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Anti-LAG-3 antibody LBL-007 plus anti-PD-1 antibody toripalimab in advanced nasopharyngeal carcinoma and other solid tumors: an open-label, multicenter, phase Ib/II trial

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Abstract

Purpose Open-label phase Ib/II study to investigate the safety and efficacy of LBL-007, an anti-LAG-3 antibody, plus toripalimab, an anti-PD-1 antibody, in patients with previously treated advanced nasopharyngeal carcinoma (NPC) and other solid tumors.

Methods Patients with advanced tumors refractory to prior standard therapies were enrolled. In phase Ib, patients received LBL-007 200 mg or 400 mg and toripalimab 240 mg intravenously once every 3 weeks. In phase II, all patients received LBL-007 at the recommended phase II dose (RP2D) and toripalimab 240 mg intravenously once every 3 weeks. The primary end points were safety in phase Ib and objective response rate (ORR) in phase II. The exploratory end point was the predictive capability of LAG-3 and PD-L1 expression for efficacy.

Results Between November 30, 2021, and December 1, 2023, 80 patients were enrolled, including 30 (37.5%) with NPC and 50 (62.5%) with other tumors. Median follow-up was 26.0 months. In Phase Ib, LBL-007 was administered at 200 mg to four patients and 400 mg to six patients, with no dose-limiting toxicities observed. Therefore, the 400 mg dose of LBL-007 was established as the RP2D and administered to 70 patients in phase II. Nine (11.3%) of 80 patients had grade 3 or 4 treatment-related adverse events, the most common of which included anemia (2.5%), hyponatremia (2.5%), increased alanine aminotransferase (2.5%), increased aspartate aminotransferase (1.3%), and

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fatigue (1.3%). Eight patients (10.0%) had treatment-related serious adverse events. No treatment-related deaths were reported. In immunotherapy-naive NPC patients ($n=12$), ORR was 33.3%, disease control rate (DCR) was 75%, and median progression-free survival (PFS) was 10.8 months (95% CI, 1.3 to not estimated). In IO-treated NPC patients ($n=17$), ORR was 11.8%, DCR was 64.7%, and median PFS was 2.7 months (95% CI, 1.4 to 4.9). For other tumors, ORRs were 15.8% in immunotherapy-naive patients and 3.7% in immunotherapy-treated patients. Patients with ≥ 2 + LAG-3 expression had a higher ORR of 28.0%, compared to 7.7% in those with < 2 + LAG-3 expression.

Conclusion LBL-007 plus toripalimab exhibited a manageable safety profile in patients with advanced solid tumors and demonstrated promising antitumor activity in NPC, especially in immunotherapy-naive patients. These findings warrant further validation in future studies.

Introduction

Immunotherapy with immune-checkpoint inhibitors (ICIs) has transformed cancer treatment, offering significant survival benefits across various malignancies [1]. Despite their success, anti-PD-(L)1 monotherapy achieves only modest overall response rates in patients with advanced cancers [2–4]. As a result, combination therapies targeting PD-(L)1 and other immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and lymphocyte activation gene-3 (LAG-3), have been investigated to enhance clinical outcomes [5–9].

LAG-3 is an inhibitory receptor that is highly expressed on exhausted T cells [10]. It limits T cell function by interacting with major histocompatibility complex (MHC) class II molecules [11]. Co-expression of LAG-3 and PD-1 has been observed on tumor-infiltrating T cells in several cancers, including melanoma and nasopharyngeal carcinoma (NPC) [12–14]. Recent studies have elucidated the underlying mechanisms that co-blockade of LAG-3 and PD-1 enhances the proliferation, cytotoxicity and interferon-gamma production of exhausted CD8 + T cells [15, 16]. These findings support the rational for evaluating this combination therapy in tumors with elevated LAG-3 and PD-(L)1 expression. The RELATIVITY-047 trial demonstrated that dual blockade of PD-1 and LAG-3 results in synergistic anti-tumor activity, leading to FDA approval of this combination therapy for patients with advanced melanoma [5]. However, the efficacy and safety of anti-LAG-3/PD-1 combination therapy in other cancers, particularly in NPC, requires further investigation.

LBL-007 is an innovative, fully human, IgG4/κ subtype monoclonal antibody designed to selectively bind and inhibit LAG-3. Preclinical study suggested that the endocytosis efficiency of LBL-007 was superior to that of another anti-LAG-3 antibody, relatlimab [17]. In addition, the combination of LBL-007 and an anti-PD-1 antibody resulted in enhanced inhibition of tumor growth compared to either monotherapy in mouse allograft models. In this trial, we evaluate the safety profile, preliminary antitumor activity, and potential biomarkers of LBL-007 combined with toripalimab in patients with advanced NPC and other solid tumors. To our knowledge, this is the first clinical trial to assess the efficacy of anti-LAG-3/PD-1 combination therapy in NPC patients.

Methods

Study design and participants

This is an open-label, single-arm, multicenter, dose escalation and expansion, phase Ib/II trial to assess the safety and preliminary antitumor activity of LBL-007 combined with toripalimab in patients with advanced malignant tumors (ClinicalTrials.gov identifier: NCT05102006). This study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and amendments received approval from the institutional review board or independent ethics committee at each site. Patients provided written informed consent before enrollment and agreed to comply with the study protocol and visit schedule.

