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Invited Mini Review

Update of early phase clinical trials in cancer immunotherapy

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Immunotherapy has revolutionized the landscape of cancer treatment and become a standard pillar of the treatment. The two main drivers, immune checkpoint inhibitors and chimeric antigen receptor T cells, contributed to this unprecedented success. However, despite the striking clinical improvements, most patients still suffer from disease progression because of the evolution of primary or acquired resistance. This mini-review summarizes new treatment options including novel targets and interesting combinational approaches to increase our understanding of the mechanisms of the action of and resistance to immunotherapy, to expand our knowledge of advances in biomarker and therapeutics development, and to help to find the most appropriate option or a way of overcoming the resistance for cancer patients. [BMB Reports 2021; 54(1): 70-88]

INTRODUCTION

During the last decade, immunotherapy has become a standard pillar of cancer treatment with already existing pillars of surgery, radiation, cytotoxic chemotherapy, and molecular-targeted therapy. Two main derivers have contributed to this unprecedented success; one is immune checkpoint (IC) inhibitors and the other is chimeric antigen receptor (CAR) T cells. ICs, such as cytotoxic T-lymphocyte-associated protein (CTLA-4) and programed cell-death protein-1/programmed cell-death protein ligand-1 (PD-1/PD-L1), are exploited by cancer cells to evade host immunity, and their blocking monoclonal antibodies can restore or reinvigorate the host immunity. At first, the disruption of the pathway was shown to induce durable remission or even cures in patients with advanced or metastatic melanoma or Non-small cell lung cancer (NSCLC). More success has followed in different tumor types, including renal cell carcinoma (RCC) and urothelial tumors, and in different clinical situations, including adjuvant therapy after surgery, consolidation therapy after chemoradiotherapy, and even in neo-adjuvant therapy before surgery. On the other hand, CAR-T cells also showed very impressive clinical outcomes in hematologic malignancies despite their specific life-threatening toxicities. Two CAR-T cell therapeutics, tisagenlecleucel and axicabtagen-ciloleucel, were approved by the US FDA and EMA for acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). In fact, CAR-T cells are different from IC inhibitors in that they are genetically engineered T cells, whereas IC inhibitors are a kind of classical monoclonal antibodies, giving different technical, regulatory, and economic challenges.

Immunotherapy can be categorized into 'passive' or 'active'. The former is to give directly immune molecules that can kill tumor cells, such as specific tumor molecule-targeting monoclonal antibodies or immune cells, such as CAR-T cells or CAR-NK cells. The latter is to give patients molecules that can activate their own immune system, including cytokines such as IFN-gamma or IL-2, cancer vaccines and immunomodulators, such as IC inhibitors or other co-stimulatory agonists, which finally kill tumor cells indirectly. The movement of CAR-T cells toward solid tumors was sometimes blocked by the lack of appropriately identified cancer-specific antigens, meaning that passive immunotherapy needs cancer-specific antigens or suitable targets. On the other hand, the success of IC therapy did not always repeat in all patients, because of difference in individuals' immune responses. As a result, many patients do not respond to IC inhibitors at all, or some patients may lose their initial responsiveness during their treatment, perhaps because of a failure to provoke or maintain the host immunity, or perhaps partly because of a defect of their own immune system itself.

This review focuses mainly on clinical and some pre-clinical studies of immunotherapy, especially targeting immune molecules, other than passive or adoptive immunotherapy and cancer vaccines, considering that they have rather different or unique challenges. However, an improved understanding of immunotherapy might help to create new therapeutic approaches or optimize the therapeutic options including CAR-T cells or cancer vaccines.

CO-INHIBITORY IMMUNE CHECKPOINT INHIBITORS OR ANTAGONISTS (Table 1)

Currently approved IC inhibitors target CTLA-4 and PD-1/PD-L1 co-inhibitory pathways. However, as mentioned above, despite their continuing success, most patients are still unresponsive

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Table 1. Co-inhibitory immune checkpoint inhibitors or antagonists

Target	Agent	Company	Clinical phase	Findings
TIGIT	Tiragolumab (MTIG7192A)	Roche	II/III	• Phase I trial - Monotherapy: ORR 0% - Tiragolumab/atezolizumab for NSCLC: ORR 46% & DCR 85% • Phase II trial of tiragolumab/ atezolizumab - All NSCLC, ORR 37% & mPFS 5.6 months (HR 0.58, 95% CI 0.38-0.89) - High PD-L1 (≥ 50%), ORR 66% & mPFS not reached (HR 0.30, 95% CI 0.15-0.61)
	Vibostolimab (MK-7684)	Merck Sharp & Dohme	II	• Phase I trial - Monotherapy: ORR 7% - Vibostolimab/pembrolizumab: ORR 5% • Phase I part B for anti-PD-1/PD-L1 therapy-naïve patients: - ORR 29% & mPFS 5.4 mo - PD-L1 ≥ 1%, ORR 46% & mPFS 8.4 mo - PD-L1 <1%, ORR 25% & mPFS 4.1 mo
	BMS-986207	Bristol-Myers Squibb	I/II	• ± Nivolumab
	ASP8374	Astellas	I	• ± Pembrolizumab
	AB154	Arcus Bioscience	I/II	• Zimberelimab (AB122, anti-PD-1) vs zimberelimab+ANB154 vs zimberelimab+ANB154+AB928 (dual adenosine receptor antagonist)
	BGB-A1217	Beigene	I	• + Tislelizumab (anti-PD-1)
	Eigliimab (OMP-313M32)	Mereo BioPharma (OncoMed Pharmaceuticals)	I	• ± Nivolumab
	COM902	Compugen	I	
	IBI939	Innovent Biologics	I	
	EOS884448	iTeos Therapeutics	I	
LAG-3	Relatlimab (BMS-986016)	Bristol-Myers Squibb	II	• Relatlimab/nivolumab for melanoma, ORR 11.5% & DCR 49% - LAG-3 ≥ 1%, ORR 18% & DCR 64%
	Eftilagimod alpha (IMP321)	Immutep	II	• Eftilagimod/pembrolizumab for NSCLC as first-line, ORR 53% for HNSCC as second-line, ORR 39%
	Leramilimab (LAG525/IMP701)	Novartis	II	• Leramilimab/spartalizumab - For mesothelioma, 25% (2/8) - For TNBC, 40% (2/5) • ± NIR178 ±canakinumab
	MK-4280	Merck Sharp & Dohme	II	• Phase I trial - monotherapy: ORR 6% & DCR 17% - MK-4280/pembrolizumab: ORR 27% & DCR 40%
	Fianlimab (REGN3767)	Regeneron	III	• + Cemiplimab (REGN2810, Anti-PD-1)
	TSR-033	Tesaro	I	• ± Dostarlimab (TSR-042, anti-PD-1)
	BI-754111	Boehringer Ingelheim	I	• ± BI-754091 (anti-PD-1) • BI-754091 ± BI-754111
	Sym-022	Symphogen	I	• Sym-021 (anti-PD-1) ± Sym-022
	INCAGN02385	Incyte	I/II	• + INCAGN02390 (anti-TIM3) • + INCAGN02390/INCMGA00012 (anti-PD-1)
	Tebotelimab (MGD013)	MacorGenics	I	• ± Brivanib (VEGFR2 inhibitor) or margetuximab (anti-HER2)
	RO7247669	Roche	I	
TIM-3	Cobolimab (TSR-022)	Tesaro	I	• Combination with dostarlimab; - ORR 15% & DCR 40% • TSR-022 ± TSR-042 or nivolumab ± TSR-033 or docetaxel
	MBG453	Novartis	I/II	• ± Spartalizumab
	Sym023	Symphogen	I	• Sym-021 (anti-PD-1) ± Sym-023

Table 1. Continued

Target	Agent	Company	Clinical phase	Findings
	SHR1702	Jiangsu HengRui Medicine	I	• ± Camrelizumab (SHR-1210, anti-PD-1)
	LY3321367	Eli Lilly	I	• ± LY3300054 (Anti-PD-L1)
	BMS986258	Bristol-Myers Squibb	I/II	• ± Nivolumab
	INCAGN2390	Incyte	I	• +INCAGN02385 (anti-LAG3) • +INCAGN02385/INCMGA00012
	RO7121661	Roche	I	
VISTA (B7-H5)	CA-170	Curis	II	• For Hodgkin disease: CBR 52% • For NSCLC; ORR 0%
	JNJ-61610588	Janssen	I	
	HMBD-002	Hummingbird Bioscience	I	
B7-H3 (CD276)	Enoblituzumab (MGA271)	MacroGenics	II	• Enoblituzumab/pembrolizumab - Anti-PD1/PD-L1 naïve patients NSCLC: ORR 35.7% & DCR 92.9% HNSCC: ORR 33.3% & DCR 61.1% - Naïve patients with B7-H3 ≥ 10% NSCLC: ORR 45.5% & DCR 90.9% HNSCC: ORR 40.0% & DCR 73.3%
	MGD009	MacroGenics	I	• Partial clinical hold due to hepatotoxicity
	Omburtamab (8H9)	Y-mAbs Therapeutic	II/III	
BTLA	TAB004/JS004	Shanghai Junshi Bioscience	I	

BTLA: B- and T-lymphocyte attenuator, DCR: disease-control rate, HNSCC: head and neck squamous cell carcinoma, LAG-3: Lymphocyte activation gene-3, NSCLC: Non-small cell lung cancer, mo: month, mPFS: median progression-free survival, ORR: overall response rate, PD-1: programed cell death protein-1, PD-L1: programmed cell death protein ligand-1, TIGIT: T cell immunoglobulin and ITIM domain, TIM-3: transmembrane immunoglobulin and mucin domain 3, TNBC: triple negative breast cancer, VISTA: V-domain Ig Suppressor of T-cell Activation.

and show intolerable immune-mediated toxicity or disease progression in their treatment. Therefore, interest has grown towards other co-inhibitory ICs to overcome their refractoriness or resistance. The front runners include co-inhibitory ICs co-expressing PD-1/CTLA-4, such as LAG-3, TIM-3, and TIGIT, which are highly expressed on dysfunctional or exhausted T cells (1, 2). Many agents targeting one of them have been explored as monotherapy, but their efficacies were not as good as those of anti-PD-1/PD-L1 monotherapy. They are often investigated in combination with anti-PD-1/PD-L1, especially based on preclinical studies which showed that combinational receptor blockade has strong synergistic effects and results in improved effector $CD8^+$ T cell and Natural Killer (NK) cell function as well as decreased regulatory T cell (Treg)-mediated suppression. Other co-inhibitory ICs, such as VISTA, B7-H3 and BTLA, are also being explored. However, because their roles in tumors showing primary or acquired resistance are not known well yet and need to be elucidated further, a few agents are being investigated under early clinical development.

T cell immunoglobulin and ITIM domain (TIGIT)

TIGIT is an Ig-like protein homologous to CD28 interfering with the co-stimulatory axis of the CTLA-4/B7/CD28 axis and plays a key role in the suppression of T-cell proliferation and activation and promotion of T-cell exhaustion. In fact, TIGIT inhibits innate and adaptive immunity by means of, multiple mechanisms, including direct inhibition of T cells through binding CD155 on T cells, indirect inhibition of T cells via increasing interleukin (IL)-10 production, decreasing IL-12 production by binding CD155 on antigen-presenting cells (APCs), and increasing immunosuppressive functions of Tregs. NK cells are also inhibited by TIGIT (3). In mice, dual TIGIT and PD-1/PD-L1 blockade synergize to increase the proliferation and function of antitumor $CD8^+$ T cells, resulting in prolonged overall survival (4). In melanoma patients, dual PD-1/TIGIT blockade also increases the proliferation and function of tumor antigen-specific $CD8^+$ T cells and tumor-infiltrating lymphocytes (TILs) when compared to single blockade (5).

Tiragolumab (MTIG7192A) showed good tolerability as both monotherapy and combinational therapy with atezolizumab, an anti-PD-L1 antibody, and preliminary but promising clinical activity in a phase I trial. In the trial, no response was observed from monotherapy, although the patients included were known to be resistant; however, out of 13 NSCLC patients receiving the combination, the response rate (RR) was 46% and disease-control rate (DCR) was 85% (6). In a following randomized

phase II CITYSCAPE trial, an atezolizumab/tiragolumab combination compared with atezolizumab alone resulted in improved progression-free survival (PFS) with medians of 5.6 months versus 3.9 months, respectively, or 42% reduction in the risk of disease progression or death (stratified hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.38-0.89). Overall response rate (ORR) was also almost doubled, from 21% to 37%. Of more note, explorative analysis did show 70% reduction in the risk in patients with PD-L1 expression $\geq$ 50% (stratified HR, 0.30; 95% CI, 0.15-0.61) with an RR of 66%, but did not in patients with PD-L1 $<$ 50% (7). The two phase 3 trials are ongoing; the SKYSCRAPER-01 trial is exploring atezolizumab with or without tiragolumab in patients with previously untreated advanced or metastatic PD-L1-selected NSCLC; and the SKYSCRAPER-02 trial is exploring atezolizumab plus carboplatin or etoposide with or without tiragolumab in patients with untreated extensive-stage SCLC.

Vibostolimab (MK-7684) also showed good tolerability with or without pembrolizumab, anti-PD-1 antibody and preliminary efficacy in a phase I trial. The ORR was 7% with vibostolimab monotherapy and 5% with a vibostolimab/pembrolizumab combination, whereas the corresponding median duration of response was reportedly 9 months and 13 months, respectively (8). In part B of the trial for anti-PD-1/PD-L1 therapy-naïve patients, the vibostolimab/pembrolizumab combination demonstrated an ORR of 29% and a median PFS of 5.4 months. The ORR and median PFS were 46% and 8.4 months, respectively, in patients with PD-L1 $\geq$ 1%, whereas that was 25% and 4.1 months, respectively, in patients with PD-L1 $<$ 1% (9).

Other anti-TIGIT antibodies are under clinical investigation, including BMS-986207, ASP8374, AB154, BGB-A1217, and OMP-313M32. Many new agents, such as COM902, IBI939, and EOS884448, are also going into early clinical development or are in preclinical development.

Lymphocyte activation gene-3 (LAG-3)

LAG-3/CD223 is a surface molecule located close to CD4 but sharing less than 20% homology. Like CD4, LAG-3 binds to a major histocompatibility complex-II (MHC-II) but with much stronger affinity, prohibits the binding of the same MHC molecule to T-cell receptor (TCR) and CD4, and thus directly hinders TCR signaling in the immune response. However, since its genetic or pharmacological deficiency makes it ineffective alone, it requires cooperation with other signals, such as blockade of the PD-1/PD-L1 pathway. In addition, LAG-3/MHC-II interaction may act as bi-directional inhibitory signaling shared by tumor cells and immune cells. Actually, aberrant LAG-3 expression is observed in many tumor types.

Relatlimab (BMS-986016) showed its efficacy with nivolumab in malignant melanoma patients who had already been exposed to anti-PD-1/PD-L1 therapy. The combination resulted in an ORR of 11.5% including one complete response (CR) and DCR of 49%. An exploratory analysis in patients with LAG-3 $\geq$ 1% showed an RR of 18% and DCR of 64%. Of note, RRs differed according to PD-L1 expression; for PD-L1 $\geq$ 1%, the RR was 6.3%; but for PD-L1 $<$ 1%, that was 27%. For LAG-3 $<$ 1%, PD-L1 expression did not influence responses. For those who had been exposed to anti-CTLA-4 therapy, the RR was 24% when LAG-3 was $\geq$ 1%, whereas that was 8.3% when LAG-3 $<$ 1% (10).

Eftilagimod alpha (IMP321) is a soluble LAG-3 protein that binds MHC-II molecules to mediate antigen-presenting cells (APCs) and then activate CD-8+ T-cell, whereas anti-LAG-3 antibodies inhibit LAG-3 on T cells to restore T-cell activity. Combined with pembrolizumab, the ORR was 53% as first-line therapy for NSCLC patients and 39% as second-line therapy for immunotherapy-naïve head and neck squamous-cell carcinoma (HNSCC) patients (11).

Leramilimab (LAG525 or IMP701), when combined with spartalizumab (PDR001), an anti-PD-1 antibody, led to enduring responses in a phase I trial, including 2 of 8 mesothelioma patients and 2 of 5 triple-negative breast-cancer (TNBC) patients (12).

MK-4280 monotherapy demonstrated an RR of 6% and DCR of 17% in patients with advanced solid tumors, whereas an MK-4280/pembrolizumab combination had an RR of 27% and DCR of 40% (13). Of note, a biomarker-directed randomized phase II (MK-3475-95/KEYNOTE-495) study of pembrolizumab in combination with MK-1308 (anti-CTLA4), MK-4208 or lenvatinib for treatment-naïve NSCLC patients is ongoing. In the study, participants will be defined by gene-expression profiles and tumor-mutation burden before randomization.

In addition to classic IgG4 anti-LAG-3 antibodies, including relatilimab, leramilimab, MK-4280, fianlimab (REGN3767), TSR-033, and BI-754111, different types of anti-LAG-3 antibodies are also under development. Sym022 is an Fc-inert human antibody and INCAGN02385 is an Fc-engineered IgG1k antibody. Of more interest, bi-specific antibodies targeting both LAG-3 and PD-1 were explored based on preclinical findings that both are highly upregulated on dysfunctional TILs and thus co-blockade demonstrates synergistic improvement of antitumor responses. Bi-specific antibodies are under clinical investigation, including tebotelimab (MGD013) and RO7247669. Tebotelimab is being explored not only as monotherapy but also in combination with either brivarinib, VEGFR2 inhibitor, or margetuximab, an anti-HER2 antibody.

Transmembrane immunoglobulin and mucin domain 3 (TIM-3)

TIM-3 is a glycoprotein with poorly understood signaling mediators and heterogeneous ligands. TIM-3 is often co-expressed with PD-1 in exhausted CD8+ cells in tumors that exhibit defects in proliferation and cytokine production. In addition, TIM-3+ and FoxP3+ Tregs seem to be a significant common feature across many tumor types. These cells are more suppressive than are TIM-3- and FoxP3+ Tregs owing to increased production of IL-10, and so promote dysfunctional CD8+ TILs. In preclinical models, its blockade synergizes with blockade of PD-1

despite its lack of efficacy as a single agent.

