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REVIEW

Targeting ILT4 to Improve Immunotherapy Efficacy in Solid Tumour: From Bench to Bedside

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Abstract: Immunotherapy, especially immune checkpoint inhibitors (ICIs), has greatly changed the paradigm of cancer treatment in the past decade. However, the efficacy of ICIs in solid tumors is still limited. Even in patients with high PD-L1 expression, the response rate is less than 40%. The immunosuppressive tumour microenvironment (TME) represents a major cause of ICI hyporesponsiveness due to its inhibition on effective T-cell trafficking and immunity. Exploring novel immunotargets and developing combination therapeutics represent promising strategies to improve tumor response to immunotherapy. Immunoglobulin-like transcript (ILT) 4 is a classical inhibitory molecule in myeloid cells. Recently, ILT4 expression was discovered in tumour cells and multiple immunocytes in the TME, functionally inducing tumour growth, metastasis, and immune escape. Our group proposed ILT4 as a novel checkpoint molecule for tumour immunotherapy in 2018. In the past 5 years, translational research on ILT4 has made remarkable advances. Here, we update recent findings on ILT4 function in the TME, summarize the translational research on the development of therapeutic ILT4 antibodies, and highlight emerging clinical trial data supporting the role of ILT4 blockade in improving immunotherapy efficacy.

Keywords: ILT4, immunosuppression, translational research, clinical trials, immunotherapy

Introduction

Immunotherapy, especially immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 pathways, has greatly changed the paradigm of cancer treatment over the last decade. However, the response rate of ICIs in solid tumours is still low, at no more than 40%, due to primary resistance.[1] Even in the initial responders, most relapse after a period of response, namely, acquired resistance. It is well accepted that both tumour cell-intrinsic and -extrinsic factors contribute to immunotherapy resistance.[2] Intrinsically, tumour cells can express a series of genes and pathway molecules to decrease their immunogenicity, inhibit antigen presentation, and prevent immune cell infiltration and function in the tumour microenvironment (TME).[3,4] Extrinsically, an immunosuppressive TME, including inhibitory immunocytes, cytokines, checkpoint molecules and metabolites, restricts the intra-tumoural infiltration and anti-tumour immune response of T cells.[3–5] Therefore, utilizing combination strategies to potentiate antigen presentation and reverse the immunosuppressive TME represents a promising approach to improve immunotherapy response.[6,7] In fact, the combination of PD-1/PD-L1 inhibitors with other anti-tumour strategies, especially with novel immunotherapeutics, has become a main direction in clinical trials over the past year.[8]

Immunoglobulin-like transcript (ILT) 4, also called leukocyte immunoglobulin-like receptor B2 (LILRB2), was initially defined as an inhibitor of myeloid cell activation.[9] It is mainly expressed in myeloid cells, including monocytes, macrophages, dendritic cells (DCs), neutrophils, and platelets.[10] Furthermore, ILT4 expression can be induced in activated T cells.[11] The orthologue of ILT4 in mice is PIR-B.[12] As a classic type I transmembrane receptor in the immunoglobulin superfamily, ILT4 transduces inhibitory signals using immunoreceptor tyrosine inhibitory motifs (ITIMs) in the cytoplasm. Upon engagement with different ligands, ILT4 in these immunocytes induces M2-like polarization of macrophages, inhibits the antigen presentation of

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DCs, decreases the phagocytic activity of neutrophils, prevents platelet aggregation, and drives Th2 differentiation of $CD4^+$ T cells.[10,11] Recently, ILT4 expression was discovered in multiple tumour cells and immune cells in the TME, supporting its role in tumour promotion. In our previous publication, we mainly focused on its general biological features, expression and functions in the TME.[13–17] We also summarized the underlying mechanisms for ILT4-mediated tumour promotion, highlighting ILT4 as a novel immune checkpoint target for tumour immunotherapy.[10] In the past 5 years, translational research on ILT4 has made remarkable advances. Here, we review the emerging evidences in preclinical translational research and clinical trials on ILT4 inhibition, highlighting the potential of ILT4 blockade as a novel combination strategy to improve immunotherapy efficacy.

ILT4 Expression and Function in the TME

ILT4 in Tumour Cells

Many immune checkpoint molecules, including ILT4, are highly expressed in tumour cells, contributing to both tumorigenesis and immune escape.[18] The expression of ILT4 in solid tumours was first reported by our group in 2008.[14] Since then, our findings have been reinforced by a large body of studies (Table 1). It has been demonstrated that ILT4 is highly expressed or induced in multiple solid tumour cells, including non-small cell lung cancer (NSCLC), breast cancer, oesophageal carcinoma, pancreatic cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma (HCC), melanoma, endometrial cancer and renal clear cell carcinoma.[13–17,19–25] The expression of ILT4 correlates with

Table 1 The Distribution and Functions of ILT4/PIR-B in Tumour Cells and Immune Cells of TME

