Immune Checkpoint Receptors

Subjects: Oncology

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Anticancer therapy based on the inhibition of immune checkpoints (ICs) is an actively developing field of study, and it has been widely used. Antibodies blocking immune checkpoints are used as therapeutics. The targeted checkpoints are mainly the PD-L1 (programmed death-ligand 1), expressed by the tumor, and the PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) immune cell receptors. To increase the effectiveness of therapy by blocking ICs, additional receptors and ligands are being investigated as targets of immunotherapy.

Keywords: immune checkpoint ; expression ; therapy

1. TIM-3

TIM-3 (T-cell immunoglobulin and mucin domain-3) is a transmembrane protein, expressed by T-cells, IFNγ-secreting T-regulatory cells (Treg), natural killer cells (NK cells), dendritic cells (DCs), macrophages, and mast cells [1]. TIM-3 is a receptor, an immune response regulator that ensures the formation of immunological tolerance and prevents the occurrence of autoimmune diseases by regulating the homeostasis of T-helper type 1 [2]. A decreased expression level of TIM-3 is associated with the development of diabetes and multiple sclerosis [3]. At the same time, the overexpression of Tim3 can contribute to the depletion of T-cells by limiting the pool of memory T-cells while enhancing the initial activation of T-cells and the generation of short-lived effector cells in acute and chronic infections [4]. In addition, the participation of TIM-3 in the activation of mast cells was revealed [5]. Increased TIM-3 expression by tumor-infiltrating lymphocytes (TILs) is indicated in many malignant neoplasms and is characteristic of effector lymphocytes with a depleted phenotype [6][7]. On the other hand, TIM-3 expression is characteristic of activated regulatory T-cells with immunosuppressive activity [8]. A significant role of TIM-3, expressed in antigen-presenting cell (APC) and T-cells, in the regulation of CD8+ TILs trogocytosis in tumors has been shown. The use of mAb to TIM-3 is able to counteract the fratricidal process undergone by trogocytosed CD8+ T-cells [9].

2. LAG-3

The LAG-3 (lymphocyte-activation gene 3) gene (CD223) encodes a protein that negatively regulates the activation, proliferation, effector functions, and homeostasis of T-cells [10][11] and dendritic cells participating in preventing the development of autoimmune reactions in normal tissues [12] and regulating the immune response in chronic infections [13]. Due to the partial similarity of extracellular domains, LAG-3 and CD4 were presumably developed by gene duplication. However, differences in their intracellular domains result in their opposite functions [14]. The LAG-3 protein is presented in a transmembrane and soluble form (sLAG-3) formed by alternative splicing. It has been shown that under the action of ADAM10 and ADAM17 metalloproteases, the extracellular part of the receptor also passes into a soluble form [15]. LAG-3 is constitutively expressed by natural T-regulatory cells (Tr1), DCs, NK cells, and B-cells and is not found on naive T-cells; however, its expression is strongly increased after the activation of CD4+ and CD8+ lymphocytes, including TILs [16]. The modulating functions of LAG-3 correlate with the level of receptor expression [17]. The activation of LAG-3 reduces the production of various immunostimulatory interleukins (IL) and increases sensitivity to Treg signaling, thereby increasing T-cell tolerance and accelerating their depletion [16].

3. TIGIT

TIGIT (T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains) is a co-inhibitory receptor, expressed by all types of T-lymphocytes, as well as NK cells [18]. The receptor is involved in maintaining self-tolerance. The positive effect of TIGIT in regenerative hyperplasia was revealed: the absence of the receptor impairs liver regeneration in vivo [19].

Several immunoregulatory mechanisms involving TIGIT have been described to date. The interaction of TIGIT with the ligand causes the phosphorylation of its cytoplasmic domain, which triggers processes that block the transmission of intracellular signals along the PI3K and MAPK pathways and the activation of NF-κB, which, in turn, leads to the suppression of the cytotoxic functions of NK cells [20]. In addition, the interaction of this receptor with the ligand leads to the phosphorylation of the latter and the triggering of modulating signals in DCs [21]. TIGIT has been reported to directly inhibit T-cell proliferation and effector functions by downregulating T-cell receptor (TCR) and activating CD28 signaling [22].