Cobolimab (TSR022) was evaluated as monotherapy or in combination with TSR-042, an anti-PD-1 antibody. The benefit was observed in combination, with an ORR of 15% and DCR of 40% (14). Cobolimab is also being investigated in combination with either TSR-042 and TSR-033, anti-LAG-3 antibody, or TSR-042 and docetaxel.

Like anti-LAG-3 antibodies, many agents are under clinical investigation, including MBG453, Sym023, INCAGN2390, LY 3321367, BMS-986258 and SHR1702. A bispecific antibody, RO712661, targeting both TIM-3 and PD-1, also entered into clinical investigation.

V-domain Ig suppressor of T-cell activation (VISTA or B7-H5 or PD-1 homolog)

VISTA is highly expressed on mature APCs and, to a lesser extent, on Tregs and TILs. In addition, VISTA expression on infiltration myeloid cells is also consistently observed in many tumor types and increases with tumor progression, meaning that VISTA is active in regulating T-cell and myeloid functions in the tumor microenvironment (TME) (15, 16). Releasing suppressive activity of myeloid cells by the blockade of VISTA could synergize blockade of other IC inhibitors. In fact, the synergic effect of dual VISTA/PD-L1blockage was observed in animal models.

Anti-VISTA antibodies, such as JNJ-61610588 and HMBD-002, are under clinical investigation or about to enter clinical trials. Of interest, CA-170, an oral inhibitor targeting both PD-L1 and VISTA, showed preliminary efficacy. In a phase II trial, the clinical benefit rate (CBR) by irRECIST was 52% in treated Hodgkin lymphoma and more than 70% in treated NSCLC, but no objective response was observed (17, 18).

B7-H3 (CD276)

B7-H3 was initially discovered as a positive co-stimulator but has been found to be involved in the inhibition of T cells in recent studies (19). B7-H3 is expressed in the TME of many tumors and its blockade controlled tumor growth. The anti-tumor immunity was dependent on $CD8^+$ T cells and NK cells (20).

Enoblituzumab (MGA271) has been studied in phase I trials, especially for B7-H3-expressing solid tumors. As monotherapy, enoblituzumab produced four partial responses (PRs) out of 54 patients with solid tumors. Of note, one PR was observed in 18 malignant melanoma patients who had already received either anti CTLA-4 or anti-PD-1 or both (21). With pembrolizumab, enoblituzumab resulted in an ORR of 35.7% for anti-PD-1/PD-L1 therapy-naïve NSCLC and an ORR of 33.3% for anti-PD-1/PD-L1 therapy-naïve HNSCC, whereas RRs ranged from 0% to 7.7% for previously anti-PD-1/PD-L1 therapy-treated patients according to tumor types. Interestingly, high B7-H3 expression was related to better clinical activity; among 11 anti-PD1/PD-L1 therapy-naïve NSCLC patients with PD-L1 $<$ 1% but B7-H3 $\geq$ 10%, there were 5 PRs and 5 SDs, giving an RR of 45.5% and DCR of 90.9%; and among 15 anti-PD1/PD-L1 therapy-naïve HNSCC patients with B7-H3 $\geq$ 10%, 6 PRs and 5 SDs were observed, giving an RR of 40.0% and DCR of 73.3% (22).

Orlotamab (MGD009) is a bispecific antibody binding both CD3 on T cells and B7-H3 on tumor cells. However, it was placed on partial clinical hold because of hepatic adverse events. Omburtamab (8H9), an antibody drug conjugate labeled with radioactive iodine-131, is also being investigated in a phase II and III study for CNS tumors, including leptomeningeal metastases, based on clinical activity seen in two pivotal phase II studies.

B- and T-lymphocyte attenuator (BTLA, CD272)

BTLA is another inhibitory receptor that belongs to the CD28 immunoglobulin superfamily and is expressed on mature lymphocytes,-including Tregs, macrophages, and mature bone-marrow-derived DCs. Co-signaling molecules can be classified into two families based on their structure. One is the CD28 immunoglobulin superfamily, which includes co-stimulatory molecules, such as CD28, inducible co-stimulatory molecule (ICOS), and co-inhibitory molecules, such as CTLA-4, PD-1, TIM-3, LAG-3, TIGIT, and BTLA. The other is the tumor necrosis factor receptor superfamily (TNFRSF), which includes co-stimulatory molecules, such as CD27, CD30, 4-1BB, CD40, OX40 and GITR. Therefore, BTLA is similar to PD-1 and CTLA4, inhibiting T-cell activation and cytokine production. TAB004/JS004, the first anti-BTAL antibody, entered into clinical investigation.

CO-STIMULATORY IMMUNE-CHECKPOINT AGONIST (Table 2)

Co-stimulatory ICs are also the target of clinical development. Unlike IC inhibitors targeting co-inhibitory ICs, development of agonists is complicated for several reasons. One problem is the geometric constraints of the peculiar structure of receptors. The cross-linking properties, which are influenced by the interaction between targeting antibodies and Fcγ receptors on surrounding cells, may be a key for their efficacy, and therefore synthetic ligands could be more effective than are antibodies. A further complication is the contradictory role of co-stimulatory ICs on inducible effector T cells and on constitutively expressed regulatory T cells. The different expressions in T cells might allow designing dual activity agents that productively engage effector T cells while selectively depleting regulatory T cells, especially through antibody-dependent cellular cytotoxicity (ADCC). However, such agents might require sufficient density of ADCC-competent myeloid/NK cells or synergize by increasing innate infiltrates. They are also being investigated or developed as monotherapy or in combination with IC inhibitors, such as anti-CTLA4 or anti PD-1/PD-L1 antibodies.

Table 2. Co-stimulatory immune checkpoint agonists

Target	Agent	Company	Clinical phase	Findings
ICOS	Vopratelimab (JTX-2011)	Jounce Therapeutics	I/II	• As monotherapy - For ICOS high: ORR 22.2%, mPFS 6.2 mo & mOS 21.4 mo - For ICOS low: ORR 0%, mPFS 2 mo & mOS 9 mo • ± Nivolumab or ipimilumab
	GSK3359609	GlaxoSmithKline	III	• For HNSCC, - Onotherapy; ORR 8% - GSK3359609/pembrolizumab; ORR 28%
	MEDI-570	MedImmune	I	• T-cell lymphoma
	KY1044	Kymab Limited	I/II	• ± Atezolizumab
OX40 (CD134)	PF-0451860	Pfizer	II	• Monotherapy; ORR 4% • Avelumab ± PF-0451860 or axitinib ± PF-0451860 • PF-0451860 ± utomilumab (4-1BB agonist)
	Tavolimab (MEDI-0562)	MedImmune	I	• Monotherapy; 2 immune-related PR
	MEDI6962	MedImmune	I/II	• Monotherapy or MEDI6962/tremelimumab or MEDI6962/ritiximab; ORR 0% • MEDI6962/durvalumab; ORR 5%
	GSK3174998	GlaxoSmithKline	I/II	• Monotherapy: ORR 2.2% • GSK3174998/pembrolizumab; ORR 7.3%
	Vonlerolizumab (MOXR0916)	Genentech	I	• Vonlerolizumab/atezolizumab; ORR 4%
	BMS-986178	Bristol-Myers Squibb	I/II	
	INCAGN01949	Incyte	I/II	• Monotherapy: ORR 0% • + Nivolumab or ipilimumab or both
	ABBV-368	AbbVie	I	
	ATOR-1015	Alligator Bioscience	I	
GITR (CD357)	TRX 518	Leap Therapeutics,	I/II	• Monotherapy: ORR 0% • ± Nivolumab or pembrolizumab
	MK-4166	Merck Sharp & Dohme	I	• Monotherapy: ORR 0% • MK-4166/pembrolizumab, - Escalation cohort; ORR 9% - Expansion cohort for melanoma IC inhibitor naïve; ORR 69% IC inhibitor treated; ORR 0%
	MK-1248	Merck Sharp & Dohme Corp		• Monotherapy; ORR 0% • MK-1248/pembrolizumab; ORR 18%
	BMS-986156	Bristol-Myers Squibb	I/II	• Monotherapy: ORR 0% • BMS-986156/nivolumab - HNSCC; ORR 14.3% - Cervical cancer; ORR 13.9% - Bladder cancer, ORR 10.7% - HCC, ORR 8.3% - NSCLC, ORR 2.7%
	INCAGN01876	Incyte Corporation	I/II	• ± Pembrolizumab & epacadostat • + Nivolumab or ipilimumab or both
	OMP-336B11	OncoMed Pharmaceuticals	I	Terminated by sponsor decision
	MEDI1873	MedImmune	I	• Monotherapy; ORR 0%

Inducible co-stimulator (ICOS, CD278)

ICOS/CD278 is a disulfide-linked homodimer and a member of the B7/CD28 immunoglobulin superfamily that is expressed mainly on activated T cells. It is structurally and functionally similar to CD28 Biologically, it is closely intertwined with CTLA-4 and therefore, it is required for and upregulated by CTLA-4 blockade, meaning that it strongly synergizes with CTLA-4 blockade in poorly immunogenic tumors.

