

Therapeutic advantage of combinatorial CAR T cell and chemo-therapies

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Supplementary Table 1: Expanded list of preclinical CAR T and chemotherapy studies including relevant mechanisms of action

Drug (s)		FDA Appr. (Y/N)	Drug Description	CAR Target (s)	Tumor Model (s)	CAR Limitation (s) Addressed	Relevant Biological Mechanism(s)	PMID
1	All trans retanoic acid (tretinoin)	Yes	Vitamin A Derived Retinoid	BCMA	Multiple Myeloma	Antigen Dilema	Enhanced antigen expression on primary myeloma cells	36722406
2	All trans retanoic acid (tretinoin)	Yes	Vitamin A Derived Retinoid	CD38	Multiple Myeloma	Antigen Dilema	Upregulated antigen expression on tumor cells which potentiated CAR T cell killing	36918219
3	Azacitidine	Yes	Hypomehylating Agent	CD70	Acute Myeloid Leukemia	Antigen Dilema	Increased antigen expression on tumor cells in a high tumor burden bearing model	35452603
4	Bryostatin-1	Yes	modulate Protein Kinase C	CD22	Leukemias and lymphomas	Antigen Dilema	Upregulated CD22 on different leukemia and lymphoma cells which improved CAR T cell functionality and in vivo persistence	31110075
5	Bryostatin-1	Yes	modulate Protein Kinase C	CD22	B-ALL	Antigen Dilema	Increased cytolysis through enhanced antigen expression on cancer cell lines while sparing normal cells	35222407
6	Cisplatin	Yes	Alkylating Agent	CD133	Gastric Cancer	Antigen Dilema	Pretreatment of tumor cells with drug improved tumor cell killing by CAR T cells	33635343
7	Crenolanib	Yes	Kinase Inhibitor	FLT3	Acute Myeloid Leukemia	Antigen Dilema	Upregulated antigen expression leading to increased CAR T cell mediated killing	29472720
8	Cyclophosphamide	Yes	Lymphodepleting Agent	NKG2D ligands	Off-Target Study Only	Antigen Dilema	Upregulated NKG2D ligands which improved cytotoxicity of CAR T cells	26122933

9	Decitabine	Yes	Hypomethylating Agent	CSPG4	Ovarian Cancer	Antigen Dilema	Mediated a dose dependent increase in CSPG4 on antigen negative cells enhancing recognition by CAR T cells	36291817
10	Decitabine	Yes	Hypomethylating Agent	CD19	Lymphoblastoma	Antigen Dilema	Increased antigen expression on tumor cells improving CAR T cell mediated killing	31372000
11	Decitabine and Chidamide	Yes	Hypomethylating Agent and HDAC Inhibitor	nanobodyCD70	Acute Myeloid Leukemia	Antigen Dilema	Combinatorial treatment enhanced the expression of CD70 on AML cells which facilitated greater cytotoxic activity of CAR T cell	36932256
12	Gemcitabine	Yes	Antimetabolite	GRP78	Pancreatic Cancer	Antigen Dilema	Increased surface antigen expression leading to increased tumor killing by CAR T cells	37897831
13	Ingenol-3-angelate	Yes	Protein Kinase C Agonist	B7-H3	Osteosarcoma	Antigen Dilema	Increased surface expression of B7-H3 via PKC activation	38561833
14	Lenalidomide	Yes	Immunomodulatory Agent	MUC1	Multiple Myeloma	Antigen Dilema	Increased antigen expression on tumor cells improving CAR T cell mediated killing	35840578
15	Lorlatinib	Yes	Broad Kinase Inhibitor	CD19, GD2, ALK	Leukemia, Neuroblastoma	Antigen Dilema	Increased antigen expression on low antigen density cells potentiating CAR T cell effector function	38039964
16	ABT-737	No	Bcl-2 Inhibitor	CD19	B Cell Malignancy	Tumor Burden	Increased tumor cell apoptosis	23788110
17	Azacitidine	Yes	Hypomethylating Agent	CEA	Colorectal Cancer	Tumor Burden	Increased antigen expression on tumor cells and improved cytotoxic effect of CAR T cells which may be of resistant to other chemotherapy resistant models	30075754
18	Celecoxib	Yes	COX2 Inhibitor	CD19	B Cell Malignancy	Tumor Burden	Partially reversed CAR T cell resistance of tumor cell lines	29904021

19	Dabrafenib	Yes	MAPK Inhibitor	GD2	Melanoma	Tumor Burden	Used in the clinic to treat melanoma, need to see if can be used in combination but little impact on CAR T cell function individually	25415284
20	Decitabine	Yes	Hypomethylating Agent	EGFR, CD44v6	Bladder cancer	Tumor Burden	Differential regulated the expression of cell survival and apoptosis factors skewing the balance towards more apoptosis sensitivity which enhanced CAR T cell killing	34868059
21	Fluorouracil	Yes	Anti-Metabolite	CEA	Colorectal Cancer	Tumor Burden	Increased antigen expression on tumor cells but negatively influenced the viability of the CAR T cells	30075754
22	Indometacin	Yes	NSAID	CD19	B Cell Lymphoma	Tumor Burden	Sensitized tumor cells to CAR T cells by inducing oxidative stress which led to increased death receptor surface expression	35882449
23	Paclitaxel	Yes	Anti-Microtubule Agent	T4	Epithelial Ovarian Cancer	Tumor Burden	Induced tumor cell apoptosis and promoted cell cycle arrest offering additive benefit to CAR T cell therapy	30167862
24	Rimiducid	Yes	Dimerizing Agent	IL-1RAP	Acute Myeloid Leukemia	Tumor Burden	Eliminated tumor cells that were resistant to CAR T cell therapy whose resistance was driven by epitope masking	33414517
25	Sodium Butyrate	No	HDAC Inhibitor	CEA	Colorectal Cancer	Tumor Burden	Increased antigen expression on tumor cells and improved cytotoxic effect of CAR T cells which may be of resistant to other chemotherapy resistant models	30075754
26	THZ1	No	Broad Kinase Inhibitor	EGFR	Triple Negative Breast Cancer	Tumor Burden	Overcame tumor acquired CAR T cell resistance through transcriptional reprogramming preventing further resistance, tumor growth, and metastasis	33875483

27	Trametinib	Yes	MEK Inhibitor	GD2	Melanoma	Tumor Burden	Used in the clinic to treat melanoma, need to see if can be used in combination but little impact on CAR T cell function individually	25415284
28	Vemurafenib	Yes	MAPK Inhibitor	GD2	Melanoma	Tumor Burden	Used in the clinic to treat melanoma, need to see if can be used in combination but compound did impair CAR T cells at plasma relevant concentrations	25415284
29	Zanubrutinib	Yes	Src Kinase Inhibitor	CD19	Lymphoblastoma	Tumor Burden	Induced dose dependent toxicity on tumor cells and CAR T cells	36254554
30	DMXAA	No	STING Agonist	Neu	Breast Cancer	Infiltration	Improved infiltration of traditional Th1 type CAR T cells but more significantly synergized with Th/Tc17 CAR T cell phenotypes	33382402
31	Docetaxel	Yes	Anti-Neoplastic Agent	HER-2	Non-Small Cell Lung Cancer	Infiltration	Increased the recruitment and infiltrative capacity of CAR T cells through a potential CXCL11 mechanism	30744691
32	Rapamycin	Yes	mTOR Inhibitor	EpCAM	Acute Myeloid Leukemia	Infiltration	Improved the capacity of CAR T cells to infiltrate into the bone marrow by modulating mTOR target CXCR4	34233960
33	All trans retanoic acid (tretinoin)	Yes	Vitamin A Derived Retinoid	FGFR4	Rhabdomyosarcoma	Immune Microenvironment	Targets myeloid derived suppressor cells	35877472
34	BLZ945	No	CSF1R Inhibitor	B7-H3	Glioma	Immune Microenvironment	Depleted tumor associated macrophages but was actually detrimental to CAR T cell efficacy	37971169
35	Carboplatin	Yes	Alkylating Agent	Lewis Y antigen (LeY)	Prosate cancer	Immune Microenvironment	Improved the efficacy of CAR T cell treatment but the response was dependent on the changes induced by the tumor microenvironment	37660083

36	Cyclophosphamide	Yes	Lymphodepleting Agent	CD19	Raji tumors	Immune Microenvironment	Depleted tumor associated Tregs	21487038
37	Cyclophosphamide	Yes	Lymphodepleting Agent	CD19	Raji tumors	Immune Microenvironment	Contributed to tumor clearance in combination with CAR T cells	18477047
38	Cyclophosphamide	Yes	Lymphodepleting Agent	CEA	Colon Cancer, Breast Cancer	Immune Microenvironment	Aided in tumor clearance of initially established tumors and helped induce tumor immunity in re-challenged settings	33796409
39	Cyclophosphamide	Yes	Lymphodepleting Agent	PSCA	Prostate, Pancreatic	Immune Microenvironment	Dampened immunosuppressive microenvironment and supported pro-inflammatory microenvironment	33647456
40	Cyclophosphamide and Fludarabine	Yes	Lymphodepleting Agent	CD19	B Cell Leukemia	Immune Microenvironment	Downregulated IDO expression	25940712
41	Cyclophosphamide and Fludarabine	Yes	Lymphodepleting Agent	B7-H3	Canine Sarcoma	Immune Microenvironment	Demonstrated efficacy of CAR T cells in canine sarcoma with cyclophosphamide and fludarabine successfully used as lymphodepleting agents	35405743
42	Docetaxel	Yes	Anti-Neoplastic Agent	PSMA	Prostate Cancer	Immune Microenvironment	Improved cytotoxic effect of CAR T cells by diminishing the frequency and immunosuppressive capacity of MDSCs	35962287
43	Epacadostat	Yes	IDO1 Inhibitor	FGFR4	Rhabdomyosarcoma	Immune Microenvironment	Prompted the successful clearance of RMS tumors using a polypharmacy approach	35877472
44	Epacadostat	Yes	IDO-1 Inhibitor	MSLN	Esophageal Squamous Cell Carcinoma	Immune Microenvironment	Prevented the accumulation of the immunosuppressive metabolite, kynurenine, which enhanced cytotoxic potential	33828565
45	L-NAME	No	iNOS Inhibitor	FGFR4	Rhabdomyosarcoma	Immune Microenvironment	Prompted the successful clearance of RMS tumors using a polypharmacy approach	35877472

46	Oxamate	No	Lactate Dehydrogenase A Inhibitor	EGFRvIII	Glioblastoma	Immune Microenvironment	Modulated the immunosuppressive microenvironment by reducing promoter activity of Treg populations and restraining chemokine activity in macrophages	37770937
47	Pexidartinib	Yes	CSF1R Inhibitor	FGFR4	Rhabdomyosarcoma	Immune Microenvironment	targets M2 like TAMs	35877472
48	PI-3065	No	PI3K Inhibitor	ROR1, EGFRvIII	Breast	Immune Microenvironment	Nanoparticle loaded sheets improved CAR T cell effector function through remodeling of the immune microenvironment	29760047
49	SD-208	No	TGF β Inhibitor	FGFR4	Rhabdomyosarcoma	Immune Microenvironment	Protected CAR T cells from inhibitory effect of TGF- β and reduced PD-1 expression within a polypharmacy approach	36722406
50	SD-208	No	TGF β Inhibitor	ROR1	Triple-Negative Breast Cancer	Immune Microenvironment	Protected CAR T cells from inhibitory effect of TGF- β and reduced PD-1 expression within a polypharmacy approach	32303620
51	7DW8-5	No	Immunostimulatory Glycolipid	ROR1, EGFRvIII	Breast	Immune Microenvironment	Nanoparticle loaded sheets improved CAR T cell effector function through remodeling of the immune microenvironment	29760047
52	Acalabrutinib	Yes	Src Kinase Inhibitor	CD19	Lymphoblastoma	Fitness	Improved in vitro persistence and in vivo tumor clearance,	31899702
53	AKT Inhibitor VIII	No	PI3K Inhibitor	CD19	B cell leukemia	Fitness	Minimized differentiation of CAR T cells through induced regulation of the FOXO1 transcription factor	29212954
54	Carboplatin	Yes	Alkylating Agent	ErbB	Epithelial ovarian cancer	Fitness	Tumor pre-treatment with noncytotoxic doses of carboplatin sensitized EOC tumors to CAR T cells resulting in better disease regression while using lower doses of CAR T cells	23898037

