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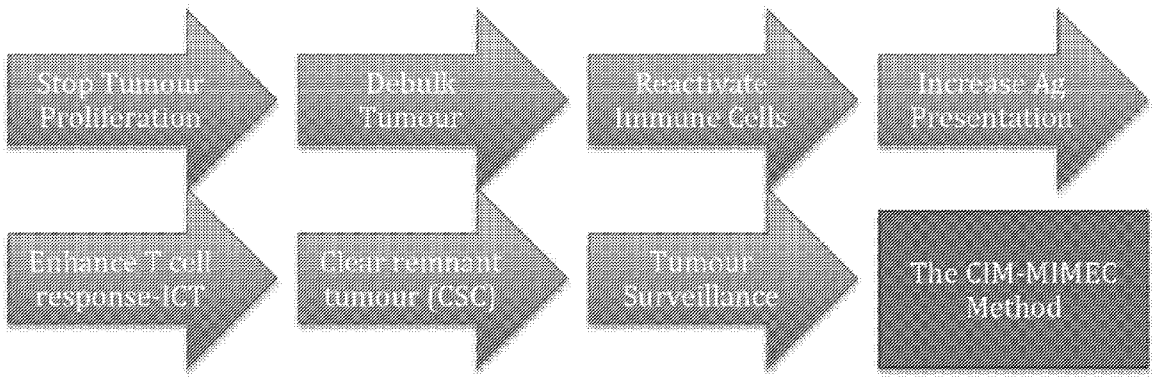
(54) Title: METHOD OF TREATING CANCER

[FIGURE 1 One Embodiment of The CIM-MIMEC Method]



(57) Abstract: Disclosed herein is a method of treating cancer, comprising: a) reducing or stopping cancer proliferation, b) debulking tumour mass, c) activating immune cells, d) increasing antigen presentation and/or enhancing T cell response, and e) clearing residual tumour cells.

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METHOD OF TREATING CANCER

The present disclosure relates to a method of treating cancer, use of medicaments in a staged combination therapy for the treatment of cancer (also referred to herein as multimodal cancer therapy), and use of a medicament or medicaments in the manufacture of a multimodal therapy for the treatment of cancer, for example linked with dynamic input of tumor status, to optimise intervention and timing.

BACKGROUND

The treatment of cancer is still a huge challenge and burden to society. The present inventor believes that the effectiveness of cancer therapy can be greatly increased by employing a multimodal method of treatment. That is conscious choice of sequence and the timing of multiple treatments to achieve improved outcomes, for patients.

The involvement of the immune system in defense against cancer growth has been evident for a long time but with the emergence of the immune check-point inhibitor therapies (for example, PD-1, PDL-1, CTLA4) the understanding of the field has rapidly expanded. It is clear that tumors attract immune cells. However, it is also clear that many of these cells that are effective against viral and bacterial infections, offer little effect against cancer, and may even be counterproductive and cancer supporting.

It is now thought that tumor associated macrophages actually feed and protect the cancer cells. Stroma, containing immune cells, builds up around cancer cells and creates a protected environment where the cancer flourishes.

Cancer cells are highly adapted to corrupting and hijacking many natural biological processes that exist in the body. Cancers are sometimes based on mutations and modifications of cells and thus can readily change and adapt. Given this the present inventor believes that is unlikely that one or two modes of treatment will be effective for the treatment of the majority of cancers.

Therefore, the inventor has designed a new method to treat cancer, which involves a radical resetting of the immune system, which will be much more efficacious than just using simple steps, such as immune check point inhibitors or combinations thereof.

In some ways, the method of present disclosure can be considered a “reboot” of the immune system, which after treatment is then able to fight the cancer.

SUMMARY OF THE DISCLOSURE

Thus, the present disclosure provides a method of treating cancer comprising the steps;

a) reducing or stopping cancer proliferation,

a1) declutter of tumor infiltrating immune cells,

b) debulking tumour mass, and/or increasing antigen presentation,

c) activating immune cells,

d) increasing antigen presentation and/or enhancing T cell response, and

e) clearing residual tumor cells.

The treatment schedule of the present disclosure is a paradigm shift in cancer treatment, because at the present time standard of care cancer treatment generally only involves one or two of the above steps.

Whilst some cancer therapy regimes (like chemotherapy regimens) are a combination or cocktail of the therapeutic agents from the outset, and cancer adjuvant therapy is known (i.e. chemotherapy or radiation therapy after surgery to excise a tumor) subsequent cancer therapies are not employed until the first line or second therapy has failed.

The multimodal therapy of the present disclosure is not the same as simply trying different treatments after the failure of a treatment. Instead it involves pro-actively employing multiples modes of treatment, in particular in the order specified herein.

In one embodiment the method comprises the further step of tumour surveillance.

In one embodiment the therapeutic steps are taken in fast succession, in particular while surveying and reading "efficacy", for example by studying effects on immune parameters and/or variables showing circulating tumor components. Efficacy here is not employed in the strict technical sense but simply to effects more generically.

The fast delivery of a sequence of therapies and the elected timing of the next treatment step may be important to reset the immune system while stopping further cancer growth. Thus in one embodiment the present multimodal treatment comprises multiple treatment steps, which are employed at specific times, for example over a period of 1 to 12 months, such as 1 to 2 months, 1 to 3 months, 1 to 4 months, 1 to 5 months, 1 to 6 months, 1 to 7 months, 1 to 8 months, 1 to 9 months, 1 to 10 months or 1 to 11 months.

This fast succession of different modes of treatment is highly advantageous because it minimises the time available for the cancer cells to "regroup" and develop strategies to make them resistant to treatment.

In one embodiment the "subsequent" therapies are **not** employed because a therapy has failed i.e. the further therapy is not started because there is resistance to "first line or second line" therapy.

In one embodiment step **b)** follows step **a)** or step **a1)**. In one embodiment step **c)** follows step **b)**. In one embodiment step **d)** follows step **c)**. In one embodiment step **e)** follows step **d)**.

In one embodiment one or more treatment steps may overlap or be at the same time.

In one embodiment step **a)** and **a1)** overlap or are at the same time. In one embodiment step **a)** and **b)** overlap or are at the same time. In one embodiment step **a1)** and **b)** overlap or are at the same time. In one embodiment step **b)** and **c)** overlap or are at the same time. In one embodiment step c) and d) overlap or are at the same time. In one embodiment step **d)** and **e)** overlap or are at the same time.

In one embodiment step **a)**, **a1)** and **b)** overlap or are at the same time. In one embodiment step **a)**, **b)** and **c)** overlap or are at the same time. In one embodiment step **a1)**, **b)** and **c)** overlap or are at the same time. In one embodiment step **b)**, **c)** and **d)** overlap or are at the same time. In one embodiment step **c)**, **d)** and **e)** overlap or are at the same time.

In one embodiment step **a)**, **a1)**, **b)** and **c)** overlap or are at the same time. In one embodiment step **a)**, **b)**, **c)** and **d)** overlap or are at the same time. In one embodiment step **a1)**, **b)**, **c)** and **d)** overlap or are at the same time. In one embodiment step **b)**, **c)**, **d)** and e) overlap or are at the same time.

In one embodiment step **a)**, **b)**, **c)**, **d)** and **e)** overlap or are at the same time. In one embodiment step **a1)**, **b)**, **c)**, **d)** and **e)** overlap or are at the same time

In one embodiment one or more of the steps do not overlap, for example 2, 3, 4 or all of the step do not overlap.

In one embodiment step **b)** and **d)** do not overlap and are not at the same time.

In one embodiment step **e)** does not overlap with step **c).**

In one embodiment the method comprises a pre-step of surgery, for example to remove tumour mass and/or lymph nodes and the like.

In one embodiment the method comprises irradiation.

In one embodiment step **a)** is a treatment selected from the group comprising irradiation, chemotherapy, anti-proliferation pathway therapy (for example anti-oestrogen, anti-androgen, anti-HER, anti-BCR/ABL, anti-VEGF, anti-PDGF, anti-BRAF antibody molecule [including a bispecific antibody, full-length or an antibody binding fragment], with or without combining with the appropriate chemotherapy) and a combination of two or more of the same.

In one embodiment at least one agent employed in step **a)** is an antiproliferative agent, for example selected from the group 25-hydroxcholesterol, 3-hydroxtyrosol, 7β-hydroxycholestrol, aloe-emodin, apigenin, artesunate, berberine, caffeine power (C0750), dichloromethylenediphosphonic acid (for example as a salt, such as a disodium salt), emodin, HA 14-1, hyperforin, N-acetyl-D-sphingosine, N-hexanoyl-D-sphingosine, oleuropein, pathenolide, tangeretin, tanshinone IIA, β-cryptoxanthine, β-cryptoxanthin, β-lonone, *trans*-cinnamaldehyde and combinations thereof.

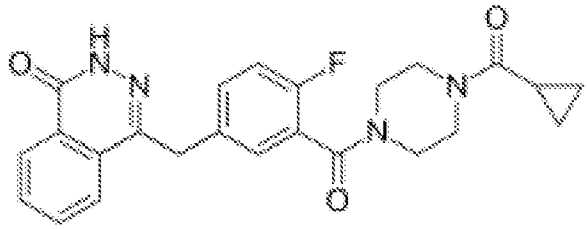
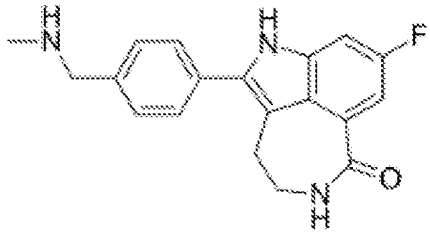
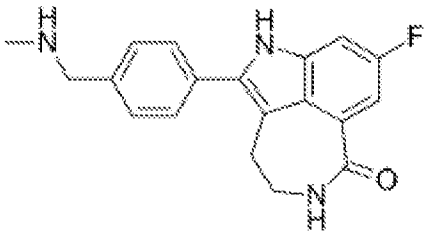
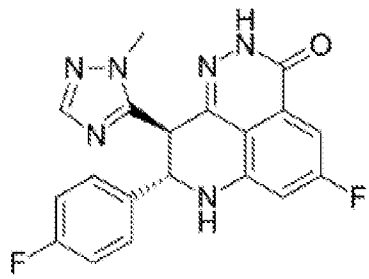
Other agents that can be employed alone or in a combination in step **a)** include high doses of vitamin B1, parp inhibitors, a gene product of NME2, myrtillin (delphinidin-3-O-glucoside), tulipanin (delphinidin-3-O-rutinoside), violdelphin (delphinidin 3-rutinoside-7-*O*-(6-*O*-(4-(6-O-(4-hydroxybenzoyl)-β-D-glucosyl)oxy benzoyl)-β-D-glucoside), nasunin (delphinidin-3-(p-coumaroylrutinoside)-5-glucoside) and combinations of two or more of the same.

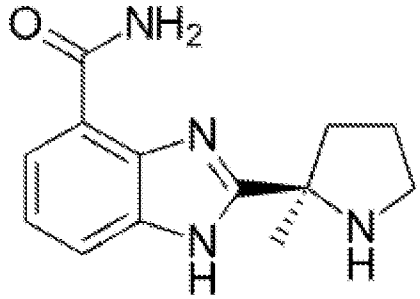
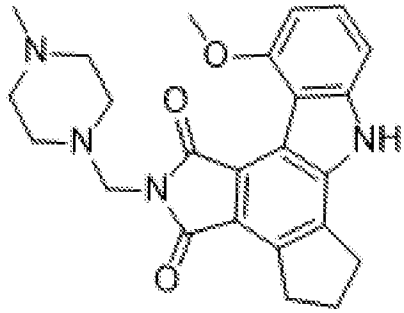
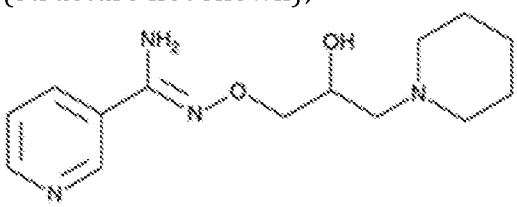
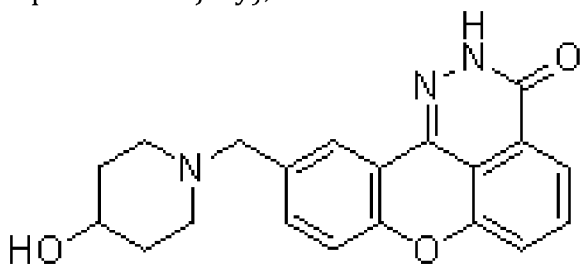
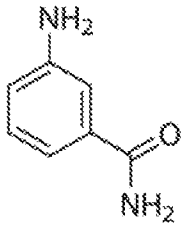
In one embodiment therapy employed in step **a)** is Varlitinib [(*R*)-N4-[3-Chloro-4-(thiazol-2-ylmethoxy)-phenyl]-N6-(4-methyl-4, 5,-dihydro-oxazol-2-yl)-quinazoline-4,6-diamine] or a pharmaceutically acceptable salt thereof, which may be employed alone or in a combination therapy.

The Varlitinib, is administered at a dose in the range 100mg to 900mg on each occasion, in particular 200 mg, 300mg, 400mg or 500mg each dose, such as 400mg, for example administered once or twice daily, such as twice daily.

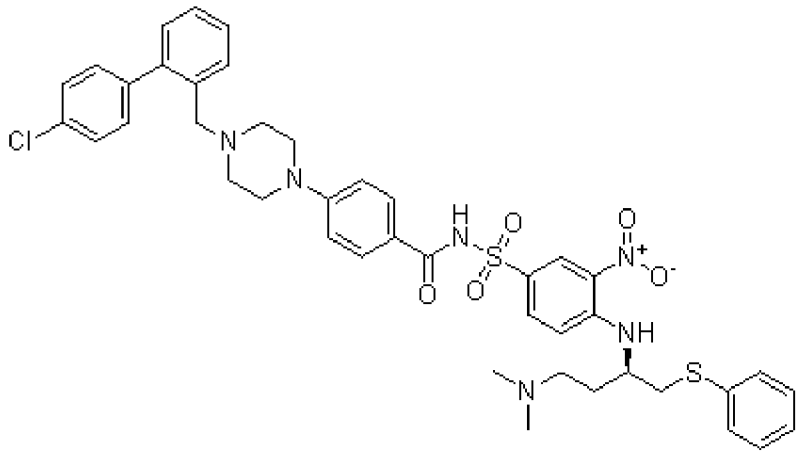
In one embodiment the therapy of step a) comprises a DHODH inhibitor, such as 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt thereof.