The first agent is vopratelimab (JTX-2011), which was designed to achieve dual agonist/Treg-depleting activity. The phase I/II ICONIC trial as monotherapy or combinational therapy with nivolumab for heavily treated patients did show that the emer-

Table 2. Continued

Target	Agent	Company	Clinical phase	Findings
4-1BB (CD137)	Urelumab (BMS-663513)	Bristol-Myers Squibb	I/II	• Monotherapy for R/R NHL: - DLBCL; ORR 6% - FL; ORR 12% - Other NHL; ORR 17% • Urelumab/rituximab: - DLBCL; ORR 10% - FL; ORR 35% • Urelumab/nivolumab - Melanoma; ORR 50% - NSCLC; ORR 5% - HNSCC, ORR 4.5%
	Utomilumab (PF-05082566)	Pfizer	I/II	• Monotherapy; ORR 3.8% - Merkel cell carcinoma; ORR 13.4% • Utomilumab/rituximab for R/R NHL; ORR 21.2% • Utomilumab/pembrolizumab; ORR 26.1% • Utomilumab/mogamulizumab (CCR4 inhibitor); ORR 4.2%
	PRS-343	Pieris Pharmaceuticals	I	• Monotherapy for heavily treated HER2+ patients; ORR 11%
	INBRX-105	Inhibrx	I	
CD27	Varlilumab (CDX-1127)	Celldex Therapeutics	I/II	• Monotherapy - HD; ORR 10% - NHL; ORR 0%
CD70	Cusatuzumab (ARGX-110)	Argenx	I/II	• Monotherapy for solid tumor; ORR 0% • Monotherapy for CTCL, ORR 23% • Cusatuzumab/azacitidine for AML, ORR 92%
CD40	CP-870893	Pfizer	I	• Monotherapy for solid tumor; ORR 0% • CP-870893/paclitaxel/carboplatin for solid tumors; ORR 20% • CP-870893/gemcitabine for pancreatic cancer; ORR 24% • CP-870893/pemetrexed/cisplatin for mesothelioma; ORR 40%
	APX005M	Bristol-Myers Squibb	I/II	• APX005M/gemcitabine/nab-paclitaxel for pancreatic cancer; ORR 58%
	ChiLob7/4	Cancer Research UK	I	
	SEA-CD40	Seattle Genetics	I	• ± Pembrolizumab or pembrolizumab/gemcitabine/nab-paclitaxel
	CDX-1140	Celldex Therapeutics	I	• ± Pembrolizumab or gemcitabine/nab-paclitaxel

AML: acute myelogenous leukemia, CCR4: C-C chemokine receptor 4, CTCL: cutaneous T-cell lymphoma, DLBCL: diffuse large B-cell lymphoma, GITR: glucocorticoid-induced TNFR-related, FL: follicular lymphoma, HCC: hepatocelluar carcinoma, HD: Hodgkin disease, HER2: human epidermal growth factor receptor 2, HNSCC: head and neck squamous cell carcinoma, ICOS: Inducible co-stimulator, NHL: non-Hodgkin lymphoma, NSCLC: Non-small cell lung cancer, mo: month, mOS: median overall survival, mPFS: median progression-free survival, ORR: overall response rate, RR: relapsed/refractory.

gence of ICOS-high CD4+ cells was associated with the ORR, PFS, and OS. Out of 18 ICOS-high patients, 4 showed responses, giving an ORR of 22.2% with median PFS and OS of 6.2 months and 21.4 months, respectively, whereas 32 ICOS-low patients did not show any response with median PFS and OS of 2 months and 9 months, respectively (23). Following a phase II EMERGY study of vopratelimab in combination with ipilimumab, an anti-CTLA4 antibody, in NSCLC and urothelial tumors, is now recruiting after failure of anti PD-1/PD-L1 therapy. A combination study with nivolumab or ipilimumab for advanced/refractory solid tumors is also ongoing.

GSK33359609 is a pure agonist and is investigated with or without pembrolizumab in the INDUCE-1 study, in which an ORR of 8% and 28% was observed in monotherapy and combination therapy, respectively, in an expansion cohort of previously treated HNSCC patients with median PFS of 5.6 months (24). MEDI-570, which has strong ADCC-mediated T-cell-depleting activity, is under investigation in T-cell lymphoma. KY1044 is a dual agonist/depleting activity and is under clinical investigation with or without atezolizumab, anti-PD-L1 antibody.

OX40 (CD134 or TNFRSF4)

OX40, GITR, and 4-1BB are structurally related as members of TNFRSF and inducible T-cell co-stimulators like ICOS. OX40 has important co-stimulatory functions during T-cell activation, mediating the survival and expansion of both $CD4^+$ and $CD8^+$

T cells in cancer as well as in auto-immunity and infectious diseases. OX40 also involves in controlling effector and memory T-cell responses. So, targeting OX40-OX40L interaction can promote non-regulatory $CD4^+$ and $CD8^+$ T-cell survival, sustain anti-apoptotic protein expression like BCL-XL, BCL-2 and survivin, increase cytokine production like IL-2 and IFN-γ, boost tumor-specific effector T-cell responses, and augment tumor-specific memory T-cell generation following antigen challenge. Of interest, the application of an anti-OX40 agonist was shown to induce activation and proliferation of T-cell populations, but also resulted in upregulation of PD-L1 in tumors occurring between 2 and 3 weeks after the administration. These findings suggested synergism with anti-PD/PD-L1 inhibitors.

Most OX40-targeting agents were in development as monoclonal antibodies and their safety profiles were reportedly manageable in early-phase trials. They include PF04518600, GSK 3174998, MEDI0562, MEDI6469, BMS986178, INCAGN01949, and MOXR0916. Some of them showed preliminary but limited clinical activity. New agents such as KY-B602 are still under preclinical development. Less conventional molecules are also under clinical investigation. MEDI1109 is a bispecific antibody co-targeting OX40 and PD-L1, and ATOR-1015 is a bispecific antibody co-targeting OX40 and CTLA-4. The one has not entered into clinical development yet, but the latter has already entered early clinical investigation.

PF-04518600 showed only one PR out of 25 evaluable patients in a phase I trial (25). PF-04518600 is being explored in combination with either FDA-approved agents or new agents. For example, not only avelumab, an anti-PD-L1 inhibitor, or axitinib, a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI), with or without PF-04518600, is being investigated. PF-04518600 with or without utomilumab, an anit-4-1 BB agonist, is also being studied. However, disappointingly, PF-04518600 was not seen in the sponsor's pipeline.

GSK3174998 was studied with or without pembrolizumab. There was one PR out of 45 patients enrolled in the monotherapy part, and 2 CRs and 7 PRs out of 96 patients enrolled in the combination part (26). GSK3174998 is now being explored in combination with other agents, such as pembrolizumab or GSK1795091, a toll-like receptor 4 agonist (TLR4).

MEDI0562 as a single agent showed 2 immunity-related partial responses and 44% stable disease in 55 patients enrolled, 47% of whom had HNSCC (27). A study of MEDI0562 in combination with either durvalumab, anti-PD-L1, or tremelimumab, an anti-CTLA4, for advanced solid tumor completed the enrollment but the results are not reported yet.

MEDI6469 was also investigated but as monotherapy; there was no response (28). Like MEDI0562, MEDI6469 was also investigated with durvalumab, tremelimumb, or rituximab. However, only one PR was observed in MEDI6469/durvalumab combination, but no response was observed as a single agent or when combined with tremelimumab or ritixumab. Accordingly, the sponsor discontinued the development of the two agents.

Vonlerolizumab (MOXR0916) was evaluated with or without atezolizumab. A phase Ib dose-escalation study of MOXR0916 and atezolizumab showed 2 PRs out of 51 patients or an ORR of 4% (29). So, the sponsor discontinued the MOXR916 program.

INCAGN01949 did not induce any response in a phase I/II study (30). A study of a combination of INCAGN01949 with either nivolumab or ipilimumab or both has completed the enrollment.

Glucocorticoid-induced TNFR-related (GITR, TNFRSF18)

GITR is also known as activation-inducible tumor necrosis factor. It is constitutively and highly expressed in CD4+/CD25+ regulatory T cells but expressed inducibly on NK and effector T cells. On the other hand, its ligand (GITRL) is also expressed on non-lymphoid activated APCs and endothelial cells. Its role is complex and context-dependent. GITR-null T cells show increased proliferation upon TCR engagement and increased antigen-induced cell death. Conversely, the engagement of GITR through ligands or agonistic antibodies promotes the expansion of effector T cells and production of cytokines.

TRX518, a first IgG1 anti-GITR antibody, showed unremarkable toxicity but little efficacy as monotherapy (30). It reduced circulating and intratumoral Tregs and increased the T_{eff}/T_{reg} ratio. In preclinical models using TRX518, GITR agonism was not sufficient to activate cytolytic T cells, because of persistent exhaustion, but combination with PD-L1 blockade reinvigorated T cells, suggesting the possibility of overcoming resistance (31).

In fact, as single anti-GITR antibodies, TRX518, MK-4166, MK-1248, BMS986156, and MEDI1837 demonstrated a manageable safety profile but disappointingly limited clinical activity or no objective response. When combined with anti-PD-1/PD-L1 antibody, preliminary clinical activity was observed without dose-limiting toxicities (DLTs).

MK4166, humanized IgG1 antibody, in combination with pembrolizumab, showed 4 PRs out of 45 patients or an ORR of 9% in a dose-escalation cohort. There were 4 CRs and 5 PRs or an ORR of 69% in 13 IC inhibitor-naïve melanoma patients in an expansion cohort, whereas there was no response in previously IC-inhibitor-treated patients (32).

