**SUPPLEMENTARY INFORMATION**

**Table S1. Immunomodulatory strategies proposed as cancer immunotherapies**.

Immune modulated strategies proposed on clinical trial interventional studies for cancer immunotherapies for breast, lung, colorectal and prostate cancer patients in the last years. In the table, information about the biological target, type of agent, name of pharmaceutical formulation and its effect on immune cell population and its effector functions are described below. These data were obtained from the ClinicalTrials.gov database, according to the following search parameters: (1) Study type: interventional studies, (2) Recruitment status: not stopped studies (i.e. not yet recruiting, recruiting, enrolling by invitation, active not recruiting and completed), (3) Study results: all studies, (4) Study start: from 01/Jan/2010 to 04/Dec/2019.

|  |  |  |  |
| --- | --- | --- | --- |
| **Target** | **Type** | **Formulation name** | **Effects on immune response a** |
| Adenosine A2A receptor | Recombinant protein | AZD4635, AB928, NIR178, CPI-444, PBF-509 | Competes with tumour-released adenosine for binding to A2AR expressed on intra-tumoral immune cells. The binding inhibits regular A2AR/A2BR activation, enhancing immune cells proliferation and activation. |
| B7.1 | MVA, FPV | TRICOM | Co-stimulatory molecules regularly expressed on APC. Introduced in combination with a TAA cancer vaccine may enhance TAA-specific T-cell responses. |
| CCL21 | Tumour cell | GM.CD40L.CCL21 | Chemokine responds by attracting APCs and NK cells and T-cells to induce a cytotoxic immune response. |
| CD137 | Antibody | PF-05082566  Utomilumab | CD137 activation stimulates T cell proliferation and survival. This may result in enhanced immune activation. |
| CD3 | Bispecific antibody, T cell | AMG 160, RO6958688, CYAD-101, NKR-2 cells, EGFRBi armed activated T cell | Co-stimulatory molecule expressed in T cells, it participates in T cell activation. |
| CD39 | Antibody | TTX-030 | CD39 inhibition on tumour microenvironment promotes high extracellular ATP and low extracellular adenosine leading to immune T cell activation. |
| CD40 | Antibody, bispecific antibody, recombinant protein, RNA | Selicrelumab, APX005M, ABBV-927, ABBV-428, SEA-CD40, Trimix | Enhance immune response, triggers activation of APCs and induce T cell effector response. |
| CD40L | Tumour cell | GM.CD40L.CCL21 | Co-stimulatory molecules allow strong cell activation, proliferation and pro-inflammatory cytokine production. |
| SIRP | Fusion protein | TTI-621 | SIRP is usually expressed on macrophages and it is responsible for effector function suppression and inhibition of phagocytosis. Synthetic SIRP binds to CD47 receptors expressed on tumour cells avoiding macrophage suppression. |
| CD70 | RNA | Trimix | Co-stimulatory molecule, binding to CD27 on T cells is responsible for activation and maintenance of T cell effector functions. |
| CD73 | Antibody | NZV930, Oleclumab, MEDI9447 | Allows CD73 internalization and prevents conversion of extracellular AMP to adenosine, then prevents suppression of lymphocyte effector functions. |
| CD80/86 | CAR T cell | - | Co-stimulatory molecules generally expressed on APC and mediate T cell activation. CD80/CD86 CAR T cells produce a transformed receptor which specifically binds the B7 proteins CD80 (B7-1) and CD86 (B7-2). |