In one embodiment the PARP inhibitor one or more compounds independently selected from of the following:

	**AZD-2281 (Olaparib)** a PARP-1 and PARP-2 inhibitor (which is the first PARP inhibitor to gain US FDA approval); 
AG-014699 (Rucaparib) a PARP-1 inhibitor (currently in Phase III trials for ovarian and pancreatic cancer); 	**MK-4827 (Niraparib)** a PARP-1 and PARP-2 inhibitor (currently in Phase III trials for ovarian, breast cancer and Ewing sarcoma); 
BMN-673 (Talazoparib) a PARP-1 and PAR-2 inhibitor (which is currently in	**ABT-888 (Veliparib)** a PARP-1 and PARP-2 inhibitor (which is currently being

Phase III trials for ovarian, breast and other solid cancers); 	evaluated in Phase III studies for breast, pancreatic, non-small cell lung cancer, lymphoma and multiple myeloma); 
CEP-9722 a PARP-1 and PARP-2 inhibitor;	**INO-1001 (3-aminobenzamide)** a potent inhibitor of PARP (with IC50 of <50 nM in CHO cells and a mediator of oxidant-induced myocyte dysfunction during reperfusion)
BGB-290 a PARP-1 and PARP-2 inhibitor (structure not shown); 	**BGP-15** a PARP inhibitor (which has been shown to protect against ischemia-reperfusion injury); 
E7016 (previously known as GPI-21016) a PARP inhibitor (undergoing Phase I trials in combination with temozolomide for advanced solid tumours and gliomas); 	

MP-124 a PARP-1 inhibitor (structure not shown);



ABT-737 a PARP-1 and PARP-2 inhibitor,

or a pharmaceutically acceptable salt or solvate of any one of the same.

In one embodiment the therapy in step **a1)**, i.e. the decluttering of immune cells, is performed by administering a compound, such as a CXCR2 antagonist, an anti-GCF, cyclophosphamide and/or irradiation, and a combination of two or more of the same.

As used herein, decluttering refers to neutralisation of immune cells. This neutralisation may, for example include reduction in number of immune cells. Generally speaking, decluttering results in a reduction in overall number of immune cells, but may also encompass total depletion, including local and systemic depletion.

In one embodiment decluttering of immune cells is performed by removing specific immune cell populations, for example using medication and/or techniques such as a dialysis.

In one embodiment the immune cells that are "decluttered" are selected from a lymphocyte (such as a T lymphocyte, such as a T cell or a NKT cell), a B cell, a natural killer cell and a combination of two or more of the same.

In one embodiment the immune cells which are decluttered are tumor associated macrophages. Tumor associated macrophages can be decluttered by NKT cells engineered to encode a cytokine, for example as disclosed in WO2013/040371, incorporated herein by reference.

In one embodiment the immune cell, which is decluttered is a lymphocyte, for example a NK cell or a T lymphocyte, such as a T cell or a NKT cell.

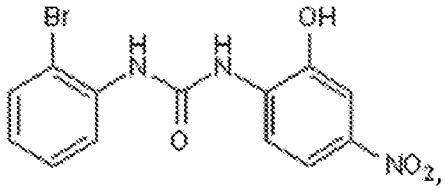
In one embodiment the immune cells that are decluttered are B cells.

In one embodiment the immune cell that is decluttered is a natural killer cell. NK cells can be targeted by monoclonal antibodies or binding fragments specific to CD56.

Mature T lymphocytes can be removed by medicaments such as alemtuzumab.

Immune cells with surface expression of CD52 can be removed by Campath.

In one embodiment the CXCR2 antagonist is selected from an antibody or binding fragment thereof, MK-7123, SB265610, SB 225002:



GSK1325756, AZD5069, and combinations thereof.

In one embodiment the CXCR2 antagonist is SCH-527123.

In one embodiment the decluttering step **a1)** is performed by employing anti-neutrophil antibodies.

In one embodiment the step **a1)** is performed using a G-CSF antibody, for example CSL324, which is a humanized G-CSFR antibody.

In one embodiment the debulking in step **b)** is surgery to reduce a tumor mass. In one embodiment the surgery is followed by chemotherapy and/or (in particular or) irradiation therapy.

Debulking as employed herein refers to a reduction in the total mass of a tumor. This includes breaking a tumor mass into smaller fragments as well as shrinking the tumor mass. Methods of reducing a tumor mass include cutting (excising), ablating (including cryoablation, liquid nitrogen treatment of topical cancer cells and combinations of two or more of the same.

In one embodiment the debulking in step **b)** is performed by administering chemotherapy selected from alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents, such as doxorubicin, 5-fluorouracil (5-FU), paclitaxel, gemcitabine, capecitabine, irinotecan, and platins such as cisplatin and oxaliplatin.

In one embodiment the debulking in step **b)** is selected from treatment with an oncolytic virus, an antibody drug conjugate and a combination thereof.

In one embodiment the oncolytic virus is a virus selected from an adenovirus, herpes simplex virus, reovirus, measles virus, Newcastle disease virus, Seneca Valley virus, Vesicular stomatitis virus, polio virus, ECHO enterovirus, Coxsackie virus, and vaccinia virus.

In one embodiment the oncolytic virus is selected from Enadenotucirev, talimogene laherparepvec, RIGVIR, Ad5-yCD/mutTKSR39rep-hIL12, Cavatak™, CG0070, DNX-2401, G207, HF10, Imlygic®, JX-594, MG1-MA3, MV-NIS, OBP-301, Reolysin®, Toca 511.

In one embodiment the antibody drug conjugate (ADCC) is selected from the group comprising AGS-15E, AGS-16C3F, AGS-22M6E, AMG-172, AMG-595, ASG-5ME, brentuximab vedotin, DEDN-6526A, DMUC-5754A, gemtuzumab ozogamicin, glembatumumab vedotin, GSK2857916, hRS7-SN-38, IMGN-242, IMGN-289, IMGN-388, IMGN-529, IMGN-633, IMGN-853, Indatuximab, indatuximab ravtansine, Inotuzumab

ozogamicin, lorvotuzumab mertansine, MEDI-547, milatuzumab doxorubicin, MLN-0264, MLN-2704, PF-06263507, pinatuzumab vedotin, polatuzumab, PSMA-ADC, RG-7450, RG-7599, SAR-3419, SAR-566658, SC16LD6.6, SGN-15, SGN-19A, SGN-CD33A, SGN-LIV1A, trastuzumab emtansine and combinations thereof.

In one embodiment step **b)** comprises administering varlitinib or a salt thereof, as a monotherapy or as part of a combination therapy, for example as disclosed elsewhere herein.

In one embodiment step **b)** comprises administering a DHODH inhibitor, such as as 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt thereof.

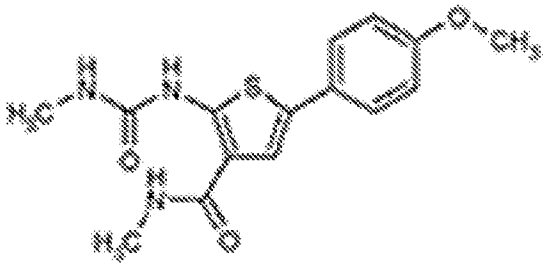
In one embodiment activating the immune cells in step **c)** comprises administering a RON inhibitor, an AXL kinase inhibitor, a MER kinase agonist, a cytokine (such as IL-13, IL-15, IL-4 or IL-2), a tumour vaccine for example comprising a tumour antigen and adjuvant, a dendritic cell vaccine and a combination of two or more of the same.

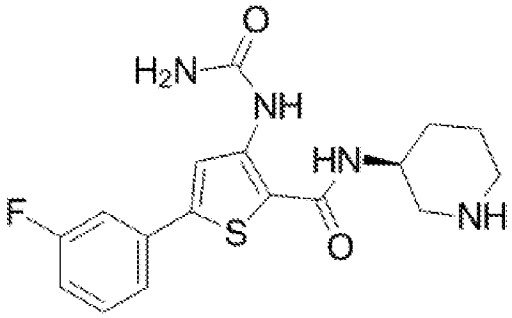
As used herein activating immune cells refers to the functional activation of the immune cells, for example the activation of T cells by stimilulation with antigens (including where the antigen is provided on antigen presenting cells), and the activation of B cells to produce tumor specific antibodies. Activating may also include the recruitment of immune cells to the tumor site. Use of appropriate cytokines can stimulate and/or activate immune cells.

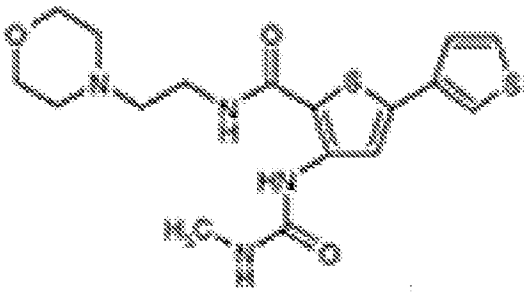
In one embodiment the RON inhibitor is N-(4-(2-Amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide disclosed in WO 2008/058229.

In one embodiment activating the immune cells in step **c)** comprises administering one or more check-point inhibitors.

In one embodiment the checkpoint inhibitor is one or more compounds independently selected from:

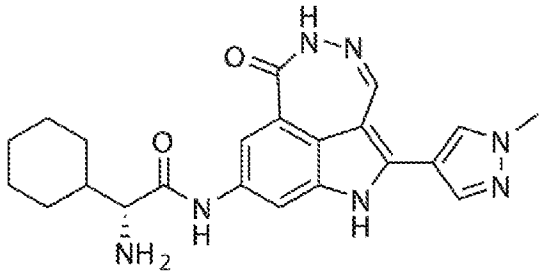
AZD-6672 a CHK1 and CHK2 inhibitor (with an IC50 of about 5 nM in a cell-free assay, with less potent activity against CAM, Yes, Fyn, Lyn, Hck an Lck);	 ;



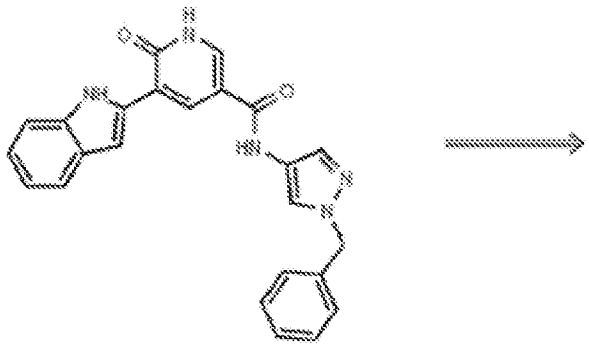


;

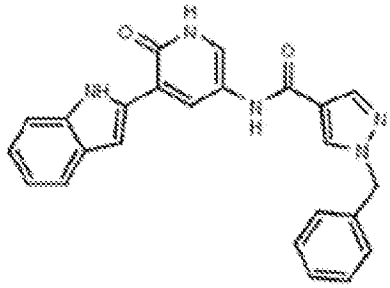
PF-477736 is a CHK1 & 2 inhibitor (ATP-competitive CHK1 inhibitor with a K_I of 0.49 nM in a cell free assay. The molecule also VEGFR2, Aurora-A, FGFR3, Flt3, Fms (CSF-1R), Ret and Yes. It shows approximately 100 fold selectivity for CHK1 over CHK2);



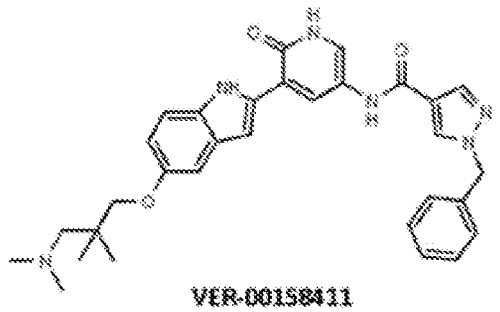
V155422, V155991 and V158411 are CHK1 and CHK2 inhibitors,:



VER-00155422
Chk1 IC_{50} = 0.017 μM
LE = 0.35



VER-00155991
Chk1 IC_{50} = 0.0076 μM
LE = 0.37

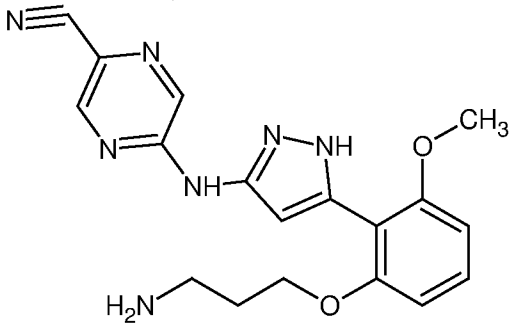


VER-00158411
Chk1 IC_{50} = 0.0044 µM
LE = 0.30

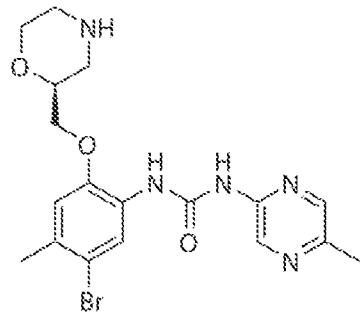
Kinase	IC_{50} (nM)	*In vitro* PD Assay	IC_{50} or EC_{50} (nM)
Chk1	4.4 ± 2.1	Chk1 (pS296)	48
Chk2	4.5	Chk2 (pS516)	904
CDK1	>50 000	Gem pH2AX (S139)	51
		Gem pHH3 (S10) MI	79