MK1248, a humanized IgG4 antibody, in combination with pembrolizumab, resulted in 1 CR and 2 PRs out of 17 patients, giving an ORR of 18%, whereas there was no response with monotherapy (33).

BMS-986156 when combined with nivolumab showed some clinical activity with ORRs of 0% to 11.1% across the different dose cohorts. Of note, responses were observed in different tumor types with ORRs of 14.3% for HNSCC, 13.9% for cervical cancer, 10.7% for bladder cancer, 8.3% for hepatocellular carcinoma (HCC), and 2.7% for NSCLC (34). INCAGN01876 was studied alone or with pembrolizumab and epacadostat, and is now being studied with either nivolumab or ipilimumab or both.

However, AMG228 was not under further development, because of a business decision based on a phase I study in which there was no evidence of T-cell activation or anti-tumor activity with AMG 228 monotherapy (35).

Besides antibodies, other agents, including OMP-336B11, a synthetic GITR ligands-Fc fusion protein, and MEDI1873, a homogenous hexameric GITRL fusion protein, were investigated. However, further clinical development of OMP-336B11 and MEDI8373 is not planned, because of the sponsor's decision or lack of anti-tumor activity, respectively (36, 37).

4-1BB (CD137 or TNFRSF9)

4-1BB provides CD28-independent co-stimulation that can overcome anergy, since 4-1BB can play a role of cytokine induction, prevent activation-induced cell death, and upregulate cytotoxic T-cell activity, but also may also be involved in reduction of the infiltration of Tregs into tumors. Agonists can eradicate established tumors even in monotherapy or in combination with anti-PD-1, inducing memory CD8-mediated long-term rejection of poorly immunogenic tumors. Two agonistic antibodies have been studied well to date.

The clinical development of IgG4 urelumab (BMS-663513) has been held up transiently because of the occurrence of target dose-dependent and fatal liver toxicity, but was restarted after lowering doses as monotherapy and combination therapy (38). The toxicity is related to the S100A4 protein secreted by tumors and stromal cells and thus close monitoring of liver enzymes is needed (39). A preliminary clinical activity was observed in lymphoma patients. With urelumab monotherapy who were refractory or resistant to rituximab. The ORR was 6% in patients with DLBCL, 12% in follicular lymphoma (FL), and 17% in other types of non-Hodgkin's lymphoma (NHL). With a urelumab and rituximab combination, the ORR was 10% for DLBCL and 35% for FL (40). In another study of combination with nivolumab, encouraging efficacy was observed in melanoma patients, with RR of 50%. However, in NSCLC and HNSCC patients, clinical activity was disappointingly limited, with RRs of 5% and 4.5%, although no significant added toxicity was observed (41).

The other IgG2 utomilumab (PF-05082566) did show a better safety profile with no dose-limiting toxicities (DLTs). It also showed preliminary clinical activity, in that ORR was 3.8% for solid tumors and 13.3% for Merkel cell carcinoma with a complete response (42). With rituximab for refractory and resistant NHL, it showed an ORR of 21.2%, including 4 CRs and 7 PRs (43). Many combinations of utomilumab with other agents were also explored. The combination with pembrolizumab showed a favorable safety profile and preliminary clinical activity with an ORR of 26.1% (44). The combination with mogamulizumab, an anti-C-C chemokine receptor 4 (CCR4) antibody, showed a favorable safety profile but limited clinical activity, with an ORR of 4.2% (45).

In fact, urelumab caused dose-dependent hepatitis, limiting the dose, whereas utomilumab had a better safety profile but lower agonistic potency. To overcome these limitations, different approaches are being investigated, such as Fc-free tumor-targeted 4-1BB-agonistic trimer body, or bispecific antibodies co-targeting 4-1 BB and HER2 or PD-1.

1D8 N/C EGa1 is a 4-1BB-agnostic trimeric antibody. Trimeric antibodies have two major advantages compared to conventional IgG monoclonal antibodies; one is they lack the fragment crystallizable (Fc) region involved in 4-1BB-mediated toxicity; and the other is that they are trimeric or more physiological 4-1BBL. In a preclinical study, 1D8 N/C EGa1 did induce potent anti-tumor activity without systemic toxicity (46). However, it has not entered into clinical investigation yet.

PRS-343 co-targets 4-1BB and HER2 and showed a preliminary but promising RR of 11%. Out of 18 evaluable but heavily treated HER2+ patients, 2 PRs were observed (47). However, PRS-343 trials are now suspended because of a partial clinical hold. INBRX-105 co-targets both 4-1BB and PD-1 and is now recruiting.

CD27 (TNFRSF7) and CD70

CD27 is another member of TNFRSF and a costimulatory molecule on T cells, mediating cellular activation, proliferation, effector function, and cell survival on binding to its unique ligand, CD70. Expression of CD70 is tightly controlled and upregulated exclusively upon activation on T cells, B cells, and certain subsets of dendritic cells (DCs).

Varlilumab (CDX-1127), an anti-CD27 agonistic antibody, launched a first-in-human, dose-escalation, and expansion study for hematologic malignancies. The study showed a favorable safety profile with no DLTs. One out of 10 HD patients experienced CR, but out of 18 NHL patients, none experienced any response (48).

Cusatuzumab (ARGX-110), an anti-CD70 antibody, was also investigated in solid tumors and hematologic malignancies. In a phase I study for solid tumors, neither DLTs nor an anti-tumor response was observed (49). However, for heavily treated CD70+ cutaneous T-cell lymphoma patients, as monotherapy the ORR was 23% with 1 CR and 5 PRs, whereas, combined with azacitidine for newly diagnosed AML patients, ORR was amazingly 92%, including 9 CR/CRi and 1 morphologically leukemia-free statues (50, 51).

During the last decade, three antibody-drug conjugates targeting CD70, including vorsetuzumab mafodotin (SGN-75), MDX-1203 (BMS-936561) and SGN-CD70A, reached clinical development for lymphoma but now all have been discontinued.

CD40 (TNFRSF5)

CD40 is expressed on a wide range of hematopoietic and non-hematopoietic cells, but its ligand, CD154 or CD40L, is restrictedly expressed on activated T cells, B cells and platelets. The activation of CD40 leads to upregulation of MHC molecules, immunoglobulin superfamily co-stimulatory molecules, such as CD86, and other TNFRSF ligands, such as CD137, GITR, and OX40.

Selicrelumab (CP-870893) produced an RR of 27% in advanced melanoma, whereas none of the 14 patients with other solid tumors responded. Interestingly, one patient experienced long-lasting remission for more than 15 years (52). However, in a subsequent trial, including malignant melanoma patients, there was no response in solid tumors (53). Following combinations with cytotoxic chemotherapy were studied. With carboplatin/paclitaxel, selicrelumab produced an ORR of 20% in advanced solid tumors; with gemcitabine for metastatic pancreatic cancer, it produced an ORR of 24%, and with cisplatin/pemetrexed for malignant pleural mesothelioma, it resulted in an ORR of 40% (54-56).

Other agonistic anti-40 agonists, including APX005M, ChiLob 7/4, SEA-CD40, and CDX-1140, did not result in meaningful clinical activity (57-60). Recently, for newly diagnosed metastatic pancreatic cancer patients, a result of a phase Ib trial of APX005M and chemotherapy with or without nivolumab reported an ORR of 58% (61). A randomized phase II study of gemcitabine/nab-paclitaxel with or without APX005M (0.3 mg/kg) and with or without nivolumab is under way. Other anti-CD40 agonists are also being investigated with pembrolizumab or gemcitabine/nab-paclitaxel or both.

OTHER IMMUNOMODULATORS OR MEDIATORS (Table 3)

Adenosine pathway

Adenosine (ADO) is an effective endogenous immunosuppressant in cancer as well as in normal condition. It is excreted by stressed or injured cells or is generated through dephosphorylation of adenosine-monophosphate by the enzyme CD73, ecto-5′-nucelotidase. Hypoxia and TGF-β are key determinants of producing adenosine derivatives. Hypoxia induces release of ATP or NAD+, a possible source of bioactive adenosine, through the activity of multiple enzymes expressed on cancer cells, such as CD39 or CD73. ADO acts by binding the amine receptors expressed on immunity cells, especially T and NK cells, of which the cAMP-increasing adenosine receptor 2a and 2b, A2aR and A2bR, play a key role. As a result, ADO provokes Tregs and myeloid-derived suppressor cells (MDSCs) accumulation, T_{eff} and NK inhibition, or cancer-associated fibroblast proliferation, finally generating tumorigenic TME. In fact, ADO and CD73 are widely expressed on a variety of cells in the TME. Therefore, inhibition of either CD73 or A2aR or both could improve the activity of cytotoxic lymphocytes and reduce tumor growth. Synergy with anti-PD1 or anti-PDL1 and anti CTLA-4 therapies was also observed in preclinical studies. Agents targeting CD73, such as oleclumab or BMS-986179, are under clinical development alone or with anti-PD1/PD-L1 or anti-CTLA4 antibody.