55	Carboplatin	Yes	Alkylating Agent	EGFR	Breast cancer (TNBC; MDA-MDB-468 cells)	Fitness	Improved CAR T cell cytotoxic activity in vitro	35813488
56	Celecoxib and aspirin	Yes	COX1/2 Inhibitors	CD19	B Cell Lymphoma	Fitness	COX inhibition induced tumor cell apoptosis but impaired quality of CAR T cells	34122428
57	Dasatinib	Yes	Src Kinase Inhibitor	GD2	B Lymphoid Leukemia	Fitness	Promoted memory phenotype, decreased exhaustion markers, and increased effector cytokine production	33795428
58	Dasatinib	Yes	Src Kinase Inhibitor	GRP78	Acute Myeloid Leukemia	Fitness	Prevented CAR T cell antigen mediated differentiation which improved cytotoxicity	35102167
59	Dasatinib	Yes	Src Kinase Inhibitor	CD19	B Lymphoid Leukemia	Fitness	Served as a safety switch for CAR T cell by limiting cytotoxicity, cytokine secretion, and proliferation	30814055
60	Dasatinib	Yes	Src Kinase Inhibitor	CD19	Lymphoblastoma	Fitness	Paused CAR T cell intracellular signaling transduction by interfering with upstream kinase activity	31270272
61	Dasatinib	Yes	Src Kinase Inhibitor	CD19	B Lymphoid Leukemia	Fitness	Decreased exhaustion, differentiation and apoptosis related gene signatures	34289897
62	Dasatinib and Ibrutinib	Yes	Src Kinase Inhibitor	CD7	T cell Leukemia	Fitness	Minimized tonic signaling induced fratricide on the CAR T cell and improved persistence and tumor control	36086817
63	Decitabine	Yes	Hypomethylating Agent	CD19	Lymphoblastoma	Fitness	Enhanced memory phenotype, proliferation, and cytokine production of CAR T cells while also mitigating exhaustion	33462245

64	Decitabine	Yes	Hypomethylating Agent	CD123	Leukemia	Fitness	Epigenetically reprogrammed CAR T cells which decreased methyltransferase expression leading to decreased exhaustion markers and enhanced memory phenotype	32973749
65	Dexamethasone	Yes	Anti-Inflammatory Synthetic Glucocorticoid	IL13Ra2	Glioblastoma	Fitness	Identified threshold that which dexamethasone is harmful for CAR T cells	35081104
66	Dexamethasone	Yes	Anti-Inflammatory Synthetic Glucocorticoid	IL13Ra2	Glioblastoma	Fitness	Dex is commonly used in GBM treatment, low doses do not impact CAR T cell functionality - but do not necessarily help either	29103912
67	Dexamethasone	Yes	Anti-Inflammatory Synthetic Glucocorticoid	CD19, CS-1, TAG-72	ALL, Multiple Myeloma, Ovarian Cancer	Fitness	Dex increases IL-7 receptor expression on CAR T cells, further combination with IL-7 enhanced anti-tumor activity	38140726
68	Dexamethasone and methylprednisone	Yes	Anti-Inflammatory Synthetic Glucocorticoid	CD19, MSLN	Leukemia	Fitness	Exposure to GCs impairs CAR T cell activity but is reversed when GCs are removed, Important when GCs are used to control CRS but cytotoxicity is still desired	38475830
69	Docetaxel	Yes	Anti-Neoplastic Agent	PSMA	Prostate Cancer	Fitness	Combinatorial treatment proved to have additive effect at killing antigen positive tumor cells	32728611
70	Enasidenib	Yes	IDH2 Inhibitor	CD19	Leukemia, Osteosarcoma	Fitness	Enhances persistence, expansion, and memory CAR T cell formation through enhanced glycolytic activity and reduced reactive oxygen species formation	38171332
71	Ibrutinib	Yes	Src Kinase Inhibitor	CD19	Chronic Lymphocytic Leukemia	Fitness	Increased CAR T cell viability and expansion while decreasing differentiation and exhaustion markers and improving cytokine release	32683672