Patients enrolled in the trial had histologically or cytologically confirmed advanced (metastatic and/or unresectable) malignant tumors and had progressed after standard treatment. Eligible patients were either immunotherapy-naive (IO-naive) or had prior exposure to immunotherapy (IO-treated). Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), adequate organ function, and a life expectancy of at least 12 weeks. Key exclusion criteria included a history of or active autoimmune disease, active hepatitis B or C virus infection and active brain metastases. The full inclusion and exclusion criteria and criteria for withdrawal from treatment are listed in the protocol (Supplement protocol).

Study treatment

Based on data from two unpublished phase I trials (CTR20191854, NCT04640545), we selected LBL-007 at doses of 200 mg (equivalent to 3 mg/kg for a 65 kg subject) or 400 mg (equivalent to 6 mg/kg for a 65 kg subject) once every 3 weeks for patients in the phase Ib study. The 240 mg dose of toripalimab was administered once every

3 weeks according to the commercial recommendation. The recommended phase II dose (RP2D) of LBL-007 was determined based on safety and pharmacokinetic profile from phase Ib. In phase II, all patients received LBL-007 at the RP2D and toripalimab 240 mg once every 3 weeks. Treatment continued for two years or until confirmed disease progression (PD), intolerable toxicity, withdrawal of consent, or patient/physician decision. Continued treatment beyond initial progression was allowed if clinically beneficial and without unacceptable toxicities, until imaging-confirmed disease progression 4 weeks later. The study diagram is shown in Supplement Figure S1.

Assessments

Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-relate AEs (TRAEs) were attributed to either LBL-007, toripalimab, or both. Immune-related AEs (irAEs) were considered by investigators to be potentially related to immune mechanisms. The detailed definition of dose-limiting toxicity (DLT) is listed in the protocol (Supplement protocol). DLTs were evaluated in patients enrolled in the dose escalation phase (phase Ib). The maximum tolerated dose (MTD) was determined as the highest dose level with ≤ one out of six patients experiencing a DLT.

Radiologic tumor response was assessed using RECIST version 1.1 via computed tomography or magnetic resonance imaging. Evaluation was performed every 6 weeks in the first 24 weeks, and then every 9 weeks for up to two years. Complete response and partial response were confirmed by investigators at least 4 weeks after the initial documentation.

Formalin-fixed, paraffin-embedded baseline tumor samples were used to determine LAG-3 and PD-L1 expression levels via validated immunohistochemistry assays, as described previously [18]. Archived tissue samples obtained within one year were acceptable. LAG-3 expression was graded based on staining intensity as follows: 0 (no staining), 1+ (weak), 2+ (moderate), or 3+ (strong). High expression of LAG-3 was defined as intensity ≥ 2+. PD-L1 expression was assessed using the standardized SP263 assays (Ventana Medical Systems) and was scored as the proportion of tumor cells (TCs) showing PD-L1 membrane staining.

End points

In Phase Ib, the primary end points were to evaluate safety and tolerability of LBL-007 combined with toripalimab, and the determination the RP2D. Safety data, including AEs, serious AEs (SAEs), TRAEs, irAEs and DLTs, were summarized descriptively. In phase II, the primary end point was the preliminary efficacy of LBL-007 plus toripalimab, as measured by the objective response rate (ORR). Secondary end points included safety, progression-free survival (PFS), disease control rate (DCR) and duration of response (DOR). The exploratory end point was the correlation between efficacy and expression levels of LAG-3 and PD-L1.

Statistical analysis

Safety analysis was conducted in all patients who received at least one dose of study drugs. Antitumor activity was evaluated in patients who had at least one post-baseline imaging evaluation. Biomarker analysis was performed in patients with available data on PD-L1 and LAG-3 expression levels, as well as tumor response outcomes.

ORR and DCR were calculated with corresponding 95% confidence intervals using the Clopper-Pearson method. PFS and DOR were plotted using the Kaplan-Meier method for time-to-event data. Categorical variables were summarized using frequency counts and percentages, while continuous variables were summarized using descriptive statistics, including mean, standard deviation (SD), median, and range (min, max). We performed all statistical tests using SAS v9.4.

Results

Patient baseline characteristics

From November 30, 2021, to December 1, 2023, 93 patients were screened for eligibility and 80 patients were enrolled from 11 centers (10 in phase Ib and 70 in phase II), including 30 patients with NPC, 13 with small cell lung cancer (SCLC), 12 with lung adenocarcinoma (adNSCLC), 9 with squamous non-small cell lung cancer (sqNSCLC), 8 with esophageal squamous cell carcinoma (ESCC), 5 with head and neck squamous cell carcinoma (HNSCC), and 3 with cervical cancer (CCA). All patients had progressed after standard therapies, and 35 patients (43.8%) had received two or more prior lines of treatment. Additionally, 47 patients (58.8%) had previously received anti-PD-(L)1 immunotherapy. The baseline characteristics of the enrolled patients are summarized in Table 1.

At the data cutoff on July 26, 2024, the median follow-up was 26.0 (range, 0.6–29.4) months. The median duration of therapy was 5.0 months (range, 0.3–24.7). All 80 patients discontinued the study treatment for the following reasons: 59 due to disease progression, seven due to withdrawal of consent, five after completing 2 years of treatment, seven due to AEs and two due to death. Among the five patients who completed 2 years of treatment, two IO-naïve and one IO-treated NPC patient achieved PRs, while one IO-naïve and one IO-treated NPC patient achieved SDs.