A phase I first-in-human study with oleclumab (MEDI9447) alone or in combination with durvalumab for patients with advanced pancreatic or microsatellite-stability colorectal cancer (CRC) showed a safety profile as manageable as that of monotherapy, but showed a preliminary clinical activity in the combination arm only like that of many other new immunotherapeutic agents. There was 1 PR out of 21 CRC patients, giving an RR of 4.7%, and 2 PRs out of 20 pancreatic-cancer patients, giving an RR of 5% (62).

A phase I study of BMS-986179 in which patients received 2-week BMS-986179 monotherapy, followed by the combination with nivolumab, also showed a finding similar to that of oleclumab, in that a single BMS-986179 therapy demonstrated complete and persistent CD73 target engagement in the tumor and periphery, and then the combination produced a PR in 7 out of 52 patients (63).

CPI-006, an anti-CD73 antibody, alone or in combination with pembrolizumab or ciforadenant (CPI-444), an A2aR antagonist, is under clinical investigation. AK119, an anti-CD73 antibody recently entered clinical investigation with or without AK104, a PD-1/CTLA-4 bispecific antibody. LY3475070, a CD73 oral inhibitor, is also being explored as monotherapy or combinational therapy with pembrolizumab. GS-1423, an anti-CD73-TGFβ-Trap bifunctional antibody, is being clinically investigated with or without chemotherapy.

On the other hand, small molecules targeting A2aR were also developed to competitively inhibit ADO binding. Ciforadenant (CPI-444), originally investigated for Parkinson's disease, was tested alone or with atezolizumab and showed a good safety profile as a single agent or in combinational therapy. However, the clinical activity was relatively disappointing. For previously treated RCC patients, ciforadenant alone resulted in an RR of 3% with a median PFS of 4.1 months, whereas a ciforadenant/atezolizumab combination resulted in an RR of 11% with a median PFS of 5.8 months (64). For 18 NSCLC patient, only one PR was observed (65). Another study of ciforadenant with or without atezolizumab for heavily treated metastatic castration-resistant prostate cancer (CRPC) did not produce any objective response (66).

A phase I study of NIR178 as a single agent showed a favorable safety profile and clinical benefits in heavily treated NSCLC patients, with an RR of 11.8% including 1 CR (67). A subsequent phase I/II study of NIR178 and spartalizumab (PDR001), an anti-PD-1 antibody, showed clinical benefits in 2 patients including 1 CR, giving an RR of 8% (68). Following phase II studies in combination with spartalizumab are ongoing.

AZD4635 also showed clinical activity with manageable toxicities in a phase Ia study. Interestingly, at first 3 PRs were observed in 8 evaluable metastatic CRPC patients, including 1 PR in monotherapy and 1 CR and 1 PR in combination with durvalumab (69). More data with more metastatic CRPC patients were reported; in the monotherapy group, the ORR was 6.1%, and in the combination group, it was 16.2%, interestingly including 2 CRs. Of note, patients with a high adenosine gene signature in the peripheral blood showed longer PFS than did those with a low signature (median PFS 21 weeks vs 8.7 weeks; HR 0.5; 95 CI, 0.3-0.9) (70). A following phase II study for mCRPC patients is ongoing.

Table 3. Other immunomodulators or mediators

Target	Agent	Company	Clinical phase	Findings
CD73	Oleclumab (MEDI9447)	AstraZeneca	I/II	• Monotherapy for solid tumors; ORR 0% • Oleclumab/durvalumab, - CRC; ORR 4.7% - Pancreatic cancer; ORR 5%
	BMS-986179	Bristol-Myers Squibb	I	• BMS-986179/nivolumab; ORR 13.4%
	CPI-006	Corvus Pharmaceuticals	I	
	AK-119	Akeso	I	• ± AK104 (PD-1/CTLA-4 bispecific antibody)
	LY3475070	Eli Lilly	I	
A2aR	Ciforadenant (CPI-444)	Corvus Pharmaceuticals	I	• For previously treated RCC, - Monotherapy; ORR 3% & mPFS 4.1 mo - Ciforadenant/atezolizumab; ORR 11% & mPFS of 5.8 mo • For previously treated NSCLC; ORR 5.5% • For previously treated CRPC; ORR 0%
	NIR178	Novartis	I/II	• For previously treated NSCLC, - Monotherapy; ORR 11.8% - NIR178/spartalizumab; ORR 8%
	AZD4635	AstraZeneca	I/II	• For metastatic CRPC, - Monotherapy; ORR 6.1% - AZD4635/durvalumab; ORR 16.2%
A2bR	PBF-1129	Palobiofarma SL	I	
A2aR & A2bR	AB928	Arcus Biosciences	I	
IDO-1,2	Indoximod	New Link Genetics	II	• Sipuleucel-T ± indoximod for refractory metastatic prostate cancer, mPFS 10.3 mo vs 4.1 mo • Indoximod/gemcitabine/nab-paclitaxel for pancreatic cancer, ORR 46.2% • Indoximod/pembrolizumab for melanoma, ORR 53% & mPFS 12.4 mo
	Epacadostat	Incyte Biosciences	III	• Pembrolizumab ± epacadostat for melanoma, mPFS 4.7 mo vs 4.9 mo (HR 1.00, 95% CI 0.83-1.21; one-sided P = 0.52) & OS (HR 1.13, 95% CI, 0.86-1.49; one-sided P = 0.81)
CSF-1/CSF-1R	Emactuzumab (RG7155)	Roche	I/II	• Emactuzumab/paclitaxel; ORR 7%
	Lacnotuzumab (MCS110)	Novartis	I	• Lacnotuzumab/spartalizumab; ORR 2%
	PD-0360324	Pfizer	I	
	BMS-986227	Bristol-Myers Squibb	I	
	IMC-CS4	Eli Lilly	I	
CD47	Hu5F9-G4	Gilead Sciences	I	• Hu5F9-G4/rituximab for rituximab-refractory NHL; ORR 50% • Hu5F9-G4/azacitidine for chemotherapy-ineligible untreated AML or high risk MDS;ORR 53% • + Rituximab, cetuximab, avelumab or atezolizumab
	CC-90002	Celgene	I	• CC-90002/rituximab; ORR 13%
	AK117	Akeso	I	
	IBI188	Innovent Biologics	I	• ± Rituximab
	IBI322	Innovent Biologics	I	
	TTI-622	Trillium Therapeutics	I	• ± Rituximab, nivolumab or carfilzomib (proteasome-inhibitor)
	ALX-148	ALX Oncology	I/II	• ALX-148/rituximab; ORR 35% - Indolent NHL, ORR 50% - Aggressive NHL, ORR 31% • ALX-148/pembrolizumab for HNSCC - IC inhibitor naïve; ORR 40% - IC inhibitor treated; ORR 0% • ALX-148/trastuzumab for HER2+ G/GEJ cancer; ORR 21%

Table 3. Continued

Target	Agent	Company	Clinical phase	Findings
Chemokine-chemokine receptor inhibitor	PF-04136309 (CCR2 inhibitor)	Pfizer	I	• PF-04136309/FOLFIRINOX; ORR 48.5% • PF-04136309/gemcitabine/nab-paclitaxel; ORR 60%
	BMS-813160 (CCR2/CCR5 inhibitor)	Bristol-Myers Squibb	I/II	• BMS-813160/nivolumab/gemcitabine/nab-paclitaxel
	Carlumab (CNTO888, anti-CCL2),	Centocor Research & Development	I	• Monotherapy for metastatic CRPC; ORR 0%
	Mogamulizumab (KW0761, anti-CCR4)	Kyowa Kirin	I/II	• Mogamulizumab/nivolumab, - For HCC, ORR 27% - For pancreatic cancer, ORR 20% • Mogamulizumab/durvalumab or mogamulizumab/tremelimumab; ORR 5.3% • Mogamulizumab/utomilumab; ORR 4.2%
	Reparixin (DF1681Y, CXCR1/CXCR2 inhibitor)	Dompé Farmaceutici S.p.A	II	• Reparixin/paclitaxel; ORR 29.6%
	Navarixin (MK-7123, CXCR2 inhibitor)	Merck Sharp & Dohme Corp	II	
	AZD5069 (oral CXCR2 inhibitor)	Astra Zeneca	II	• AZD5069/durvalumab for pancreatic cancer; ORR 5.6%
	Plerixafor (AMD3100, oral CXCR4 inhibitor)	Merck Sharp & Dohme Corp	II	
	LY2510924, (CXCR4 peptide antagonist)	Eli Lilly	II	• LY2510924/durvalumab for pancreatic cancer; ORR 0%
	Balixafortide (POL6326, CXCR4 peptide antagonist)	Polyphor	III	• Balixafortide/eribulin for HER- breast cancer, ORR 30% • Eribulin ± balixafortide for HER- breast cancer
KIRs	IPH2011	Innate Pharma	I	• Monotherapy; ORR 0%
	Lirilumab (IPH2102/BMS-986015)	Bristol-Myers Squibb	I/II	• Monotherapy; ORR 0% • Lirilumab/nivolumab for HNSCC; ORR 24% • + Nivolumab/ipilimumab
	Lacutamab (IPH4102)	Innate Pharma	II	• Monotherapy for CTCL; ORR 36.4%
NKG2A	Monalizumab (IPH2201)	Innate Pharma	II	• Monalizumab/cetuximab for HNSCC; ORR 20%
STING agonist	MK-1454	Merck Sharp & Dohme	I	• MK-1454/pembrolizumab; ORR 24%
	ADU-S100 (MIW815)	Aduro Biotech	I	• MIW815/spartalizumab, ORR 3% • + Pembrolizumab or ± ipilimumab
	GSK3745417	GlaxoSmithKline	I	• ± Pembrolizumab
	TAK-676	Takeda	I	• ± Pembrolizumab
	E7766	Eisai	I	