4. VISTA

VISTA (V-domain Ig suppressor of T-cell activation) or PD-1H (programmed death-1 homolog) is predominantly expressed by myeloid cells, as well as by CD4+ and Foxp3+ T-regulatory cells [23]. Studies of VISTA expression in cancer diseases have shown the presence of protein on TILs and macrophages and its absence on cells of most types of tumors [24]. However, in a number of studies, the expression of VISTA by tumor cells was detected in different proportions of samples in non-small cell lung cancer (NSCLC), [25], hepatocellular carcinoma [26], ovarian and endometrial cancer [27], melanoma, stomach cancer, and breast cancer [28]. VISTA negatively regulates T-cell activation, proliferation, and cytokine production [29] and specifically suppresses the immune response mediated by CD4+ T-cells [30]. However, in a study by Mercier et al., the suppression of lymphocyte functions was mediated by the activation of cell receptors by a fusion protein (VISTA-Ig) acting as a ligand [31]. On the other hand, the increased proliferation and production of VISTA−/− cytokines by CD4+ T-cells indicates VISTA receptor function [30]. In addition, VISTA directly regulates the effector functions of myeloid cells [32]. Thus, understanding the complex functioning of VISTA requires a detailed study of the associated immune regulatory mechanisms.

5. BTLA

BTLA (B- and T-lymphocyte attenuator) or CD272 is a transmembrane receptor expressed by naive T-lymphocytes, B-cells, macrophages, DCs, and natural killer T-cells (NKT) [33][34]. BTLA is involved in the regulation of immune cell homeostasis by inhibiting proliferation, the activation of B- and T-cells, and the production of cytokines [35]. In particular, BTLA negatively regulates the expansion and function of γδ T-cells [36], various subtypes of which both contribute to the progression of cancer and have antitumor activity [37]. A soluble form of the BTLA protein (sBTLA) is described as a potential prognostic and predictive marker in patients with clear cell renal cell carcinoma, pancreatic adenocarcinoma, and prostate cancer [38][39][40].

A recent study in patients treated with immune checkpoint (ICT) inhibitors for solid tumors found an association between serum levels of soluble BTLA (sBTLA) and median overall survival [41].

Data on the clinical significance of the molecules considered in the table, as well as the results of preclinical studies, are presented in **Table 1**.

Table 1. Clinical significance and results of preclinical studies of immune checkpoints (ICs) and their ligands.

Receptor	Results of Preclinical Stydies	Ligands	Clinical Significance/ Results of Preclinical Stydies
TIM-3	The use of mAbs against TIM-3 stimulates the production of IFNγ. The antitumor efficacy of anti-TIM-3 is associated with the ratio of CD8+:CD4+ T-cells in the TILs pool. The combined use of mAbs targeting TIM-3, PD-1 (programmed cell death protein 1), and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) has been shown to be more effective and well tolerated [42]. In models of lung adenocarcinoma, it was found that the use of mAbs targeting PD-1 can increase the expression of TIM-3. The effectiveness of the use of TIM-3 in overcoming resistance to therapy with mAbs targeting PD-1 has been shown [43]. The expression of LAG-3 and CTLA-4 was increased on CD8+ T-lymphocytes bound by the used mAbs targeting TIM-3 and PD-1. The combined use of mAbs targeting TIM-3 and CTLA-4 shows a synergistic effect in models [44].	Phosphotidylserine	-
		Galectin-9	Resistance to anti-PD-1 therapy has been observed in the presence of TIM-3+ lymphocytes and galectin-9-expressing myeloid-derived suppressor cells (MDSC) [45]. The co-expression of galectin-9 and TIM-3 has been detected in various types of cancer [46][47]. The correlation of galectin-9 expression with better overall survival (OS) (in hepatocellular carcinoma (HCC) and colorectal cancer (CRC)) or progression-free survival (PFS) (in gastric cancer (GC) and NSCLC) has been shown [48]. The opposite data are available [49].
		Alarmin-1 (HMGB1)	HMGB1 is associated with progression and metastasis in NSCLC and CRC [50] [51].
		CEACAM1	A synergistic antitumor effect has been shown with the simultaneous blockade of TIM-3 and CEACAM1, as well as CEACAM1 and PD-L1 (programmed death-ligand 1), on CRC models [52]. In the early stages of CRC, CEACAM1 inhibits tumor cell proliferation [53]. However, CEACAM1 is a diagnostic and prognostic marker in melanoma, and CEACAM1 is found in tumor samples and sera from patients with pancreatic cancer (PC) and is overexpressed in advanced stages of CRC, NSCLC, and other cancers [54].
LAG-3	It has been shown that the therapeutic use of PD-1 leads to an increase in the expression level of LAG-3 [55]. In NSCLC, the co-expression of LAG-3 and PD-1 on TILs and PD-L1 on tumor cells is shown [56]. A synergistic effect was observed from the combined use of mAbs binds LAG-3 and PD-1 in various tumor models [57].	MHC class II	MHC class II molecule (MHCII) is associated with survival, increased numbers of CD4+ and CD8+ T -cells in the TILs, and a good response to anti-PD-1 and PD-L1 immunotherapy in some cancers [58].
		Fibrinogen-like protein (FGL-1)	The FGL-1/LAG-3 interaction blockade stimulates tumor immunity [59]. The reduced expression of FGL-1 increases the efficiency of CD8+ T-cell activation during LAG-3 blockade [60].
		Galectin-3	The restoration of cytolytic functions of CD8+ T- cells in response to the inhibition of galectin-3 was shown, which indicates the role of galectin-3 in the suppression of antitumor immunity. The direct involvement of galectin-3 in the processes of metastasis was revealed [61][62][63], as well as the association of galectin-3 expression with poor clinical prognosis [64]. However, in melanoma and glioblastoma, the presence of galectin-3 is beneficial for patients [65].
		LSECtin	A high level of soluble LSECtin in the blood serum of patients with CRC is associated with the presence of liver metastases [66]. The expression of LSECtin and its interaction with LAG-3 molecules are shown on B16 melanoma cells. It is accompanied by the suppression of the T-cell antitumor response, and the blockade of LSECtin/LAG-3 interaction restores the secretion of IFNγ [67].