72	Ibrutinib	Yes	Src Kinase Inhibitor	CD19	Lymphoblastoma	Fitness	Decreased exhaustion marker and displayed better combined tumor control when added to CAR T cells	32876369
73	Ibrutinib	Yes	Src Kinase Inhibitor	CD19	Mantle Cell Lymphoma	Fitness	Enhanced CAR T cell killing and improved long term remission of mice and exhaustion markers in vivo	26819453
74	Ibrutinib	Yes	Src Kinase Inhibitor	CD19	Chronic Lymphocytic Leukemia	Fitness	Improves CAR T cell engraftment supporting greater tumor clearance	26813675
75	Ibrutinib	Yes	Src Kinase Inhibitor	CD19	Lymphoblastoma	Fitness	Improved in vitro persistence, in vivo tumor clearance, and promoted a memory phenotype.	31899702
76	Idelalisib	Yes	PI3K Inhibitor	CD19	Chronic Lymphocytic Leukemia	Fitness	Enriched the naive T CAR T cell fraction, increased lymph node homing markers, and decreased exhaustion marker expression	30737788
77	IPI-145,CAL-101, or TGR-1202	No	PI3K Inhibitor	MSLN	Melanoma	Fitness	Dual blockade of the gamma and delta subunits of PI3K impaired cell function but individual use with either inhibitor improved anti-tumor function	32383488
78	JQ1	No	BET Bromodomain Inhibitor	EGFR	Glioblastoma	Fitness	Suppressed the transcriptional expression of CAR T cell induced immunosuppressive genes supporting cytotoxic targeting of tumor cells	34058385
79	JQ1	No	BET Bromodomain Inhibitor	CD19	Chronic Lymphocytic Leukemia	Fitness	Reinvigorated exhausted CAR T cells through increased CAR expansion, proliferation, and metabolic fitness	34396987
80	Lenalidomide	Yes	Immunomodulatory Agent	CD133, HER2	Glioblastoma, Breast Cancer	Fitness	Increased CAR T effector function (proliferation, cytokine secretion, and killing) through drug regulated degradation of T cell essential transcription factors	32967454

81	Lenalidomide	Yes	Immunomodulatory Agent	CD19, BCMA	Lymphoblastoma	Fitness	Drug regulated degradable IL-7 system that enhanced CAR T cell expansion, memory status, and persistence and antitumor activity of CAR T cells	38123696
82	Lenalidomide	Yes	Immunomodulatory Agent	NKG2D	Colorectal Cancer	Fitness	Improved in vitro cytotoxicity and effector cytokine production	37790973
83	Lenalidomide	Yes	Immunomodulatory Agent	CD23	Chronic Lymphocytic Leukemia	Fitness	Improved CAR T cell migration and preserved the functionality of CAR T cell immune synapse improving effector function	35259043
84	Lenalidomide	Yes	Immunomodulatory Agent	CD19	Lymphoblastoma	Fitness	Served as an "ON" and "OFF" supporting the activation or degradation of CAR T cells which improved antitumor activity while limiting inflammatory cytokine release	33408186
85	Lenalidomide	Yes	Immunomodulatory Agent	CD19	Lymphoblastic Leukemia	Fitness	Controlled effector function of degranulated CAR T cells to better regulate activity and minimize off-target toxicities	33333026
86	Lenalidomide	Yes	Immunomodulatory Agent	BCMA	Multiple Myeloma	Fitness	Enhanced cytokine production, cytolytic activity, activation, and decreased exhaustion markers improving in vivo tumor clearance	31395689
87	Lenalidomide	Yes	Immunomodulatory Agent	CS1	Multiple Myeloma	Fitness	Supported increased cytotoxicity and persistence in vivo with improved memory phenotype, Th1 cytokine production, and immune synapse formation	29061640
88	LY294002	No	PI3K Inhibitor	NKG2D	Breast Cancer, Lung Cancer	Fitness	Supported CAR T cell survival and prevented exhaustion by upregulating anti-apoptotic proteins	35965586
89	LY294002	No	PI3K Inhibitor	NKG2D	Chronic Myeloid Leukemia, Pancreatic Cancer	Fitness	Decreased antigen expression on activated CAR T cells diminishing fratricidal cell death	30619300

