

Roles of Tumor-associated Macrophages (TAMs) in Tumor Environment and Strategies for Targeting Therapy

Meng-Qi Liu^{1#}, Jia-wei Zhang^{1#}, Jian-Wei Zhu^{1,2*}

¹School of Pharmacy, Shanghai Jiao Tong University, Shanghai, People's Republic of China

²Jecho Laboratories, Inc., Maryland, United States

[#]These authors contribute to this work equally.

Address for correspondence

Jian-Wei Zhu, PhD, School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China (e-mail: jianweiz@sjtu.edu.cn).

Supplementary Information

Table Content

Table. S1	Representative clinical trials of tumor-associated macrophages-targeting agents.
Table. S2	Chemical structural formulas and targets of small molecule compounds mentioned.
Table. S3	TAMs targeting-related studies: significance, advantages, and limitations.

Table 1 Representative clinical trials of tumor-associated macrophages-targeting agents

Agent (company)	Format	Indication	Co-therapy	Clinical Phase	Reference
CSF-1R blockade					
LY3022855 (IMC-CS4; Eli Lilly)	Antibody	Advanced solid tumors	Durvalumab/Tremelimumab	Phase I	NCT02718911
		Melanoma	Vemurafenib/Cobimetinib	Phase I/II	NCT03101254
		Advanced solid tumors	-	Phase I	NCT01346358
Cabiralizumab (Five Prime & BMS)	Antibody	Pancreatic cancer stage IV	Gemcitabine and Nivolumab	Phase II	NCT03697564
		Pigmented villonodular synovitis/Diffuse type tenosynovial giant cell tumor	-	Phase I/II	NCT02471716
		Selected advanced tumors	Nivolumab	Phase I	NCT02526017
		Advanced melanoma/NSCLC/RCC	APX005M and Nivolumab	Phase I	NCT03502330
		Advanced pancreatic cancer	Nivolumab/Chemotherapy	Phase II	NCT03336216
SNDX-6352 (Axatilimab; Syndax Pharmaceuticals)	Antibody	Solid tumors	Durvalumab	Phase I	NCT03238027
		Intrahepatic Cholangiocarcinoma	Durvalumab	Phase II	NCT04301778
Emactuzumab (RO5509554;RG7155; Roche)	Antibody	Advanced solid tumors	Paclitaxel	Phase I	NCT01494688
		Advanced solid tumors	Atezolizumab	Phase I	NCT02323191
		Tenosynovial giant cell tumor	-	Phase III	NCT05417789
		Advanced solid tumors	RO7009789	Phase I	NCT02760797
		Platinum-resistant ovarian, Fallopian tube, or Primary peritoneal cancer	Paclitaxel and Bevacizumab	Phase II	NCT02923739
AMG 820 (AmMax Bio, Inc)	Antibody	Select advanced solid tumors	Pembrolizumab	Phase Ib/II	NCT02713529
BLZ945 (Novartis)	Small molecule	Advanced solid tumors	PDR001	Phase I/II	NCT02829723
(PLX3397; Daiichi Sankyo, Inc)	Small molecule	Advanced melanoma, NSCLC/Ovarian cancer	Pembrolizumab	Phase I/II	NCT02452424
		Sarcoma and Malignant peripheral nerve sheath tumors	Sirolimus	Phase I/II	NCT02584647
CCR2- CCL2					
MLN1202 (Takeda oncology)	Antibody	Metastatic Cancer	-	Phase II	NCT01015560
Carlumab (CNTO 888; Janssen)	Antibody	Prostate Cancer	-	Phase II	NCT00992186

