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ORIGINAL RESEARCH

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A phase 2, multicenter, open-label study of anti-LAG-3 ieramilimab in combination with anti-PD-1 spartalizumab in patients with advanced solid malignancies

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ABSTRACT

Ieramilimab, a humanized anti-LAG-3 monoclonal antibody, was well tolerated in combination with the anti-PD-1 antibody spartalizumab in a phase 1 study. This phase 2 study aimed to further investigate the efficacy and safety of combination treatment in patients with selected advanced (locally advanced or metastatic) solid malignancies. Eligible patients with non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), mesothelioma, and triple-negative breast cancer (TNBC) were grouped depending on prior anti-PD-1/L1 therapy (anti-PD-1/L1 naive or anti-PD-1/L1 pretreated). Patients received ieramilimab (400 mg) followed by spartalizumab (300 mg) every 3 weeks. The primary endpoint was objective response rate (ORR), along with safety, pharmacokinetics, and biomarker assessments. Of 235 patients, 142 were naive to anti-PD-1/L1 and 93 were pretreated with anti-PD-1/L1 antibodies. Durable responses (>24 months) were seen across all indications for patients naive to anti-PD-1/L1 and in melanoma and RCC patients pretreated with anti-PD1/L1. The most frequent study drug-related AEs were pruritus (15.5%), fatigue (10.6%), and rash (10.6%) in patients naive to anti-PD-1/L1 and fatigue (18.3%), rash (14.0%), and nausea (10.8%) in anti-PD-1/L1 pretreated patients. Biomarker assessment indicated higher expression of T-cell-inflamed gene signature at baseline among responding patients. Response to treatment was durable (>24 months) in some patients across all enrolled indications, and safety findings were in accordance with previous and current studies exploring LAG-3/PD-1 blockade.

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Introduction

The use of anti-programmed cell death-1/programmed death ligand 1 (PD-1/PD-L1) has emerged as an effective anti-cancer strategy in multiple types of cancer.[1] However, dysregulation of additional immune checkpoints may be a key mechanism of tumor immune evasion and resistance to available treatments.

Lymphocyte-activation gene 3 (LAG-3) is a type I transmembrane protein expressed in various immune cells.[2–4] The interaction of LAG-3 with its lignads[2] inhibits T-cell response. LAG-3 expression and tumor infiltration of LAG-3$^+$ cells were found to be associated with tumor progression, poor prognosis, and negative clinical outcomes in a variety of cancers.[5,6] Blockade of LAG-3 in combination

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with anti-PD-1 agents has demonstrated improved cytotoxic T-lymphocyte activation and proliferation, enhanced effector function, and improved anti-tumor efficacy[3,4,7,8] supporting the hypothesis that the combination of anti-LAG-3 and anti-PD-1 therapies may have potentially synergistic effects on immune checkpoint pathways. In melanoma, the anti-LAG-3 relatlimab (BMS-986016) in combination with nivolumab demonstrated improved efficacy with a manageable safety profile, leading to approval of combination treatment.[9]

Ieramilimab is a humanized immunoglobulin (Ig)G4 monoclonal antibody (mAb) that inhibits LAG-3 interaction with MHC class II molecules.[10] Spartalizumab is a humanized IgG4 anti-PD-1 mAb that binds to PD-1 and blocks interaction with its ligands – programmed cell death ligand 1 and 2 (PD-L1/L2).[11] Clinical trials of spartalizumab demonstrated safety and promising activity in advanced cancers, including in anaplastic thyroid cancer (ORR of 24% by irRC).[5] We previously presented the preclinical characterization of ieramilimab, as well as clinical data from the phase 1 part of a multicenter, open-label, non-randomized study (ClinicalTrials.gov: NCT02460224).[10] The phase 1 study showed that ieramilimab was well tolerated both as monotherapy and in combination with spartalizumab, and immune-mediated toxicities of the combination were comparable to those seen with spartalizumab alone.[10] In some cases, durable responses were achieved, further supporting the potential contribution of LAG-3 blockade to anti-PD-1 response durability. Here, we report assessment of the ieramilimab/spartalizumab combination in advanced/metastatic NSCLC, melanoma, TNBC, RCC, and mesothelioma naive to or previously treated with PD-1/L1 inhibitors.