| CSF1  (M-CSF) | Antibody | PD 0360324, MCS110 | Prevents the binding to and activation of the M-CSF receptor (M-CSFR) present in macrophages, which is related to immune suppression. |
| CSF1R | Small molecule | JNJ-4034652 | Inhibitory molecule that blocks the interaction of CSF1 with CSF1R, avoiding immune suppression. |
| CTLA4 | Antibody | REGN4659 | Immune checkpoint receptor which mediates immune suppression on T cells. |
| DEC-205 | Fusion protein | CDX-1401 | DEC-205 binds to the endocytic DC receptor, leading to neoantigen internalization to induce specific immune response. |
| FLT3 | Recombinant protein | CDX-301 | Stimulate hematopoietic cells proliferation and migration from the bone marrow, including DC. |
| Furin | Tumour cell expressing shRNA | Vigil | shRNA decreases furin protein production on T cells and inhibits TGFβ gene expression, preventing its immunosuppressive role. |
| G-CSF | Recombinant protein | pegfilgrastim, HM10460A, eflapegrastim | Induce neutrophil proliferation and activation, improvement chemotherapy-induced neutropenia. |
| GM-CSF | Tumour cell, recombinant protein, HSV | GVAX, SV-BR-1-GM, Vigil, Proscavax, 1650-G, GM.CD40L.CCL21 , rhu GM-CSF, Talimogene Laherparepvec, T-Vec | GM-CSF expression induces local migration of granulocytes and monocyte/macrophages, promoting antigen presentation. |
|
| ICAM-1 | MVA, FPV | TRICOM | Co-stimulatory molecules regularly expressed on APC. The interaction with its receptor located in the T cell contributes to enhancing T cell effector response. |
|  |  |  |  |
| IFN 2a/2b | Recombinant protein | - | Mediate activation and proliferation of various immune cells populations, including B cells and monocytes. |
| IL10 | Recombinant protein | Pegilodecakin | Induce differentiation and proliferation of tumour specific CD8+ T cells. |
| IL12 | Plasmid | INO-9012, MEDI0457 | The induced expression of IL-12 by tumour tissues promotes the activation of NK cells. |
| IL13 | Antibody | QBX258 | Cytokine related to allergic inflammatory response, also could stimulate tumour cell proliferation. Antibody prevents tumour progression. |
| IL15/ IL15R | Fusion protein, recombinant protein | ALT-803, N-803 | Super agonist of IL-15R which mediates efficient NK and CD8+ T cell effector functions. Cytokine induces activation of DC, T and NK cells. |
|
| IL17a | Antibody | CJM112 | Prevents inflammation mediated through the pro-inflammatory cytokine IL17, which is usually related to autoimmune diseases. |
| IL1b | Antibody | Canakinumab, ACZ885 | Suppress inflammatory responses mediated by IL-1b, resulting in suppression of inflammation related to autoimmune diseases. |
| IL2 | Recombinant protein, fusion protein, MVA | Proscavax, Aldesleukin, Bempegaldesleukin, NKTR-214, ALKS 4230, Darleukin, RO6874281, TG4010 | Binds to IL2Rb where induce proliferation and activation of effector T cells. PEG conjugation prevents IL-2 binding to the IL2Ra, preventing regulatory T cell activation. |
| IL4 | Antibody | QBX258 | Antibody blocks lymphedema-related cytokines. They work blocking IL-4 produced by T cells with a Th2 profile. |
| IL6R | Antibody | Tocilizumab | Anti-IL6R blocks the interaction of IL-6 to the receptor. This prevents IL-6-mediated signalling related to autoimmune disorders. |
| IL7 | Recombinant protein | - | Induce T and B cell production in hematopoietic organs, aside from to induce proliferation and differentiation of mature NK and T cells. |