		Solid tumors	DOXIL®/gemcitabine/ Paclitaxel plus carboplatin	Phase I	NCT01204996
CCR5					
Leronlimab (PRO 140; CytoDyn)	Antibody	Advanced or metastatic solid tumors	-	Phase II	NCT04504942
		Triple-negative breast carcinomas	Carboplatin	Phase Ib/II	NCT03838367
BMS-813160 (Bristol Myers Squibb)	Small molecule	Pancreatic Ductal Adenocarcinoma	Nivolumab and Gemcitabine and Nab-paclitaxel	Phase I/II	NCT03496662
		NSCLC/HCC	Nivolumab	Phase II	NCT04123379
Ang-2					
CVX-241 (PF-05057459; Pfizer)	Ang-2-VEGF-fused peptibody	Advanced solid tumor	-	Phase I	NCT01004822
CVX-060 (PF-04856884; Pfizer)	Covx-Ang-2 peptibody	Advanced solid tumor	-	Phase I	NCT00879684
		Metastatic renal cell carcinoma	Axitinib (VEGFR inhibitor)	Phase II	NCT01441414
		Advanced renal cell carcinoma	Sunitinib (VEGFR inhibitor)	Phase II	NCT00982657
MEDI3617 (MedImmune LLC)	Antibody	Advanced solid tumor	Carboplatin/Paclitaxel/Bevacizumab (anti-VEGF)	Phase I	NCT01248949
		Metastatic melanoma	Tremelimumab	Phase I	NCT02141542
Vanucizumab (RO5520985; Roche)	Anti-Ang-2/VEGF-A bispecific antibody	Metastatic solid tumor	Selicrelumab (CD40 agonist)/bevacizumab (anti-VEGF)	Phase Ib	NCT02665416
		Metastatic Colorectal Cancer	FOLFOX and bevacizumab	Phase II	NCT02141295
		Locally advanced or metastatic solid tumors	Atezolizumab	Phase I	NCT01688206
LY3127804 (Eli Lilly)	Anti-Ang2 antibody	Advanced solid tumor	Ramucirumab (Anti-VEGFR2)	Phase I	NCT02597036
CD40					
CDX-1140 (Providence Health& Services)	Antibody	Malignant epithelial neoplasms	TCR-transduced T cells /Pembrolizumab	Phase I	NCT04520711
		NSCLC/Lung cancer	CDX-301(FLT3 ligand)/SBRT	Phase I/II	NCT04491084
		NSCLC /Melanoma /Breast Cancer	CDX-301/Pembrolizumab/Chemotherapy	Phase I	NCT03329950
		Recurrent ovarian cancer	Pembrolizumab, Bevacizumab	Phase II	NCT05231122