Table 1 Patients' demographics and baseline characteristics

Characteristic	IO-naive NPC (*n* = 12)	IO-treated NPC (*n* = 18)	IO-naive other tumors (*n* = 21)	IO-treated other tumors (*n* = 29)
Age, years, median (range)	44.5 (31–68)	40.0 (28–61)	56.0 (38–69)	58.0 (41–73)
Sex, No. (%)				
Female	3 (25.0)	4 (22.2)	2 (9.5)	9 (31.0)
Male	9 (75.0)	14 (77.8)	19 (90.5)	20 (69.0)
Race, No. (%)				
Asian	12 (100.0)	18 (100.0)	21 (100.0)	29 (100.0)
ECOG Performance Status, No. (%)				
0	3 (25.0)	12 (66.7)	3 (14.3)	11 (37.9)
1	9 (75.0)	6 (33.3)	18 (85.7)	18 (62.1)
TNM stage, No. (%)				
IIIA	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)
IIIB	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)
IV	12 (100.0)	18 (100.0)	16 (76.2)	28 (96.6)
Previous lines of therapy, No. (%)				
1	10 (83.3)	6 (33.3)	13 (61.9)	15 (51.7)
≥ 2	2 (16.7)	12 (66.7)	7 (33.3)	14 (48.3)
Tumor types, No. (%)				
Nasopharyngeal Cancer	12 (100.0)	18 (100.0)	0 (0.0)	0 (0.0)
Small Cell Lung Cancer	0 (0.0)	0 (0.0)	5 (23.8)	8 (27.6)
Lung Adenocarcinoma	0 (0.0)	0 (0.0)	2 (9.5)	10 (34.5)
Lung Squamous Cell Carcinoma	0 (0.0)	0 (0.0)	7 (33.3)	2 (6.9)
Esophageal Squamous Cell Carcinoma	0 (0.0)	0 (0.0)	1 (4.8)	7 (24.1)
Head and Neck Squamous Cell Cancer	0 (0.0)	0 (0.0)	5 (23.8)	0 (0.0)
Cervical Cancer	0 (0.0)	0 (0.0)	1 (4.8)	2 (6.9)
PD-L1 expression, No. (%)				
< 1%	4 (33.3)	2 (11.1)	11 (52.4)	8 (27.6)
1%≤PD-L1<25%	2 (16.7)	4 (22.2)	2 (9.5)	4 (13.8)
≥25%	1 (8.3)	3 (16.7)	0 (0.0)	0 (0.0)
Unknown/missing	5 (41.7)	9 (50.0)	8 (38.1)	17 (58.6)
LAG-3 expression, No. (%)				
0	1 (8.3)	1 (5.6)	0 (0.0)	1 (3.4)
1+	1 (8.3)	3 (16.7)	2 (9.5)	5 (17.2)
2+	2 (16.7)	2 (11.1)	3 (14.3)	2 (6.9)
3+	3 (25.0)	3 (16.7)	8 (38.1)	4 (13.8)
Unknown/missing	5 (41.7)	9 (50.0)	8 (38.1)	17 (58.6)

Abbreviations: ECOG: eastern cooperative oncology group; IO: immuno-oncology therapy; LAG-3: Lymphocyte-activation gene 3

Antitumor activity

Five patients discontinued treatment without any post-baseline imaging evaluations. Thus, antitumor activity was assessed in the remaining 75 patients (93.8%). Ten patients (13.3% [95% CI, 6.6–23.2%]) achieved a confirmed objective response. No CRs were reported, while PRs were observed in patients with NPC ($n = 6$), sqNSCLC ($n = 2$), HNSCC ($n = 1$) and ESCC ($n = 1$). The DCR was 54.7% (95% CI, 42.7–66.2%). Efficacy results are summarized in Table 2; Figs. 1 and 2 and Supplement Figure S2.

Among the 12 IO-naive NPC patients, the ORR was 33.3% (95% CI, 9.9–65.1%), the DCR was 75.0% (95% CI, 42.8–94.5%), the median PFS was 10.8 months (95% CI, 1.3 to NE), and the median DOR was 15.0 months (95% CI, 5.5 to NE). Among the 17 IO-treated NPC patients, the ORR was 11.8% (95% CI, 1.5–36.4%), the DCR was 64.7% (95% CI, 38.3–85.8%), the median PFS was 2.7 months (95% CI, 1.4 to 4.9), and the median DOR was 13.5 months (95% CI, 12.5 to NE). Notably, among the six NPC responders, 83.3% maintained partial responses for more than 12 months. The one-year PFS rate was 40% for IO-naive NPC patients and 21.2% for IO-treated NPC patients.

Among patients with other tumors, the ORR was 8.7% (95% CI, 2.4–20.8%), and the DCR was 45.7% (95% CI, 30.9–61.0%). Among the eight patients with sqNSCLC, one out of six IO-naive patients achieved a PR, and one out of two IO-treated patients achieved a PR. Among the eight patients with ESCC, the only IO-naive patient

Table 2 Antitumor activity

Outcome	IO-naive NPC (*N* = 12)	IO-treated NPC (*N* = 17)	IO-naive other tumors (*N* = 19)	IO-treated other tumors (*N* = 27)
Best overall response[a], No. (%)				
CR	0	0	0	0
PR	4(33.3)	2(11.8)	3(15.8)	1(3.7)
SD	5(41.7)	9(52.9)	9(47.4)	8(29.6)
PD	3(25.0)	6(35.3)	7(36.8)	18(66.7)
ORR[b]				
n (%)	4(33.3)	2(11.8)	3(15.8)	1(3.7)
95% CI[c]	(9.9,65.1)	(1.5,36.4)	(3.4,39.6)	(0.1,19.0)
DCR[d]				
n (%)	9(75.0)	11(64.7)	12(63.2)	9(33.3)
95% CI[c]	(42.8,94.5)	(38.3,85.8)	(38.4,83.7)	(16.5,54.0)
PFS, months, median (95% CI[e])	10.8 (1.3, NE)	2.7 (1.4, 4.9)	3.1 (1.3, 5.7)	1.4 (1.3, 1.6)
1-year PFS rate (95% CI[f])	40.0% (13.5%, 65.7%)	21.2% (5.6%, 43.4%)	5.8% (0.4%, 23.3%)	0% (NE, NE)
DOR, months, median (95% CI[e])	15.0 (5.5, NE)	13.5 (12.5, NE)	5.3 (4.3, NE)	2.7 (NE, NE)
1-year DOR rate (95% CI[f])	75.0% (12.8%, 96.1%)	100.0% (100.0%, 100.0%)	0% (NE, NE)	0% (NE, NE)