90	LY294002	No	PI3K Inhibitor	CD33	Acute Myeloid Leukemia	Fitness	Improved persistence by mediating a less differentiated state and decreasing tonic CAR T cell signaling	29479065
91	Metformin	Yes	Antihyperglycemic	CD19	Lymphoma	Fitness	Suppressed the AMPK pathway which negatively influenced proliferation and cytotoxicity of CAR T cells	29662316
92	Paclitaxel	Yes	Anti-Microtubule Agent	ICAM-1	Gastric Cancer	Fitness	Enhanced anti-tumor activity of CAR T cells in vivo	32995483
93	Rapamycin	Yes	mTOR Inhibitor	CD123,HER2, CD33	Acute Myeloid Leukemia	Fitness	Used as a pro-apoptotic compound that allowed for in vivo clearance control of CAR cells to better mitigate off target toxicities	32384544
94	Rapamycin	Yes	mTOR Inhibitor	BCMA,CD123 (Natural Killer Cells)	Acute Myeloid Leukemia	Fitness	Used as a safety switch to regulate the elimination of expanded effector cells	32384544
95	Rapamycin	Yes	mTOR Inhibitor	IL-1RAP	Acute Myeloid Leukemia	Fitness	Used as a safety switch to regulate the elimination of expanded effector cells	37173386
96	Rapamycin	Yes	mTOR Inhibitor	CD19,BCMA	Lymphoma	Fitness	Allowed for selective activation of CAR T cells only in the presence of both the antigen and the dimerizing compound	31039141
97	Rapamycin	Yes	mTOR Inhibitor	CD19	Lymphoblastoma	Fitness	Promoted a less differentiated, stem cell like memory phenotype	30890531
98	Rapamycin	Yes	mTOR Inhibitor	CD19	Lymphoblastoma	Fitness	Utilized rapamycin as a caspase regulating compound to initiate CAR T cell suicide and minimize toxicity	29661681
99	Regorafenib	Yes	Broad Kinase Inhibitor	EpCAM (Natural Killer Cell)	Colorectal Cancer	Fitness	Supported greater in vivo tumor control through enhanced persistence	30410941
100	Rimiducid	Yes	Dimerizing Agent	SLAMF7	Multiple Myeloma	Fitness	Performed as a suicide switch on CAR T cells to better control off target toxicities to antigen containing leukocytes	30740516