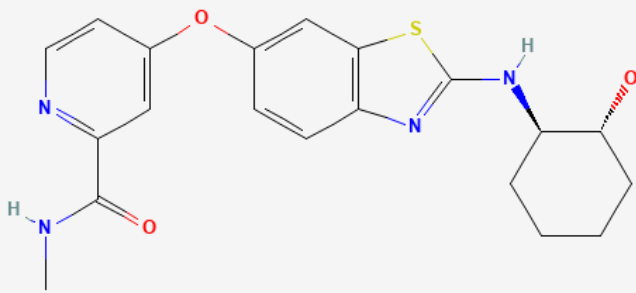
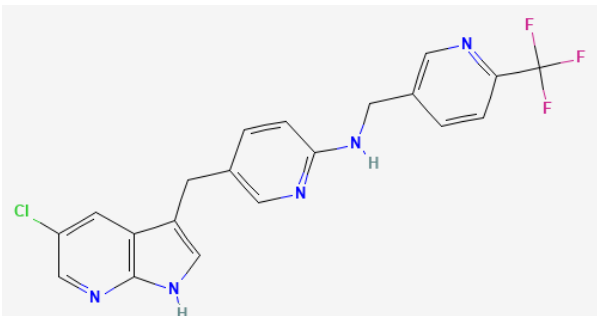
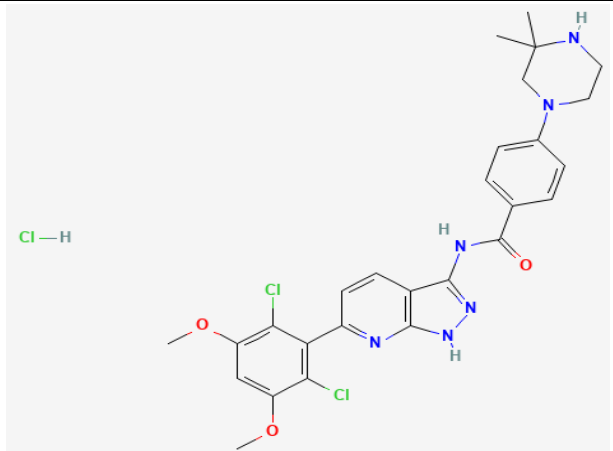
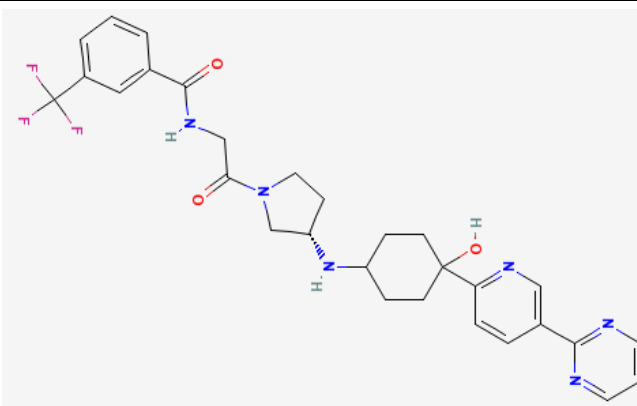
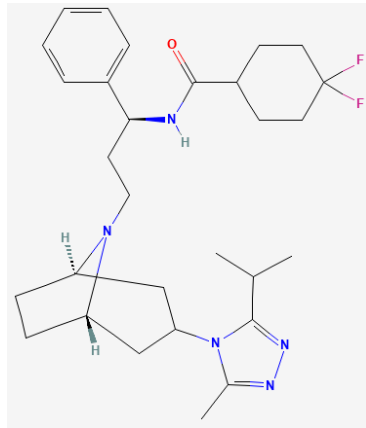
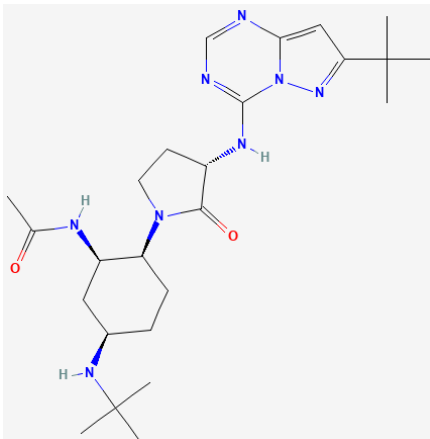
Chi Lob 7/4 (Cancer Research UK)	Antibody	Non-Hodgkin/B cell /lymphoma	-	Phase I	NCT01561911
APX005M (Apexigen)	Antibody	Solid tumors	-	Phase I	NCT02482168
		NSCLC/Metastatic melanoma	Nivolumab	Phase I/II	NCT03123783
		Metastatic Pancreatic adenocarcinoma	Nivolumab/ Gemcitabine/Nab-Paclitaxel	Phase I/II	NCT03214250
		CNS tumor	-	Phase I	NCT03389802
		Soft Tissue sarcoma	Doxorubicin	Phase II	NCT03719430
		Locally advanced rectal adenocarcinoma	mFOLFOX /Radiation	Phase II	NCT04130854
		Unresectable/Metastatic melanoma	-	Phase II	NCT04337931
		Metastatic melanoma	Pembrolizumab	Phase I/II	NCT02706353
		Advanced melanoma /NSCLC/RCC	Cabiralizumab /Nivolumab	Phase I	NCT03502330
SGN-40 (Seagen Inc)	Antibody	Multiple myeloma	-	Phase I	NCT00079716
		Multiple myeloma	Bortezomib	Phase I	NCT00664898
		Non-Hodgkin's Lymphoma	Rituximab	Phase I	NCT00556699
		Diffused large B cell lymphoma	R-ICE	Phase IIb	NCT00529503
		Multiple myeloma	Lenalidomide/Dexamethasone	Phase I	NCT00525447
		Diffused large B cell lymphoma	-	Phase II	NCT00435916
		Non-Hodgkin's Lymphoma	-	Phase I	NCT00103779
		Diffused large B cell lymphoma	Rituximab /Gemcitabine	Phase I	NCT00655837
Selicrelumab (RO7009789; Roche)	Antibody	Solid tumors	Atezolizumab	Phase I	NCT02304393
		Advanced/Metastatic solid tumors	Vanucizumab /Bevacizumab	Phase I	NCT02665416
		Refractory or Relapsed B cell lymphoma	Atezolizumab	Phase I	NCT03892525
		Pancreatic Carcinoma	Nab-paclitaxel, Gemcitabine	Phase I	NCT02588443
Mitazalimab (ADC-1013; JNJ-64457107; Alligator Bioscience)	Antibody	Neoplasms/Solid tumors	-	Phase I	NCT02379741
		Advanced solid neoplasms	-	Phase I	NCT02829099
		Metastatic Pancreatic Ductal Adenocarcinoma	Chemotherapy	Phase Ib/II	NCT04888312
		Metastatic Pancreatic Cancer	MesoPher	Phase I	NCT05650918
CP-870,893 (Roche)	Antibody	Advanced solid tumors	-	Phase I	NCT02225002
		Reccurant melanoma/IV stage melanoma	Tremelimumab	Phase I	NCT01103635
		Neoplasms	Paclitaxel, Carboplatin	Phase I	NCT00607048