Materials and methods

Study design and patient eligibility

This study was a phase 1/2 multicenter, open-label, international, non-randomized study comprising a phase 1 dose-escalation part followed by a phase 2 part which investigated the combination in NSCLC, melanoma, RCC, mesothelioma, and TNBC (Figure S1). Patients were assigned to different groups depending on indication and prior anti-PD1/L1 therapy (i.e., anti-PD1/L1 naive or anti-PD1/L1 pretreated). Each group was to enroll approximately 20 patients, and the sample size could expand to approximately 40 patients if at least three patients (or if at least two patients for TNBC) had an objective response (partial response [PR] or complete response [CR]) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or immune-related response criteria (irRC). The data cutoff date was December 31, 2020.

Eligible patients were required to be ≥18 y old and have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1. Enrolled patients had advanced (locally advanced or metastatic) solid tumors with at least one measurable lesion as determined by RECIST v1.1.

For detailed patient eligibility criteria, see supplementary material

Treatment

Patients received ieramilimab (400 mg) followed by spartalizumab (300 mg) via intravenous (IV) infusion once every 3 weeks (Q3W) until unacceptable toxicity, progressive disease per irRC, or treatment discontinuation at the discretion of the investigator or the patient. An alternative dose and schedule of ieramilimab 600 mg IV combined with spartalizumab 400 mg IV once every 4 weeks (Q4W) was explored in 21 patients with anti-PD-1/L1-naive TNBC.

For detailed methods, see supplementary material