Note: 75 of 80 patients had at least one post-baseline scan available and were included in the activity population

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; n, number; IO, immuno-oncology therapy; ND, not determined; NE, not estimated; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease

[a]Per RECIST 1.1

[b]ORR=CR + PR

[c]95% CI is based on Clopper-Pearson method

[d]DCR= CR + PR + SD

[e]95% CI is based on Brookmeyer Crowley method

[f]95% CI is based on Greenwood formula

achieved a PR, while no PRs were observed in the seven IO-treated patients. Among the four IO-naive HNSCC, one patient achieved a PR. No objective responses were observed in three patients with CCA and 13 patients with SCLC.

Safety

In phase Ib, LBL-007 was administered intravenously at doses of 200 mg in four patients and 400 mg in six patients once every 3 weeks. No dose-limiting toxicities were observed. Therefore, the 400 mg dose of LBL-007 was selected as the RP2D and administered to 70 patients in phase II. All 80 patients received toripalimab at a fixed dose of 240 mg once every 3 weeks and were included in the safety population.

Any-grade TRAEs were reported in 61 patients (76.3%) (Table 3). Grade 3 or 4 TRAEs occurred in 9 patients (11.3%). The most common grade 3 or 4 TRAEs included anemia (2.5%), hyponatremia (2.5%), increased alanine aminotransferase (2.5%), increased aspartate aminotransferase (1.3%), and fatigue (1.3%). Serious TRAEs were reported in 10.0% of patients, and 8.8% of patients experienced TRAEs leading to treatment discontinuation, including one patient with grade 4 neutropenia and grade 4 leukopenia, one patient with grade 3 anemia, one patient with grade 4 paralysis of the lower limbs, one patient with grade 4 constrictive pericarditis, one patient with grade 2 myocarditis, one patient with grade 2 elevated myocardial enzymes and one patient with grade 3 hyponatremia. No treatment-related deaths occurred. The most common immune-related adverse events were hypothyroidism (10.0%), increased aspartate aminotransferase (5.0%), increased alanine aminotransferase (3.8%), fatigue (3.8%) and increased gamma-glutamyl transferase (2.5%). Grade 3 or 4 irAEs occurred in 3.8% of patients. All irAEs were well manageable with corticosteroids.

Exploratory analyses

Exploratory analysis based on LAG-3 and PD-L1 expression was performed in 38 patients with available efficacy data. High LAG-3 expression (≥ 2+) was observed in 25 patients (65.9%), and 12 patients (31.6%) showed positive PD-L1 expression (TC ≥ 1%).

Among the 38 patients, those with LAG-3 expression ≥ 2 + had an ORR of 28.0% versus 7.7% in those with LAG-3 expression < 2+ (Table 4). Among the 15 NPC patients, those with LAG-3 expression ≥ 2 + had an ORR of 40% versus 20% in those with LAG-3 expression < 2+. To note, of the eight patients achieving a confirmed objective response in the biomarker-evaluable population, seven (87.5%) had LAG-3 expression ≥ 2+. However, the association between efficacy and PD-L1 expression was elusive, as similar ORR was observed in PD-L1 positive and negative populations (25.0% versus 19.2%).