| IL8 | Antibody | BMS-986253 | Inhibits IL-8-mediated tumour cell proliferation and reduces inflammation on tumours with IL-8 upregulation, prevents neutrophil recruitment. |
| LAG3 | Antibody, recombinant protein | Relatlimab, TSR-033, LA525, IMP321 | Anti-LAG3 binds to the LAG3 receptor expressed on TILs, which prevents its interaction with MHC class II expressed in tumours and subsequent induction of immune checkpoint inhibition. The soluble version of LAG3 binds to MHC class II expressed on DC inducing the maturation and migration of these cells to lymph nodes to induce T cells activation. |
| LFA-3 | MVA, FPV | TRICOM | Cell adhesion molecules regularly expressed on APC, specifically macrophages. It is important to improve the interaction between T cells and APC. |
| NKG2A | Antibody | Monalizumab, IPH2201 | Inhibits NKG2A activation on NK and CD8+ T cells, to avoid subsequent inhibition of their cytotoxic activities. |
| OX40 | Antibody | PF-04518600, MEDI6469 | Binds to OX40 and induce T cell proliferation and antitumor effector functions. |
| PD1 | Antibody, bispecific antibody, fusion protein | PF-06801591, AB122, PDR001, spartalizumab, SHR-1210, camrelizumab, AK105, toripalimab, JS001, ABBV-181, budigalimab, RO7121661, Sintilimab, TSR-042, dostarlimab, M7824, BGB-A317, tislelizumab | Target PD1 receptor expressed on T cells and prevents the interaction with PDL1/PDL2 and subsequent T cell inactivation. |
| PDL1 | Antibody, fusion protein | MSB0011359C, M7824, TTI-621 | Binds to PD-L1 and avoid its interaction to PD-1 receptors expressed on T cells. This avoids T cell inactivation. |
| S15 | Antibody | NC318 | Targets and binds to S15 on the surface of tumour-associated macrophages with a pro-tumoral profile to disrupt its activity. |
| TGFβRII | Fusion protein | MSB0011359C, M7824 | Neutralizes TGFβ, avoiding its interaction to receptors located in NK and CD8+ T cells which have been related to immune surveillance depression. |
| TIM3 | Bispecific antibody, antibody | RO7121661, TSR-022 | Blocks interaction with its physiological ligand, prevents immune checkpoint T cell suppression and allows T cell effector functions. |
| a Drugs function mined from NCI Drug Dictionary, National Cancer Institute at the National Institutes of Health (www.cancer.gov/publications/dictionaries/cancer-drug/). AMP: adenosine monophosphate, APC: antigen-presenting cells, ATP: adenosine triphosphate, CAR T CELL: chimeric antigen receptor T cells, DC: dendritic cell, FPV: fowlpox virus, HSV: herpes simplex virus, MHC: major histocompatibility complex, MVA: Modified Vaccinia Ankara, NK: natural killer, PEG: Polyethylene glycol, shRNA: short hairpin RNA, TAA: tumour-associated antigens | | | |

**Table S2. Neoantigens proposed as target for cancer immunotherapies**.

Description of neoantigen-based immunotherapeutic vaccines currently studied through clinical interventional trials proposed for breast, lung, colorectal and prostate cancer in the past ten years. In the table, the information about the vaccination strategy, the type of cancer, clinical trial phases and codes are listed below. These data were extracted from ClinicalTrials.gov database, according to the following search parameters: (1) Study type: interventional studies, (2) Recruitment status: not stopped studies (i.e. not yet recruiting, recruiting, enrolling by invitation, active not recruiting and completed), (3) Study results: all studies, (4) Study start: from 01/Jan/2010 to 04/Dec/2019.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NEOANTIGEN | STRATEGY | CANCER TYPE | PHASE | CLINICAL TRIAL CODE |