Results

A total of 235 patients with advanced mesothelioma ($n = 57$), NSCLC ($n = 42$), melanoma ($n = 42$), RCC ($n = 38$), or TNBC ($n = 56$), was enrolled between August 2017 and December 2020 in the phase 2 part of the study from 25 sites in 12 countries. Of these patients, 142 (60.4%) were naive to PD-1/L1 inhibitors and 93 (39.6%) patients were previously treated with PD-1/L1 inhibitors.

Patient characteristics

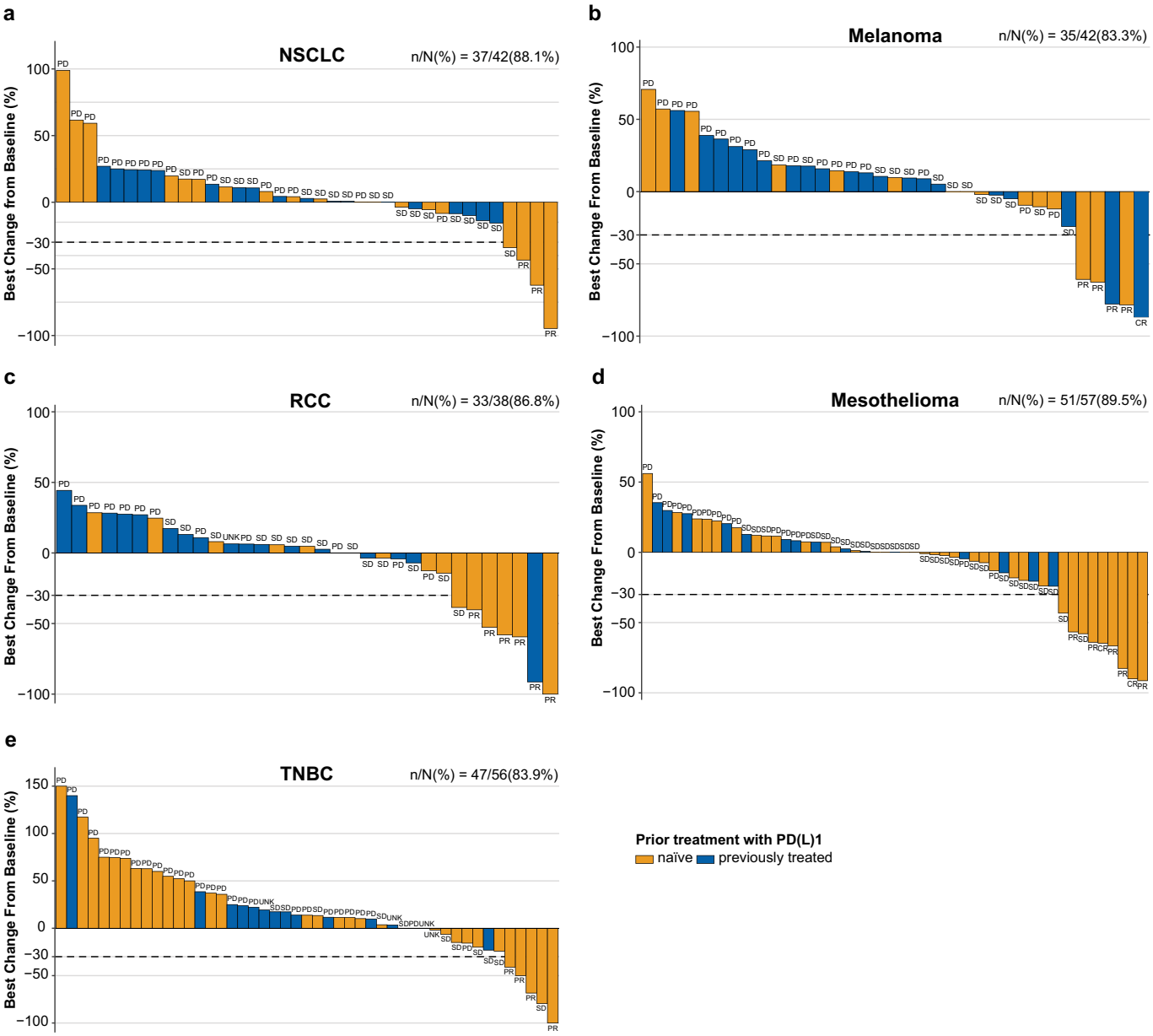
The baseline characteristics and demographics of patients are provided in Table S1. In the anti-PD-1/L1 naive and pretreated cohorts, 92.3% and 100% of patients, respectively, had received prior systemic antineoplastic therapies; and 47.9% and 58.1% of patients had received prior radiotherapy, respectively. In the anti-PD-1/L1-naive melanoma group, 8/20 patients had non-cutaneous melanoma and 12/20 patients had cutaneous melanoma (10 Asian, 1 Caucasian, 1 race unknown). Of 22 patients in the anti-PD-1/L1-pretreated melanoma cohort, 18 (82%) patients had cutaneous melanoma and four (18%) patients had non-cutaneous melanoma. Duration of exposure to ieramilimab and spartalizumab by treatment group is provided in Supplementary Table S3. The median (range) duration of exposure to study treatment was ~15.1 weeks (3.0 weeks–2.6 y) in anti-PD-1/L1-naive patients and 14.7 weeks (3.0 weeks–2.5 y) in anti-PD-1/L1-pretreated patients. In the anti-PD-1/L1-naive cohort, 71.8% of patients discontinued study treatment due to progressive disease, whereas in patients pretreated with PD-1/L1 inhibitors, 82.8% discontinued treatment due to progressive disease (Supplementary Table S3).