Values are the average of at least 2 determinations ± SD

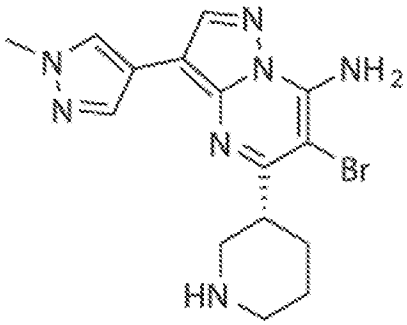
LY2606368;



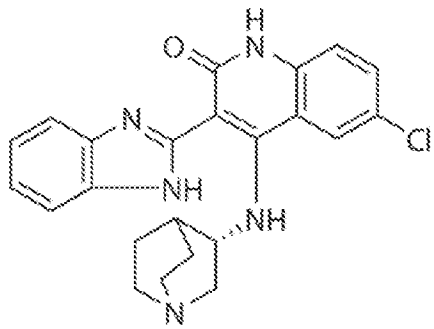
LY2603618 a selective potent CHK1 inhibitor;



MK-8776 is a selective CHK1 inhibitor (with an IC50 of 3 nM in a cell-free assay. The molecule shows 500-fold selectivity against CHK2);

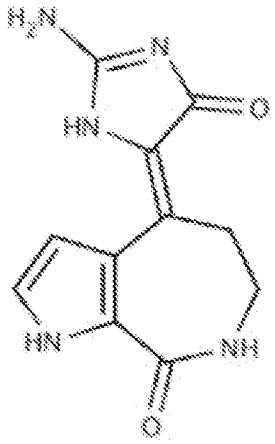


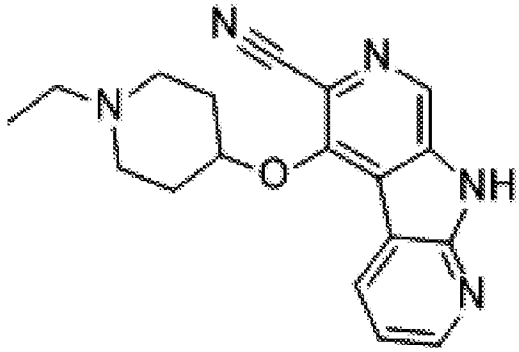
CHIR124 is CHK1 inhibitor (is a novel and potent inhibitor with IC50 of 0.3 nM in a cell-free assay. It shows 2,000-fold selectivity against CHK2 and 500 to 5000 fold less activity against CDK2/4 and Cdc2);



Debromohymenialdisine (SKF 108753) is a natural product derived from sponges that in inhibits CHK1 and CHK2;

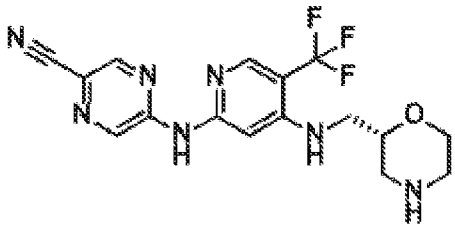
GDC-0425 is a selective CHK1 inhibitor;

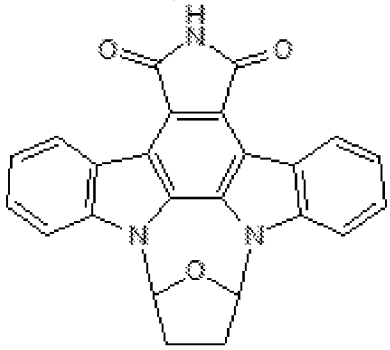




GDC-0575 (structure not given);

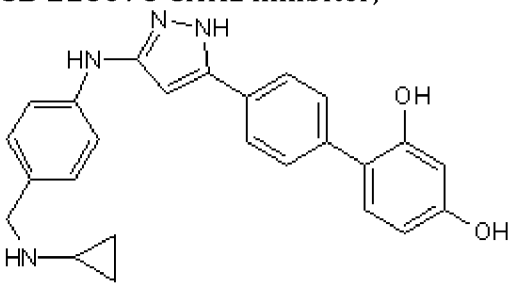
CCT245737;

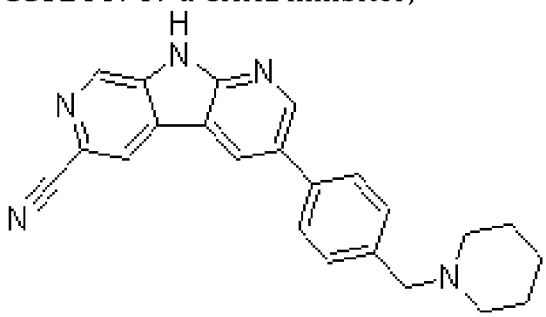




SB 218078 CHK1 inhibitor;

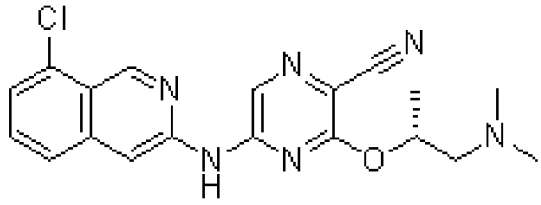
CCT244747 a CHK1 inhibitor;

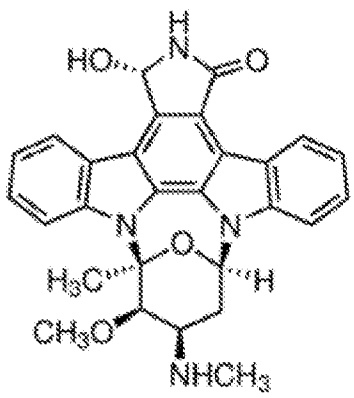




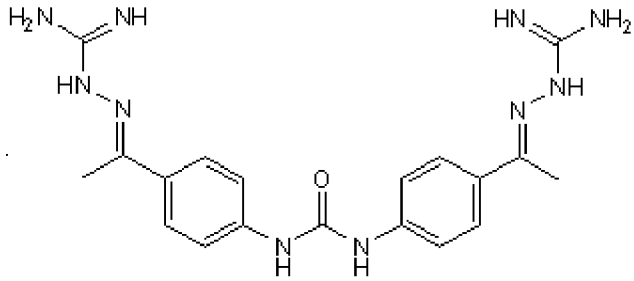
GNE-900 a CHK1 inhibitor;

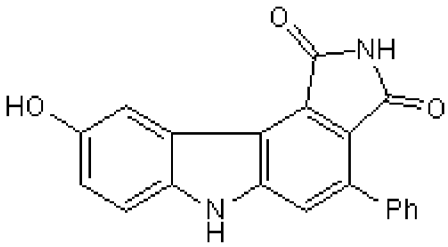
SAR-020106 a CHK1 inhibitor;

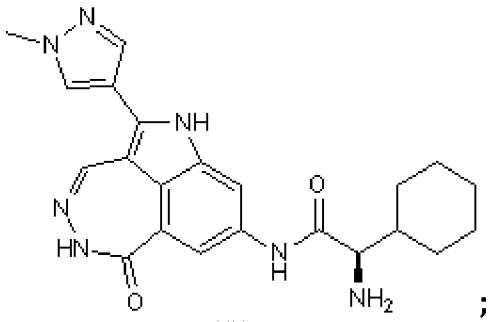




UCN-01 non-selective CHK1 inhibitor;







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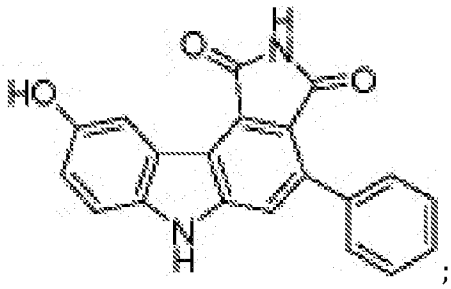

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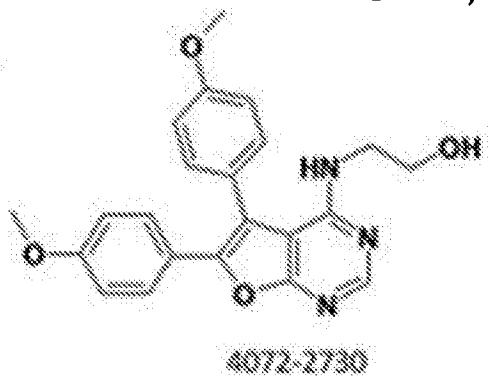
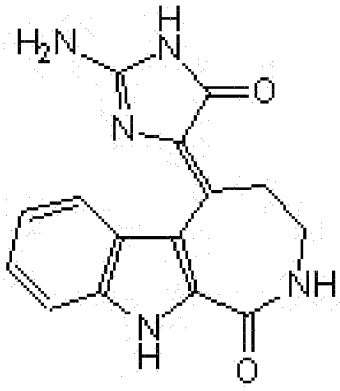


4072-2730



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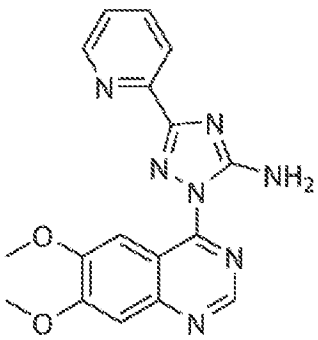
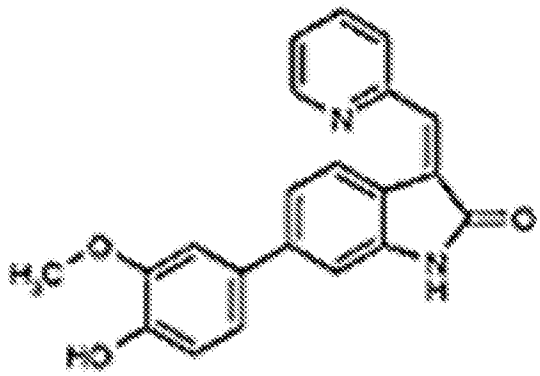
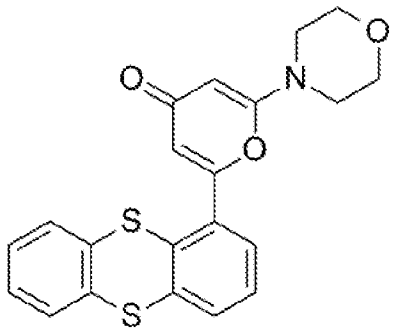


;

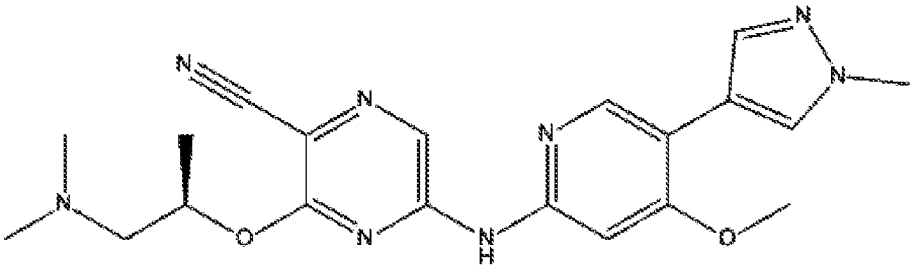
CP-466722 is a potent ATM inhibitor, which does not inhibit ATR. The molecule also inhibits Pi3K and PIKK;



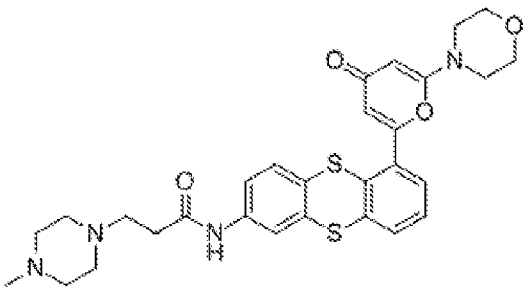


;

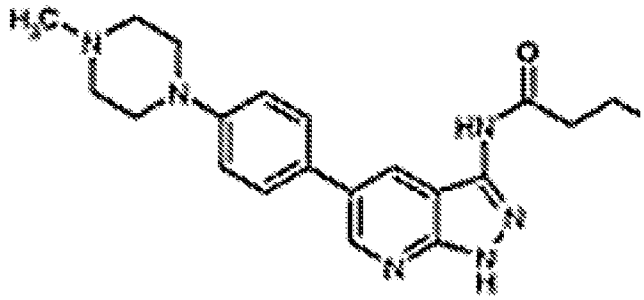
TCS 2312 a CHK1 inhibitor KI 0.38 nM, EC50 60 nM;



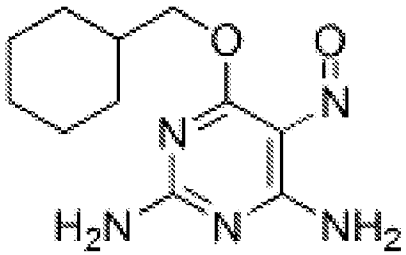
KU55933 is a potent and selective ATM inhibitor (vis-a-vie DNA-PK, Pi3K/Pi4K, ATR and mTOR) with an IC50 of 13 nM and KI of 2.2 mM;

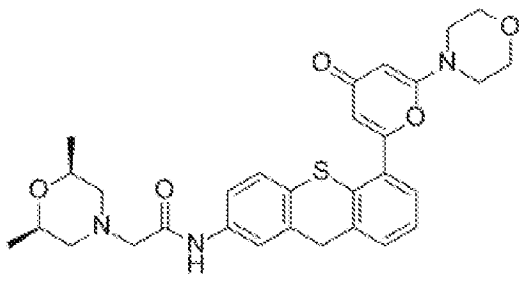


KU59403 is an ATM inhibitor;