Tumour Types	Expression Cells	Biological Features	References
NSCLC	Tumour cells	Promote proliferation, invasion and metastasis of tumour cells; Prognostic marker of worse cell differentiation, lymph node metastasis, advanced cancer stages, less tumour-infiltrating lymphocyte (TIL) infiltration and poor patient overall survival (OS); Lead to the recruitment and M2-like polarization of tumour-associated macrophages (TAMs) and impair T-cell killing ability; Promote immune senescence of naive and effector T cells	[13–16,29]
Colorectal cancer	Tumour cells	Prognostic biomarker for advanced cancer stages and poor patient OS; Promote the proliferation, migration, invasion and pro-angiogenic ability of tumour cells; Decrease TIL infiltration in the stroma; Prevent $CD8^+$ T-cell infiltration, induce the accumulation of regulatory T cells (Tregs) and M2-like polarization of TAMs	[17,20,21,30]
Breast cancer	Tumour cells	Promote proliferation, invasion and metastasis of tumour cells; Prognostic biomarker of advanced cancer stages, less TIL infiltration and poor patient OS	[24,26,31]
Melanoma	Tumour cells	Induce immune senescence of naive and effector T cells; Promote proliferation, invasion and metastasis of tumour cells	[24]
Gastric cancer	Tumour cells	Prognostic biomarker of advanced cancer stages and poor patient OS	[23]
Esophageal cancer	Tumour cells	Diagnostic biomarker	[25]
Pancreatic ductal carcinoma	Tumour cells	Facilitate epithelial-to-mesenchymal transition (EMT) and early metastasis	[32]
CLL	Neoplastic B cells	Promote malignant transformation of B cells	[27]
AML	Neoplastic cells and hematopoietic stem cells (HSCs)	Inhibit differentiation of AML cells, support HSC renewal; Facilitate AML development and infiltration	[28]
Lung Cancer	Myeloid cells	Inhibit the maturation of macrophages and promote the M2-like phenotypic differentiation of TAMs and myeloid-derived suppressor cells (MDSCs), leading to effector T-cell anergy, Treg proliferation and tumour promotion	[33,34]
Clear cell renal cell carcinoma (ccRCC)	TAMs	Induce an immune-tolerant microenvironment	[35]
HCC	DCs	Promote the secretion of IL-1β and IL-6, inhibit the generation of IL-10 and IL-23, and impair T cell proliferation and killing activity	[36–38]

poorer cell differentiation, increased regional lymph node metastasis, advanced tumour stages and shorter patient survival.[13,15,17,19,21,23,26] Moreover, ILT4 gene expression is suggested as a diagnostic signature in both early stage and advanced oesophageal cancer.[25] In addition to solid tumors, ILT4 is also enriched in haematological tumours, including neoplastic cells of human chronic B lymphocytic leukaemia (CLL) and acute monoblastic and monocytic leukaemia (AML).[27,28] ILT4 in these tumour cells represents a phenotypic abnormality and correlates with tumour progression.[27,28] These findings support that ILT4 is a diagnostic and prognostic biomarker for malignancies.

Functionally, enriched ILT4 in tumour cells not only directly regulated their malignant behaviours but also induced an immunosuppressive TME (Figure 1). In NSCLC, breast cancer, colorectal cancer, melanoma, and endometrial cancer, ILT4 expression promoted the proliferation, migration, invasion and pro-angiogenic ability of tumour cells.[13,17,19,24,26,29–31,39] In pancreatic ductal carcinogenesis, ILT4 induced the EMT and the early metastatic behaviour of tumour cells in preneoplastic lesions.[32] In addition, radiotherapy-induced ILT4 expression facilitated tumour cell senescence and a senescence-associated secretory phenotype (SASP), which in turn enhances tumor proliferation and radiation resistance.[40] These findings suggest that ILT4 is an important driver for tumour development, progression and treatment resistance. In this process, HLA-G and ANGPTL2, two well-recognized ligands for ILT4, act as important initiators.[17,24,29,32,39] HLA-G is expressed and secreted by tumour cells and T cells. HLA-G not only binds to but also upregulates ILT4 in tumour cells, resulting in migration and metastasis