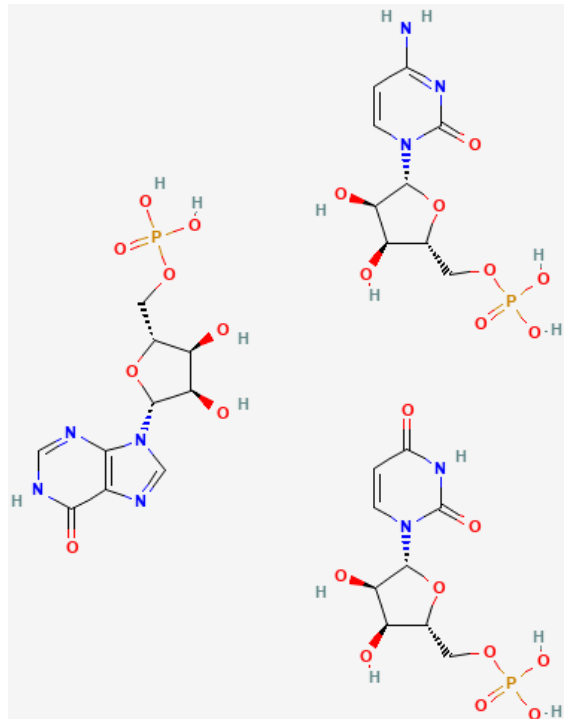
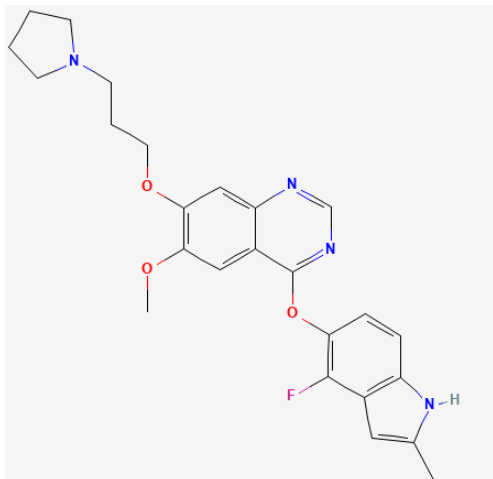
		Adenocarcinoma pancreas	Gemcitabine	Phase I	NCT01456585
SEA-CD40 (Seagen Inc)	Antibody	NSCLC/Squamous cell carcinoma	Pembrolizumab /Gemcitabine/Nab-paclitaxel	Phase I	NCT02376699
GM.CD40L (H. Lee Moffitt Cancer Center and Research Institute)	Cell vaccine	Lung cancer/ Adenocarcinoma	CCL21	Phase I/II	NCT01433172
		Lung cancer/ Adenocarcinoma of the Lung	Nivolumab	Phase I/II	NCT02466568
CD47					
TTI-621 (PF-07901800; Pfizer)	SIRPα-IgG1-Fc fusion protein	Hematologic malignancies/Solid tumors	Rituximab/Nivolumab	Phase I	NCT02663518
Maplirpacept (TTI-622; PF-07901801; Pfizer)	SIRPα-IgG4 Fc fusion protein	Lymphoma/Multiple myeloma/Diffuse large B-cell lymphoma	Monotherapy/ Azacitidine/Venetoclax/Carfilzo mib/Dexamethasone/Anti-CD20 Targeting agent/Isatuximab	Phase I	NCT03530683
		Lymphoma/Multiple Myeloma	-	Phase I	NCT05567887
		Diffuse large B-cell lymphoma	Tafasitamab, Lenalidomide	Phase Ib/II	NCT05626322
		Platinum-resistant ovarian cancer	Pegylated Liposomal Doxorubicin	Phase I/II	NCT05261490
		Relapsed or refractory diffuse large B-cell lymphoma	TTI-621, Pembrolizumab	Phase II	NCT05507541
Hu5F9-G4 (Gilead)	Antibody	Solid tumors	-	Phase I	NCT02216409
		Acute myeloid leukemia/Myelodysplastic Syndrome	-	Phase I	NCT02678338
		Non-Hodgkin’s Lymphoma	Rituximab ±Chemotherapy	Phase Ib/II	NCT02953509
AO-176 (Arch Oncology)	Antibody	Solid tumors	Monotherapy/Paclitaxel/Pembroli zumab	Phase I/II	NCT03834948
		Multiple myeloma	Bortezomib/Dexamethasone	Phase I/II	NCT04445701
ALX148 (ALX Oncology)	SIRPα-IgG1 Fc fusion protein	Metastatic cancer /Solid tumor /Advanced cancer /NonHodgkin lymphoma	Pembrolizumab /Trastuzumab /Rituximab/Ramucirumab plus Paclitaxel/ 5-FU plus Cisplatin	Phase I	NCT03013218
		Ovarian Cancer	Liposomal Doxorubicin and Pembrolizumab	Phase II	NCT05467670
		Microsatellite stable metastatic colorectal	Cetuximab and Pembrolizumab	Phase II	NCT05167409