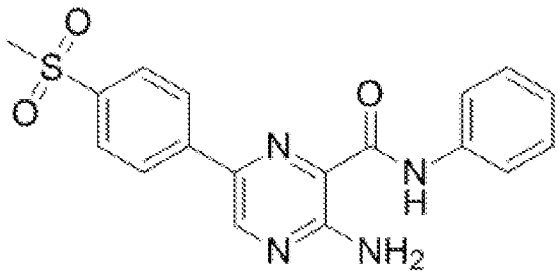
KU60019 is an ATM inhibitor;



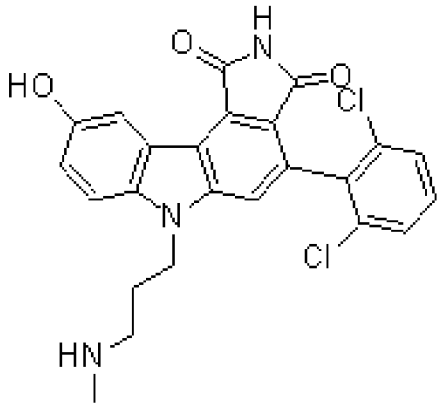


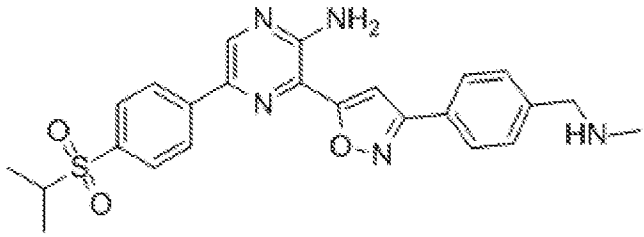
VE-822 is a selective ATR inhibitor with a K_I of 0.2 nM and an about 150 selectivity over ATM;

NU6027 is a potent ATR inhibitor;

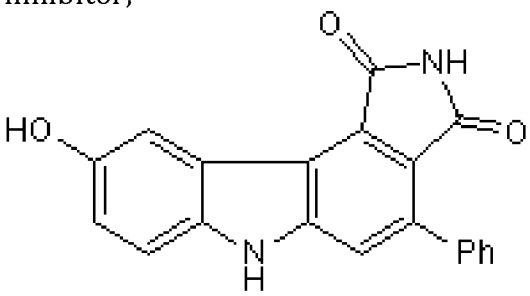


VE-821 is a potent and selective ATP competitive inhibitor of ATR with a K_I of 13 nM and an IC50 of 26 nM;

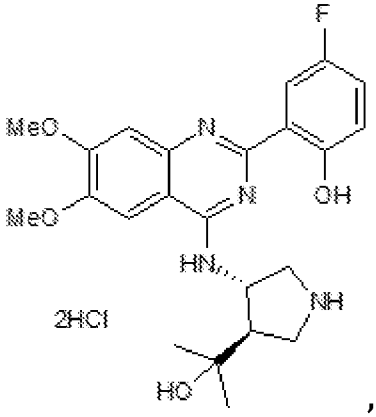




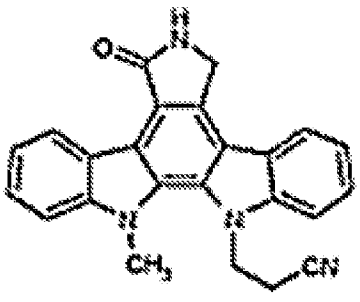
PD-321852 is a CHK1 and WEE1 inhibitor;



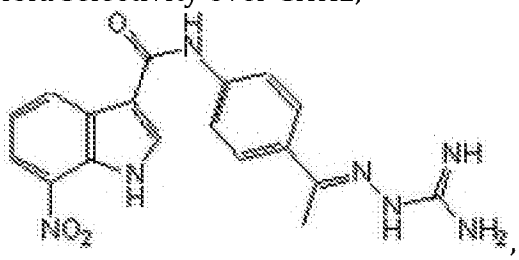
PD-407824 is a CHK1 and WEE1 inhibitor;

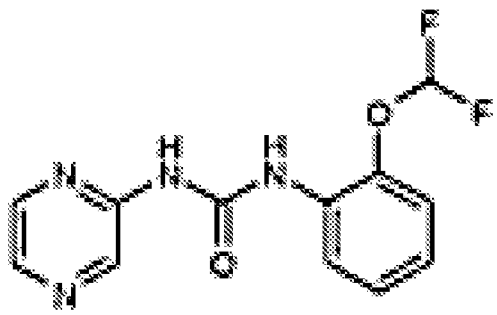


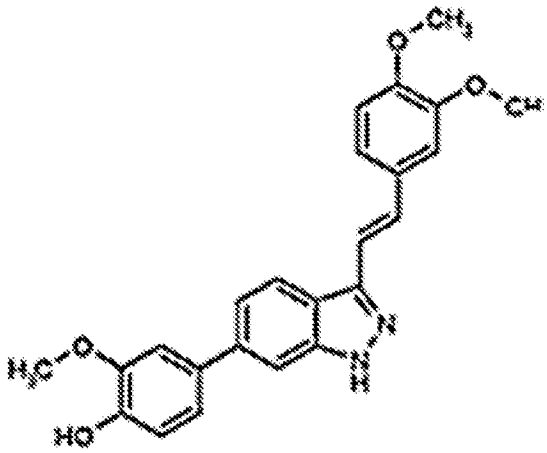
PV1019 is a CHK2 inhibitor;

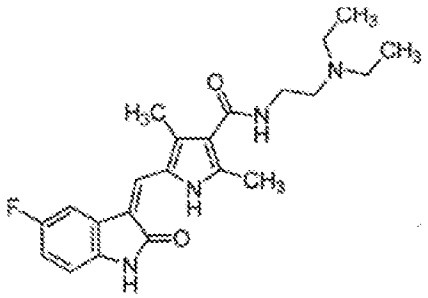


CCT241533 is a CHK2 inhibitor with about 63 fold selectivity over CHK1;

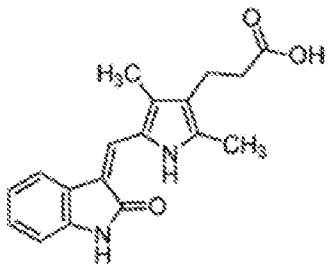




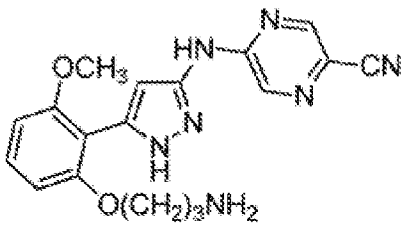




Sunitinib



SU6668



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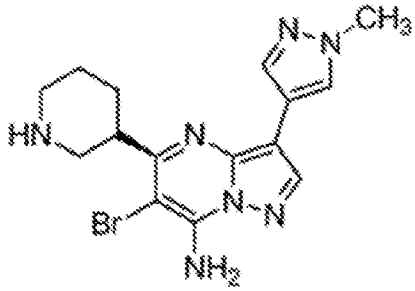


SCH900776

In one embodiment the check-point inhibitor is a PD-1 or PD-L1 inhibitor.

In one embodiment the checkpoint inhibitor is a combination of 2 or several immune checkpoint inhibitors such as PD-1 plus CTL4, or PD-1 plus LAG3 (or TIM3 or GITR).

In one embodiment step **d)**, i.e. increasing antigen presentation and/or enhancing T cell response, comprises administering a therapy selected from the group comprising a T cell therapy (for example where T cells are activated *in vitro* to generate CTLs specific to an antigen), a cell therapy comprising engineered chimeric receptors, a PD1 inhibitor, a PD-L1 inhibitors, a CTLA4 inhibitor, a LAG3 inhibitor and a combination of two or more of the same.

Increasing antigen presentation as used herein refers to the enhancement of the presentation of antigens to antigen presenting cells, for example by using a combination of treatments to make tumors necrotic, thereby providing a lot of potential antigenic material for presentation by antigen presenting cells. Other examples of increasing

antigen presentation include enhancing the ability of dendritic cells and macrophages to phagocytose tumor and present tumor antigen; and blocking or inhibiting do-not-eat-me signals (CD47) on tumour cells that prevent phagocytosis of tumour cells.

Alternatively or in addition onclotytic viruses carrying a transgene can be used to infect the cancer cell and express the "protein or peptide" encoded on the cancer cells surface to increase antigen expression. Antigen in this context simply means a target for therapy or immune cells, in particular a target for immunotherapy.

In one embodiment step **d)** comprises administering a therapy selected from the group comprising an oncolytic virus, a DLL inhibitor, ADH-1 molecular targeting therapy and combinations of two or more of the same, for example the oncolytic virus is a virus selected from an adenovirus, herpes simplex virus, reovirus, measles virus, Newcastle disease virus, Seneca Valley virus, Vesicular stomatitis virus, polio virus, ECHO enterovirus, Coxsackie virus, and vaccinia virus, such as Enadenotucirev, talimogene laherparepvec, RIGVIR, Ad5-yCD/mutTKSR39rep-hIL12, Cavatak™, CG0070, DNX-2401, G207, HF10, Imlygic®, JX-594, MG1-MA3, MV-NIS, OBP-301, Reolysin®, or Toca 511.

Residual tumor cells as used herein refers to tumor cells that remain after the previous therapy, for exampleat the primary tumor site or in the vicinity, including circulating tumor cells, dormant cancer cells, cancer stems cells and combinations of the two or more of the sameThe goal of this step is to eradicate any remaining traces of cancer cells and minimise recurrence of the cancer.

In one embodiment step **e)**, i.e. clearing residual tumor cells comprises targeting cancer stem cells.

In one embodiment the cancer stem cell therapy comprises targeting one or surface markers, for example with one or more monoclonal antibodies. In one embodiment the marker is selected from CD133, CD44, CD24, ESA, CD34 + CD38, and CD47.

In one embodiment step **e)** comprises an agent, such as an antibody or binding fragment thereof, specific to TRAIL or NF-αB.

In one embodiment step **e)** comprises an agent, such as an antibody or binding fragment thereof, specific to a cell marker Epcam, CD133, CD44, CD24, ESA, $CD34^{+}/CD38^{-}$ and CD47.

In one embodiment the cell markers are targeted by a chimeric antigen receptor.

In one antibody or antibody binding fragment is in the format of an antibody drug conjugate.

DETAILED DISCLOSURE

Multimodal or stage cancer therapy as employed herein refers to discrete phases of therapy, for example each phase lasting in the region of 1 week to 6 months, such as

2 weeks to 1 month, 2 weeks to 2 months, 2 weeks to 3 months, 2 weeks to 4 months or 2 weeks to 5 months. The therapies may overlap but generally will not simply be a combination therapy.

Combination therapy as employed herein is two or more active agents both administered over the same period of treatment.

The theory behind the method of the present disclosure is as follows:

1. Stop cancer continuing growing via use of cell cycle inhibitors and proliferation pathway inhibitors, and nutrient pump/metabolic inhibitors, to decrease growth of tumor burden:
    a. Cancers use de-breaking of cell cycle to go on fast growth (1)
    b. Proliferation pathway inhibitors and metabolic inhibitors can slow cancer growth (2)
2. Remove Neutrophils and Tregs and de-clog cancer (remove non-functional immune cells and other cancer supportive elements) to make it accessible to immune therapy and to stop building of cancer tissue
    a. Mesenchymal stem cells and Neutrophils are steered by cancer G-CSF (2)
    b. Mesenchymal stem cell (MSC) are attracted to early stage tumor (2)
    c. MCS steer Neutrophils via G-CSF to become tumor supportive (2)
    d. Inhibitors of G-CSF slow cancer (3)
    e. Tumors with higher blood Neutrophil to Lymphocyte ratio have worse prognosis (4)
    f. Patients who become neutropenic during chemotherapy have better prognosis (5)
    g. Neutrophils steer dendritic cells and Tregs (6)
    h. Neutrophils are key for angiogenesis, which turns cancers to fast growth via the so called angiogenic shift (7)
    i. Tumor associated Macrophages (TAMs) support tumor growth (8)
    j. Removing Neutrophils using an antibody, increases survival in PDX model (9)
    k. In order for allogenic T-cell transplantation to work, best results are achieved by combination of cyclophosphamide and radiation to remove Tregs and other immune cells (10)
3. Then shift dendritic cells and macrophages to macrophage type 1, the inflammatory kind
    a. Macrophage type 2 is the most prevalent TAM and is not effective in antigen presentation (11)
    b. Intervention with inhibitor of RON kinase shifts macrophages to Type 1 and increase efficacy of PD-1 therapy (12)

c. Potential steering of M2 macrophage to M1 subtype with inhibition of IL-4 and 1L-13 since these gluococorticoid hormones have been shown to induce M2 Macrophage phenotype. (12)
d. Dendritic cells capture antigens from tumour and migrate into the draining lymph nodes for presentation. The antigens can be presented with MHC class I and class II molecules. (13)
e. Tumours interfere with DC maturation through IL-10 and TSLP. The DCs are skewed towards a Th2 lineage which promotes tumour development. (14)
f. pDCs are also inhibited due to ligation of ILT7 with BST2 on tumour cells. The inhibited pDCs induce CD4+ T cells to differentiate to become immunosuppressive. (15)
g. GM-CSF, in combination with other chemokines, can induce differentiation of inflammatory DCs that in turn will activate T cell functions. (16, 17, 18)
h. Antibody therapy for engagement of surface molecules on DCs such as dectin1, DCSIGN/CD209 and CD40 putatively polarize DCs towards the pro-inflammatory phenotype. (19, 20, 21)