Receptor	Results of Preclinical Stydies	Ligands	Clinical Significance/ Results of Preclinical Stydies
TIGIT	The blockade of TIGIT has been shown to prevent the depletion of NK cells and stimulate NK-mediated tumor immunity, activate antitumor T-cell immunity, and promote the formation of immune memory [68][69]. The co-inhibition of TIGIT and PD-1 or PD-L1 with mAbs exhibited a significant therapeutic effect, up to the complete elimination of tumors [68][70][71][72]. Using mAb against TIGIT showed: restoration of the functions of effector T-cells; the induction of cellular cytotoxicity against regulatory T-cells; a direct cytotoxic effect on TIGIT+ tumor cells [73][74]. The high efficiency of the combined inhibition of PD-1 and CD96 or TIGIT and CD96 has been shown [75].	Nectin-2 (CD112)	Interaction with TIGIT leads to the corresponding transmission of inhibitory signals to immune cells. Nectin-2 is expressed in breast and ovarian tumors [76].
		Nectin-4 (PVRL4)	Nectin-4 blocking Abs stimulates an NK-mediated antitumor response [77]. The participation of nectin-4 in the processes of proliferation, invasion, and metastasis through the activation of Pi3k/Akt and WNT/β-catenin signaling pathways has been shown [78]. The revealed hyperexpression of nectin-4 by tumor tissues is associated with tumor aggressiveness and poor clinical prognosis [79][80].
		PVR (CD155)	Overexpression and the presence of a soluble form of CD155 in the blood serum of patients are associated with a poor clinical prognosis [81][82][83]. The association of the co-expression of TIGIT and CD155 with an unfavorable disease course in lung adenocarcinoma and primary SCC of the esophagus has been shown [82][84].
VISTA	In response to blocking VISTA with the use of mAbs, an increase in the number of TILs and the restoration of the functions of CD8+ T-cells were observed [32]. An increase in the expression of chemokines (CXCL9/10, CCL4/5) as well as cytokines (IFNβ, IL6, IL12, IL23, IL27, TNFα) was observed in tumor tissues [31]. However, the effective suppression of tumor growth was observed only when anti-VISTA mAbs was used in combination with anti-PD-1 mAbs [85][86] or CTLA-4 [87]. The blockade of VISTA caused an increase in tumor infiltration by immune cells and a decrease in the number of myeloid suppressor cells (MSCs). The therapeutic effect of anti-VISTA antibodies has been demonstrated in ovarian cancer (OC) models highly expressing VISTA [28].	VSIG-3 (IGSF11)	The expression of VSIG-3 by tumor tissues was found in CRC, HCC, and in intestinal-type GC [88]. The overexpression of VSIG-3 is associated with the expression of VISTA, as well as with PD-L1 and PD-1, with a high degree of tumor malignancy, and a poor clinical prognosis in glioblastoma has been revealed [89]. Experimental models show the antitumor efficacy of the SG7 Ab, which inhibits VISTA binding to VSIG-3 and PSGL-1 [90].
		PSGL-1	The ability of PSGL-1 to bind to VISTA was shown at acidic values of the medium (pH 6.0). At lower pH values, an enhanced inhibitory effect of VISTA was shown, and the use of Abs capable of blocking the VISTA/PSGL-1 interaction restored the proliferative and secretory functions of T-cells [91]. Experimental models show the antitumor efficacy of the SG7 Ab, which inhibits VISTA binding to VSIG-3 and PSGL-1 [90].
		Galectin-9	The study of samples from patients with peritoneal carcinomatosis showed a high level of expression of galectin-9, VISTA and TIM-3 depleted TILs [92].