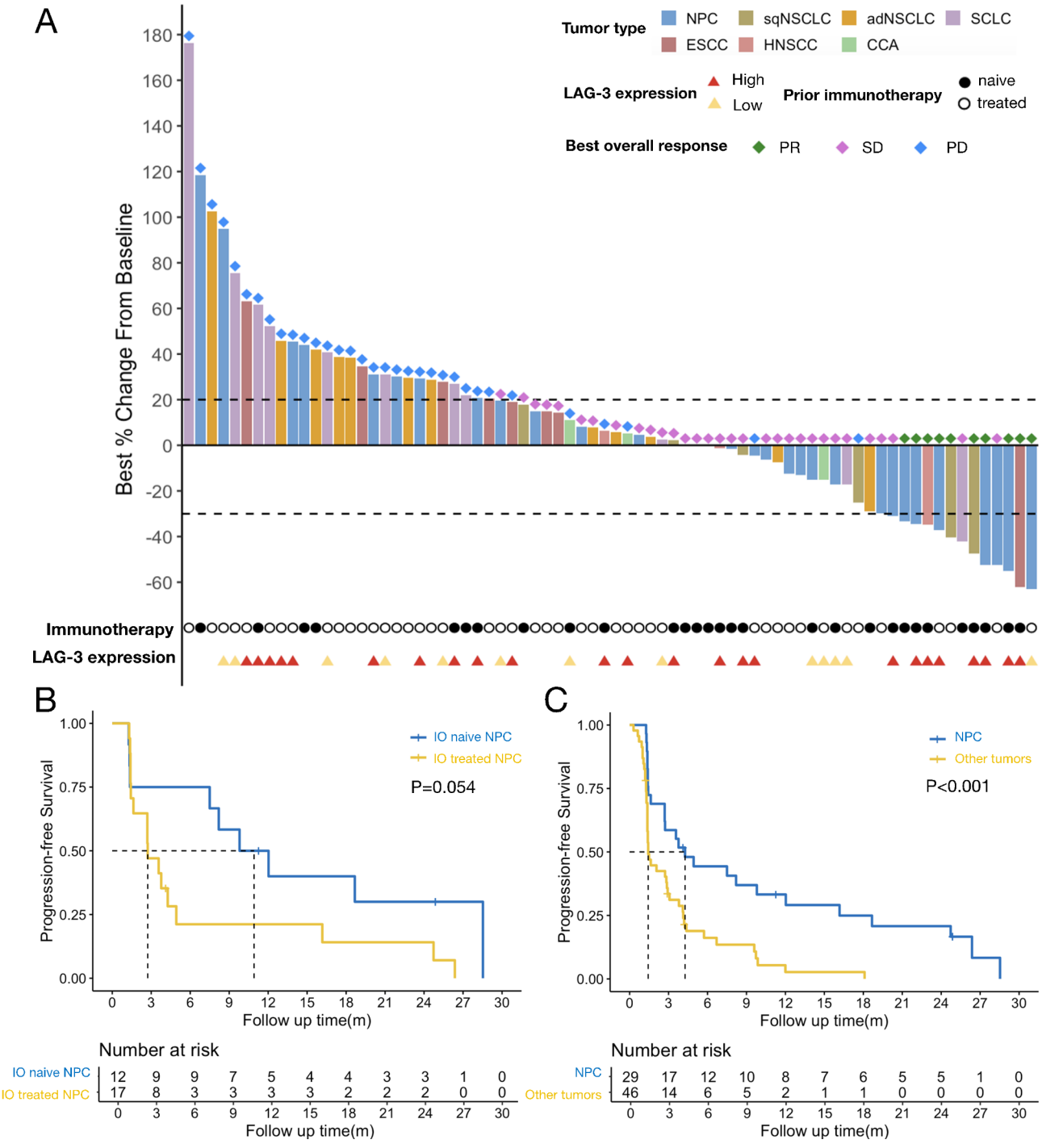

Fig. 1 Tumor response assessment and Kaplan-Meier survival plots. Efficacy of LBL-007/toripalimab combination in patients with advanced solid tumors. Five patients who had nonvaluable response and were not included. (**A**) Waterfall plot showing the maximum changes in tumor size. (**B**) Kaplan-Meier plot of progression-free survival in NPC patients stratified by prior immunotherapy. (**C**) Kaplan-Meier plot of progression-free survival in patients stratified by NPC and other tumors. Abbreviations: adNSCLC: lung adenocarcinoma; CCA: cervical cancer; ESCC: esophageal squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; IO: immunotherapy; NPC: nasopharyngeal carcinoma; PD: progressive disease; PR: partial response; SCLC: small cell lung cancer; SD: stable disease; sqNSCLC: squamous non-small cell lung cancer