4. Secure major antigen presentation to make dendritic cells and macrophages phagocytose tumor and present tumor antigen
    a. Use either of a series of technologies (radiation, chemo, oncolytic virus, cancer vaccine, toxin loaded antibodies, cancer metabolism inhibitors or nutrient pump inhibitors or other) to make tumor necrotic and allow APCs lots of material to present. (40)
    b. A specific example of cancer metabolism inhibitor would be DHODH inhibitors that inhibit de novo synthesis of pyrimidines. This inhibition will specifically inhibit rapidly dividing cells. DHODH inhibition will also lead to induction of p53 and resulting apoptosis once a threshold of p53 levels is breached. (39)
    c. With findings that the neoantigen repertoire for tumours vary greatly across tumours, exome sequencing for tumours can yield personalized vaccine targets based on predicted MHC binding capacity. (22, 23)
    d. Neo-antigen presentation can also be greatly enhanced by blocking or inhibiting do-not-eat-me signals (CD47) on tumour cells that prevent phagocytosis of tumour cells. (24)
5. Use immune checkpoint inhibitor (ICI) to enhance T-cell response (or use highly targeted CAR-T construct to seek out and destroy tumor tissue
    a. Single or combinations or sequences of ICIs can be used and have shown additive effects in the clinic (25)

b. These ICI therapies are not limited to T cell mediators and may also affect DCs, NK, NKT cells. They are a combination of antagonists to inhibitory signals and agonists to activation signals on the immune cells. (25)

6. Eradicate remnant tumor by using either of the following technologies to specifically kill Circulating tumour cells (CTC) and Cancer Stem Cells (CSC) dormant cancer cells (DCC)
    a. Oncolytic virus kills CTC (26)
    b. Inhibition of ALDH by eg. disulfiram increases reactive oxygen species (ROS) and kills CSC (27)
    c. Inhibition of NANOG indirectly through HIF1a inhibition by eg. disulfiram may inhibit CSCs (28)
    d. The phenotype of CSCs will differ depending on the cellular context. In well-validated systems, such as breast and hemaotopoietic cancers, therapies against CSC have also shown efficacy, in reducing tumour recurrence and demonstrating long-term efficacy. (29, 30, 31, 32)
    e. Starting proliferation of dormant cells by eg. Lithium turns DCCs non-dormant and accessible for killing via eg. chemo, irradiation or other means. Chemotherapy and irradiation methods may only impact cycling cells. By driving cells out of G0 into the cell cycle – you would be able to trigger apoptosis at cell cycle checkpoint. (33)
7. Use fast dynamic diagnostics to follow immune status in the tumor and direct therapy
    a. Tumors signal via exosomes in the circulation to seeding areas about status and to steer grafting probabilities (34)
    b. Thrombocytes carry RNA and other tumor markers that tell status in tumor (35)
    c. Survey both CTC and circulating immune cell subsets to gain an idea about heightened nature of immune system in response to tumour, as well as, resolution of immune response. (36)
    d. This is particularly important as several immune checkpoint therapies have demonstrated pseudo-progression, increase in tumour size via RECIST due to immune cell infiltration and inflammation. The anti-tumour effect is only visible after several weeks. Hence it would be critical to have a dynamic marker of immune activity that can be read out at earlier timepoints. (37)
    e. Use combination of RNA, DNA, cell and immune diagnostics to determine response to therapy and best next steps (38)

Tumors recruit a number of cells and they are either supporting cells, or just bystanders, which are likely to physically block access to the cancer. It may also be that

these supporting or bystander cells, feed of fuel the cancer cell growth. Therefore we hypothesise therapy should focus on removing these before shifting to changing the macrophage and dendritic cell infiltration.

In turn changing the macrophage and dendritic cell set up is important to perform before applying ICIs since these activated M1 and active dendritic cells can provide immunogenic material to the T-cells.

Generally it is useful in the present method that the immunostimulation, by the means of making antigens available en masse, to the macrophages and the dendritic cells, should occur after the macrophages and the dendritic cells have been activated, and should precede application of the immune checkpoint inhibitors.

Killing circulating tumor cells and cancer stem cells and dormant cancer cells is described as the last step. However this step can be applied at initiation and/or during the subsequent steps, and may be repeated together with immune reactivation at subsequent sessions.

The timely feedback of the status of the tumor is important, since this multi-stage immuno, pathway and tumor escape/survival directed therapy needs to be steered and directed. For example daily measures of anti-tumour activity may enable one to be able to direct the therapy better (i.e. understanding when the neutrophils are down and depleted, and when the myeloid derived suppressor cells have been turned off, and when the macrophages have turned to M1 phenotype and how the immune checkpoint inhibition is successful in attacking the tumor).

Additionally, the detection of circulating tumor cells and RNA and DNA products from the tumor provides an indication whether the strategies to kill cancer stem cells have been successful.

Furthermore, the diagnosis of autoimmune reactions early allowing early intervention will be key, since several of the immunostimulation combos and efforts will elicit autoimmune reactions that need to be staved off quickly. The learning from this monitoring is likely to be important since individuals' response to these combined therapies may be highly specific both in kind, quality, quantity and timing.

The method is different from other methods in that it foresees usage of key therapies for a limited period of time, for a therapy period of less than 2 months is envisioned for one or more stages. This therapy in parts or in full may need to be repeated at a later stage, potentially with changes that may take instruction from the ongoing immune and cancer diagnostics.

In one embodiment we expect that a 2 week period of proliferation and nutrient/metabolic inhibition may be sufficient before taking down neutrophils and debulking of tumor. This step may take a week, followed by macrophage/dendritic cell type change (3-7 days), and then turning on the antigen production and presentation (1

to 2 weeks) before turning on the immune defense with T-cells and NK cells via the immune checkpoint inhibitors for at least 2 weeks. During the latter period, if not before, the killing of circulating and dormant cancer cells should be started, along with attempts to eradicate cancer stem cells.

This new method represents a way to declare total war against the cancer and is believed to cause maximal effect in the shortest period of time, while keeping side effects to a minimum. It also is a new way to try to learn as much possible about the specific cancer and to be able to adapt therapy to achieve best effect and avoid side effects.

The method should be meaningful both in early cancer (e.g. neo-adjuvant setting pre surgery) as well as a treatment alternative later in the cancer development.
The tumor mass and whether or not mass metastasis has occurred will be key factors whether or not the therapy will be effective. However, given the reported cases of durable responses in melanoma with immune checkpoint inhibitors, even after many lines of therapy, make it possible to believe in efficacy even at protracted and far progressed disease.

Treatment of cancer as employed herein refers to administration of the combination therapy of the present disclosure for the purpose of reducing symptoms, ameliorating symptoms, slowing progressing (including spreading) of the cancer or a form thereof (such as metastatic cancer), stopping progression (including spreading) of the cancer or a form thereof (such as metastatic cancer), shrinking tumors, reducing metastases, reducing or eliminating certain populations of cancer cells, for example cancer stem cell populations, sending the cancer into remission, maintaining the cancer in remission, prophylactic treatment of cancer, curing cancer or a combination of one or more the same, as appropriate.

Treatment of cancer as employed herein also refers to administration of the combination therapy of the present disclosure for the purpose of enhancing concomitant anti-cancer therapy, and for the purpose (at least in part) to reduce side effects and/or reducing the dose required of concomitant anti-cancer therapy.

Lithium compound as employed herein refers to an active agent employed in therapy comprising the alkali metal lithium, for example lithium salts comprising a counter-ion such as selected from the group comprising aspartate, bromide, chloride, citrate, lithium carbonate, lithium sulfate and orotate.

Lithium salts are well established treatments for mood disorders. The main side effects are taste derangement, tremor and kidney side effects. However, these side effects are much less toxic than those encountered by patients receiving normal traditional cancer therapy, and the doses employed for cancer therapy may be lower

than those employed for the treatment of mood disorders, especially when the lithium is employed in combination of disulfiram.

It is common clinical practice to monitor plasma levels of lithium, so that the likelihood of toxicity is reduced. Therefore, in one embodiment the patient receiving the combination therapy of the present disclosure is monitored for plasma levels of lithium, for example when the treatment is started and/or on a monthly, three monthly, six monthly or annual basis.

Thus in one embodiment the dose of lithium employed is a dose that does not elicit side effects in the majority of patients.

The majority of patients as employed herein refers to wherein at 51% of patients who receive that dose do not encounter therapy limiting side effects or only encounter minor side effects associated with the lithium such as 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100% of patients do not encounter therapy limiting side effects.

Minor side effects as employed herein are effects that a negligible i.e. that do not significantly impact on the patients' quality of life and thus at most are slightly inconvenient.

It is believed by the present inventors that the lithium acts in cancer cells (for example cancer cells which are differentiated, i.e. non-cancer-stem-cells) at least via inhibiting the enzyme glycogen synthase kinase-3 (GSK-3), which is linked to the insulin and the Wnt pathways. The inhibition of GSK-3 may be associated with anti-proliferative effects. However, lithium may also be linked to hormone receptors such as estrogen and androgen. Thus other effects of lithium may be exerted on bone marrow and on adaptive and innate immune defenses which are not necessarily associated to the GSK3 mediated effects.

Paradoxically, lithium seems to increase the proliferation and self-renewal of stem cells, including cancer stem cells. That could be seen as a negative in terms of cancer therapy. However, in this instance it may be positive because it prevents the cancer cells evading treatment.

Thus lithium driving proliferation and self-renewal prevents the cancer cells becoming dormant. The latter is thought to be a mechanism for cancer cell resistance. Thus preventing the option for the cancer cells to become dormant may enhance immediate efficacy of cancer therapy and may allow more or all of the cancer cell populations present to be treated. This in turn may improve the effectiveness of the cancer therapy and/or reduce the risk for cancer relapse.

Furthermore, self-renewal may also mean that the effectiveness of concomitant therapies (such as traditional cancer therapies or therapies directed to cancerous at renewal mechanisms) may have an increased therapeutic window or have a therapeutic

window which is shifted towards more "selectively" effecting cancer cells (or certain types of cancer cells, such as cancer stem cells).

Another mechanism of lithium efficacy may be on the bone marrow and the T-cells, which through the inhibition of GSK3 may become more effective, for example providing prolonged T cell proliferation and increased IL-2 production. Thus, there may be immune-stimulatory effects provided by employing the combination therapy of the present disclosure which renders the patient more receptive to therapy, for example in the form of immune-oncology compounds.

Immune-oncology compounds also referred to as cancer immune therapy herein refers to therapies that target tumor associated antigens (TAAs) and stimulate immune responses to the cancer.

Thus lithium and disulfiram may work additively or in synergy, to decrease the survival of cancer cells, such as cancer stem cells.

Disulfiram inhibits the aldehyde dehydrogenase, which is a key marker for cancer stem cells, and is a key enzyme for defense against reactive oxygen species (ROS), which may otherwise harm the cancer stem cell. Thus disulfiram may cause cancer stem cell reduction, for example via accumulation of reactive oxygen species leading to necrosis, apoptosis or autophagy thereby increasing death of cancer stem cells.

Necrosis as employed herein refers to cell death through injury or damage to the cell.

Apoptosis as employed herein refers to hastening programmed cell death, which is sometimes referred to as cell assisted suicide.

Autophagy as employed herein refers to a complex process of intracellular degradation, which may deliver nutrients and/or energy to other cells.

We hypothesize that the combination therapy of the present disclosure makes it difficult for cancer cells to stay in quiescent dormant mode, for example by provoking self-renewal stimulated by the lithium part of the combined therapy. This renders the cancer stem cells vulnerable to cancer treatments, either via the disulfiram part or by other anti-cancer therapeutics.

However, if the cancer cells manage to stay in quiescent dormant mode the disulfiram part of the therapy may be deleterious to them through, for example the accumulation of reactive oxygen species (ROS).

Reactive oxygen species (ROS) as employed herein refers to peroxides, superoxides, hydroxyl radicals, singlet oxygen and the like. The accumulation of reactive oxygen specifies causes significant damage to cell structure, which ultimately is likely to cause cell death.

Disulfiram (DSF) is a widely used anti addiction medicine (ethanol addiction). Its main target is aldehyde dehydrogenase, and its' inhibition causes upstream accumulation of ethanol aldehyde which is linked to physical discomfort.

Aldehyde dehydrogenase is also a marker of cancer stem cells and the present inventors believe that disulfiram via inhibition of aldehyde dehydrogenase increases the concentration of reactive oxygen species. This increased concentration of reactive oxygen species in turn damages the cancer stem cells. Thus is hypothesized that DSF suppresses self-renewal capability mainly through the activation of reactive oxygen species (ROS)-p38 MAPK pathway.

In addition disulfiram, via inhibition of SOD-1, is thought to inhibit the release of TNF-alpha, vascular endothelial growth factor, and MMP-2 and MMP-9 from cultured macrophages, which may contribute to the overall effectiveness of the combination therapy.

It is believed that by attacking cancers cell via two independent pathways, using well tolerated drugs, and particularly the ability to target cancer stems cells will lead to significant improvements of cancer treatment.

In addition, effects of lithium on the bone marrow and on the immune system may add to the breadth of potential positives of the therapy of the present disclosure.

Furthermore it may be that the combination therapy of the present disclosure has beneficial effects in protecting non-cancerous tissue from the toxic effect of cancer therapy that may be employed in combination with the therapy comprising disulfiram and a lithium compound.

Combination treatment as employed herein refers to a treatment wherein the duration of time when the patient is on or taking the medicament comprising a lithium compound is also the time when the patient is taking or is administered a medicament comprising the disulfiram (i.e. treatment regimens for lithium and disulfiram at least overlap).

In one embodiment a lithium compound and a disulfiram are administered or taken in the same 7 days period. In one embodiment the disulfiram is administered or taken on the same day as the lithium compound.

In one embodiment the combination therapy of the present disclosure is employed as adjuvant therapy, for example post-surgery or post-chemotherapy.

In one embodiment the combination therapy of the present disclosure is employed as neo-adjuvant therapy.

The combination treatment of the present disclosure may be employed in combination with one or more further cancer treatments, for example

- concomitant with chemotherapy (including where chemotherapy follows radiation therapy), or

- concomitantly with radiation therapy (including where radiation therapy follows chemotherapy)
- concomitant with chemotherapy and radiation therapy
- concomitant with immune-modulating agents such as PD-1 inhibitors and IDO1-inhibitors and agents active on the macrophage type shift (type 2 to type 1 shift)

In one embodiment the therapy may reduce the side effects of such and may allow usage of higher and more effective doses of other cancer therapies to be employed and tolerated.