Receptor	Results of Preclinical Stydies	Ligands	Clinical Significance/ Results of Preclinical Stydies
BTLA	The antitumor efficacy of anti-BTLA mAbs has been shown [93][94]. In the blockade of BTLA, an increase in the proliferation and expansion of NY-ESO-1-specific CD8+ T-cells was observed, and an increased efficiency of the use of mAbs targeting BTLA in combination with anti-PD-1 and anti-Tim-3 in melanoma was shown [95]. An increase in median OS [96], as well as the enhancing T-cell proliferation and cytokine production, was observed with the combination of anti-BTLA and anti-PD-1 therapies [97].	HVEM (TNFRSF14)	T-cell activation is observed as a result of HVEM suppression in OC cells and in the ESCC cell line [98][99]. HVEM expression is associated with a decrease in the number of TILs and with a poor prognosis in ESCC and CRC, including in patients with CRC metastases to the liver and other oncological diseases [99][100][101][102][103]. The high expression of HVEM is associated with an increased risk of transformation, while transformed FL is characterized by a low level of BTLA expression and a high level of HVEM [104]. In GC, an overexpression of BTLA and HVEM is associated with a poor clinical prognosis [105].

Data on current clinical trials utilizing the considered immune checkpoints are presented in **Table 2**.

Table 2. Summary of ongoing clinical trials of receptor inhibitors.

Target	Drug	Number of Current Trials/ Phase	Type of Tumor	Some Published Results of Clinical Trials	
				Trial	Clinical Safety and Efficacy
TIM-3	Sabatolimab (MBG453)	16 I, II, III	Advanced or metastatic solid tumors Bone marrow diseases Glioblastoma Hematologic malignancies	NCT02608268 Phase I-Ib/II	Patients received sabatolimab (*n* = 133) or sabatolimab plus spartalizumab (*n* = 86). The MTD was not reached. No responses were seen with sabatolimab. Five patients receiving combination treatment had PR (6%; lasting 12–27 months) [106]
	TSR-022	4 I, II	Advanced or metastatic solid tumors Melanoma	NCT02817633 Phase I	In the group of 20 patients who received the TSR-022+TSR-042 combination, the ORR was 15% (3/20), and disease stabilization reached 40% (8/20) [107].
	LY3321367	1 I	Solid tumors	NCT03099109 Phase I	No DLTs were observed in the monotherapy (*n* = 30) or combination (*n* = 28) therapy. LY3321367 treatment-related adverse events (TRAEs) occurred in ≥2 patients. In the NSCLC monotherapy expansion cohort, outcomes varied: anti-PD-1/L1 refractory patients [N = 23, objective response rate (ORR) 0%, DCR 35%, PFS 1.9 months] versus anti-PD-1/L1 responders (*n* = 14, ORR 7%, DCR 50%, PFS 7.3 months). In combination expansion cohorts (*n* = 91), ORR and DCR were 4% and 42% [108]
	LY3415244, BsAb for PD-L1/TIM-3	1 I	Advanced solid tumors	NCT03752177 Phase Ia/Ib	Two patients (16.7%) developed clinically significant anaphylactic infusion-related reactions. One patient with PD-1 refractory NSCLC had a near partial response (−29.6%) [109]
	INCAGN02390	5 I	Solid tumors Melanoma	-	-
	BGB-A425	1 I	Advanced or metastatic solid tumors	-	-
	BMS-986258	1 I	Advanced cancer	-	-
	SHR-1702	2 I	Hematologic malignancies Advanced solid tumors	-	-
	RO7121661, BsAb for PD-1/TIM-3	2 I, II	Advanced or metastatic solid tumors Melanoma	-	-