101	Rimiducid	Yes	Dimerizing Agent	CD123,HER2, CD33	Acute Myeloid Leukemia	Fitness	Used as a pro-stimulatory compound that enhanced CAR T cell proliferation, cytokine secretion, and cytotoxicity	30740516
102	Ruxolitinib	Yes	Janus Kinase Inhibitor	CD19	Lymphoblastoma	Fitness	Inhibited proliferation without damaging viability or effector function of the CAR T cells which helped mitigate cytokine release syndrome related toxicities	35101664
103	SCH-58261	No	A2a Receptor Inhibitor	CD19	Leukemia	Fitness	CAR T cells were loaded with vesicles carrying SCH supporting higher CAR T cell engraftment and enhanced functionality	29720380
104	SCH-58261	No	A2a Receptor Inhibitor	MSLN	Ovarian Adenocarcinoma	Fitness	Adenosine signaling was exogenously activated and co-incubation with SCH reversed loss of CAR T cell effector function and cytokine secretion	32151275
105	Temozolomide	Yes	Alkylating Agent	EGFRvIII	Glioblastoma	Fitness	Served as a lymphodepleting agent prior to CAR delivery which improved the abundance and persistence of cells	29872570
106	THZ1	No	Broad Kinase Inhibitor	CD19	Lymphoma	Fitness	Protecte against cytokine release syndrome associated toxicities by diminishing polymerase mediated transcriptional activity	33397398
107	Trametinib	Yes	MEK Inhibitor	GD2	Neuroblastoma	Fitness	Enhanced in vitro tumor cell killing while sparing exhaustion and promoting expansion	34382720
108	Azacitidine	Yes	Hypomehylating Agent	CD123	Acute Myeloid Leukemia	Antigen Dilemma, Fitness	Upregulated antigen expression and induced clonal outgrowth of exhaustion marker negative, CAR positive T cells that had increased killing potency	34750374

109	Decitabine	Yes	Hypomethylating Agent	NY-ESO-1	Breast Cancer, Multiple Myeloma	Antigen Dilemma, Fitness	Upregulated antigen expression on tumor cells leading to increased killing which also correlated with higher interferon gamma production	26447882
110	S63845	No	Mcl-1 Inhibitor	CD19	B-cell Malignancies	Antigen Dilemma/ Tumor Burden	Increased CD19 expression and induced tumor cell apoptosis	33362794
111	Venetoclax	yes	Bcl-2 Inhibitor	CD19	B-cell Malignancies	Antigen Dilemma/ Tumor Burden	Increased CD19 expression and induced tumor cell apoptosis where one out of three delivery methods tested was able to prevent CAR T cell damage	33362794
112	Venetoclax	yes	Bcl-2 Inhibitor	CD19	Multiple Lymphoma Models	Antigen Dilemma/ Tumor Burden	Overexpressed Bcl2(F104L) to protect CAR T cell from venetoclax toxicities	35904479
113	Cisplatin	Yes	Alkylating Agent	HER2	Lung Cancer	Fitness, Infiltration	Cisplatin-loaded CAR T cells (via membrane coated polymeric nanoparticles) resulted in better anti-tumor response and homing.	38282968
114	Lenalidomide	Yes	Immunomodulatory Agent	CD19	B Cell Lymphoma	Fitness, Infiltration	Polarized CD8+ cells to less differentiated state, increased expansion, suppressed VEGF production supporting infiltration, and minimized exhaustion	37219767
115	Lenalidomide	Yes	Immunomodulatory Agent	Wilms Tumor 1	Chronic Myelogenous Leukemia	Fitness, Infiltration	Increased infiltration of both CD3/8+ T cells and improves anti-tumor activity	34674611
116	Lenalidomide	Yes	Immunomodulatory Agent	CD19,CD20	B-cell non-Hodgkin Lymphoma	Fitness, Infiltration	Increased interferon gamma production and infiltration of CAR positive cells which supported greater anti-tumor activity	27141398
117	Lenalidomide	Yes	Immunomodulatory Agent	EGFRvIII	Glioblastoma	Fitness, Infiltration	Improved interferon gamma production, migration of CAR T cells to tumor site, and enhanced immune synapse formation improving tumor control	26450624