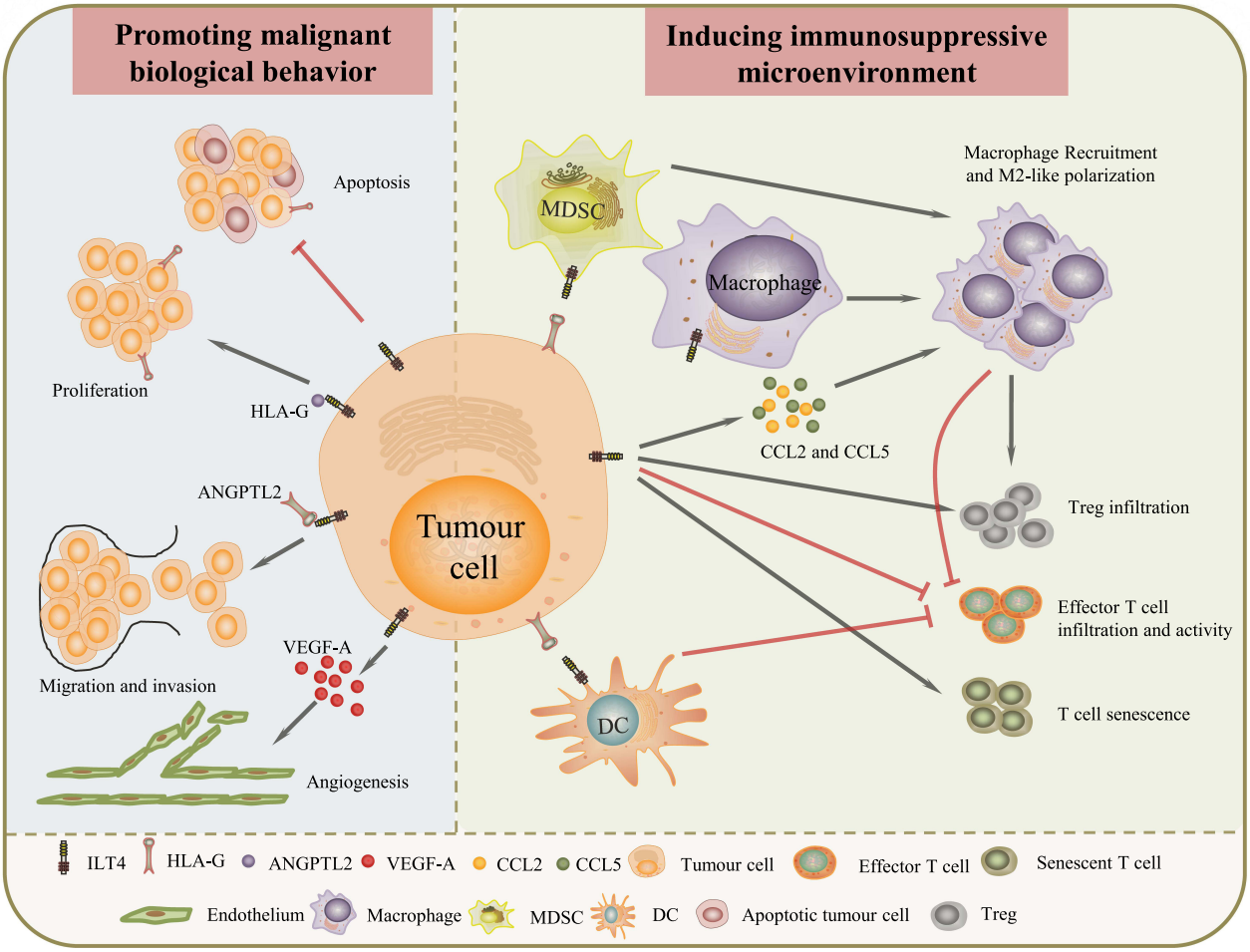

Figure 1 ILT4 promotes tumour progression directly by inducing malignant behaviors of tumour cells or indirectly by creating immunosuppressive TME. (Left) Tumour-derived ILT4 enhances the proliferation, invasion, migration, and pro-angiogenic ability of tumour cells, meanwhile inhibits their apoptosis via interaction with its ligands HLA-G or ANGPTL2. These abilities of ILT4 directly promote tumour progression. (Right) ILT4 can mediate tumour progression indirectly via creating immunosuppressive TME. ILT4 expression in tumour cells, MDSCs and TAMs induce the recruitment and M2-like polarization of TAMs, which subsequently leads to effector T-cell anergy and Treg proliferation. In addition, ILT4 expression in tumour cells and DCs prevents $CD8^+$ T cell infiltration, induces Treg accumulation, promotes T cell anergy and senescence, and finally impairs the tumoricidal ability of T cells.

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of tumour cells.[13,41–43] Meanwhile, we also find that ILT4 can in turn upregulate HLA-G expression in tumour cells, forming a positive feedback loop to facilitate tumour progression.[41,44,45] In addition to HLA-G, the ligation of ANGPTL2 to ILT4 also promote tumor growth and metastasis by increasing their proliferation, EMT, pro-angiogenic ability, as well as by inhibiting their apoptosis and differentiation.[29,32,39] These studies emphasize the promotion of ILT4 on tumor malignant behaviors.

In addition to direct regulation of tumour biologies, tumour-derived ILT4 also acts as a crucial suppressor in anti-tumour immune response. In NSCLC, colorectal cancer and breast cancer, high ILT4 expression was correlated with increased IL-10 levels in tumour cells and decreased TIL infiltration in the stroma.[13,15,21,26,46] Further subset analysis revealed that tumour-derived ILT4 prevented $CD8^+$ T-cell infiltration, and induced the accumulation of Tregs and M2-like TAMs, creating a suppressive TME for tumour growth.[15,21,46] More importantly, tumour-derived ILT4 also directly impaired the tumoricidal ability of T cells.[24,46] Using in vitro and in vivo studies, our group identified that ILT4 promoted tumour cell-induced immune senescence of naive and effector T cells, and finally impaired their proliferation and cytotoxicity.[16,24] Mechanistically, ILT4 increased fatty acid synthesis and lipid accumulation in tumour cells, leading to T-cell senescence and dysfunction.[24] Moreover, EGFR activation in NSCLC dramatically upregulated ILT4 expression, which then leads to the recruitment and M2-like polarization of TAMs and indirectly impairs T-cell killing ability.[16] In glioblastoma tissues, high ILT4 level is correlated with increased infiltration of Tregs and MDSCs, but decreased infiltration of $CD4^+$ and $CD8^+$ T cells.[47] Furthermore, ILT4 induced the formation and expansion of MDSCs, and finally inhibited the immune response of $CD8^+$ T cells.[47] These findings suggest that ILT4 is an important mediator for immunosuppression. Given that immunosuppressive TME causes tumor hyporesponsiveness to T cell-based immunotherapy (especially PD-1 and PD-L1 inhibitors),[48] these findings provide new ideas for improving immunotherapy efficacy via ILT4 blockade.

ILT4 in Immune Cells

It is reported that a variety of immune cells, especially myeloid cells in the TME show abundant ILT4 or PIR-B expression (Table 1). In the stroma of lung cancers, ILT4 is overexpressed in monocytes, TAMs and MDSCs.[16,33,34] ILT4 in these myeloid cells inhibits the maturation of macrophages and induces the M2-like phenotypes of TAMs and MDSCs, subsequently leading to effector T cell anergy, Treg proliferation and tumour promotion.[33,34] The macrophages in ccRCC tissues also show high ILT4 expression, which interacts with enriched HLA-G in tumour cells to induce an immune-tolerant microenvironment.[35] Moreover, peripheral blood granulocytes and mature DCs (mDCs) from HCC patients shows markedly higher ILT4 levels compared with those from healthy donors.[36–38] Functionally, ILT4 inhibits the secretion of IL-1β and IL-6 and promotes the generation of IL-10 and IL-23 in monocyte-derived DCs, which are responsible for impaired T-cell proliferation and killing activity against HCC.[37] These studies suggest that myeloid-derived ILT4 plays an important role in tumour immune escape (Figure 1). ILT4 blockade might reprogram the immunosuppressive TME and be used as a potential target for tumour immunotherapy.