| 5T4 | Adenovirus | PC | I/II | NCT03815942 |
| MVA | PC | I/II | NCT03815942 |
| RNA | LC | I/II | NCT03164772 |
| Abl-2 | Peptide | BC, PC | I | NCT01095848 |
| ADAM 17 | Peptide | BC, PC | I | NCT01095848 |
| BAP31 | Peptide | BC, PC | I | NCT01095848 |
| Brachyury | Adenovirus | BC | I/II | NCT03387085 |
| BC, PC, LC, CC | I | NCT03384316 |
| FPV | PC | I/II | NCT03493945 |
| MVA | BC, PC, LC | I | NCT02179515 |
| PC | I/II | NCT03493945 |
| S. cerevisiae | BC | I/II | NCT03387085 |
| CD138 | Peptide | BC | I | NCT03362060, NCT02826434 |
| CD38 | Antibody | CC | I/II | NCT03555149 |
| CD40 | Antibody | BC | I/II | NCT03424005 |
| CC | I/II | NCT03555149 |
| LC | I | NCT02376699 |
| I/II | NCT03123783 |
| Bispecific antibody | LC | I | NCT02955251 |
| CEA | Adenovirus | BC | I | NCT03384316 |
| I/II | NCT03387085, NCT01147965 |
| LC, CC | I | NCT03384316 |
| I/II | NCT01147965 |
| PC | I | NCT03384316 |
| Bispecific antibody | LC | I/II | NCT01221675, NCT03337698 |
|
| CAR T cell | BC, CC | I | NCT03682744, NCT02850536, NCT02416466 |
| DNA | LC | III | NCT02654587 |
| MVA | PC | II | NCT03315871 |
| S. cerevisiae | BC | I/II | NCT03387085 |
| VRP | CC | I | NCT01890213 |
| CS1 | Peptide | BC | I | NCT03362060, NCT02826434 |
| DLL3 | CAR T cell | LC | I | NCT03392064 |
| EDDR1 | Peptide | BC, PC | I | NCT01095848 |
| EGFR | Bispecific | CC | I | NCT01420874 |
| EpCAM | CAR T cell | BC | I | NCT02915445 |
| FAP | Fusion protein | BC | I/II | NCT03424005 |
| -catenin | Peptide | BC, PC | I | NCT01095848 |
| Globo H | Carbohydrate | BC | II | NCT01516307 |
| BC, LC, CC | I | NCT02310464 |
| GPC3 | CAR T cell | LC | I | NCT03198546 |
| Her2 | BAT (bispecific armed T cell) | BC | I | NCT03661424 |
| I/II | NCT03272334 |
| II | NCT01147016 |
| Bispecific antibody | BC, LC | I | NCT02892123 |
| CAR T cell | LC | I | NCT03198052 |
| Conjugated antibody | BC, LC, CC | I | NCT03821233 |
| DC | BC | I | NCT02063724, NCT02061423 |
| DNA | LC | III | NCT02654587 |
| Peptide | BC | I | NCT01376505 |
| I/II | NCT00194714 |
| II | NCT02297698, NCT01570036 |
| Plasmid | BC | II | NCT03384914 |
| VRP | BC | I | NCT01526473 |
| II | NCT03632941 |
| HPV genes | HPV vaccine | LC | II | NCT01909752 |
| PC | I | NCT02234921 |
| L. monocytogenes | CC | I/II | NCT02164461 |
| Plasmid | CC | II | NCT03439085 |
| T cell | CC | I/II | NCT02280811 |
| HSV-tk | Adenovirus | BC | I | NCT01997190 |
| LC | I | NCT03131037, NCT01997190 |
| II | NCT02831933 |
| PC | II | NCT02768363 |
| III | NCT01436968 |
| IGF1R | Plasmid | BC | II | NCT03384914 |
| IGFBP2 | Plasmid | BC | II | NCT03384914 |
| Integrin β8 | Peptide | BC, PC | I | NCT01095848 |
| L19 | Antibody | LC | II | NCT03705403 |
| LAG-3 | Antibody | CC | II | NCT02060188 |
| LAGE-1 | T cell | LC | II | NCT03709706 |
| LAMP | DC | LC | I | NCT03371485 |
| Lewis-Y | CAR T cell | LC | I | NCT03198052 |
| LIV1 | Antibody | BC | I/II | NCT03424005 |
| MAGE | Adenovirus | LC | I/II | NCT02879760 |
| DNA | LC | III | NCT02654587 |
| Exosomes | LC | II | NCT01159288 |
| Maraba virus | LC | I/II | NCT02879761 |
| RNA | LC | I/II | NCT03164772 |
| T cell | BC | I/II | NCT02111850 |
| MART-1 | Exosome | LC | II | NCT01159288 |
| Mesothelin | Bispecific antibody | LC | I | NCT02955251 |