Efficacy

As anticipated, overall anti-tumor efficacy was higher in patients who had not received previous treatment with anti-PD-1/L1 antibodies. In patients with mesothelioma naive to anti-PD-1/L1, the ORR was 17.1% (90%-CI: 8.3–29.7%) with clinical activity reported in seven patients (two patients with CR and five patients with PR) compared to 6.3% (one patient with PR; 90%-CI: 0.3–26.4%) in anti-PD-1/L1-pretreated patients. In patients with NSCLC unselected for PD-L1 status, the ORR was 15% (three patients with PR; 90%-CI: 4.2–34.4%)

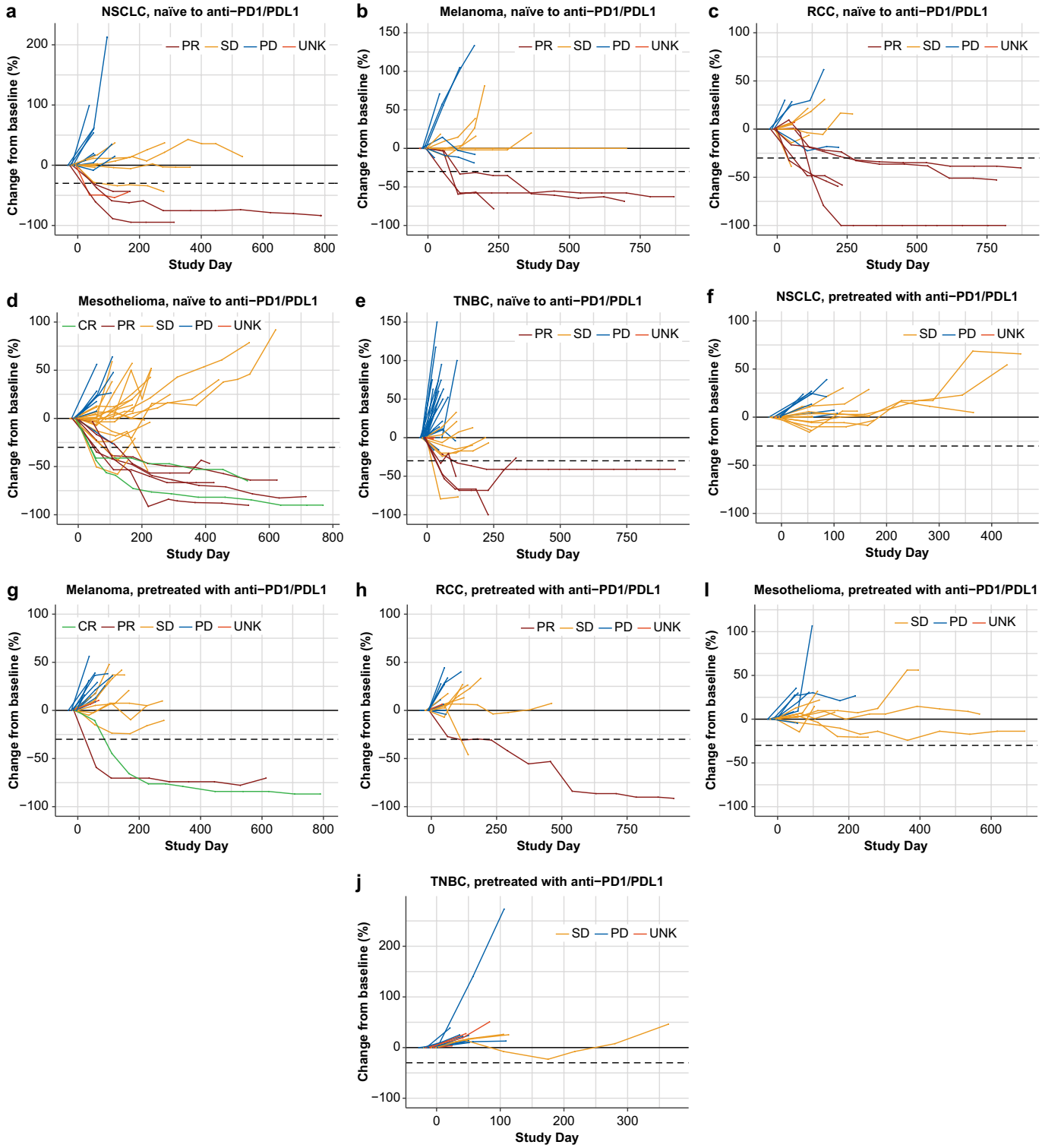
in those naive to anti-PD-1/L1 compared to no responses in the anti-PD-1/L1-pretreated cohort. The melanoma cohort naive to anti-PD-1/L1 included 8 patients with non-cutaneous melanoma (such as ocular/uveal or mucosal melanoma), and 12 patients with cutaneous melanoma. The ORR was 15% (three patients with PR; 90%-CI: 4.2–34.4%). When considering only the 12 patients in the anti-PD-1/L1 naive melanoma group who had cutaneous disease, the ORR was 25% (3 patients with PR). In the anti-PD-1/L1-pretreated melanoma cohort, one patient each experienced a CR and PR (ORR 9.1%; 90%-CI: 1.6–25.9%). In patients with RCC naive to and pretreated with anti-PD-1/L1, the ORR was 26.3% (five patients with PR; 90%-CI: 11.0–47.6%) and 5.3% (one patient with PR; 90%-CI: 0.3–22.6%), respectively. In the TNBC group, patients naive to anti-PD-1/L1 treated Q3W and Q4W reported an ORR of 14.3% (90%-CI: 4.0–32.9%) and 4.8% (90%-CI: 0.2–20.7%), respectively, whereas patients with TNBC pretreated with anti-PD-1/L1 reported no evidence of clinical responses. Waterfall plots for best percentage change from baseline per RECIST v.1.1 for all patient groups are shown in Figure 1.

Duration of response by indication and prior treatment with anti-PD-1/L1 is shown in Figure 2. Durable responses (>24 months) were seen across all indications for anti-PD-1/L1-naive patients, as well as for melanoma and RCC patients pretreated with anti-PD-1/L1 (Figure 2). The median PFS per RECIST v1.1/irRC for anti-PD-1/L1-naive patients was 5.5/5.6 months for mesothelioma, 3.9/4.2 months for NSCLC, 2.2/5.4 months for melanoma (cutaneous and non-cutaneous), 4.4/5.8 months for RCC, 1.9/1.9 months for TNBC Q3W, and 1.8/1.9 months for TNBC Q4W. The



Abbreviations: PD-1, programmed cell death-1; PD-L1, programmed death ligand 1.