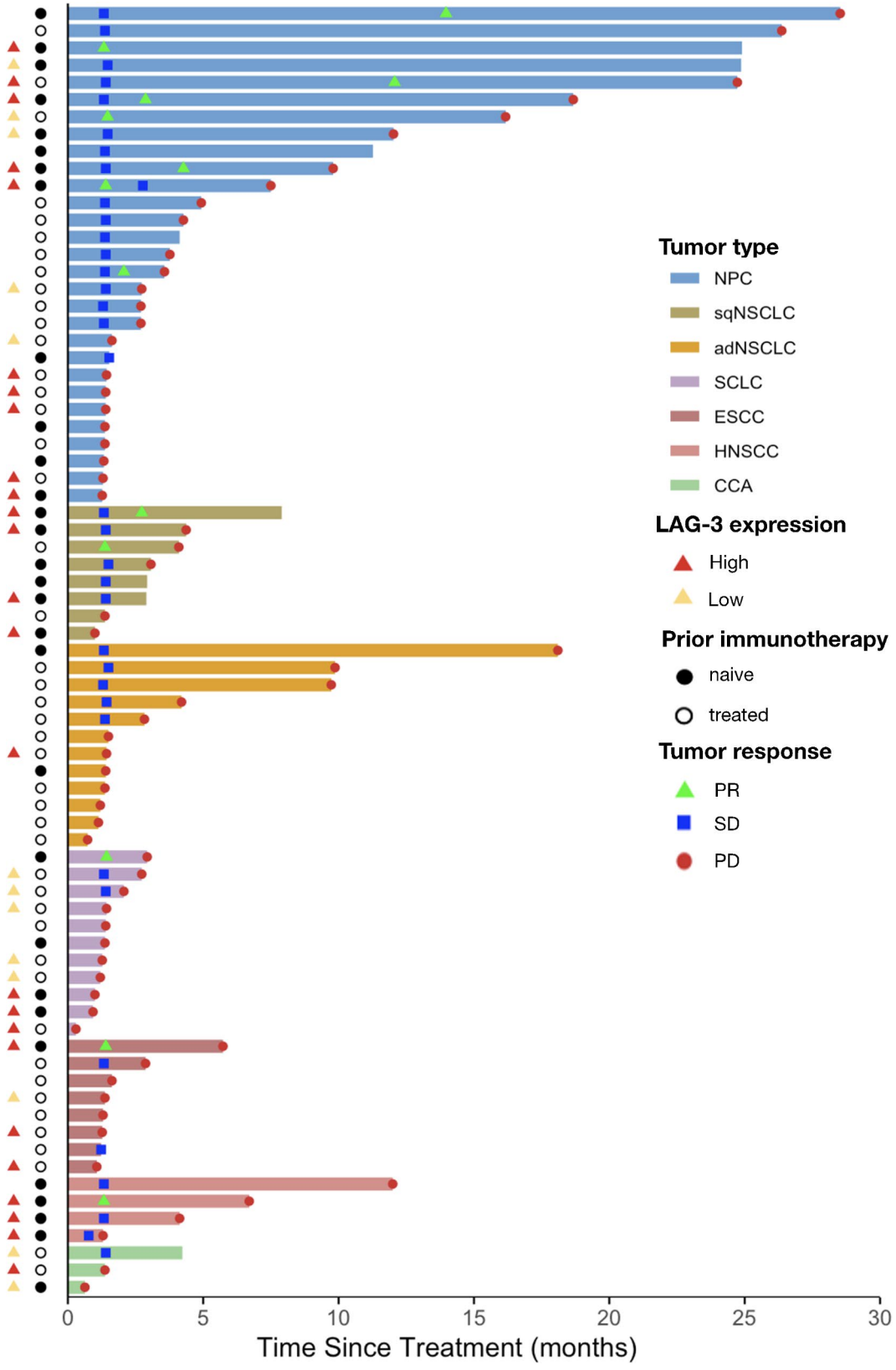

Fig. 2 Swimmer plot showing tumors responses and duration of treatment in patients. Five patients who had nonvaluable response and were not included. Abbreviations: adNSCLC: lung adenocarcinoma; CCA: cervical cancer; ESCC: esophageal squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; NPC: nasopharyngeal carcinoma; PD: progressive disease; PR: partial response; SCLC: small cell lung cancer; SD: stable disease; sqNSCLC: squamous non-small cell lung cancer

Table 3 Safety

Safety Outcome	Total ($n=80$), No. (%)	
	Any Grade	Grade 3 or 4
Any AE[a]	73 (91.3)	18 (22.5)
Serious AEs	16 (20.0)	11 (13.8)
AEs leading to discontinuation[b]	10 (12.5)	7 (8.8)
Any TRAE	61 (76.3)	9 (11.3)
Serious	8 (10.0)	5 (6.3)
AEs leading to discontinuation[b]	7 (8.8)	4 (5.0)
TRAEs reported in ≥ 10% of patients		
Anemia	24 (30.0)	2 (2.5)
Aspartate aminotransferase increased	12 (15.0)	1 (1.3)
Proteinuria	12 (15.0)	0 (0.0)
Hypoalbuminaemia	10 (12.5)	0 (0.0)
Rash	10 (12.5)	0 (0.0)
Hypothyroidism	9 (11.3)	0 (0.0)
Weight decreased	9 (11.3)	0 (0.0)
Alanine aminotransferase increased	9 (11.3)	2 (2.5)
Hyponatremia	9 (11.3)	2 (2.5)
Fatigue	8 (10.0)	1 (1.3)
Immune-related AE[c]	15 (18.8)	3 (3.8)
Hypothyroidism	8 (10.0)	0 (0.0)
Aspartate aminotransferase increased	4 (5.0)	1 (1.3)
Fatigue	3 (3.8)	1 (1.3)
Alanine aminotransferase increased	3 (3.8)	2 (2.5)
Gamma-glutamyl transferase increased	2 (2.5)	1 (1.3)

Note: All of 80 patients received at least one dose of study drugs and were included in the safety population

Abbreviations: AEs, adverse events; TRAEs, treatment-related adverse events

[a]Grade 5, $n=0$

[b]Discontinuation of any or both treatment components

[c]Immune-related adverse events included adverse events of any grade that occurred in at least 2% of patients that were potentially immune-mediated by investigators

Table 4 Efficacy per LAG-3 and PD-L1 tumor expression

LAG-3/PD-L1 Expression	ORR, No. (%)		
	NPC ($n=15$)	Other tumors ($n=23$)	All tumors ($n=38$)
LAG-3 expression ≥ 2+	4 (40.0%)	3 (20%)	7 (28.0%)
LAG-3 expression < 2+	1 (20.0%)	0 (0.0%)	1 (7.7%)
PD-L1 expression ≥ 1%	2 (22.2%)	1 (33.3%)	3 (25.0%)
PD-L1 expression < 1%	3 (50.0%)	2 (10.0%)	5 (19.2%)

Note: 38 of 80 patients had known expression of LAG-3 and PD-L1 as well as tumor response data

Abbreviations: NPC, nasopharyngeal carcinoma; ORR, objective response rate; LAG-3, lymphocyte-activation gene 3

Discussion

While anti-LAG-3/PD-1 combination therapy has been established as a standard treatment for advanced melanoma [5], it has shown only modest anti-tumor efficacy in several other cancers [19–21]. Thus, it is of significant scientific and clinical meanings to investigate LAG-3/PD-1 co-blockade in cancers with high LAG-3 and PD-1 expression, such as nasopharyngeal carcinoma. To our knowledge, this is the first phase Ib/II trial to investigate dual inhibition of LAG-3 and PD-1 in NPC patients. The combination of LBL-007 and toripalimab demonstrated encouraging antitumor activity in patients with advanced NPC, particularly in immunotherapy-naive patients. Improved tumor responses were observed in patients with high expression of LAG-3. This combination therapy had a manageable safety profile, with no new safety signals identified. Based on these encouraging findings, a phase II trial (ClinicalTrials.gov: NCT04252768) evaluating co-blockade of LAG-3 and PD-1 in combination with gemcitabine and cisplatin chemotherapy in patients with previously untreated advanced NPC is currently ongoing.