A suitable dose may be chosen by the practitioner based on the nature of the cancer being treated.

Chemotherapeutic agent as employed herein is intended to refer to specific antineoplastic chemical agents or drugs that are selectively destructive to malignant cells and tissues. Chemotherapeutic agent and chemotherapy or cytotoxic agent are employed interchangeably herein unless the context indicates otherwise. Examples inlcude alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. Other examples of chemotherapy include doxorubicin, 5-fluorouracil (5-FU), paclitaxel, capecitabine, irinotecan, and platins such as cisplatin and oxaliplatin.

Examples of alkylating agents, which may be employed in the method of the present disclosure include an nitrogen mustards alkylating agent, nitrosoureas, tetrazines, aziridines, platins and derivatives, and non-classical alkylating agents.

Examples of a platinum containing chemotherapeutic agent (also referred to as platins), such as cisplatin, carboplatin, oxaliplatin, satraplatin, picoplatin, nedaplatin, triplatin and lipoplatin (a liposomal version of cisplatin), in particular cisplatin, carboplatin and oxaliplatin.

The dose for cisplatin ranges from about 20 to about 270 mg/m^2 depending on the exact cancer. Often the dose is in the range about 70 to about 100mg/m^2.

The dose for cisplatin ranges from about 20 to about 270 mg/m^2 depending on the exact cancer. Often the dose is in the range about 70 to about 100mg/m^2.hemotherapeutic agent is a topoisomerase inhibitor.

Nitrogen mustards include mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide and busulfan. Nitrosoureas include N-Nitroso-N-methylurea (MNU), carmustine (BCNU), lomustine (CCNU) and semustine (MeCCNU), fotemustine and streptozotocin. Tetrazines include dacarbazine, mitozolomide and temozolomide.

Aziridines include thiotepa, mytomycin and diaziquone (AZQ).

Examples of antimetabolites, which may be employed in the method of the present disclosure, include anti-folates (for example methotrexate and pemetrexed), purine analogues (for example thiopurines, such as azathiopurine, mercaptopurine,

thiopurine, fludarabine (including the phosphate form), pentostatin and cladribine), pyrimidine analogues (for example fluoropyrimidines, such as 5-fluorouracil and prodrugs thereof such as capecitabine [Xeloda®]), floxuridine, gemcitabine, cytarabine, decitabine, raltitrexed(tomudex) hydrochloride, cladribine and 6-azauracil.

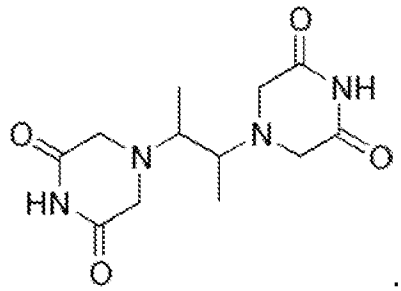
Examples of anthracyclines, which may be employed in the method of the present disclosure, include daunorubicin (Daunomycin), daunorubicin (liposomal), doxorubicin (Adriamycin), doxorubicin (liposomal), epirubicin, idarubicin, valrubicin currenlty used only to treat bladder cancer and mitoxantrone an anthracycline analog, in particular doxorubicin.

Examples of anti-microtubule agents, which may be employed in the method of the present disclosure, include include vinca alkaloids and taxanes.

Vinca alkaloids include completely natural chemicals for example vincristine and vinblastine and also semi-synthetic vinca alkaloids, for example vinorelbine, vindesine, and vinflunine.

Taxanes include paclitaxel, docetaxel, abraxane, carbazitaxel and derivatives of thereof. Derivatives of taxanes as employed herein includes reformulations of taxanes like taxol, for example in a micelluar formulaitons, derivatives also include chemical derivatives wherein synthetic chemistry is employed to modify a starting material which is a taxane.

Topoisomerase inhibitors, which may be employed in a method of the present disclosure include type I topoisomerase inhibitors, type II topoisomerase inhibitors and type II topoisomerase poisons. Type I inhibitors include topotecan, irinotecan, indotecan and indimitecan. Type II inhibitors include genistein and ICRF 193 which has the following structure:



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Type II poisons include amsacrine, etoposide, etoposide phosphate, teniposide and doxorubicin and fluoroquinolones.

In one embodiment he chemotherapeutic agent is a parp inhibitor, in particular as disclosed herein.

In one embodiment the combination therapy is administered with or following a treatment regime comprising a platinum containing chemotherapeutic agent, for example cisplatin, carboplatin or oxaliplatin.

In one embodiment a combination of chemotherapeutic agents employed is, for example a platin and 5-FU or a prodrug thereof, for example cisplatin or oxaplatin and capecitabine or gemcitabine, such as FOLFOX.

In one embodiment the chemotherapy comprises a combination of chemotherapy agents, in particular cytotoxic chemotherapeutic agents.

In one embodiment the chemotherapy combination comprises a platin, such as cisplatin and fluorouracil or capecitabine.

In one embodiment the chemotherapy combination in capecitabine and oxaliplatin (Xelox).

In one embodiment the chemotherapy is a combination of folinic acid and 5-FU, optionally in combination with oxaliplatin.

In one embodiment the chemotherapy is a combination of folinic acid, 5-FU and irinotecan (FOLFIRI), optionally in combination with oxaliplatin (FOLFIRINOX). The regimen consists of: irinotecan (180 mg/m^2 IV over 90 minutes) concurrently with folinic acid (400 mg/m^2 [or 2 x 250 mg/m^2] IV over 120 minutes); followed by fluorouracil (400–500 mg/m^2 IV bolus) then fluorouracil (2400–3000 mg/m^2 intravenous infusion over 46 hours). This cycle is typically repeated every two weeks. The dosages shown above may vary from cycle to cycle.

In one embodiment the combination employs a microtubule inhibitor, for example vincristine sulphate, epothilone A, N-[2-[(4-Hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide (ABT-751), ataxol derived chemotherapeutic agent, for example paclitaxel, abraxane, or docetaxel or a combination thereof.

In one embodiment the combination employs an mTor inhibitor. Examples of mTor inhibitors include: everolimus (RAD001), WYE-354, KU-0063794, papamycin (Sirolimus), Temsirolimus, Deforolimus(MK-8669), AZD8055 and BEZ235(NVP-BEZ235).

In one embodiment the chemotherapy combination employs a microtubule inhibitor, for example vincristine sulphate, epothilone A, N-[2-[(4-Hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide (ABT-751), a taxol derived chemotherapeutic agent, for example paclitaxel, abraxane, or docetaxel or a combination thereof.

In one embodiment the chemotherapy combination employs a MEK inhibitor. Examples of MEK inhibitors include: AS703026, CI-1040 (PD184352), AZD6244 (Selumetinib), PD318088, PD0325901, AZD8330, PD98059, U0126-EtOH, BIX 02189 or BIX 02188.

In one embodiment the chemotherapy combination employs an AKT inhibitor. Examples of AKT inhibitors include: MK-2206 and AT7867.

In one embodiment the combination employs an aurora kinase inhibitor. Examples of aurora kinase inhibitors include: Aurora A Inhibitor I, VX-680, AZD1152-HQPA (Barasertib), SNS-314 Mesylate, PHA-680632, ZM-447439, CCT129202 and Hesperadin.

In one embodiment the chemotherapy combination employs a p38 inhibitor, for example as disclosed in WO2010/038086, such as *N*-[4-({4-[3-(3-*tert*-Butyl-1-*p*-tolyl-1*H*-pyrazol-5-yl)ureido]naphthalen-1-yloxy}methyl)pyridin-2-yl]-2-methoxyacetamide.

In one embodiment the combination employs a Bcl-2 inhibitor. Examples of Bcl-2 inhibitors include: obatoclax mesylate, ABT-737, ABT-263(navitoclax) and TW-37.

In one embodiment the chemotherapy combination comprises an antimetabolite such as capecitabine (xeloda), fludarabine phosphate, fludarabine (fludara), decitabine, raltitrexed (tomudex), gemcitabine hydrochloride and cladribine.

In one embodiment the chemotherapy combination comprises ganciclovir, which may assist in controlling immune responses and/or tumour vasculation.

Cancer Types In more Detail

In one embodiment the gastric cancer is selected from the group comprising adenocarcinoma of the stomach, squamous cell carcinomas, lymphoma of the stomach, gastric stromal tumour, and neuroendocrine tumours.

In one embodiment the liver cancer is, for example selected from the group hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, and hepatoblastoma, in particular hepatocellular carcinoma. In one embodiment the primary liver cancer is stage 1, 2, 3 or 4. In one embodiment the liver cancer is secondary or metastasized liver cancer.

Prostate cancer as employed herein refers to cancer of the prostate, for example ductal adenocarcinoma, transitional cell (urothelial cancer), squamous cell cancer, carcinoid of the prostate, small cell cancer or sarcoma and sarcomatoid cancer.

Pancreatic cancer as employed herein includes exocrine cancers (including rare forms thereof such as cystitic tumours, and cancer of the acinar cells), endocrine pancreatic tumours (including gastrinomas, insulinomas, somatostatinomas, VIPomas, glucagonomas), pancreatoblastoma, sarcomas of the pancreas and lymphoma.

Biliary tract cancer as employed herein refers to cholangiocarcinoma (intrahepatic, extrahepatic), gall bladder cancer and ampullary carcinoma.

Colorectal cancer as employed herein refers to cancer or the colon and/or rectum and includes squamous cell cancers, carcinoid tumours, sarcomas and lymphomas.

Breast cancer as employed herein refers to cancer of the breast and includes ductal carcinoma in situ, lobular carcinoma in situ, invasive ductal breast cancer, invasive lobular breast cancer, invasive breast cancer, Paget's disease, angiosarcoma of

the breast and rare types of breast cancer such as medullary breast cancer, mucinous breast cancer, tubular breast cancer, adenoid cystic carcinoma of the breast metaplastic breast cancer, basal type breast cancer and papillary breast cancer.

Lung cancers are classified according to histological type and are categorized by the size and appearance of the malignant cells seen by a histopathologist under a microscope. For therapeutic purpose, two broad classes are distinguished: non-small cell lung carcinoma and small cell lung carcinoma.

In one embodiment the epithelial cancer is lung cancer, for example small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

Non-small-cell lung carcinoma-The three main subtypes of NSCLC are adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma.

Nearly 40% of lung cancers are adenocarcinoma, which usually originates in peripheral lung tissue. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may be associated with a better long term survival.

Squamous-cell carcinoma accounts for about 30% of lung cancers. They typically occur close to large airways. A hollow cavity and associated cell death are commonly found at the center of the tumor. About 9% of lung cancers are large-cell carcinoma. These are so named because the cancer cells are large, with excess cytoplasm, large nuclei and conspicuous nucleoli.

Small-cell lung carcinoma-In small-cell lung carcinoma (SCLC), the cells contain dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association. Most cases arise in the larger airways (primary and secondary bronchi). These cancers grow quickly and spread early in the course of the disease. Sixty to seventy percent have metastatic disease at presentation.

In one embodiment the cancer is non-small lung carcinoma.

In one embodiment the cancer is liver cancer, for example a liver metastasis from a primary cancer, for example colon cancer, which has spread to the liver. In one embodiment the liver cancer is HCC hepatocellular carcinoma.

In one embodiment there is provided treatment of renal cancer, for example renal cell carcinoma and/or urothelial cell carcinoma. Other examples of renal cancer include squamous cell carcinoma, juxtaglomerular cell tumor (reninoma), angiomyolipoma, renal oncocytoma, Bellini duct carcinoma, clear-cell sarcoma of the kidney, mesoblastic nephroma, Wilms' tumor, mixed epithelial stromal tumor, clear cell adenocarcinoma, transitional cell carcinoma, inverted papilloma, renal lymphoma, teratoma, carcinosarcoma, and carcinoid tumor of the renal pelvis.

In one embodiment the cancer is bladder cancer, for example is any of several types of malignancy arising from the epithelial lining (i.e. the urothelium) of the urinary bladder. About 90% of bladder cancers are transitional cell carcinoma. The other 10% are squamous cell carcinoma, adenocarcinoma, sarcoma, small cell carcinoma, and secondary deposits from cancers elsewhere in the body. The staging of this cancer is given below.

T (Primary tumour)

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Ta Non-invasive papillary carcinoma
- Tis Carcinoma in situ ('flat tumour')
- T1 Tumour invades subepithelial connective tissue
- T2a Tumour invades superficial muscle (inner half)
- T2b Tumour invades deep muscle (outer half)
- T3 Tumour invades perivesical tissue:
- T3a Microscopically
- T3b Macroscopically (extravesical mass)
- T4a Tumour invades prostate, uterus or vagina
- T4b Tumour invades pelvic wall or abdominal wall

N (Lymph nodes)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
- N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3 Metastasis in a lymph node more than 5 cm in greatest dimension

M (Distant metastasis)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis.

The current disclosure extends to any stage of bladder cancer.

There are more than 30 different types of ovarian cancer which are classified according to the type of cell from which they start. Cancerous ovarian tumours can start from three common cell types:

- Surface Epithelium - cells covering the lining of the ovaries
- Germ Cells - cells that are destined to form eggs

- Stromal Cells - Cells that release hormones and connect the different structures of the ovaries

The present disclosure relates to treatment of ovarian cancer from any source, for example as described herein, in particular epithelium cells. Epithelial ovarian carcinomas (EOCs) account for 85 to 90 percent of all cancers of the ovaries.

Common Epithelial Tumors - Epithelial ovarian tumors develop from the cells that cover the outer surface of the ovary. Most epithelial ovarian tumors are benign (noncancerous). There are several types of benign epithelial tumors, including serous adenomas, mucinous adenomas, and Brenner tumors. Cancerous epithelial tumors are carcinomas - meaning they begin in the tissue that lines the ovaries. These are the most common and most dangerous of all types of ovarian cancers. Unfortunately, almost 70 percent of women with the common epithelial ovarian cancer are not diagnosed until the disease is advanced in stage.