		cancer			
CC-90002 (Celgene)	Antibody	Hematologic Neoplasms	Rituximab	Phase I	NCT02367196
IBI188 (Innovent Biologics (Suzhou) Co. Ltd.)	Antibody	Advanced malignancies	-	Phase I	NCT03717103
IBI322 (Innovent Biologics (Suzhou) Co. Ltd.)	CD47/ PD-L1 bispecific antibody	Advanced malignancies	-	Phase I	NCT04328831
		Advanced malignant tumors lymphomas	-	Phase I	NCT04338659
SL-172154 (Shattuck Labs, Inc)	SIRPα-Fc-CD40L bispecific recombinant protein	Cutaneous squamous cell carcinoma /Squamous cell carcinoma of head and neck	-	Phase I	NCT04502888
		Ovarian cancer	-	Phase I	NCT04406623
		Ovarian cancer	Pegylated Liposomal Doxorubicin/ Mirvetuximab	Phase I	NCT05483933
SIRPα					
BI 765063 (OSE Immunotherapeutics)	Antibody	Solid tumor	BI 754091 (Anti-PD-A antibody)	Phase I	NCT03990233
		Colorectal Cancer	Ezabenlimab/ Pembrolizumab	Phase I	NCT05446129
CC-95251 (CC-95251)	Antibody	Neoplasms	Rituximab/ Cetuximab	Phase I	NCT03783403
GS-0189 (FSI-189; Gilead Sciences)	Antibody	Non-hodgkin lymphoma	Rituximab	Phase I	NCT04502706
TREM					
PY159 (PIONYR)	Antibody	Advanced Solid Tumors	Pembrolizumab	Phase I	NCT04682431
PY314 (PIONYR)	Antibody	Advanced Solid Tumors	-	Phase I	NCT04691375
TLRs					
Rintatolimod (Hemispherx Biopharma Inc)	Small molecule	Locally Advanced Pancreatic Adenocarcinoma	FOLFIRINOX	Phase II	NCT05494697
		Metastatic Pancreatic Ductal Adenocarcinoma	Durvalumab	Phase I/II	NCT05927142
		Refractory Metastatic or Unresectable Colorectal Cancer	Pembrolizumab	Phase II	NCT04119830
		Colorectal Cancer Metastatic to the Liver	Celecoxib, and Recombinant Interferon Alfa-2b	Phase II	NCT03403634
		Prostate Cancer Before Surgery	Aspirin	Phase II	NCT03899987
		Recurrent Platinum-sensitive Ovarian	Cisplatin and pembrolizumab	Phase II	NCT03734692