Blocking ILT4 as a Promising Anti-Tumour Strategy: Preclinical Studies

ILT4 Inhibition as an Anti-Tumour Strategy

Along with the above basic researches, a large number of translational studies have been performed to evaluate the role of ILT4 inhibition in cancer treatment. In transplanted tumour models of NSCLC, breast cancer and endometrial carcinoma constructed with immunodeficient mice, ILT4 inhibition significantly induced tumour cell apoptosis, and restricted tumour growth, invasion, and lung metastases,[13,19,24,29] indicating that ILT4 inhibition is a potential strategy to restrict tumour biologies. In addition, when we constructed the same transplanted breast cancer model in immunocompetent C57BL/6 mice, ILT4/PIR-B blockade showed more obvious anti-tumour effect than that in immunodeficient mice, suggesting the important role of immune system in ILT4-regulated tumour growth.[24] Further analysis of the immune microenvironment showed that ILT4/PIR-B blockade reprogrammed the immunosuppressive TME towards the immune-activated phenotypes, and increased the proliferation and killing ability of tumour-specific T cells.[16,21,24,34] NSCLC patients with sensitive EGFR mutation but progressed from EGFR-TKIs are considered less effective to immunotherapy against PD-1/PD-L1 pathways.[16] Exploring novel immunotargets and treatment strategies is an urgent need in clinical practice. Using tumour transplantation models, we demonstrated that ILT4 inhibition but not PD-L1 blockade can

suppress tumour progression and immune evasion in EGFR-mutant but EGFR-TKI-resistant NSCLC, raising a novel immunotherapeutic strategy for this ICI-unfriendly subpopulation.[16]

Combination with ILT4 Blockade to Improve Immunotherapy Efficacy

ICIs have made an indelible mark in cancer immunotherapy and have been approved for the treatment of a wide array of cancer types. However, the majority of patients do not benefit from ICIs (intrinsic resistance), and some responders relapse after a period of response (acquired resistance).[3] It is reported that suppressive TME is the main contributor to ICI resistance.[49] Recently, the identification of ILT4-mediated immunosuppression has elicited great interest in attenuating ICI resistance by ILT4 blockade (Figure 2). In a Lewis lung carcinoma model, PD-L1 blockade showed mild anti-tumour effect. However, combination blockade of ILT4 and PD-L1 markedly suppressed tumour growth.[34] Similarly, in EGFR wild-type NSCLC, either ILT4 or PD-L1 blockade showed moderate anti-tumour efficacy, while blockade of both molecules induced the most significant suppression of tumour growth.[16] These studies reveal that ILT4 blockade has great potential in overcoming ICI resistance and improving their anti-tumour efficacy.

Adoptive T-cell therapy (ACT) is another important modality of immunotherapy beyond ICIs. By ex vivo expansion and reinfusion of gene-modified or re-engineered T cells, ACT augments the number, specificity, and reactivity of T cells against tumour tissues.[7] However, the immunosuppressive TME in solid tumours hinders T-cell infiltration and induces their anergy, representing a key obstacle for ACT treatment.[50] ORR of ACT in solid tumours is about 20–50%.[51,52] In our effort to improve ACT efficacy, we found that ILT4 blockade increased the infiltration of melanoma antigen-specific T cells, reversed their senescence-associated phenotypes and enhanced their tumoricidal ability.[24] The combination of