There are some ovarian epithelial tumors whose appearance under the microscope does not clearly identify them as cancerous. These are called borderline tumors or tumors of low malignant potential (LMP tumors). The method of the present disclosure includes treatment of the latter.

Germ Cell Tumors - Ovarian germ cell tumors develop from the cells that produce the ova or eggs. Most germ cell tumors are benign (non-cancerous), although some are cancerous and may be life threatening. The most common germ cell malignancies are maturing teratomas, dysgerminomas, and endodermal sinus tumors. Germ cell malignancies occur most often in teenagers and women in their twenties. Today, 90 percent of patients with ovarian germ cell malignancies can be cured and their fertility preserved.

Stromal Tumors - Ovarian stromal tumors are a rare class of tumors that develop from connective tissue cells that hold the ovary together and those that produce the female hormones, estrogen and progesterone. The most common types are granulosa-theca tumors and Sertoli-Leydig cell tumors. These tumors are quite rare and are usually considered low-grade cancers, with approximately 70 percent presenting as Stage I disease (cancer is limited to one or both ovaries).

Primary Peritoneal Carcinoma-The removal of one's ovaries eliminates the risk for ovarian cancer, but not the risk for a less common cancer called Primary Peritoneal Carcinoma. Primary Peritoneal Carcinoma is closely rated to epithelial ovarian cancer (most common type). It develops in cells from the peritoneum (abdominal lining) and looks the same under a microscope. It is similar in symptoms, spread and treatment.

Stages of Ovarian Cancer

Once diagnosed with ovarian cancer, the stage of a tumor can be determined during surgery, when the doctor can tell if the cancer has spread outside the ovaries. There are

four stages of ovarian cancer - Stage I (early disease) to Stage IV (advanced disease). The treatment plan and prognosis (the probable course and outcome) will be determined by the stage of cancer.

Following is a description of the various stages of ovarian cancer:

Stage I - Growth of the cancer is limited to the ovary or ovaries.

Stage IA - Growth is limited to one ovary and the tumor is confined to the inside of the ovary. There is no cancer on the outer surface of the ovary. There are no ascites present containing malignant cells. The capsule is intact.

Stage IB - Growth is limited to both ovaries without any tumor on their outer surfaces. There are no ascites present containing malignant cells. The capsule is intact.

Stage IC - The tumor is classified as either Stage IA or IB and one or more of the following are present: (1) tumor is present on the outer surface of one or both ovaries; (2) the capsule has ruptured; and (3) there are ascites containing malignant cells or with positive peritoneal washings.

Stage II - Growth of the cancer involves one or both ovaries with pelvic extension.

Stage IIA - The cancer has extended to and/or involves the uterus or the fallopian tubes, or both.

Stage IIB - The cancer has extended to other pelvic organs.

Stage IIC - The tumor is classified as either Stage IIA or IIB and one or more of the following are present: (1) tumor is present on the outer surface of one or both ovaries; (2) the capsule has ruptured; and (3) there are ascites containing malignant cells or with positive peritoneal washings.

Stage III - Growth of the cancer involves one or both ovaries, and one or both of the following are present: (1) the cancer has spread beyond the pelvis to the lining of the abdomen; and (2) the cancer has spread to lymph nodes. The tumor is limited to the true pelvis but with histologically proven malignant extension to the small bowel or omentum.

Stage IIIA - During the staging operation, the practitioner can see cancer involving one or both of the ovaries, but no cancer is grossly visible in the abdomen and it has not spread to lymph nodes. However, when biopsies are checked under a microscope, very small deposits of cancer are found in the abdominal peritoneal surfaces.

Stage IIIB - The tumor is in one or both ovaries, and deposits of cancer are present in the abdomen that are large enough for the surgeon to see but not exceeding 2 cm in diameter. The cancer has not spread to the lymph nodes.

Stage IIIC - The tumor is in one or both ovaries, and one or both of the following is present: (1) the cancer has spread to lymph nodes; and/or (2) the deposits of cancer exceed 2 cm in diameter and are found in the abdomen.

Stage IV - This is the most advanced stage of ovarian cancer. Growth of the cancer involves one or both ovaries and distant metastases (spread of the cancer to organs located outside of the peritoneal cavity) have occurred. Finding ovarian cancer cells in pleural fluid (from the cavity which surrounds the lungs) is also evidence of stage IV disease.

In one embodiment the ovarian cancer is: type I, for example IA, IB or IC; type II, for example IIA, IIB or IIC; type III, for example IIIA, IIIB or IIIC; or type IV.

In one embodiment the breast cancer is one selected from the group comprising ductal carcinoma in situ, lobular carcinoma in situ, invasive breast cancer, invasive lobular breast cancer, Paget's disease, angiosarcoma of the breast, medulllary breast cancer, mucinous breast cancer, tubular breast cancer, adenoid cystic carcinoma of the breast, metaplastic breast cancer, lymphoma of the breast, basal type breast cancer, phyllodes or cystosarcoma phyllodes and papillary breast cancer.

In one embodiment the prostate cancer is selected from the group comprising ductal adenocarcinoma, transitional cell (urothelial) cancer, squamous cell cancer, carcinoid, small cell cancer, sarcomas and sarcomatoid cancers.

In one embodiment the prostate cancer is selected from the group comprising ductal adenocarcinoma, transitional cell (urothelial) cancer, squamous cell cancer, carcinoid, small cell cancer, sarcomas and sarcomatoid cancers and a combination of two or more of the same.

Thyroid cancer as employed herein refers to cancer of the thyroid originating from follicular or parafollicular thyroid cells and includes papillary thyroid cancer (75% to 85% of cases); follicular thyroid cancer (10% to 20% of cases); medullary thyroid cancer (5% to 8% of cases)- cancer of the parafollicular cells, often part of multiple endocrine neoplasia type 2; poorly differentiated thyroid cancer; anaplastic thyroid cancer (less than 5% of cases) is not responsive to treatment and can cause pressure symptoms, thyroid lymphoma, squamous cell thyroid carcinoma, sarcoma of thyroid.

Renal cancer as employed herein refers to cancer of the kidney, for example renal cell carcinoma and transitional cell carcinoma of the renal pelvis, such as squamous cell carcinoma, juxtaglomerular cell tumor (reninoma), angiomyolipoma, renal oncocytoma, bellini duct carcinoma, clear-cell sarcoma of the kidney, mesoblastic nephroma, Wilms' tumor, mixed epithelial stromal tumor, clear cell adenocarcinoma, transitional cell carcinoma, inverted papilloma, renal lymphoma, teratoma, carcinosarcoma; carcinoid tumor of the renal pelvis.

Bladder cancer as employed herein refers to cancer of the bladder including transitional cell bladder cancer, carcinoma in situ, papillary cancer and rarer types of bladder cancer such as squamous cell cancer, adenocarcinoma and a combination of two or more of the same.

Esophageal cancer as employed herein refers to cancer of the oesphagus including esophageal squamous-cell carcinomas, esophageal adenocarcinomas, and variants of squamous-cell carcinoma, and non-epithelial tumors, such as leiomyosarcoma, malignant melanoma, rhabdomyosarcoma, lymphoma, among others and a combination of two or more of the same.

Head and neck cancer as employed herein refers to cancer of the neck and/or head, including mouth cancer, nasopharyngeal cancer, oropharyngeal cancer, paranasal sinus cancer, salivary gland cancer and a combination of two or more of the same.

In one embodiment the chemotherapy combination comprises ganciclovir, which may assist in controlling immune responses and/or tumour vasculation.

In the context of this specification "comprising" is to be interpreted as "including".

Aspects of the invention comprising certain elements are also intended to extend to alternative embodiments "consisting" or "consisting essentially" of the relevant elements.

Where technically appropriate, embodiments of the invention may be combined. Embodiments are described herein as comprising certain features/elements. The disclosure also extends to separate embodiments consisting or consisting essentially of said features/elements.

Technical references such as patents and applications are incorporated herein by reference.

Any embodiments specifically and explicitly recited herein may form the basis of a disclaimer either alone or in combination with one or more further embodiments.

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BRIEF DESCRIPTION OF FIGURES

Figure 1 Flow diagram showing process of the CIM-MIMEC method

Figure 2 Schematic diagram showing multimodal cancer treatment according to the present method

EXAMPLES

Example 1 Protocol for treating a cholangiocarcinoma patient.

As a pre-step as much cancerous tissue as possible is removed by surgery. The patient is then given a dose of 300-400mg bidaily of varlitinib together with a chemotoxic agent (eg capecitabine or gemcitabine) for 12-28 days. Following this, AZD5069 is given as a monotherapy or concomitantly with a T-cell stimulator for 4 to 6 weeks. After completing the latter 4, 5 or 6 cycles of chemotherapy comprising gemcitabine and cisplatin are given.

After chemotherapy is complete or concomitantly, treatment with permbrolizumab is given at 2 mg/Kg or 200mg every 3 weeks for 3, 6, 9, 12, 15 or 18 weeks.

The final stage of the therapy is one cycle of antibody drug conjugate, wherein the antibody is specific to Epcam, potentially in combination with an immune-oncology (IO) agent such as pemrolizumab.

Example 2 Protocol for treating a cholangiocarcinoma patient.

As a pre-step as much cancerous tissue as possible is removed by surgery. The patient is then given a dose of 300-400mg bidaily of varlitinib together with a chemotoxic agent (eg capecitabine or gemcitabine) for 12-28 days. Following this AZD5069 is given as a

monotherapy for 4 to 6 weeks. After completing the latter 4, 5 or 6 cycles of chemotherapy comprising 5-FU and leucovorin are given.

After or concomitantly chemotherapy is complete, treatment with permbrolizumab is given at 2 mg/Kg or 200mg every 3 weeks for 3, 6, 9, 12, 15 or 18 weeks.

The final stage of the therapy is one cycle of antibody drug conjugate, wherein the antibody is specific to Epcam, potentially in combination with an IO agent such as pemrolizumab.

Example 3 Protocol for treating a cholangiocarcinoma patient.

As a pre-step as much cancerous tissue as possible is removed by surgery. The patient is then given a dose of 300-400mg bidaily of varlitinib together with a chemotoxic agent (eg capecitabine or gemcitabine) for 12-28 days. Following this AZD5069 is given as a monotherapy for 4 to 6 weeks. After completing the latter 4, 5 or 6 cycles of chemotherapy comprising gemcitabine and cisplatin are given potentially in combination with an IO agent such as pemrolizumab.

After chemotherapy is complete or concomitantly, treatment with permbrolizumab is given at 2 mg/Kg or 200mg every 3 weeks for 3, 6, 9, 12, 15 or 18 weeks.

The final stage of the therapy targeted radiation therapy in combination with a PARP inhibitor, potentially in combination with an IO agent such as pemrolizumab.

Example 4 Protocol for treating a cholangiocarcinoma patient.

As a pre-step as much cancerous tissue as possible is removed by surgery. The patient is then given a dose of 300-400mg bidaily of varlitinib together with a chemotoxic agent (e.g. capecitabine or gemcitabine) for 12-28 days. Following this AZD5069 is given as a monotherapy for 4 to 6 weeks. After completing the latter 4, 5 or 6 cycles of chemotherapy comprising 5-FU and leucovorin are given.

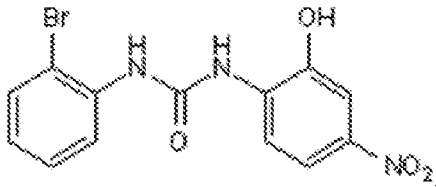
After chemotherapy is complete or concomitantly, treatment with permbrolizumab is given at 2 mg/Kg or 200mg every 3 weeks for 3, 6, 9, 12, 15 or 18 weeks.

The final stage of the therapy targeted radiation therapy in combination with a PARP inhibitor potentially in combination with an IO agent such as pemrolizumab.

In all of these examples, a careful assessment of the immune status of the patient and the presence or absence of circulating tumor material like circulating tumor cells and circulating tumor DNA, is monitored on a weekly basis, and changes in the treatment regimen may be considered based on these findings.