		Cancer			
		Metastatic or Unresectable Triple Negative Breast Cancer	Celecoxib, Interferon Alpha 2b and Pembrolizumab	Phase I/IIa	NCT05756166
Poly-ICLC (Oncovir, Inc)	Double-stranded RNA	Metastatic Mismatch Repair-proficient (MRP) Colon Cancer	Pembrolizumab	Phase I/II	NCT02834052
		Solid Cancer	Nivolumab/Pembrolizumab/Cemiplimab/Atezolizumab/Durvalumab	Phase II	NCT02423863
BO-112 (Highlight Therapeutics SL)	Double-stranded RNA	Advanced and Metastatic Melanoma	Pembrolizumab	Phase II	NCT04570332
		Metastatic Refractory NSCLC	Nivolumab	Phase Ib/II	NCT05265650
		Advanced Hepatocellular Carcinoma	Pembrolizumab	Phase I	NCT04777708
BDC-1001 (Bolt Biotherapeutics, Inc)	Immune-stimulating antibody conjugate	HER2-Positive Metastatic Breast Cancer	Pertuzumab	Phase II	NCT05954143
		Advanced HER2-Expressing Solid Tumors	-/ Nivolumab	Phase I/II	NCT04278144
CAR-macrophage					
CT-0508 (Carisma Therapeutics Inc)	Adenovirus transfection macrophages with anti-HER2-CAR	HER2 Overexpressing Solid Tumors	-/ Pembrolizumab	Phase I	NCT04660929
MCY-M11 (MaxCyte, Inc)	mRNA transfection macrophages with anti-mesothelin-CAR	Advanced Ovarian Cancer and Peritoneal Mesothelioma	-/ Cyclophosphamide	Phase I	NCT03608618

Table S2 Chemical structural formulas and targets of small molecule compounds mentioned

					
Agent	Target	Molecular Formula	Agent	Target	Molecular Formula
BLZ945	CSF-1R	C ₂₈ H ₄₀ N ₉ O ₂₅ P ₃	Pexidartinib	CSF-1R	C ₂₀ H ₁₅ ClF ₃ N ₅
					
Agent	Target	Molecular Formula	Agent	Target	Molecular Formula
3D-185	CSF-1R and FGFR	C ₂₇ H ₂₉ Cl ₃ N ₆ O ₃	PF-04136309	CCR2	C ₂₉ H ₃₁ F ₃ N ₆ O ₃
					