Several prior studies had evaluated anti-PD-1 monotherapy in advanced NPC patients who failed platinum-based chemotherapy and did not received immunotherapy. In the POLARIS-02 study of toripalimab monotherapy, the ORR was 23.9%, and the median PFS was 2.0 months among 92 NPC patients [22]. In the CAPTAIN study, camrelizumab monotherapy showed an ORR of 28.2% and median PFS of 3.7 months in 156 NPC patients [23]. In addition, the KEYNOTE-028 study reported an ORR of 25.9% and median PFS of 6.5 months for pembrolizumab among 27 PD-L1 positive NPC patients [4]. In the NCI-9742 study, nivolumab showed an ORR of 20.5% and median PFS of 2.8 months in 44 NPC patients [24]. In our study, the combination of LBL-007 and toripalimab demonstrated an ORR of 33.3% and median PFS of 10.8 months in 12 IO-naive NPC patients. Additionally, in 17 IO-treated NPC patients, LBL-007 plus toripalimab demonstrated an ORR of 11.1%, median PFS of 2.7 months and median DOR of 13.5 months. To note, of the six NPC responders, five (83.3%) maintained PRs for more than 12 months. Above all, the combination of LBL-007 and toripalimab demonstrated improved ORR and median PFS compared to prior studies of ani-PD-1 monotherapy in IO-naïve NPC patients.

Among 46 patients with other advanced tumors, only four patients (8.7%) achieved partial responses, including sqNSCLC ($n=2$), HNSCC ($n=1$) and ESCC ($n=1$). The modest antitumor activity of anti-LAG-3/PD-1 combination therapy in other advanced malignancies is consistent with previously reported data [19–21]. In another study of mixed population of tumor types, 10.7% of patients achieved an objective response in anti-LAG-3/PD-1 combination group [20]. Given the limited sample size in these tumors, the clinical impact of the combination therapy warrants further investigation.

Recent studies have elucidated the synergistic mechanisms underlying dual inhibition of LAG-3 and PD-1 [15, 16]. This combination therapy restores the functionality of exhausted CD8 + T cells, enhancing their proliferation, cytotoxicity and interferon-gamma production [15]. Indeed, the co-expression of exhaustion and effector genes in tumor-infiltrating T cells has also been

demonstrated in NPC [25, 26]. CD8 + T cells in NPC tumor samples exhibited widespread overexpression of exhaustion markers, including LAG-3, PD-1, TIGIT, HAVCR2 and CTLA4 [26]. In addition, in a cohort of 208 NPC patients, LAG-3 and PD-L1 was positively detected in 95% and 97% of patients, respectively, by immunohistochemistry [13]. In this study, 33.3% of NPC patients exhibited high expression of both LAG-3 (≥ 2+) and PD-L1 (TC ≥ 25%), compared to 8.7% of patients with other tumors. Collectively, the distinct immune microenvironment may explain the enhanced antitumor activity of dual LAG-3/PD-1 inhibition in NPC compared to other types of cancer. Future exploration of the combination therapy should prioritize tumors that highly express these exhaustion markers.

Consistent with the proposed mechanism above, improved ORRs were noted in patients with higher LAG-3 expression across both NPC and other tumors in this study. Among the 15 NPC patients, those with LAG-3 expression ≥ 2 + had an ORR of 40% compared to 20% in those with LAG-3 expression < 2+. Similarly, in the RELATIVITY-047 trial for advanced melanoma, nivolumab plus relatlimab (a LAG-3 blocking antibody) achieved an ORR of 47.0% in patients with LAG-3 expression ≥ 1%, compared to 31.0% in those with LAG-3 expression < 1% [27]. Furthermore, in a phase I/II study of anti-LAG-3/PD-1 combinations in advanced solid tumors, responding patients tended to have higher levels of LAG-3 and PD-L1, as assessed by both immunohistochemistry and RNA sequencing [20]. However, the PD-L1 expression showed limited predictive capability for efficacy in our study, which might be attributed to the mixture of IO-treated and IO-naive patients during the analysis.

The combination of LBL-007 and toripalimab was well-tolerated in patients with advanced malignancies. Grade 3 or 4 TRAE occurred in 10% of patients and 7.5% of discontinue treatment duo to TRAEs, the most common of which were anemia (2.5%), hyponatremia (2.5%), increased alanine aminotransferase (2.5%), increased aspartate aminotransferase (1.3%), and fatigue (1.3%). No drug-related deaths were observed in all of 80 patients. The safety profile was comparable with that reported in the RELATIVITY-047 trial, where 18.9% of patients experienced grade 3 or 4 TRAEs and 14.6% of patients discontinued treatment due to TRAEs in the relatlimab-nivolumab group [5]. The most common grade 3 or 4 TRAEs in the relatlimab-nivolumab group included increased levels of lipase (1.7%), alanine aminotransferase (1.4%), and aspartate aminotransferase (1.4%), as well as fatigue (1.1%).

Our study has limitations that should be considered when interpreting these results. First, this phase Ib/II trial is limited by its relatively small sample size. Second, about half of patients had unknown LAG-3 and PD-L1 expression due to limited tumor tissue availability. As a result, the effectiveness of dual LAG-3/PD-1 inhibition, along with the predictive value of LAG-3 and PD-L1 expression, requires further validation in larger cohorts.