Target	Drug	Number of Current Trials/ Phase	Type of Tumor	Some Published Results of Clinical Trials	
				Trial	Clinical Safety and Efficacy
LAG-3	Eftilagimod alpha (IMP321)	14 I, II	Advanced or metastatic solid tumors Melanoma	NCT00732082 Phase I	None of the 6 patients received 0.5 mg IMP321 experienced TRAEs. Of the 5 patients who received IMP321 at the 2 mg dose level, 1 experienced rash, 1 reported hot flashes, and 2 had mild pain at the injection sites [110]
				NCT00349934 Phase I	Thirty patients received IMP321 in three cohorts (doses: 0.25, 1.25 and 6.25 mg). Clinical benefit was observed for 90% of patients with only 3 progressors at 6 months. Additionally, t he ORR of 50% compared favorably to the 25% rate reported in the historical control group [111].
	Favezelimab (MK-4280)	10 I, II, III	Advanced or metastatic solid tumors Hematologic malignancies Melanoma	NCT03598608 Phase I/II	Fifteen patients received MK-4280 with pembrolizumab, four of whom achieved a partial response [112]
	Relatlimab (BMS-986016)	31 I, II	Advanced or metastatic solid tumors Hematologic malignancies Melanoma	NCT01968109 Phase I/IIa	Patients received relatlimab + nivolumab. In 61 efficacy-evaluable patients, ORR was 11.5% (1 complete, 6 partial (1 unconfirmed) responses); DCR was 49%. Median DOR was not reached (min [0.1þ], max [39.3þ]). ORR was 3.5-fold higher in patients with LAG-3 expression, 1% vs. <1%, regardless of PD-L1 expression. TRAEs occurred in 41% (gr 3/4, 4.4%; DC, 1.5%) [113]
				NCT03470922 Phase II	The median PFS was 10.1 months (95% confidence interval [CI], 6.4 to 15.7) with relatlimab–nivolumab as compared with 4.6 months (95% CI, 3.4 to 5.6) with nivolumab (hazard ratio for progression or death, 0.75 [95% CI, 0.62 to 0.92]; *p* = 0.006 by the log-rank test). PFS at 12 months was 47.7% (95% CI, 41.8 to 53.2) with relatlimab–nivolumab as compared with 36.0% (95% CI, 30.5 to 41.6) with nivolumab. Grade 3 or 4 TRAEs occurred in 18.9% of patients in the relatlimab–nivolumab group and in 9.7% of patients in the nivolumab group [114].
	TSR-033	2 I	Advanced solid tumors	-	-
	REGN3767	5 I, II, III	Advanced solid tumors	-	-
	Ieramilimab (LAG525)	5 I, II	Advanced solid tumors Hematologic malignancies Melanoma	NCT02460224 Phase I/II	Patients received fermilab (*n* = 134) or fermilab + spartalizumab (*n* = 121). Four patients experienced DLT in each treatment arm. No MTD was reached. TRAEs occurred in 75 (56%) and 84 (69%) patients in the single-agent and combination arms, respectively. Seven patients experienced SAEs in the single-agent (5%) and combination groups (5.8%). Antitumor activity was observed in the combination arm, with 3 (2%) CR and 10 (8%) PR. In the combination arm, 8 patients (6.6%) experienced SD for 6 months or longer versus 6 patients (4.5%) in the single-agent arm [115]
	FS118, BsAb for LAG-3/PD-L1	1 I, II	Advanced solid tumors Hematologic malignancies Melanoma	-	-

Target	Drug	Number of Current Trials/ Phase	Type of Tumor	Some Published Results of Clinical Trials	
				Trial	Clinical Safety and Efficacy
	RO7247669, BsAb for LAG-3/PD-1	5 I, II	Advanced or metastatic solid tumors Melanoma	-	-