| CAR T cell | BC, LC | I | NCT02414269 |
| LC | I | NCT03198052 |
| T cell | BC | I | NCT02792114 |
| MUC1 | Adenovirus | BC | I/II | NCT03387085 |
| BC, PC, LC, CC | I | NCT03384316 |
| CAR T cell | LC | I | NCT03198052 |
| Liposome | LC | II | NCT00828009 |
| MVA | LC | II | NCT03353675 |
| PC | II | NCT03315871 |
| RNA | LC | I/II | NCT03164772 |
| MYB | DNA | CC | I | NCT03287427 |
| NKG2D | CAR T cell | CC | I | NCT03310008 |
| T cell | CC | I | NCT03692429 |
| NY-ESO-1 | Exosome | LC | II | NCT01159288 |
| Fusion protein | BC, PC, LC, CC | I | NCT01522820 |
| Lentivirus | LC | I | NCT02122861 |
| Protein | BC, LC | I | NCT02015416 |
| RNA | LC | I/II | NCT03164772 |
| T cell | BC | II | NCT01967823 |
| LC | II | NCT03709706 |
| P10s (TACA) | Peptide | LC | I/II | NCT02264236 |
| p53 | DC | LC | II | NCT03406715 |
| DNA | LC | III | NCT02654587 |
| Liposome | BC | I | NCT02316457 |
| PADRE | DNA | LC | III | NCT02654587 |
| Peptide | LC | I/II | NCT02264236 |
| PAP | DC | PC | I | NCT02036918 |
| II | NCT01807065, NCT01804465, NCT01818986, NCT02463799, NCT01487863, NCT01431391, NCT01477749 |
| III | NCT03686683 |
| Personalized TAA | Adenoviral | LC, CC | I/II | NCT03639714 |
| CAR T cell | BC | I | NCT03680560 |
| DC | LC | I | NCT03871205 |
| PC | II | NCT02107430, NCT02137746, NCT02107404, NCT02107391, NCT02105675 |
| DNA | PC | I | NCT03532217 |
| DRibble | LC | I | NCT03057340 |
| II | NCT01909752 |
| PC | I | NCT02234921 |
| L. monocytogenes | CC | I | NCT03189030 |
| Liposome | BC | I | NCT02316457 |
| Peptide | CC | I/II | NCT03391232 |
| LC | I | NCT03380871, NCT02897765 |
| I/II | NCT03633110 |
| Plasmid | LC | I/II | NCT03548467 |
| RNA | BC, LC, CC | I | NCT03289962 |
| LC, CC | I/II | NCT03639714 |
| T cell | BC, LC | II | NCT03412877 |
| LC | I | NCT03778814, NCT03247309, NCT02876510 |
| Tumour cells | BC | II | NCT03572361 |
| Yeast vaccine | BC, LC, CC | I | NCT03552718 |
| Phosphatidylserine | Antibody | LC | II | NCT01138163, NCT01160601 |
| PRAME | Protein | LC | II | NCT01853878 |
| PSA | MVA FPV | PC | I | NCT03532217 |
| I/II | NCT02933255 |
| II | NCT03315871, NCT02649439, NCT03579654, NCT01867333, NCT01875250, NCT02649855 |
| III | NCT01322490 |
| PSCA | CAR T cell | LC | I | NCT03198052 |
| PSMA | Bispecific antibody | PC | I | NCT03792841 |
| Ras | S. cerevisiae | BC | I/II | NCT03387085 |
| T cell | CC | I/II | NCT03190941 |
| ROR1 | CAR T cell | BC, LC | I | NCT02706392 |
| SEMA4D | Antibody | LC | I | NCT03373188 |
| I/II | NCT03268057 |
| Survivin | Peptide | LC | II | NCT03836352 |
| RNA | LC | I/II | NCT03164772 |
| TERT | DC | LC | I | NCT03371485 |
| DNA | BC, LC, CC | I | NCT02960594 |
| Peptide | LC | I/II | NCT02818426 |
| Plasmid | BC, LC, CC | I | NCT02960594 |
| Topoisomerase IIα | Peptide | BC, PC | I | NCT01095848 |
| WT1 | T cell | LC | I/II | NCT02408016 |
| XBP1 | Peptide | BC | I | NCT03362060, NCT02826434 |
| Abbreviations: BAT: bispecific armed T cell, BC: breast cancer, CAR T cell: Chimeric antigen receptor T cells, CC: colorectal cancer, DC: dendritic cell, DNA: deoxyribonucleic acid, DRibble: Tumour-derived autophagosome vaccines, FPV: fowlpox virus, HPV: Human papillomavirus, LC: lung cancer, L. monocytogenes: Listeria monocytogenes, MVA: Modified Vaccinia Ankara, PC: prostate cancer, RNA: ribonucleic acid, S. cerevisiae: Saccharomyces cerevisiae, VRP: virus replicon particle. | | | | |