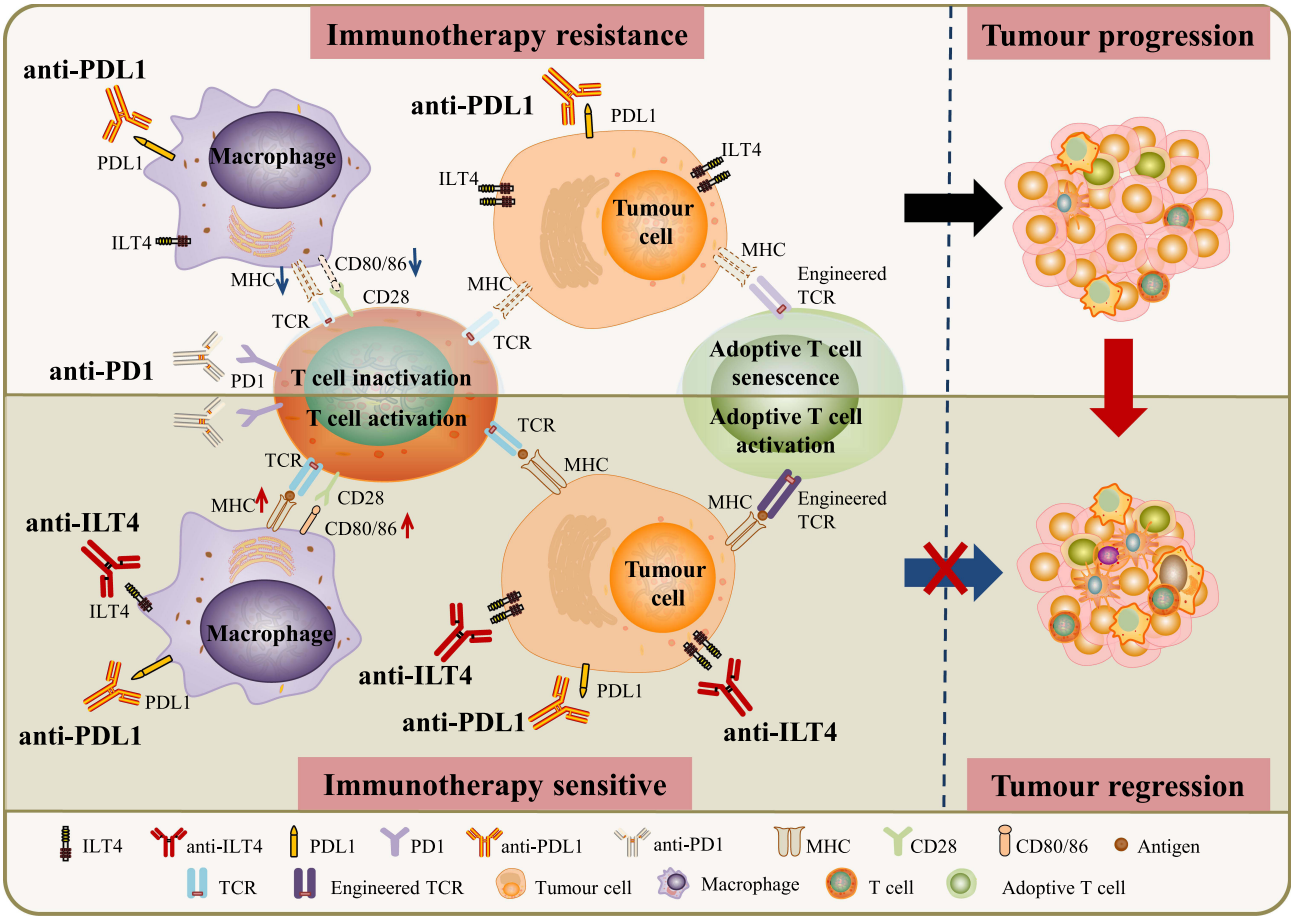

Figure 2 ILT4 blockage improved immunotherapy efficacy. Immunotherapy including anti-PD(L)1 therapy and ACT suppresses tumour progression by reactivating effector or engineered T cells in the TME. However, enriched ILT4 in the tumour cells and TAMs induces the dysfunction or senescence of these T cells, resulting in immunotherapy resistance. While blockade of ILT4 prevents tumour-induced effector and engineered T cells dysfunction, and increases the efficacy of PD(L)1 inhibitors and ACT.

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ILT4 blockade with ACT had a stronger anti-tumour effect than ACT alone.[24] This finding might reveal new opportunities for ACT application in solid tumours (Figure 2).

Development of Therapeutic ILT4 Monoclonal Antibodies and Their Preclinical Effect

The above findings promoted the development and clinical translation of therapeutic ILT4 antibodies. MK-4380 is the first humanized ILT4 antagonistic monoclonal antibody developed by Merck & Co. Through blocking the binding of ILT4 with MHC-I and ANGPTL2, MK-4380 reversed ILT4-induced immunosuppression.[53] In a preclinical mouse model of malignant melanoma, MK-4380 promoted the release of proinflammatory cytokines from peripheral blood mononuclear cells (PBMCs) and significantly inhibited tumour growth.[53]

IO-108 is another inhibitory ILT4 antibody developed by IMMUNE-ONC Therapeutics Inc. In vitro assays showed that by competitively blocking the ligation of ILT4 in the tumour microenvironment, IO-108 enhanced the production of multiple proinflammatory cytokines in lipopolysaccharide (LPS)- and anti-CD3-stimulated PBMCs, potentiated DC maturation in response to LPS, polarized $CD14^+$ cells towards a proinflammatory M1-like phenotype and attenuated their suppressive effect on autologous T-cell proliferation and the production of tumoricidal cytokines.[54] In mouse transplanted tumour models, IO-108 inhibited the growth of solid tumours and enhanced the T-cell immune response. In addition, IO-108 enhanced PD-1 inhibitor-released $CD4^+$ T-cell activity, suggesting its potential to enhance the efficacy of PD-1/PD-L1 inhibitors.[54]

JTX-8064 is a humanized IgG4 monoclonal antibody developed by Jounce Therapeutics Company. Similar to other ILT4 antagonists, JTX-8064 selectively blocks the interaction of ILT4 with MHC-I molecules and reprograms macrophages into an immunostimulatory phenotype in vitro, which is characterized by increased TNFα and decreased IL-10 production.[55] In an ex vivo human tumour histoculture system, JTX-8064 reprogrammed TAMs and indirectly activated T cells in a subset of tumour samples.[55] More importantly, when cultured with human renal cell carcinoma, head and neck cancer and lung cancer in vitro, JTX-8064 displayed remarkable tumoricidal activity, while the combination of JTX-8064 with pembrolizumab (a PD-1 inhibitor) showed a better anti-tumour effect than pembrolizumab alone, suggesting the potential of JTX-8064 in enhancing pembrolizumab efficacy.[55]

Based on the synergistic tumoricidal effect of ILT4 and PD-1/PD-L1 blockade, Celldex Therapeutics Company and Biosion jointly developed a bispecific antibody against both ILT4 and PD-1, CDX-585.[56] Preclinical data showed that CDX-585 effectively blocks ILT4 and PD-1 and mediates the activation of myeloid and T cells, especially in PD-1 inhibitor-refractory cases. Importantly, CDX-585 displayed an increased ability to activate T cells compared with the combination of ILT4 and PD-1 inhibitors. An in vivo study in transplanted melanoma mouse models verified the anti-tumour activity and safety of CDX-585, sustaining its further clinical application.[56]

