLA-4 antagonist.

10. The method according to any one of claims 1 to 9, wherein the immune checkpoint inhibitor is selected from the group consisting of Nivolumab, Pembrolizumab, Pidilizumab, Avelumab, Durvalumab Atezolimumab, Ipilimumab and Tremelimumab.
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11. The method according to any one of claims 1 to 10, wherein:

- the at least one caloric restriction mimetic is hydroxycitrate or hydroxycitrate in association with lipoic acid;
- the chemotherapy consists in administering to the patient in administering to the patient a therapeutically effective amount of a chemotherapeutic agent selected from cisplatin, oxaliplatin and carboplatin ;taxanes selected from paclitaxel, nab-paclitaxel, docetaxel and taxotere; vinca alkaloids selected from vindesine vinblastine vincristine and vinorelbine; anthracyclines selected from mitoxantrone daunorubicin, doxorubicin, epirubicin, idarubicin, valrubicin and ditrisarubicin; gemcitabine; pemetrexed; mixtures thereof and pharmaceutically acceptable salts thereof; and
- the immune checkpoint inhibitor is selected from the group consisting of Nivolumab, Pembrolizumab, Pidilizumab, Avelumab, Durvalumab Atezolimumab, Ipilimumab and Tremelimumab.

12. The method according to any one of claims 1 to 10, wherein:

- the at least one caloric restriction mimetic is hydroxycitrate or hydroxycitrate in association with lipoic acid;
- the chemotherapy consists in administering to the patient in administering to the patient a therapeutically effective amount of a chemotherapeutic agent selected from cisplatin, oxaliplatin and carboplatin; or a simultaneous or sequential administration of carboplatin and pemetrexed; or a simultaneous or sequential administration of oxaliplatin and 5-FU; taxanes selected from paclitaxel, nab-paclitaxel, docetaxel and taxotere; gemcitabine pemetrexed mitoxantrone; and mixtures thereof and pharmaceutically acceptable salts thereof; and
- the immune checkpoint inhibitor is selected from the group consisting of Nivolumab, Pembrolizumab, Pidilizumab, Avelumab, Durvalumab Atezolimumab, Ipilimumab and Tremelimumab.

13. The method according to any one of claims 1 to 10, wherein the immune checkpoint inhibitor is administrated simultaneously with the chemotherapy and/or the immune checkpoint inhibitor.

14. The method according to any one of claims 1 to 10, wherein the immune checkpoint inhibitor is administrated prior to the chemotherapy and/or the immune checkpoint inhibitor.
15. The method of claim 1 wherein the patient suffers from neoplasm, malignant;
5 carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma
10 and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; branchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell
15 carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometroid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous; adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous
20 cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; Paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; and roblastoma, malignant; Sertoli cell carcinoma; Leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant;
25 sarcoma; fibrosarcoma; fibrous histiocytooma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner
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tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; kaposi's sarcoma; hemangiopericytoma, malignant;

5 lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; Ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma;

10 fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's disease; Hodgkin's lymphoma;

15 paraganuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia;

20 basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia.