

The involvement of Lymphocyte activation gene 3 and the inhibitor in non-small cell lung cancer

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Abstract. Non-small cell lung cancer, or NSCLC, is the most typical malignant tumor in lung carcinoma. NSCLC causes a relatively high fatality and prevalence rate compared to other cancers worldwide. A combination of surgery, chemotherapy, and chemoradiotherapy interventions are commonly used as standard or front-line therapy for patients with NSCLC. However, a relatively novel treatment, immunotherapy, has become a popular target for many cancer-related clinical researches in recent years, including melanoma, urothelial cancer, and NSCLC. The general purpose of immunotherapy is to target the host's immune system and increase the immune response opposing the tumor. Within immunotherapy, immune checkpoint inhibitor (ICI) was gaining increasing attention as a therapeutic method for many cancers through recent studies. Immune checkpoints (ICs) regulate the immune response and suppress the activity of immune cells when expressed. This mechanism of action prevents immune cells from developing autoimmunity, which, if it happens, immune cells will start attacking healthy cells in the host. However, one disadvantage of IC is that they indirectly enhance tumor survival by deactivating immune cells. Thus, many ICIs are developed to directly inhibit the activity of the targeted IC. Among all types of immune checkpoints, lymphocyte activation gene 3 (LAG-3) acts as an essential IC in the host's cell. The primary objective of this article is not only to elucidate the association between LAG-3 and NSCLC but also to explain the effect of anti-LAG-3 drugs in patients with NSCLC, its synergistic effect with other checkpoint inhibitors, and the limitations of immune checkpoint inhibitors for future investigation.

Keywords: Lymphocyte Activation Gene 3, Non-Small Cell Lung Cancer, Immunotherapy.

1. Introduction

Pulmonary carcinoma has led to nearly 27.4% mortality for all cancers [1]. Among the subtypes of lung carcinoma, non-small cell lung cancer (NSCLC) is the most frequently occurring disease between all patients with lung carcinoma. Nearly 80% of all lung cancer cases are NSCLC. For many years in the past, patients with this subtype of lung carcinoma would receive surgery, radiation therapy and chemotherapy intervention [2]. A combination of these therapies is common to patients that beyond the stage 1 of NSCLC [3]. Although surgery removal of tumor has shown promising result on curing the NSCLC, it is only possible to the early-stage NSCLC cases [3]. In addition, many patients have not been cured after a surgery intervention. And even they are cured at the time, 30% to 55% of NSCLC patients would suffer from recurrence of the cancer and died after tumor resection [3]. For NSCLC patients with metastasized tumor or recurrence after surgery, it is common for them to receive chemotherapy or radiation therapy to eliminate tumor cells that are spreading inside their body. However, chemotherapy and radiation therapy could cause higher incidences of treatment related adverse events (TRAEs) than immunotherapy. In fact, advanced NSCLC patients who received chemotherapy and chemoradiotherapy had significantly increased in the occurrence of anemia, neutropenia, thrombocytopenia and vomiting according to a previous meta-analysis². Furthermore, immunotherapy in NSCLC patients have found to cause fewer cytotoxic effects than platinum-based chemotherapy [4]. Also, it has been recognized that NSCLC patients who received immunotherapy have better progression-free survival (PFS) than NSCLC patients that received chemotherapy². Therefore, immunotherapy has developed to become one of the promising treatments for NSCLC in recent years. The overall survival rate (OS) for NSCLC patients that received a combination therapy that contains both chemotherapy and checkpoint inhibitor, pembrolizumab, was 69.2% for 12-months from a phase 3 clinical research, while placebo chemotherapy alone was 49.4%

[4]. Therefore, immune checkpoint inhibitors (ICI) as one of the immunotherapies, has potential to replace chemotherapy and become the first-line treatment for NSCLC.

The immune checkpoint (IC) is an essential component of the body system. These checkpoints behave like regulators on the immune cells, which continuously suppress the activity of the immune cell. This action is crucial because IC will prevent immune cells from developing autoimmunity and attacking healthy cells in the host. However, one disadvantage of ICs is that they indirectly enhance tumor cell survival since immune cells are deactivated due to immunosuppression. Therefore, ICI has being studied right now as a type of cancer immunotherapies that inhibits ICs and prevents them from deactivating immune cells. Recent research has shown that ICI that targets the checkpoints known as programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) has a crucial tumor-suppressing effect on numerous types of solid cancers. However, a dual intervention of PD-1 and PD-L1 targeted drugs triggered up to 60% of grade 3 to 5 adverse effects (AEs) such as skin AEs, autoimmune AEs and colitis [5]. Another limitation of ICI is that the effect of a single targeted monotherapy is less likely to be successful due to resistance of tumor cells.

One of the characteristics of tumor is the capability of grow uncontrolled when there were nutrients available. While proliferating, there is a chance for the cancer cells to experience clonal and sub-clonal mutations. These mutations alter the genome of tumor cells and could potentially develop resistance to ICI. Especially in the case of sub-clonal mutations, this type of mutation could introduce intratumoural heterogeneity (ITH), which negatively affects the response to ICI [6]. Although combination of ICI therapy has shown promising result against the resistance of tumor, they also have higher toxicities than a single target inhibitor [6]. Thus, it is essential to find other ICs to target and expand the options of ICI when it comes to the immunotherapy of cancers.

Lymphocyte activating gene 3 (LAG-3) is a vital checkpoint that researchers focus on for anti-cancer treatment in recent years. LAG-3 is a transmembrane protein presented on dendritic cells, B cells, and natural-killer cells. It functions as a ligand on these immune cells and binds to the major histocompatibility complex class II (MHC-II) on antigen presenting cells (APCs). In contrast to other ICs, LAG-3 cannot be found on tumor cells. Furthermore, high LAG-3 expressions could repress T-cell activity and produce a negative prognosis in NSCLC and nasopharyngeal carcinoma patients. This review article elucidates the feature of LAG-3, anti-LAG-3 drugs effect, and certain limitations regard to the NSCLC.

2. Background of Lymphocyte activating gene 3

2.1. Structure of lymphocytes activating gene 3

LAG-3 was officially discovered in 1990. It is found in chromosome 12 and possesses a molecular weight of 70kDa. The gene of LAG-3 was found in the same region as CD4, but they only share 20% of homology. The translated LAG-3 product becomes a transmembrane protein that contains three distinct regions, including the cytoplasmic region, transmembrane region and extracellular region [7]. The cytoplasmic area of LAG-3 transmembrane protein possesses 3 components: a “KIEELE” motif, a serine phosphorylation site and a glutamate-proline dipeptide repeat sequence. Interestingly, the “KIEELE” motif was only found in LAG-3 protein and is responsible for signal transduction of intracellular activity after activation [7]. Therefore, the KIEELE motif could be a unique factor to investigate for the intracellular activity of the LAG-3 protein, and possibly a good drug targeting candidate.

2.2. Mechanism of action for LAG-3

Generally, LAG-3 suppresses the immune cells from damaging healthy cells. These LAG-3 proteins serve as regulators for autoimmune disease, but its function also helps the cancer cells to survive from the immune response and cause poor treatment outcomes. The LAG-3 gene is initially stimulated by promotion of T-cell receptor (TCR) and cytokine [8]. After the LAG-3 protein is translated and travels to the cell's surface from the late endosome [8]. Then it becomes a monomer

and expresses negative feedback on cytokine and the TCR activation pathway¹⁷. Furthermore, LAG-3 inhibits the TCR pathway in a very early stage after the signal enters the cell's cytoplasm [8]. This inhibition has led to decreased expression of transcription factors such as NFAT, which inhibit cytokine production from the T-cell [8]. A biological analysis has indicated that the dimerization of LAG-3 molecule by D1 domain when they are present on the cell surface [9]. However, there is not enough evidence to explain the relationship between the dimerization of LAG-3 and its normal functions with other ligands [8].

3. The intervention of LAG-3 in NSCLC

3.1. LAG-3 activity on the NSCLC cell lines

Before evaluating the functionality of LAG-3 on NSCLC tumors, it is vital to examine the LAG-3 protein activity on NSCLC cell lines. According to a research study, a total of 139 NSCLC specimens were acquired from NSCLC patients from surgical units [10]. Out of 139 specimens, a total of 55 cell lines were generated and further examined for the expression of PD-1, LAG-3, and PD-L1 through immunohistochemistry (IHC) [10]. Tumor infiltrating lymphocytes (TIL) examination showed that there are 36 patients (25.9%) who had LAG-3 positive [10]. In contrast to other cells, LAG-3, PD-1, and PD-L1 tested positive in 60 (43.2%) and 25 (18%) of NSCLC cell samples, respectively. And a higher intensity of LAG-3 was found in non-adenocarcinoma compared to the adenocarcinoma of NSCLC [10]. Although the activity of LAG-3 is low compared to PD-1, 25.9% of total expression is still significant in the case of NSCLC. Thus, LAG-3 remains to be a valuable checkpoint for investigation in NSCLC.

3.2. LAG-3 on TILs as prognostic factors in patients with NSCLC

LAG-3 protein has not been studied a lot in the case of NSCLC. However, due to its special component, "KIEELE" motif, and relative high expression in NSCLC cell lines [7,10], LAG-3 has some potentials to become a prognostic biomarker and a drug target for the NSCLC. In a clinical research study that comprised 553 NSCLC patients. Participants were involved within the research for examination of the prognostic effects of LAG-3 on the NSCLC. Researchers examined the expression of intraepithelial LAG-3 (T-LAG-3), extraepithelial LAG-3 (E-LAG-3) and stromal LAG-3 (S-LAG) with their relative Disease specific survival (DSS) and OS throughout all testing groups [11]. Although the result shows some correlation on DSS and OS, the result is not consistent across all testing groups. For instance, both S-LAG-3 and T-LAG-3 have shown to have a significant correlation with favorable DSS in squamous cell carcinoma (SCC). But the result is inconsistent across all pathologic stages. In other words, this finding implies that the expression of LAG-3 cannot become a strong biomarker for NSCLC [11]. In addition, some evidence from the same study suggest that each LAG-3 expression location might correspond to a specific disease or condition. Therefore, LAG-3 might still have potential to be a strong prognostic biomarker for specific conditions of NSCLC such as SCC and LN+, but further research is needed.

3.3. Correlation between ICs and TIL abundance in NSCLC patients

Contrasting to other ICs, LAG-3 protein is only found in immune cells of the host and not expressed in tumor cells. Moreover, LAG-3 are largely found on TILs. However, there could be many immune checkpoints that is activated while LAG-3 protein is presence. It is crucial to understand the correlation between LAG-3 and other ICs in the NSCLC, to provide references to combination therapy and monotherapy. In a clinical study with 139 NSCLC patients involved, strong expressions of LAG-3 were found to be correlate with intense activities of PD-1 and PD-L1 on TILs [10]. Interestingly, a similar connection did not happen between LAG-3 and TIL expression [10]. This result suggests that a dual therapy of PD-1 and LAG-3 inhibitors focusing on TILs will likely correlate with better prognosis than monotherapy in NSCLC.

Table 1. Active and or recruiting anti-LAG-3 associated clinical trials

Drug/Antibody	Clinical studies no.	Cancer targeted
IMP321	NCT03252938, NCT03625323, NCT04811027	Solid tumor(ST), peritoneal carcinomatosis, NSCLC, HNSCC
Relatlimab	NCT01968109, NCT04080804, NCT03610711, NCT03044613, NCT03459222, NCT02966548, NCT04611126, NCT02488759, NCT03607890, NCT03623854, NCT03642067, NCT04326257, NCT04913922, NCT05148546, NCT02465060, NCT05337137, NCT03743766, NCT04658147, NCT02519322	HNSCC, gastroesophageal cancer (GEC), gastric cancer (GC), esophageal cancer (EC), metastatic ovarian cancer, metastatic fallopian cancer, peritoneal cancer, MSS, acute myeloid leukemia, hepatocellular carcinoma, et, al.
REGN3767 (Fianlimab)	NCT03005782N, CT05352672	Malignances, melanoma
TSR-033	NCT03250832	Neoplasm
89Zr-DFO-REGN3767	NCT04706715, NCT04566978	Metastatic solid tumor, large B-cell lymphoma, DLBCL
Sym021	NCT04641871	Metastatic and solid cancer
Sym022	NCT04641871	Metastatic and solid cancer
Sym023	NCT04641871	Metastatic and solid cancer
BMS-986213	NCT03662659, NCT01968109, NCT05134948	Gastric cancer, stomach cancer, esophagogastric junction, Neoplasm by sites, advanced solid tumors
HLX26	NCT05078593	ST, lymphoma
EMB-02	NCT04618393	Advanced solid tumor(AST)
RO7247669	NCT04140500, NCT04785820	ST, metastatic melanoma, NSCLC, esophageal squamous cell carcinoma
INCAGN02385	NCT04370704	Melanoma
FS118	NCT03440437	Metastatic cancer, HNSCC,
tebotelimab	NCT03219268, NCT04634825, NCT04082364	AST, HER2-positive Advanced Solid Tumors, NSCLC, SCLC, HNSCC, Cholangiocarcinoma, TNBC, Gastric cancer, GEC, et,al.
BMS 986016	NCT02658981, NCT03493932	Glioblastoma, Recurrent Brain Neoplasm,
IBI323	NCT04916119	Advanced malignances
Claudin6 targeting CAR-NK cells	NCT05410717	Stage IV Ovarian Cancer, Testis Cancer, Refractory, Endometrial Cancer Recurrent, CAR NK
SRF388	NCT04374877	AST, CCRCC, Hepatocellular Carcinoma, NSCLC
INCAGN02385	NCT04463771, NCT04586244	Endometrial cancer, urothelial carcinoma
LAG525	NCT03742349, NCT03484923	TNBC, melanoma
XmAb®22841	NCT03849469	Melanoma, TNBC, Hepatocellular Carcinoma, UC, HNSCC, Nasopharyngeal Carcinoma, RCC, NSCLC, SCLC, Gastric or Gastroesophageal Junction Adenocarcinoma, et,al.
LBL-007	NCT04640545	Melanoma

3.4. RFS and OS between LAG-3 expression and NSCLC

Based on the Kaplan- Meier analysis conducted by the same research with 139 NSCLC patients involved, Recurrence free survival and OS for NSCLC patients that had LAG-3 positive expression

on TILs was shorter than patients that had negative expression¹⁹. Similarly, patients with NSCLC have shorter RFS when they have TILs that has positive PD-1 and LAG-3[10]. Interestingly, when both LAG-3 and PD-1 are negative, the OS is insignificant ($p=0.069$) [10]. This data suggests that the monotherapy of ICI that targets LAG-3 is likely to prolong both RFS and OS for the NSCLC patients, while combination therapy of ICI for LAG-3 and PD-1 may only help to boost RFS.

4. The role of LAG-3 drug in NSCLC patients

4.1. Anti-LAG-3 drugs effects in NSCLC

In the past few years, LAG-3 inhibitor is under investigated compared to other ICI in many diseases, including NSCLC. One of the reasons is that ICI that targets PD-1, PD-L1, and CTLA-4 have reached significant outcome within many clinical trials for many types of cancers such as NSCLC and melanoma (table 1). However, development of LAG-3 inhibitors has been receiving many attentions in recent years. Some researchers focus on the clinical performance of LAG-3 inhibitors in the hope that it might become a second line treatment for cancer patients who cannot receive ICI that targets other IC [12].

LAG525 or ieramilimab is a novel anti-LAG3 inhibitor that cease the immunosuppression caused by the expression of LAG-3[13]. LAG525 have undergone some clinical trials on phase I/II for safety and antitumor effectc [12]. One of the clinical trials conducted two experiment group, one with LAG525 alone, and another group comprised a combination of LAG525 and PDR001 on patients that has solid tumors including NSCLC [13]. 255 patients who are receiving the treatment are those who are unsuitable for standard treatment and are over 18 years old. Based on the result, combination therapy with PDR001 have shown promising results on overall response rate and upregulated immune activity among all types of patients including NSCLC patients²². In contrast, the data in monotherapy patients are not showing significant correlation between LAG525 and response rate. Intriguingly, even though patients that received the combined therapy have shown a substantial increase in grade 2 TRAEs, the occurrence of grade 4 and grade 3 TRAEs was more on the group of monotherapies than the combination therapy. However, the number of grade 4 and grade 3 cases between the single agent and the combination is insignificant [13]. And it is possible that the difference occurred due to individual difference on overall health. But the relationship between the occurrence of severe TRAEs and number of ICI targets needs further investigation.

Relatlimab, the first anti-LAG-3 drug that had been approved by FDA for metastatic melanoma. In a dualtreatment with PD-1 inhibitor drug, nivolumab, relatlimab has shown significant improvement on PFS in patients with untreated metastatic melanoma [14]. Patients that received combination of the relatlimab and nivolumab has an overall PFS for 10.1 months. In contrast, monotherapy of nivolumab alone has only PFS for 4.6 months ($p=0.0055$). Since relatlimab has demonstrates a significant role in this dual treatment with nivolumab. It is safe to speculate that anti-LAG-3 inhibitors has shown a considerable potential to enhance the response rate and PFS of another ICI. Furthermore, relatlimab as a drug that passed the safety protocol, it has clinical potential and deserve to be investigated on other types of cancers beside metastatic melanoma. In fact, there is one clinical trial that is investigating the dual immunotherapy of both relatlimab and nivolumab in recurrence NSCLC cases (clinical trial no. NCT04623775).

Moreover, another phase II study that focuses on Eftilagimod (Efti) and pembrolizumab dual treatment in patients with metastatic NSCLC. Efti is a soluble LAG-3 molecule that act as an immune enhancer by binding to the dendritic cells through MHC-II [15]. The study recruited 36 patients that have metastatic NSCLC. The study indicates that the disease control rate (DCR) is 69%, objective response rate (ORR) is 42% with 25.5 % to 59.2 % as 95 percent interval²⁵. Although the median OS is not collected due to the fact that the research is still active, the median PFS rate is about 8.2 months across the treatment groups²⁵. While most patients only experience grade I/II TRAEs, two patients discontinued the dual treatment due to the occurrence of grade 3 and grade 4 TRAEs, which are elevated serum AST+ALT levels and immune mediated hepatitis respectively [16].

Another phase Ia/ Ib study used IBI100, a LAG-3 inhibitor, as a mono-checkpoint therapy and dual with sintilimab, another drug that targets PD-1, on 73 patients that has solid tumors including NSCLC [17]. The result of the study indicated that the IBI100 is well tolerated for clinical use and showed no dose limiting toxicity. On the Ia group, 28 patients received dose escalating of IBI100. Among these 28 patients, 1 of them have developed partial response (PR) while 6 patients have stable disease by investigator assessment. In addition, 45 patients who received the combination therapy has reached 5 PRs and 18 SDs [17]. Among the total of 6 PRs cases, 4 of them are patients with NSCLC. Thus, this research has demonstrated the safety profile of IBI100 as a LAG-3 inhibitor and has shown a great potential for the immunotherapy approach of NSCLC.

Furthermore, many studies have shown that anti-LAG-3 drugs have the clinical potential and efficacy in immunotherapy for many types of cancers. However, LAG-3 inhibitors were more commonly used as an enhancer or supporter of other ICI treatments, such as PD-1 inhibitor, because it has shown to promote the PFS and OS of the combination therapy. Fortunately, there are more LAG-3 targeting drugs that are being investigated for the use of anti-LAG-3 drugs as an independent treatment for cancer immunotherapy

4.2. Limitations of Immune checkpoint inhibitors

As a general function of IC, they suppress immune cell production and proliferation to prevent autoimmunity and T-cell exhaustion. On the other hand, ICI increases the immune response against malignancies by disabling IC's inhibition of T-cells. Applying ICI to patients with metastatic cancers promotes T-cell activity against tumor cells, leading to a better prognosis. However, increased immune cell activity also elevates the possibility of autoimmunity. Autoimmune adverse effect (AE) is one of the most common AEs in ICI therapy, and they occur similarly in all types of ICI, besides the fact that CLTA-4 inhibitors have shown more frequent and severe AEs [18].

Besides autoimmune AEs, some other side effects are also considered to be caused by ICI treatments including LAG-3 inhibitor. These side effects include colitis, pneumonitis, skin AEs, endocrine dysfunction, hepatitis, myocarditis, and neurotoxicity.²⁷ Myocarditis and neurotoxicity are the least common AEs. Skin AEs on the other hand, is the most common AE among all other AEs. Even though there are many possible AEs with ICI immunotherapy, there are solutions for every possible side effect. Most TRAEs from grade I to grade III could be treated with glucocorticoids and steroids [17]. Moreover, these ICI induced AEs are usually considered less severe than chemotherapy [6].

Furthermore, resistance developed from cancer cells against anti-cancer drugs is always a great topic to investigate in cancer immunotherapy. Clonal mutation and sub-clonal mutation are two mutational pathways for tumor cells to develop resistance [6]. In some cases, the genetic mutation of tumor cells could lead to the change of tumor microenvironment (TME), which could cause the inhibition of immune response. Moreover, cancer cells are more prone to have mutation as checkpoint inhibitors in the cell cycle are less likely to regulate tumor cell production. Therefore, cancer cells are more likely to resist to intervention of drugs because they could become less sensitive to the drug after mutations occur. ICI treatment also has this problem. In some clinical studies, only a portion of patients has shown a positive clinical response to the ICI treatment. One approach to solve the resistance problem is the combination of ICIs. The treatment of multiple ICIs could hinder the function of multiple ICs, which could overcome the tumor resistance to a particular IC. Therefore, ICI combination therapy are being investigated more in recent years to not only improve better clinical outcomes, but also fight against the tumor resistance. However, one disadvantage of synergetic approach is that, in many clinical studies, patients who received the combination therapy for multiple ICs have shown more frequent and severe side effects than patients who received monotherapy. Therefore, further research is mandatory on reducing the TRAEs of synergetic treatments.

Another limitation for the LAG-3 inhibitor is the lack of a reliable biomarker that could be used for specificity and sensitivity of the IC intervention. The lack of a reliable biomarker in

immunotherapy could cause difficulty in choosing the most compatible inhibitor drugs for cancer patients, which could result in many patients not benefiting from the treatment²⁸. However, some potential biomarkers being used in ICI clinical research are considered useful but remain more investigations. Tumor mutation burden (TMB) is a measure of gene mutations in the Deoxyribonucleic acid (DNA) of cancer cells. It is one of the most frequently used biomarkers for ICI therapy. A high TMB indicates the presence of high gene mutations occur in the cancer genome. There is increasing evidence showing a strong correlation between TMB level and ICI response rate in recent studies, including NSCLC [20]. Most studies about TMB association with ICI response rate demonstrated that a high TMB has led to increased ICI treatment response [6]. These findings suggest that TMB could become a biomarker that predict the response rate of ICIs throughout the treatment. However, the specific mechanism between TMB and ICI response is still unclear [6]. And still, measurement of TMB cannot contribute to the sensitivity or specificity of any ICI treatment. Thus, it is necessary for a thorough investigation of TMB as a biomarker for specific inhibitors such as LAG-3 inhibitor, and other ICI immunotherapies as whole.

LAG-3 as an IC has undergone many vitro and clinical trials by researchers in the hope of becoming a treatment option for many patients with solid tumors such as NSCLC. Although relatlimab is the only FDA approved anti-LAG-3 drug to treat metastatic melanoma, as of August 2022, a total of 23 types of anti-LAG-3 drugs are being studied in clinical trials (clinicaltrials.gov, table 1). However, the number of studies about the LAG-3 inhibitor effect in patients with NSCLC is relatively small compared to other checkpoint inhibitors. Some limitations of LAG-3 and other ICIs such as resistance and biomarker could become potential topics for further investigation.

5. Conclusions

The annual incidence of cancer is increasing, and traditional treatment methods have their limitations. Immunotherapy appears to address these exposed problems. Among them, LAG-3 has undergone many in vitro and clinical trials and is promising as an immunotherapy option for NSCLC patients. Beyond the limitations of anti-LAG-3 cancer treatment, there are still many knowledge caps about the LAG-3, and many of the uncertain questions demonstrate great clinical potentials for future research. Firstly, the LAG-3 is found on many immune cells, but the specific role of LAG-3 on B cells, pDC and neurons are still unclear. Secondly, the cost of LAG-3 drugs and its inhibitor is expensive, which creates financial difficulty for some labs to run a LAG-3 related experiment. It will optimal to reduce the production cost of LAG-3 antibody in order to facilitate more LAG-3 related research. Lastly, LAG-3 molecules get dimerized by D1 domain when they are transported to the cell surface. However, whether if un-dimerized LAG-3 could still perform its normal function remains unknown, such as binds to the ligands that LAG-3 initially bound with. In conclusion, LAG-3 expression has contributed to the immunosuppression of the host and indirectly stimulate the growth of tumor cells. It shows the potential of becoming an immunotherapy treatment to patients with NSCLC. However, more research is needed to investigate the mechanisms of LAG-3 and the therapeutic outcomes of its inhibitor in NSCLC.

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