A2aR: adenosine receptor 2a, A2bR: adenosine receptor 2a, AML: acute myelogenous leukemia, CCL: C-C chemokine ligand, CCR2: C-C chemokine receptor 2, CCR4: C-C chemokine receptor 4, CCR5: C-C chemokine receptor 5, CRC: colorectal cancer, CRPC: castration resistant prostate cancer, CSF-1/CSF-1R: colony stimulating factor-1 and colony stimulating factor-1 receptor, CTCL-4: cytotoxic T-lymphocyte associate protein 4, CTCL: cutaneous T-cell lymphoma, CXCR1/CXCR2: CXC chemokine receptor 1/2, CXCR4: CXC chemokine receptor 4, HCC: hepatocelluar carcinoma, HER2: human epidermal growth factor receptor 2, HNSCC: head and neck squamous cell carcinoma, HR: hazard ratio, G/GEJ: gastric/gastroesophageal junction, IC: immune checkpoint, IDO-1,2: Indoleamine-2,3-dioxygenase 1 and 2, KIR: killer-cell immunoglobulin-like receptors, MDS: myelodysplastic syndrome, NHL: non-Hodgkin lymphoma, NSCLC: Non-small cell lung cancer, ORR: overall response rate, mo: month, OS: median overall survival, mPFS: median progression-free survival, RCC: renal cell carcinoma, STING: stimulator of interferon genes.

More A2aR inhibitors are under preclinical development. In addition, an A2aR inhibitor, PBF-1129, an A2bR antagonist, and AB928, a dual antagonist of the A2aR and A2bR, are also under clinical investigation (71).

Indoleamine-2,3-dioxygenase 1 (IDO-1) pathway

IDO1, a cytosolic heme-containing enzyme, involves in the catabolism of tryptophan, which was first shown to be critical for maternal-fetal immunity tolerance. IDO-1 inhibits activation of immune system by inhibition of mammalian target of rapamycin (mTOR) through tryptophan depletion, formation of kynurenine which promotes Tregs through the aryl hydrocarbon receptor, and non-enzymatic signaling through its ITIM domain homologous to TIGIT. Interestingly, IDO1 is induced by IFN-γ, and thus could mediate s primary or acquired resistance to anti-CTLA-4.

Indoximod showed preliminary but promising results in combination with sipuleucel-T in refractory metastatic prostate cancer, with an increase in PFS to 10.3 months vs 4.1 months and in combination with chemotherapy in pancreatic adenocarcinoma with a median OS of 10.9 months and an ORR of 46.2% (72, 73). For melanoma patients, with pembrolizumab, indoximod produced an ORR of 53% with a rate of CR of 18% and a median PFS of 12.4 months (74). Actually, indoximod is not an IDO-1 inhibitor but more of a tryptophan mimetic, directly relieving mTOR inhibition on lymphocytes.

On the other hand, epacadostat, an IDO-1-selective hydroxyamidine, showed good efficacy in initial clinical trials. However, it did not work better in the larger phase III ECHO-301 trial, in which epacadostat and pembrolizumab had been compared with pembrolizumab alone in advanced melanoma patients, thereafter blocking or slowing down the further investigation of IDO-1 inhibitors (75). However, it is still not clear if IDO1 is an inherently ineffective target or if a more potent and stable compound is needed. In fact, patients who were previously treated with CTLA-4 inhibitor or BRAF inhibitor were included in the ECHO312 trial. Those prior therapies might increase the IDO1 level and compensatory IDO2 in TME, increase cytotoxic TIL and IFN-γ, and decrease the effect of the combination.

CSF-1 (colony stimulating factor-1) pathway

CSF-1R, a tyrosine kinase receptor of the platelet-derived growth factor receptor (PDGFR) family, has two structurally unrelated ligands, CSF-1 and IL-34. Its blockade modulates the recruitment and phenotype of tumor-associated macrophages (TAMs), significantly increasing the efficacy of CTLA-4, PD-1/PD-L1, or IDO-1 inhibition. Actually, in solid tumors, macrophages represent the main immune population, consisting of up to 50% of the tumor mass. Macrophage plasticity allows these innate immune cells to adopt their M1-M2 polarization axis. TAMs usually show M2 or pro-tumor and anti-inflammatory phenotypes, whereas the M1 phenotype is associated with antitumor and pro-inflammatory functions. T cells themselves can also secrete CSF-1 upon PD-1 blockade, inducing secondary resistance. Therefore, many agents are currently in development.

Emactuzumab (RG7155), an anti-CSF-1R antibody, has been extensively studied in the CSF-1R-expressing tenosynovial giant-cell tumors and its well-known toxicity characterized by facial edema and connective-tissue autoimmunity, such as lupus erythematosus and dermohypodermitis (76). In a phase I trial as monotherapy or in combination with paclitaxel for solid tumors, the ORR of 7% was observed in combination therapy only (77).

Lacnotuzumab (MCS110), an anti-CSF-1 antibody, with spartalizumab produced an RR of 2%, although the safety profile was manageable (78).

Not only anti-CSF-1 antibodies, such as PD-0360324, but also anti-CSF-1R antibodies, such as cabiralizumab (BMS-986227) and IMC-CS4, are under clinical investigation, but many trials of anti-CSF-1 or CSF-1R antibodies were withdrawn or terminated because of a lack of interest. Recently, a phase II trial of cabiralizumab in combination with nivolumab announced that the study had failed to show improved PFS in pancreatic cancer patients.

Nevertheless, CSF1R-specific kinase inhibitors, including pexidartinib/PLX3397, linifanib/ABT869, OSI-930, GW2580, and ARRY-382, are in preclinical or early clinical development.

CD47-SIRPα signaling pathway

CD47, integrin-associated protein (IAP), belongs to the immunoglobulin superfamily and is highly overexpressed on the surface of various types of solid tumor cells. The CD47-signal-regulatory protein α (SIRPα) complex initiates inhibitory signaling pathways, leading s to the evasion of malignant cells from phagocytosis by macrophages. CD47 blockade stimulates the release of chemokines promoting the recruitment and activation of macrophage. The blockade also promotes the adaptive immunity response, such as induction of antigen-specific $CD8^+$ T-cell proliferation as well as macrophage phagocytosis, but reduces regulatory T cells.

In a phase Ib study of Hu5F9-G4 for 22 rituximab-refractory NHL patients, an Hu5F9-G4 and rituximab combination resulted in an ORR of 50% with a CR rate of 36% (79). Another phase Ib study of Hu5F9-G4 for patients with hematologic malignancy, with azacitidine, 53% of chemotherapy-ineligible untreated AML or high-risk MDS patients had a CR/CRi with good tolerability (80). In a phase I study for patients with solid tumors, Hu5F9-G4 produced 2 PRs among 62 patients, all of whom had ovarian and fallopian-tube cancers with remission duration of 5.2 months and 9.2 months, respectively (81). Studies of combination with rituximab, cetuximab, or atezolizumab are ongoing.

CC-90002, an anti-CD47 antibody, showed an ORR of 13% when combined with rituximab (82). However, a study for relapsed/refractory AML and high-risk MDS was terminated, because preliminary monotherapy data did not show a profile sufficiently encouraging for further dose escalation/expansion.

Phase I studies of AK117, IB188, and IBI322 are ongoing. The first two agents are a classical anti-CD47 antibodies and the last is an anti-CD47/PD-L1 bispecific antibody. In addition, SIRPα-Fc fusion proteins, such as TTI-622 and ALX148, block the interaction of CD47- SIRPα signaling and are under cli-

nical investigation.

ALX148 with rituximab for NHL patients produced an ORR of 35% across all tumor histologies with an RR of 50% in indolent NHL and 31% in aggressive NHL (83). With pembrolizumab or trastuzumab, AXL148 showed an RR of 40% with a median PFS of 4.6 months for IC inhibitor-naïve HNSCC, but an RR of 0% with a median PFS of 2 months for IC-inhibitor-treated HNSCC, and an RR of 21% with a median PFS of 2.2 months for HER2+ gastric or gastroesophageal junction cancer (84).

Chemokine and chemokine receptor antagonists

Chemokines are small polypeptides produced by immune cells and belong to the cytokine superfamily. To date, more than 50 chemokines are identified and classified into CC, CXC, CX3C, and C subfamilies according to the number and location of N-terminal cysteine molecules. More than 20 chemokine receptors are also identified and classified depending on their ligands. However, a chemokine can bind to multiple chemokine receptors, but also a receptor can bind to multiple chemokines. Therefore, their role depends on the specific receptors of target cells. For example, the CC chemokine receptor type 4 (CCR4) is expressed on Tregs and other circulating/tumor-infiltrating T cells as well as on T-lymphoma cells. Binding of chemokines such as CCL17 or CCL22 to CCR4 promotes recruitment of immunosuppressive Tregs. Depletion of Tregs may decrease the suppression of anti-tumor immunity and synergize with PD-1 blockade. Actually, many chemokine or chemokine receptor blockers were investigated in preclinical cancer models or in auto-immune diseases. Some of them were or are being investigated in cancer patients.