Target	Drug	Number of Current Trials/ Phase	Type of Tumor	Some Published Results of Clinical Trials	
				Trial	Clinical Safety and Efficacy
TIGIT	Vibostolimab (MK-7684)	15 I, II, III	Advanced or metastatic solid tumors Melanoma Hematologic malignancies	NCT02964013 Phase I	Part A: 56% of patients receiving monotherapy and 62% receiving a combination of vibostolimab with pembrolizumab had TRAEs. Grade 3–4 TRAEs occurred in 9% and 17% of patients, respectively. No DLT was reported. The confirmed ORR was 0% for monotherapy and 7% for combination therapy. Part B: 39 patients had anti-PD-1/PD-L1-naive NSCLC, and all received combination therapy. TRAEs occurred in 85% of patients. The confirmed ORR was 26%, with responses observed in both PD-L1-positive and PD-L1-negative tumors. Sixty-seven had anti-PD-1/PD-L1-refractory NSCLC, and 56% receiving monotherapy and 70% receiving combination therapy had TRAEs. The confirmed ORR was 3% for monotherapy and 3% for combination therapy [116]
	BMS-986207	4 I, II	Advanced solid tumors Multiple myeloma	-	-
	Etigilimab (OMP-313M32)	2 I, II	Advanced or metastatic solid tumors	NCT03119428 Phase Ia/Ib	Thirty-three patients were enrolled (Phase Ia, *n* = 23; Phase Ib, *n* = 10). There was no DLT. MTD was not determined. Six patients experienced grade ≥ 3 TRAEs. In Phase Ia, 7 patients (30.0%) had stable disease. In Phase Ib, 1 patient had a PR; 1 patient had prolonged SD of nearly 8 months. Median PFS was 56.0 days (Phase Ia) and 57.5 days (Phase Ib) [117]
				NCT02864992 Phase II	The RR by independent review was 46% (95% CI, 36 to 57), with a median DoR of 11.1 months (95% CI, 7.2 to could not be estimated) in the combined-biopsy group. The RR was 48% (95% CI, 36 to 61) among 66 patients in the liquid-biopsy group and 50% (95% CI, 37 to 63) among 60 patients in the tissue-biopsy group; 27 patients had positive results according to both methods. The investigator-assessed RR was 56% (95% CI, 45 to 66). TRAEs of grade ≥ 3 were reported in 28% [118]
	Tiragolumab	38 I, II, III	Advanced or metastatic solid tumors Melanoma Hematologic malignancies	NCT03563716 Phase II	Patients were randomly assigned to receive tiragolumab + atezolizumab (67 (50%)) or placebo + atezolizumab (68 (50%)). After a median follow-up of 5.9 months (4.6–7.6, in the intention-to-treat population, 21 patients (31.3% [95% CI 19.5–43.2]) in the tiragolumab + atezolizumab group versus 11 patients (16.2% [6.7–25.7]) in the placebo + atezolizumab group had an objective response (*p* = 0.031). Median PFS was 5.4 months (95% CI 4.2-not estimable) in the tiragolumab + atezolizumab group versus 3·6 months (2.7–4.4) in the placebo + atezolizumab group (stratified hazard ratio 0.57 [95% CI 0.37–0.90], *p* = 0.015). Fourteen (21%) patients receiving tiragolumab + atezolizumab and 12 (18%) patients receiving placebo + atezolizumab had SAEs [119]
	Domvanalimab (AB154)	9 I, II, III	Advanced or metastatic solid tumors Melanoma Glioblastoma	-	-
	ASP8374	3 I	Advanced solid tumors Glioblastoma	-	-

Target	Drug	Number of Current Trials/ Phase	Type of Tumor	Some Published Results of Clinical Trials	
				Trial	Clinical Safety and Efficacy
	CI-8993	1 I	Solid tumors	-	-
VISTA	CA-170, VISTA/PD-L1/2 antagonist	2 I, II	Advanced or metastatic solid tumors lymphomas	NCT02812875 Phase I	According to the RECIST, 33 out of 50 patients who received CA-170 showed SD. PR or CR was not achieved. Severe (grade 3 and 4) TRAEs were observed in 5 patients. No DLTs were observed [85].
	JNJ-61610588	1 I	Advanced or metastatic solid tumors	-	-
BTLA	TAB004/JS004	7 I, II	Recurrent/ refractory malignant lymphoma Advanced or metastatic solid tumors	-	

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