ILT4 Blockade Improves ICI Efficacy: Evidence from Early Phase Clinical Trials

In 2018, Merck & Co carried out the first clinical trial on the therapeutic ILT4 monoclonal antibody MK-4830 (ClinicalTrials.gov ID: NCT03564691).[57] The study enrolled 84 patients with advanced solid tumours, including NSCLC, head and neck cancer, and colorectal cancer.[58] Among them, 50 patients received MK-4830 monotherapy, and 34 received combination therapy of MK-4830 and pembrolizumab. Analysis of the baseline characteristics showed that 56% of the patients had previously received more than 3 prior lines of systemic treatment, and 23% had received PD-1/PD-L1 inhibitors. In patients treated with MK-4830 monotherapy, the objective response rate (ORR) was 2%, but in those treated with MK-4830 plus pembrolizumab, the ORR was markedly increased to 24%. Even among the 11 patients who had previously experienced PD-1/PD-L1 inhibitor treatment, 5 patients once again benefited from the combination treatment, with a duration of response (DOR) of more than 6 months. In terms of toxicity, both MK-4830 monotherapy and in combination with pembrolizumab showed acceptable safety in the dose range of 3–1600 mg Q3W. No obvious dose-limited toxicity was observed. These results demonstrated, for the first time, the great potential of ILT4 blockade in improving PD-1 inhibitor efficacy in solid tumours. Based on the above results of this phase I clinical trial, an expanded cohort of patients with different tumour types is being recruited.[57]

NCT05054348 is a phase I multi-center dose escalation clinical trial to assess the safety, tolerability and preliminary efficacy of IO-108 in patients with metastatic solid tumours. This trial was approved by the FDA in August 2021.[59] It contains an IO-108 monotherapy cohort and two combination cohorts of IO-108 with pembrolizumab or cemiplimab. At the time of abstract submission, a total of 25 patients with advanced recurrent or refractory solid tumours were enrolled.[60]

Among the 23 assessable patients (11 cases of monotherapy, 12 cases of combination therapy and 1 case of crossover therapy), 1 patient in the monotherapy group achieved complete response (CR), and 4 patients achieved stable disease (SD). In the combined treatment group, 3 patients achieved a partial response (PR), and 4 patients presented SD. Four responders experienced a treatment duration of 8–12 months and are still receiving maintenance immunotherapy. In addition, dose escalation of IO-108 from 60 mg to 1800 mg was well tolerated, and the maximum tolerated dose was not reached.[60] These results demonstrated the preliminary efficacy of IO-108 in human solid tumors, implied the role of IO-108 in improving PD-1 inhibitor response. In May 2022, the National Medical Products Administration of China (NMPA) approved the clinical trial application of IO-108 for the treatment of advanced solid tumours in Chinese patients. The phase I clinical study (NCT05508100) has a similar designation as NCT05054348 and is currently under recruitment.[61]

NCT04669899 is a Phase 1/2, open label, dose escalation and dose expansion clinical study to determine the safety, tolerability, and recommended Phase 2 dose (RP2D) of JTX-8064 alone and in combination with a PD-1 inhibitor (PD-L1) in patients with advanced refractory solid malignancies. Results from the combination cohort were presented at the American Society of Clinical Oncology (ASCO) in 2024.[62] A total of 31 patients with advanced or metastatic renal cell cancer were enrolled. Of 28 patients evaluable for response, 1 patient achieved CR, 1 patient presented PR, 14 patients achieved SD (6 SD≥ 6 months), and 11 patients achieved progressive disease (PD). Median PFS was 4 months (95% CI: 2, 6.8); 12-month OS was 75% (95% CI: 55,88). Treatment was reasonably well-tolerated. These results indicated the potential efficacy of JTX-8064 in patients with renal cell cancer.

In addition to above agents, ES009 has also advanced into phase I clinical trial (NCT06007482), which aims to determine the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary clinical activity of ES009 administered intravenously to subjects with advanced solid tumors.[63] Besides, a Phase I–II study (NCT06090266) has been designed to determine the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumour activity of OR502, a fully human ILT4 antibody, in advanced solid tumours[64] These trials are in the recruitment phase right now.

In addition to monoclonal antibodies, bispecific antibodies have been developed and advanced into early phase clinical trials. NGM-707 is an ILT2/ILT4 bispecific antibody developed by American NGM Biopharmaceutical Co., Ltd. In December 2021, the international multi-centre phase I/II clinical study (NCT04913337) was launched to assess the dose-limiting toxicity (DLT), safety, and efficacy of NGM-707 monotherapy or in combination with pembrolizumab in advanced solid tumours.[65] Moreover, PD-1/ILT4 bispecific antibody CDX-585 and PD-L1/ILT4 bispecific antibody SPX-303 are also under phase I study (NCT05788484 and NCT06259552) to evaluate their safety, tolerability, and preliminary anti-tumour efficacy in solid tumours.[66,67] These studies are currently under recruitment.

Overall, an array of therapeutic ILT4 antibodies and bispecific antibodies has entered in-human clinical trials (Table 2). Some of them have shown great potential in improving current ICI efficacy and bring hope for combination immunotherapy in the future.

Table 2 Ongoing Clinical Trials on Therapeutic ILT4 Monoclonal or Bispecific Antibodies

Study Title	NCT ID	Cancer Type	Treatment	Phase	Country or Region	STUDY STATE
A Randomized, Phase 2 Study of Pembrolizumab And Chemotherapy With or Without MK-4830 as Neoadjuvant Treatment for High-Grade Serous Ovarian Cancer	NCT05446870	High-grade Serous Ovarian Carcinoma	Pembrolizumab+ Paclitaxel+ Carboplatin+ Avastin±MK-4830	II	United states; Belgium; Canada; Chile; Israel; Italy; Korea; Poland; Singapore; Spain; Taiwan	Recruiting, without published clinical data
A Phase 1 Open Label, Multi-Arm, Multicenter Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab for Participants With Advanced Solid Tumours	NCT03564691	Neoplasms	MK-4830± Pembrolizumab ±chemotherapy/Lenvatinib	I	United states; Australia; Canada; China; France; Greece; Israel; Japan; Japan; Poland; South Africa, Spain	Recruiting

(*Continued*)

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Table 2 (Continued).