PF-04136309, an oral CCR2 inhibitor, was investigated in combination with FOLFIRINOX chemotherapy for pancreatic cancer and showed an ORR of 48.5% compared to that of 25% with FOLFIRINOX alone (85). PF-04136309 with nab-paclitaxel and gemcitabine for borderline resectable and locally advanced pancreatic cancer also showed a preliminary clinical activity with an RR of 60% (86). However, the sponsor made a business-related decision to terminate the study.

BMS-813160, an oral CCR2/5 inhibitor, is being studied with nivolumab, gemcitabine, and nab-paclitaxel for borderline resectable and locally advanced pancreatic cancer.

Carlumab (CNTO888), an anti-CCL2 antibody, failed to show efficacy in metastatic CRPC, with an ORR of 0%, perhaps because of ineffectiveness of CNTO 888 in reducing CCL2 serum level (87).

Mogamulizumab (KW0761) is an anti-CCR4 antibody and was approved first for cutaneous T-cell lymphoma based on improvement of outcomes in a phase III study in which mogamulizumab had a PFS superior to that of vorinostat (median PFS 7.7 months vs 3.1 months; HR 0.53; 95% CI, 0.41-0.69) with a manageable safety profile (88). When combined with nivolumab, it produced 4 PRs in 15 HCC patients, giving an ORR of 27%, and 3 PRs in 15 pancreatic adenocarcinomas, giving an RR of 20%. Of note, during the treatment, the decrease of effector Tregs ($CD4^+CD45RA^-FoxP3^{high}$) and increase of $CD8^+$ T cells in tumor-infiltrating lymphocytes was observed (89). However, with durvalumab or tremelimumab, it did not produce potent antitumor efficacy in solid tumors, giving an RR of only 5.3%. With durvalumab, one patient with alveolar soft-part sarcoma reached a PR, whereas with tremelimumab, one patient with prostate cancer reached a PR (90).

Reparixin, an oral CXCR1/CXCR2 inhibitor, was studied with weekly paclitaxel and showed an ORR of 29.6% (91). Navarixin (MK-7123), an oral CXCR2 antagonist, is also under investigation with pembrolizumab. AZD5069, oral CXCR2 inhibitor, is being evaluated in a phase II study in combination with durvalumab for pancreatic cancer or with enzalutamide for CRPC.

Plerixafor (AMD3100), a CXCR4 antagonist, is approved for the mobilization of hematopoietic stem cells for transplantation but also is being studied in combination.

LY2510924, a CXCR4 peptide antagonist, has also been investigated with chemotherapy or sunitinib but failed to show clinical benefits (92, 93). Recently, a phase I study of combination with durvalumab reported no response, although it was a dose-finding study with a small sample (94).

Balixafortide (POL6326), a CXCR4 peptide antagonist, produced an RR of 30% when combined with eribulin for HER2 negative breast cancer and suggested a better survival outcome (95, 96). A phase III study of the combination is in progress.

Agents targeting NK cells

NK cells play a role at the intersection between the adaptive and the immune response. In solid tumors, NK-cell function is impaired significantly during tumor development and progression. Activating receptors of NK cells, such as NKG2D, CD226, and NKp30, are downregulated, whereas inhibitory receptors, such as killer-cell immunoglobulin-like receptors (KIRs) and NKG2A/CD94, are upregulated. Other inhibitory ICs, such as PD-1, TIM-3, LAG-3, and TIGIT, are also upregulated on NK cells. Therefore, the blockades of the ICs can reverse both NK-cell and T-cell function. However, immunotherapy targeting NK-cell checkpoints is being explored to prevent tumor escape from immune surveillance and to restore the anti-tumor capacity of NK cells.

KIRs belong to the Ig superfamily and interact with MHC-I molecules on target cells, comprising both activating and inhibitory receptors. The first-in-class IgG4 monoclonal antibody was IPH2101, which targets an epitope of KIR2D and thus blocks HLA-C-binding KIR2D receptors. A phase I trial of IPH2101 for relapsed or refractory multiple myeloma reported that it was safe and tolerable, but did not produce any objective response (97). Another phase I trial for AML patients in complete remission showed a favorable safety profile without DLTs and trends toward improvement of survival outcomes (98). Subsequently, lirilumab (IPH2102/BMS-986015), the second-generation anti-KIR antibody, was found to have a good safety profile but still had

no responses in solid and hematologic malignancy, even though full KIR occupancy was sustained (99). Therefore, the sponsor decided to stop enrollment for myeloid malignancies and not pursue the development for the disease. With nivolumab, interim data of phase I/II of lirilumab for 29 HNSCC patients showed an ORR of 24% but might fail to a provide clear evidence of benefit (100). A phase I trial of combination with nivolumab and ipilimumab is open but not recruiting yet.

Lacutamab (IPH4102), a first-in-class anti-KIR3DL2 antibody, was shown to be safe and encouraging in clinical activity, with an ORR of 36.4% in a phase I clinical trial for relapsed or refractory cutaneous T-cell lymphoma (101). Phase II studies of IPH4102 alone or combined with chemotherapy are ongoing.

NKG2A (CD159) and CD94, a heterodimer inhibitory receptor of the C-type lectin family, recognizes a non-classical MHC-I molecule, HLA-E, as a ligand. Tumor cells upregulate HLA-E expression in order to avoid being killed by NK cells. Monalizumab (IPH2201, anti-NKG2A) has been explored in various tumors and shown to be well tolerated but has no responses. However, when combined with cetuximab, monalizumab produced an ORR of 20% in HNSCC patients who had been previously treated with platinum chemotherapy and anti-PD-1/PD-L1 inhibitors (102). A following phase II study is ongoing.

Stimulator of interferon genes (STING)

The stimulator of interferon genes (STING) is a cytosolic protein and is activated by the enzyme cyclic-GMP-AMP synthase (cGAS). The cGAS-STING pathway is the central cellular cytosolic DNA sensor, allowing innate immunity to respond to infection, inflammation, and even cancer. The activation of the pathway after sensing cytosolic self or foreign DNA induced the production of type I interferons and aroused immune responses mediated by immune cells, including CD8+ T cells and NK cells. The pathway is also involved in cancer-cell senescence, meaning that the cGAS-STING signaling promotes the senescence via the secretion of chemokines, pro-inflammatory cytokines, growth factors, and proteases. The STING agonists, including ADU-S100 (MIW815), MK-1454, GSK3745417, and E7766, are under clinical investigations.

MK-1454 was shown to be safe as monotherapy and in clinical activity in combination with pembrolizumab with an ORR of 24% (103).

ADU-S100 (MIW815) in combination with spartalizumab showed 2 PRs out of 66 patients treated (104). The sponsor dropped MIW815 from its portfolio, but the developer continues the development of ADU-S100 in combination.

CONCLUSION

There are many immune-oncologic (IO) agents on clinical investigation as a single agent or in combination. More agents are also in preclinical development. Actually, more agents with different targets or therapeutics with different mechanisms are not covered in this review. For example, toll-like receptors, interleukin-2 receptors, and arginase might be the targets. Cancer vaccines, oncolytic viruses, or even new CAR-T cells might be the therapeutics.

Nonetheless, many challenges are to be faced and should be overcome. As already seen in the agents mentioned above, a few agents showed promising clinical activity, but most showed no or minimal activity as monotherapy. Even the clinical activity of the combinations did not seem to be dramatically better than that of standard treatments, raising a concern whether the activity translates into a meaningful survival benefit. The first challenge might be the inability to accurately predict patient responses or to select appropriate patients because of lack of information on relevant biomarkers or surrogates. As the immune system is very dynamic and complex, identification of relevant biomarkers might be more difficult than in oncogene-driven personalized medicine. Even after the biomarkers are identified, if present, their role might change during the treatment, i.e., the spatio-temporal variation or the evolution of primary or acquired resistance.

The second issue relates to the paradox of choice. The investigation of new targets and pathways is very important in order to develop new therapeutics. However, whereas the pipeline of IO agents or therapeutics is ever-expanding, choosing the best or most appropriate treatment among many available options might become more difficult than before. The fact that we already have standard modalities to treat cancer patients other than immunotherapy, such as traditional cytotoxic chemotherapy or new oncogene-driven molecular targeted therapy, makes it much more complicated and complex. In fact, as more clinical trials of IO agents or treatments will be or are being conducted, accordingly enrolling subjects into each clinical becomes more difficult and problematic. Therefore, to find the best way to give immunotherapy concurrently or sequentially with not only standard treatment but also newly available treatment becomes more important than finding new targets and agents in a sense.

After all, the development of platforms not only to identify relevant biomarkers but also to give a comprehensive view or information should run parallel to the development of new therapeutics and discovery of new biomarkers. Despite many challenges and issues, immunotherapy is an important part of cancer treatment, giving us an opportunity of lengthening our life, improving our quality of life or even having a cancer-free life.

CONFLICTS OF INTEREST

I declare that I have received honoraria for consulting or lectures from Abbvie, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, ChongKunDang, CJ Healthcare, Eli Lilly, Green Cross, Genexine, GlaxoSmithKline, Janssen, Merck, MSD, Mundipharma, Novartis, Pfizer, Roche, Samyang Biopharm, ST Cube, and Takeda outside the submitted work.

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