In summary, LBL-007 combined with toripalimab demonstrated a manageable safety profile in advanced solid tumors. This combination therapy exhibited promising antitumor activity in advanced NPC patients, particularly in immunotherapy-naive patients. These findings warrant further investigation in future studies.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Competing interests

The authors declare no competing interests.

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Clinical trial information

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References

1. Kraehenbuehl L, Weng CH, Eghbali S, Wolchok JD, Merghoub T. Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. Nat Rev Clin Oncol. 2022;19(1):37–50.
2. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol. 2020;21(6):832–42.
3. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.
4. Hsu C, Lee SH, Ejadi S, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. J Clin Oncol. 2017;35(36):4050–6.
5. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24–34.
6. Hamid O, Lewis KD, Weise A, et al. Phase I study of Fianlimab, a human lymphocyte activation Gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma. J Clin Oncol. 2024;42(24):2928–38.
7. Luke JJ, Patel MR, Blumenschein GR, et al. The PD-1- and LAG-3-targeting bispecific molecule tebotelimab in solid tumors and hematologic cancers: a phase 1 trial. Nat Med. 2023;29(11):2814–24.
8. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus Ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122–33.
9. Dovedi SJ, Elder MJ, Yang C, et al. Design and efficacy of a monovalent bispecific PD-1/CTLA4 antibody that enhances CTLA4 blockade on PD-1(+) activated T cells. Cancer Discov. 2021;11(5):1100–17.
10. Aggarwal V, Workman CJ, Vignali DAA. LAG-3 as the third checkpoint inhibitor. Nat Immunol. 2023;24(9):1415–22.
11. Maruhashi T, Sugiura D, Okazaki IM, et al. Binding of LAG-3 to stable peptide-MHC class II limits T cell function and suppresses autoimmunity and anticancer immunity. Immunity. 2022;55(5):912–24. e8.
12. Lee WJ, Lee YJ, Choi ME, et al. Expression of lymphocyte-activating gene 3 and T-cell immunoreceptor with immunoglobulin and ITIM domains in cutaneous melanoma and their correlation with programmed cell death 1 expression in tumor-infiltrating lymphocytes. J Am Acad Dermatol. 2019;81(1):219–27.
13. Wang YQ, Zhang Y, Jiang W, et al. Development and validation of an immune checkpoint-based signature to predict prognosis in nasopharyngeal carcinoma using computational pathology analysis. J Immunother Cancer. 2019;7(1):298.
14. Minichsdorfer C, Oberndorfer F, Krall C, et al. PD-L1 expression on tumor cells is associated with a poor outcome in a cohort of caucasian nasopharyngeal carcinoma patients. Front Oncol. 2019;9:1334.
15. Cillo AR, Cardello C, Shan F, et al. Blockade of LAG-3 and PD-1 leads to co-expression of cytotoxic and exhaustion gene modules in CD8(+) T cells to promote antitumor immunity. Cell. 2024;187(16):4373–e8815.
16. Andrews LP, Butler SC, Cui J, et al. LAG-3 and PD-1 synergize on CD8(+) T cells to drive T cell exhaustion and hinder autocrine IFN-gamma-dependent antitumor immunity. Cell. 2024;187(16):4355–e7222.
17. Yu X, Huang X, Chen X et al. Characterization of a novel anti-human lymphocyte activation gene 3 (LAG-3) antibody for cancer immunotherapy. MAbs. 2019;11(6):1139-48.
18. Chen BJ, Dashnamoorthy R, Galera P, et al. The immune checkpoint molecules PD-1, PD-L1, TIM-3 and LAG-3 in diffuse large B-cell lymphoma. Oncotarget. 2019;10(21):2030–40.
19. Hegewisch-Becker S, Mendez G, Chao J, et al. First-line nivolumab and relatlimab plus chemotherapy for gastric or gastroesophageal junction adenocarcinoma: the phase II RELATIVITY-060 study. J Clin Oncol. 2024;42(17):2080–93.
20. Schoffski P, Tan DSW, Martin M et al. Phase I/II study of the LAG-3 inhibitor ieramilimab (LAG525) +/- anti-PD-1 spartalizumab (PDR001) in patients with advanced malignancies. J Immunother Cancer. 2022;10(2).
21. Yap TA, LoRusso PM, Wong DJ, et al. A phase 1 first-in-human study of FS118, a tetravalent bispecific antibody targeting LAG-3 and PD-L1 in patients with advanced cancer and PD-L1 resistance. Clin Cancer Res. 2023;29(5):888–98.
22. Wang FH, Wei XL, Feng J, et al. Efficacy, Safety, and Correlative Biomarkers of Toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II clinical trial (POLARIS-02). J Clin Oncol. 2021;39(7):704–12.
23. Yang Y, Zhou T, Chen X et al. Efficacy, safety, and biomarker analysis of Camrelizumab in previously treated recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN study). J Immunother Cancer. 2021;9(12).
24. Ma BBY, Lim WT, Goh BC, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the mayo clinic phase 2 consortium (NCI-9742). J Clin Oncol. 2018;36(14):1412–8.
25. Zhao J, Guo C, Xiong F, et al. Single cell RNA-seq reveals the landscape of tumor and infiltrating immune cells in nasopharyngeal carcinoma. Cancer Lett. 2020;477:131–43.
26. Liu Y, He S, Wang XL, et al. Tumour heterogeneity and intercellular networks of nasopharyngeal carcinoma at single cell resolution. Nat Commun. 2021;12(1):741.
27. Long GV, Stephen Hodi F, Lipson EJ, et al. Overall survival and response with nivolumab and relatlimab in advanced melanoma. NEJM Evid. 2023;2(4):EVIDoa2200239.

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