Agent	Target	Molecular Formula	Agent	Target	Molecular Formula
Maraviroc	CCR5	C ₂₉ H ₄₁ F ₂ N ₅ O	BMS 813160	CCR5	C ₂₅ H ₄₀ N ₈ O ₂



Agent	Target	Molecular Formula	Agent	Target	Molecular Formula
Cediranib	VEGFR	C ₂₅ H ₂₇ FN ₄ O ₃	Rintatolimod	TLR3	C ₂₈ H ₄₀ N ₉ O ₂₅ P ₃

Table 3 TAMs targeting-related studies: significance, advantages, and limitations

Agent	Target	Significance	Side effects	Advantages	Limitation
Pexidartinib (PLX3397)	CSF-1R	Selectively inhibits CSF1R and KIT, penetrates the blood-brain barrier in model systems	- Fatigue - Change in hair color - Nausea - Periorbital edema - Hepatotoxicity	- Enhance T-cell activity - Orally effective - Multi-target inhibitor of CSF-1R, Kit, and Flt3 receptor tyrosine kinase	- Higher doses
Emactuzumab (RG7155)	CSF-1R	Binds to CSF 1R and prevents receptor dimerization inhibits activation of signaling	- Asthenia - Peripheral edema and pyrexia	- Well tolerated - Biologically highly active	- Shows no further benefit on patients with advanced solid tumors combined with paclitaxel
Carlumab	CCR2	Binds to CCL2 with high affinity and directly Competes with the CCR2 receptor binding site	- Pneumonia - Spinal cord compression - Back pain	- Well tolerated - No antitumor activity as a single agent	- CCL2 levels increased after treatment over the pretreatment baseline
BMS-813160	CCR2 CCR5	Selective CCR2/5 dual antagonist	-	- Well-absorbed - With a good duration of action	-
Vanucizumab	Ang2	The first bispecific IgG1 monoclonal antibody that simultaneously blocks VEGF-A and Ang-2 interactions with their receptors	- Arterial - Hypertension - Asthenia - Headache	- Acceptable safety and tolerability profile	- Not show expected effect when treated as a single agent
Selicrelumab (CP-870,893)	CD40	Binds CD40 with very high affinity, a strong agonist of CD40	cytokine release syndrome	Combination therapy increased toxicity and observed pharmacodynamic markers	- Limited efficacy
Magrolimab (Hu5F9-G4)	CD47	A first-in-class antibody targeting CD47, induces tumor phagocytosis	- Anemia - Neutropenia - Thrombocytopenia	- Has no ADCC and CDC activity	- Cause anemia or thrombocytopenia because of the expression of CD47 on a variety of cells
TTI-621	SIRP α	A fully human recombinant fusion protein, promotes tumor cell phagocytosis by IFN- γ -primed macrophages	- Infusion-related reactions - Chills - Fatigue	- Well-tolerated - Demonstrated activity as monotherapy	- Cross-reactivity with other members of the SIRP family

					- Side effects of SIRP alpha on the central nervous system
PY314	TREM	Selectively binds TREM2 and depletes TREM2-expressing TAMs through ADCC and ADCP	- No infusion-related reactions, dose-limiting toxicities that resulted in treatment discontinuance	- Well tolerated - Commendable safety profile both as a standalone treatment and in conjunction with pembrolizumab	-
Rintatolimod	TLR3	A broad-spectrum active dsRNA, activate professional antigen-presenting dendritic cells	- Chronic inflammation - Sepsis - Autoimmune disorders	- Used as adjuvant of tumor vaccine	- Rapid distribution in the whole body to cause cytokine storm and other adverse reactions, - Limited application range
CT-0508	CAR-M	Macrophages were modified with CARs to improve the phagocytosis activity and antigen presentation	- CRS toxicity - OTOT toxicity	- of matrix metalloproteinase (MMP) which degrades almost all ECM - Can be generated from different sources	- Limited efficacy in CAR transduction - Need differentiation to M1 phenotype