Study Title	NCT ID	Cancer Type	Treatment	Phase	Country or Region	STUDY STATE
KEYMAKER-U01 Substudy 2: A Phase 2, Umbrella Study With Rolling Arms of Investigational Agents in Combination With Pembrolizumab in Treatment Naïve Patients With PD-L1 Positive Advanced Non-small Cell Lung Cancer	NCT04165083	Non-Small-Cell Lung Cancer	MK-4830/MK-0482 +Pembrolizumab	II	United States; Hungary; Israel; Italy; Korea; Poland; Spain	Recruiting, without published clinical data
A Phase 0 Master Protocol Using the CIVO® Platform to Evaluate Intratumoral Microdoses of Anti-Cancer Therapies in Patients With Solid Tumours	NCT04541108	Solid Tumour	MK-4830/MK-0482+ Pembrolizumab	I	United States	Recruiting, without published clinical data
KEYMAKER-U01 Substudy 3: A Phase 2, Umbrella Study With Rolling Arms of Investigational Agents in Combination With Pembrolizumab in Patients With Advanced Non-small Cell Lung Cancer (NSCLC) Previously Treated With Anti-PD-(L)1 Therapy	NCT04165096	Non-Small-Cell Lung Cancer	Pembrolizumab + MK-4830/ MK-0482/ Boserolimab	II	United States; Hungary; Israel; Italy; Korea; Poland; Spain	Active, not recruiting; without published clinical data
A Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab Plus Investigational Agents in Combination With Etoposide and Cisplatin or Carboplatin for the First-Line Treatment of Participants With Extensive-Stage Small Cell Lung Cancer (KEYNOTE-B99)	NCT04924101	Small Cell Lung Cancer	Pembrolizumab + MK-4830/ Boserolimab/ Lenvatinib + Chemotherapy	II	United States; Austria; Canada; Hungary; Israel; Italy; Korea; Poland; Russian Federation; Spain; Switzerland	Active, not recruiting; without published clinical data
A Phase 1/2 Open-Label, Umbrella Platform Design Study of Investigational Agents With Pembrolizumab (MK-3475) in Participants With Advanced Esophageal Cancer Previously Exposed to PD-1/PD-L1 Treatment (KEYMAKER-U06): Substudy 06B	NCT05319730	Esophageal Squamous Cell Carcinoma	Paclitaxel or irinotecan; Pembrolizumab + MK-4830 + paclitaxel or irinotecan/ lenvatinib	I/ II	Brazil; Chile; China; Italy; Japan; Korea; Norway; Switzerland; Taiwan	Recruiting, without published clinical data
KEYMAKER-U01 Substudy 1: A Phase 2, Umbrella Study With Rolling Arms of Investigational Agents With Pembrolizumab in Combination With Chemotherapy in Treatment-Naive Patients With Advanced Non-small Cell Lung Cancer	NCT04165070	Non-Small-Cell Lung Cancer	Pembrolizumab+Vibostolimab/ Boserolimab / MK-4830 / MK-0482 +Carboplatin + Paclitaxel/ Pemetrexed	II	United States; Hungary; Israel; Italy; Korea; Poland; Spain	Recruiting, without published clinical data
A Phase 1b/2 Study to Evaluate the Efficacy and Safety of Pembrolizumab in Combination With Investigational Agents for the Treatment of Participants With PD-1/L1-refractory Extensive-Stage Small Cell Lung Cancer in Need of Second-Line Therapy (KEYNOTE-B98)	NCT04938817	Small Cell Lung Carcinoma	Coformulation Pembrolizumab/ Quavonlimab±Lenvatinib/ MK-4830; Coformulation Favezelimab/Pembrolizumab	I/ II	United States; Australia; Austria; Canada; Hungary; Israel; Italy; Korea; Poland; Russian Federation; Spain; Switzerland	Active, not recruiting; without published clinical data

(*Continued*)

Table 2 (Continued).

Study Title	NCT ID	Cancer Type	Treatment	Phase	Country or Region	STUDY STATE
A Phase 2, Multicenter, Multi Arm, Study to Evaluate MK-1308A (Co-formulated Quavonlimab (MK-1308)/ Pembrolizumab) Versus Other Treatments in Participants With Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Cancer: (MK-1308A-008)	NCT04895722	Colorectal Cancer	Pembrolizumab/ Quavonlimab/ Favezelimab/ Vibostolimab; Pembrolizumab + MK-4830	II	United States; Belgium; Canada; Costa Rica; Denmark; Estonia; France; Germany; Greece; Guatemala; Hungary; Italy; Korea; Lithuania; Netherlands; Poland; Romania; Russian Federation; Spain; Turkey; United Kingdom	Recruiting, without published clinical data
A Phase 1b/2 Study of Immune and Targeted Combination Therapies in Participants With RCC (U03): Substudy 03B	NCT04626518	Renal Cell Cancer	Coformulation Pembrolizumab/ Quavonlimab; Coformulation Favezelimab/Pembrolizumab; Pembrolizumab + MK-4830; Pembrolizumab + Belzutifan; Belzutifan + Lenvatinib; Pembrolizumab + Lenvatinib	I/ II	United States; Australia; Canada; Chile; France; Hungary; Israel; Korea; Netherlands; New Zealand; Spain; United Kingdom;	Recruiting, without published clinical data
A Phase 1/2 Open-Label Rolling-Arm Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants With Melanoma (KEYMAKER-U02): Substudy 02C	NCT04303169	Melanoma	Pembrolizumab± Vibostolimab/ Gebasaxturev/ Favezelimab/ all-trans retinoic acid/ MK-4830	I/ II	United States; Australia; France; Israel; Italy; Switzerland	Recruiting, without published clinical data
A Phase 1/2 Open-Label, Umbrella Platform Design Study of Investigational Agents With Pembrolizumab (MK-3475) in Participants With Advanced Esophageal Cancer naïve to PD-1/PD-L1 Treatment (KEYMAKER-U06): Substudy 06A	NCT05342636	Esophageal Squamous Cell Carcinoma	Pembrolizumab plus chemotherapy; Coformulation Favezelimab/Pembrolizumab plus Chemotherapy; Pembrolizumab plus MK-4380 plus Chemotherapy; Pembrolizumab plus MK-4380 plus lenvatinib	I/ II	Brazil; Chile; France; Germany; Italy; Japan; Korea; Norway; Singapore; Switzerland; Taiwan; Thailand; Turkey	Recruiting, without published clinical data
Phase 1/2 First-in-Human (FIH) Study of Leukocyte Immunoglobulin-Like Receptor B2 (LILRB2) Inhibitor Monoclonal Antibody (mAb) JTX-8064, as Monotherapy and in Combination With a Programmed Cell Death Receptor-1 (PD-1) Inhibitor, in Adult Subjects With Advanced Refractory Solid Tumour Malignancies	NCT04669899	Cancer	JTX-8064 + pimivalimab	I/II	United States	Active, not recruiting; without published clinical data
A Phase 1, Open-Label, Multicenter Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of IO-108 as Monotherapy and in Combination With Anti-PD-1 Monoclonal Antibody in Adult Patients With Advanced or Metastatic Solid Tumours	NCT05508100	Advanced solid tumour	IO-108 ± pembrolizumab/ tislelizumab	I	China	Recruiting, without published clinical data