Claims

1. A method of treating cancer comprising the steps;
   a) reducing or stopping cancer proliferation,
   b) debulking tumour mass,
   c) activating immune cells,
   d) increasing antigen presentation and/or enhancing T cell response, and
   e) clear residual tumor cells.
2. A method according to claim 1, which comprises the further step of tumour surveillance.
3. A method according to claim 1 or 2, wherein method comprises a pre-step of surgery.
4. A method according to any one of claims 1 to 3, wherein step **a)** is selected from irradiation, chemotherapy, a CXCR2 antagonist and a combination of two or more the same.
5. A method according to claim 4, wherein the chemotherapy is selected from alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents, such as doxorubicin, 5-fluorouracil (5-FU), paclitaxel, gemcitabine, capecitabine, irinotecan, and platins such as cisplatin and oxaliplatin.
6. A method according to claim 4 or 5, wherein the CXCR2 antagonist is selected from an antibody or binding fragment thereof, MK-7123, SB265610, SB 225002, GSK1325756, AZD5069, and combinations thereof.
7. A method according to any one of claims 1 to 6, further comprising prior to step **a1)** a step of decluttering of immune cells.
8. A method according to claim 7, wherein the decluttering is selected from treatment with a CXCR2 antagonist, an anti-GCF, cyclophosphamide, irradiation and a combination of two or more of the same.
9. A method according to claim 7 or 8, wherein the decluttering is performed by removing specific immune cell populations, for example using medication and/or techniques such as dialysis.
10. A method according to claim 9, wherein the immune cell is selected from a lymphocyte (such as a T cell or NKT cell), a B cell, a natural killer cell, a tumor associated macrophage, and a combination of two or more of the same, in particular a tumor associated macrophage.
11. A method according to any one of claims 4 to 8, wherein the CXCR2 antagonist is selected from an antibody or binding fragment thereof, MK-7123, SB265610, SB 225002:



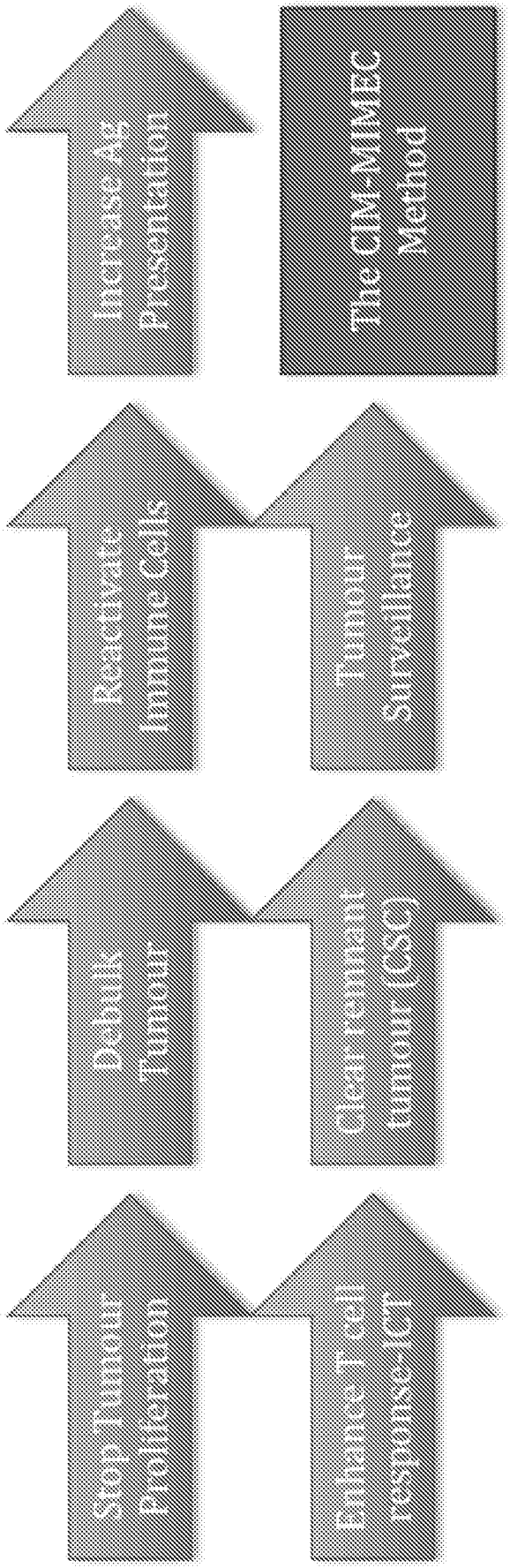
, GSK1325756, AZD5069, SCH-527123 and combinations thereof, in particular SCH-527123.

12. A method according to any one of claims 1 to 11, wherein the debulking in step b) is selected from treatment with an oncolytic virus, an antibody drug conjugate and a combination thereof.
13. A method according to claim 12, wherein the oncolytic virus is a virus selected from an adenovirus, herpes simplex virus, reovirus, measles virus, Newcastle disease virus, Seneca Valley virus, Vesicular stomatitis virus, polio virus, ECHO enterovirus, Coxsackie virus, and vaccinia virus.
14. A method according to claim 13, wherein the oncolytic virus is selected from Enadenotucirev, talimogene laherparepvec, RIGVIR, Ad5-yCD/mutTKSR39rep-hIL12, Cavatak™, CG0070, DNX-2401, G207, HF10, Imlygic®, JX-594, MG1-MA3, MV-NIS, OBP-301, Reolysin®, Toca 511.
15. A method according to claim 13 or 14, where the antibody drug conjugate (ADCC) is selected from the group comprising AGS-15E, AGS-16C3F, AGS-22M6E, AMG-172, AMG-595, ASG-5ME, brentuximab vedotin, DEDN-6526A, DMUC-5754A, gemtuzumab ozogamicin, glembatumumab vedotin, GSK2857916, hRS7-SN-38, IMGN-242, IMGN-289, IMGN-388, IMGN-529, IMGN-633, IMGN-853, Indatuximab, indatuximab ravtansine, Inotuzumab ozogamicin, lorvotuzumab mertansine, MEDI-547, milatuzumab doxorubicin, MLN-0264, MLN-2704, PF-06263507, pinatuzumab vedotin, polatuzumab, PSMA-ADC, RG-7450, RG-7599, SAR-3419, SAR-566658, SC16LD6.6, SGN-15, SGN-19A, SGN-CD33A, SGN-LIV1A, trastuzumab emtansine and combinations thereof.
16. A method according to any one of claims 1 to 15, wherein activating the immune cells in step c) comprises administering a RON inhibitor, an AXL kinase inhibitor, a MER kinase agonist, a cytokine (such as IL-13), a tumour vaccine for example comprising a tumour antigen and adjuvant, a dendritic cell vaccine and a combination of two or more of the same.
17. A method according to claim 16, wherein the RON inhibitor is N-(4-(2-Amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide disclosed in WO 2008/058229.
18. A method according to any one of claims 1 to 17, wherein activating the immune cells in step c) comprises administering a check-point inhibitor.
19. A method according to claim 18, wherein the check-point inhibitor is a PD-1 or PD-L1 inhibitor.
20. A method according to any one of claims 1 to 19, wherein step d) comprises administering a therapy from the group comprising a T cell therapy (for example where T cells are activated *in vitro* to generate CTLs specific to an antigen), a cell therapy comprising engineered chimeric receptors, a PD1 inhibitor, a PD-L1

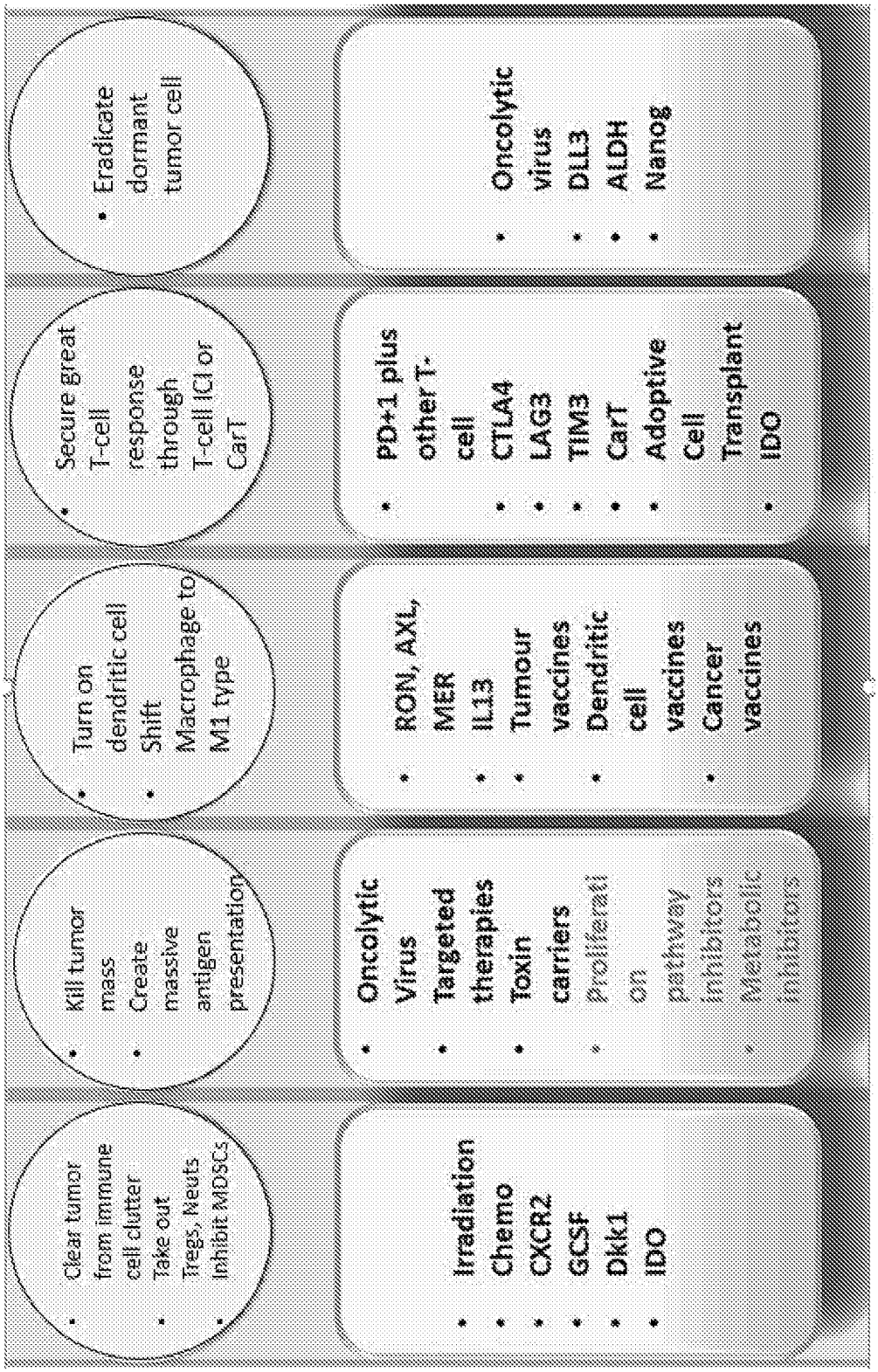
inhibitors, a CTLA4 inhibitor, a LAG3 inhibitor and a combination of two or more of the same.

21. A method according to any one of claims 1 to 20, wherein step e) comprises administering a therapy selected from the group comprising an oncolytic virus, a DLL inhibitor, ADH-1 molecular targeting therapy and combinations of two or more of the same.
22. A method according to claim 21, wherein the oncolytic virus is a virus selected from an adenovirus, herpes simplex virus, reovirus, measles virus, Newcastle disease virus, Seneca Valley virus, Vesicular stomatitis virus, polio virus, ECHO enterovirus, Coxsackie virus, and vaccinia virus.
23. A method according to claim 22, wherein the oncolytic virus is selected from Enadenotucirev, talimogene laherparepvec, RIGVIR, Ad5-yCD/mutTKSR39rep-hIL12, Cavatak™, CG0070, DNX-2401, G207, HF10, Imlygic®, JX-594, MG1-MA3, MV-NIS, OBP-301, Reolysin®, Toca 511.
24. A method according to any one of claims 1 to 23, wherein step e) comprises targeting cancer stem cells.
25. A method according to claim 24, wherein the cancer stem cells are treated with a combination therapy comprising lithium and disulfiram.
26. A method according to any one of claims 1 to 25, wherein the cancer is an epithelial cancer.
27. A method according to claim 26, wherein the epithelial cancer is selected from liver cancer (such as hepatocellular carcinoma), biliary tract cancer, breast cancer (such as non-ER+ breast cancer, in particular double negative breast cancer), prostate cancer, colorectal cancer, ovarian cancer, endometrial cancer, cervical cancer, lung cancer, gastric cancer, pancreatic, bone cancer, bladder cancer, head and neck cancer, thyroid cancer, skin cancer, renal cancer, and oesophagus cancer, for example gastric cancer.
28. A method according to claim 27, wherein the cancer is selected from the group comprising liver cancer (such as hepatocellular carcinoma), breast cancer, biliary duct cancer prostate cancer, colorectal cancer, bladder cancer, ovarian cancer, endometrial cancer, lung cancer, gastric cancer, oesophageal cancer, kidney cancer, head and neck cancers and combinations thereof.

[FIGURE 1 One Embodiment of The CIM-MIMEC Method]



[Figure 2 MultiModal Cancer Treatment According to the Present Method]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2017/050263

A. CLASSIFICATION OF SUBJECT MATTER

See Supplemental Box

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

FAMPAT/CAPLUS/BIOSIS/EMBASE/MEDLINE: irradiation, chemotherapy, CXCR2 antagonist, oncolytic virus, antibody drug conjugate, RON inhibitor, AXL inhibitor, MER agonist, cytokine, tumour vaccine, T cell therapy, chimeric receptor, PD1 inhibitor, PD-L1 inhibitor, CTLA4 inhibitor, LAG3 inhibitor, DLL inhibitor, ADH-1 molecular targeting therapy and similar terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/027915 A1 (BEIJING CONVERD CO., LTD.) 5 March 2015 & US 2016/0250292 A1 Para. [0140]-[0160] of the patent family member	1-28
Y	WO 2010/135242 A1 (EDEN PHARMACEUTICALS, INC.) 25 November 2010 Page 2 lines 6-12; Page 19 lines 8-11; Page 22 lines 5-11; Page 25 line 6-Page 26 line 25	1-28
Y	US 2015/0086541 A1 (AGUILAR-CORDOVA C.E.) 26 March 2015 Para. [0002]-[0004], [0080]-[0100]; Claim 11	1-28
Y	WO 2016/065330 A1 (SZALAY A. AND MINEV B.) 28 April 2016 Para. [0004]-[00014]	1-28

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15/08/2017 *(day/month/year)*	22/08/2017 *(day/month/year)*

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International application No.
PCT/SG2017/050263

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/022138 A2 (YEUNG A.W.H.) 6 February 2014 Page 2 line 14-Page 3 line 24; Examples	1-28
Y	WO 2015/153514 A1 (GENENTECH, INC.) 8 October 2015 Para. [0003], [0471]-[0481]; Claim 91	1-28
Y	WO 2009/083232 A1 (DEUTSCHES KREBSFORSCHUNGSZENTRUM AND RUPRECHT-KARLS-UNIVERSITÄT HEIDELBERG) 9 July 2009 Example 5	1-28
Y	WO 2013/112942 A1 (DNA TRIX, INC. AND MD ANDERSON CANCER CENTER) 1 August 2013 Para. [008], [0173]-[0187]	1-28
Y	WO 2015/061752 A1 (PHARMACYCLICS, INC. AND THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 30 April 2015 Para. [0004], Example 15; Claims 32 and 33	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2017/050263

Supplemental Box
(Classification of Subject Matter)

Int. Cl.
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