118	Sorafenib	Yes	Broad Kinase Inhibitor	GPC3	Hepatocellular Cancer	Immune Microenvironment, Tumor Burden	Promoted IL-12 secretion in tumor associated macrophages and induced tumor cell apoptosis	31078430
119	Oxaliplatin (with cyclophosphamide)	Yes	Alkylating Agent	ROR1	Lung Cancer	Infiltration, Immune Microenvironment	Improves CAR-T cell-mediated tumor control and survival when combined with cyclophosphamide by activating tumor macrophages to express T-cell-recruiting chemokines, resulting in improved CAR-T cell infiltration, remodeling of the tumor microenvironment, and increased tumor sensitivity to anti-PD-L1	33357452
120	Azacitidine	Yes	Hypomethylating Agent	CD44v6	Acute Myeloid Leukemia	Tumor Burden, Fitness	Increased the activation, persistence, and promoted a memory phenotype of CAR T cells while also inducing tumor cell apoptosis	37180104
121	Decitabine	Yes	Hypomethylating Agent	CD44v6	Acute Myeloid Leukemia	Tumor Burden, Fitness	Increased the activation, persistence, and promoted a memory phenotype of CAR T cells while also inducing tumor cell apoptosis (more profound than azacitidine)	37180104
122	Eltanexor	No	XPO-1 Inhibitor	CD19	Lymphoma, Acute Myeloid Leukemia	Tumor Burden, Fitness	Pretreatment of tumor cells with inhibitor sensitized them to CAR T cell therapy by decreasing tumor cell viability and mitigating exhaustion	34165175
123	Ibrutinib	Yes	Src Kinase Inhibitor	CD19	Lymphoblastoma	Tumor Burden, Fitness	Induced dose dependent toxicity on tumor cells and CAR T cells but decreased exhaustion markers and had better anti-tumor effect	36254554

124	JQ1	No	BET Bromodomain Inhibitor	CD19,CD123	Acute Myeloid Leukemia	Tumor Burden, Fitness	Decreased immunosuppressive ligand on tumor cells and their respective receptors on CAR T cells supporting anti-tumor activity	36038554
125	Linsitinib	Yes	IGF1R/IR Inhibitor	GD2	Diffuse Midline Glioma	Tumor Burden, Fitness	Induced tumor cell apoptosis while not affecting CAR T cell viability and increased memory phenotype expression as well as decreased exhaustion markers	34964902
126	Metformin	Yes	Antihyperglycemic	CEA	Gastric Cancer	Tumor Burden, Fitness	Blocked tumor specific aerobic glycolysis while upregulating CAR T cell oxidative phosphorylation and energy metabolism	36827893
127	Rapamycin	Yes	mTOR Inhibitor	CD19	B cell Lymphoma	Tumor Burden, Fitness,	Inhibited tumor specific immune evasion and anti-apoptic mechanisms while working in tandem with engineered rapamycin resistant CAR T cells	21878902
128	Selinexor	Yes	XPO-1 Inhibitor	CD19	Lymphoma, Acute Myeloid Leukemia	Tumor Burden, Fitness	Pretreatment of tumor cells with inhibitor sensitized them to CAR T cell therapy by decreasing tumor cell viability and mitigating exhaustion	34165175
129	JK184	No	Hedgehog Inhibitor	B7-H3	Breast Cancer	Tumor Burden, Infiltration	Promoted tumor cell apoptosis and CAR T cell trafficking and infiltration to the tumor site which corresponded to increased inflammatory cytokine production	36635683
130	Sunitinib	Yes	Broad Kinase Inhibitor	CAIX	Renal Cancer	Antigen Dilemma, Infiltration, Immune Microenvironment	Upregulated antigen expression on tumor cells, promoted CAR T cell infiltration, and reduced the abundance and frequency of myeloid derived suppressor cells	31574023

131	Metformin and Rapamcyin	Yes	AMPK Activator, mTOR Inhibitor	EGFRvIII	Glioblastoma	Fitness, Immune Microenvironment, Tumor Burden	Pretreated CAR T cells had better persistence and anti-tumor activity under impairing hypoxic conditions along with fewer MDSCs	38386420
132	TY-52156	No	S1P3 Receptor Antagonist	EpCAM	Breast Cancer, Colon Cancer	Fitness, Infiltration, Immune Microenvironment	Improved infiltration and effector function by remodeling the TME to promote pro-inflammatory macrophage polarization and recruitment	37591632