(*Continued*)

Table 2 (Continued).

Study Title	NCT ID	Cancer Type	Treatment	Phase	Country or Region	STUDY STATE
A Phase 1b, Open-Label, Dose-Escalation, Dose-Expansion, and Dose-Randomization Study of IO 108 as Monotherapy and in Combination With Either Pembrolizumab or Cemiplimab in Adult Patients With Advanced Solid Tumours	NCT05054348	Solid tumour, Adult	IO-108±pembrolizumab/ cemiplimab	I	United States	Recruiting
A Study of OR502, a Monoclonal Antibody Targeting LILRB2, Alone and in Combination With Anticancer Agents	NCT06090266	Advanced solid tumours	OR502	I/II	United States	Recruiting, without published clinical data
A Study of ES009 in Subjects With Locally Advanced or Metastatic Solid Tumours	NCT06007482	Advanced solid tumours	ES009	I	Australia	Recruiting, without published clinical data
A Study of SPX-303, a Bispecific Antibody Targeting LILRB2 and PD-L1 in Patients With Solid Tumours (SPX-303)	NCT06259552	Solid Tumour	SPX-303	I	United States	Recruiting, without published clinical data
A Study of CDX-585 in Patients With Advanced Malignancies	NCT05788484	Advanced solid tumours	CDX-585	I	United States	Recruiting, without published clinical data
A Study of CHS-1000 in Participants With Advanced or Metastatic Solid Tumors	NCT06389526	Advanced solid tumors	CHS-1000	I	United States	Not yet recruiting

Conclusion and Prospectives

Immunotherapy using ICIs has transformed the landscape of cancer treatment and become a standard option for most solid tumours. However, the response rate in most solid tumors is still limited and less than 50%.[68] This represents a major bottleneck in immunotherapy. As a newly defined immune checkpoint molecule, ILT4 is enriched not only in multiple tumour cells but also in a variety of immune cells, including TAMs, DCs and $CD8^+$ T cells, in the immune microenvironment. ILT4 in the TME supports tumour progression by directly inducing their malignant behaviours, as well as by indirectly creating an immunosuppressive microenvironment leading to T-cell dysfunction. Moreover, ILT4 leads to the hyporesponsiveness of tumour cells to immunotherapy. Recently, therapeutic ILT4 monoclonal antibodies and bispecific antibodies against ILT4 plus ILT2/PD-1/PD-L1 have achieved great breakthrough in clinical transformation. Some have shown promising potential in the combination therapy with PD-(L)1 inhibitors in early phase clinical trials. These agents and results raises new hope for improving ICI efficacy.

However, there are still a series of challenges to be addressed before therapeutic ILT4 antibodies be widely used in clinical practice. First, due to different levels of ILT4 expression in different cancer types and individuals, the efficacy of therapeutic ILT4 antibodies might be heterogenous. Clinical trials with larger sample sizes and biomarker exploration are needed to further verify clinical efficacy and select beneficiary populations. Second, whether combination treatment with ILT4 antibodies can break through the bottleneck of ICI hyporesponsiveness in patients with active driver genes needs further clinical verification. The synergistic effect of anti-ILT4 with ACT, like chimeric antigen receptor (CAR)-T-cell therapy, also needs further investigation. Third, given that ILT4 antibodies monotherapy is less effective, the combination strategies of anti-ILT4 with other therapeutic modalities, such as chemotherapy, radiation therapy and targeted therapy, need to be explored. Finally, ILT4 is highly expressed in platelets, neurons and epithelial cells, which might cause adverse effects related to anti-ILT4 treatment. Therefore, advanced biomaterials and drug delivery systems are needed to accurately enrich ILT4 antibodies in the TME to prevent their nonspecific binding to

platelets and nervous system cells. Exploration of these questions will facilitate the precision translation of ILT4 blockade from bench to bedside.

In conclusion, immunotherapy targeting ILT4 has shown promising potential in cancer treatment, especially in improving PD-1 inhibitor efficacy. However, the transformation on anti-ILT4 treatment is still in its infancy, and many important problems need to be solved in clinical trials and practice.

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Disclosure

The authors report no conflicts of interest in this work.

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