Figure 1. Best percentage change from baseline and best overall responses in all patients (naive to prior anti-PD-1/L1 and pretreated) with mesothelioma, NSCLC, melanoma, RCC, and TNBC.



Abbreviations: CR, complete response; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-1, programmed cell death-1; PDL1, programmed death ligand 1; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; TNBC, triple-negative breast cancer; UNK, unknown.

Figure 2. Duration of response per RECIST v1.1 in patients naive to prior anti-PD-1/L1 and pretreated patients.

median PFS per RECIST v1.1/irRC for anti-PD-1/L1-pretreated patients was 3.4/3.4 months for mesothelioma, 3.5/3.5 months for NSCLC, 1.9/1.9 months for melanoma (cutaneous and non-cutaneous), 3.0/3.0 months for RCC, and 1.7/1.7 months for TNBC (Table 1, and Supplementary Fig. S2). DCR by indication is provided in Table S2. At the time of study completion, 17 patients were continuing treatment with ieramilimab and spartalizumab.

Table 1. Summary of best overall response, disease control rate, and progression-free survival by RECIST v1.1.

RECIST v1.1	Naive to anti-PD-1/PD-L1, *n* (%)						Pretreated with anti-PD-1/PD-L1, *n* (%)				
Response by RECIST v1.1	Mesothelioma *n* = 41	NSCLC *n* = 20	Melanoma *n* = 20	RCC *n* = 19	TNBC Q3W *n* = 21	TNBC Q4W *n* = 21	Mesothelioma *n* = 16	NSCLC *n* = 22	Melanoma *n* = 22	RCC *n* = 19	TNBC *n* = 14
Best overall response											
Complete response (CR)	2 (4.9)	0	0	0	0	0	0	0	1 (4.5)	0	0
Partial response (PR)	5 (12.2)	3 (15.0)	3 (15.0)	5 (26.3)	3 (14.3)	1 (4.8)	1 (6.3)	0	1 (4.5)	1 (5.3)	0
Stable disease (SD)	20 (48.8)	7 (35.0)	6 (30.0)	7 (36.8)	4 (19.0)	4 (19.0)	8 (50.0)	11 (50.0)	7 (31.8)	7 (36.8)	3 (21.4)
Progressive disease (PD)	9 (22.0)	9 (45.0)	6 (30.0)	4 (21.1)	11 (52.4)	12 (57.1)	7 (43.8)	8 (36.4)	12 (54.5)	9 (47.4)	8 (57.1)
ORR (CR+PR), [90% CI]	7 (17.1), [8.3–29.7]	3 (15.0), [4.2–34.4]	3 (15.0), [4.2–34.4]	5 (26.3), [11.0–47.6]	3 (14.3), [4.0–32.9]	1 (4.8), [0.2–20.7]	1 (6.3), [0.3–26.4]	0, [0.0–12.7]	2 (9.1), [1.6–25.9]	1 (5.3), [0.3–22.6]	0, [0.0–19.3]

Abbreviations: CI, confidence interval; DOR, duration of overall response; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death-1; PD-L1, programmed death ligand 1;, RECIST, Response Evaluation Criteria in Solid Tumors; RCC, renal cell cancer; TNBC, triple-negative breast cancer; Q3W, every 3 weeks; Q4W, every 4 weeks.

Safety

Most of the patients that were naive to anti-PD-1/L1 (98.6%) and all pretreated patients experienced at least one AE of any grade regardless of study treatment. In the anti-PD-1/L1-naive cohort, the most frequently reported AEs regardless of relationship to study treatment were arthralgia (23.9%), nausea (23.2%), pyrexia (22.5%), constipation (21.8%), fatigue (21.1%), dyspnea (20.4%), cough (20.4%), and pruritus (20.4%). In patients pretreated with PD-1/L1 inhibitors, nausea (28.0%), fatigue (24.7%), dyspnea (21.5%), and decreased appetite (20.4%) were the most frequently reported AEs regardless of study treatment (Figure 3a).

AEs suspected to be study drug related were comparable between patients naive to prior anti-PD-1/L1 (66.2%) and pretreated patients (63.4%). In patients who had not received prior anti-PD-1/L1 therapy, the most frequent AEs suspected to be study drug related were pruritus (15.5%), fatigue (10.6%), and rash (10.6%). In anti-PD-1/L1-pretreated patients, the most frequent AEs suspected to be study drug related were fatigue (18.3%), rash (14.0%), and nausea (10.8%) (Figure 3b).

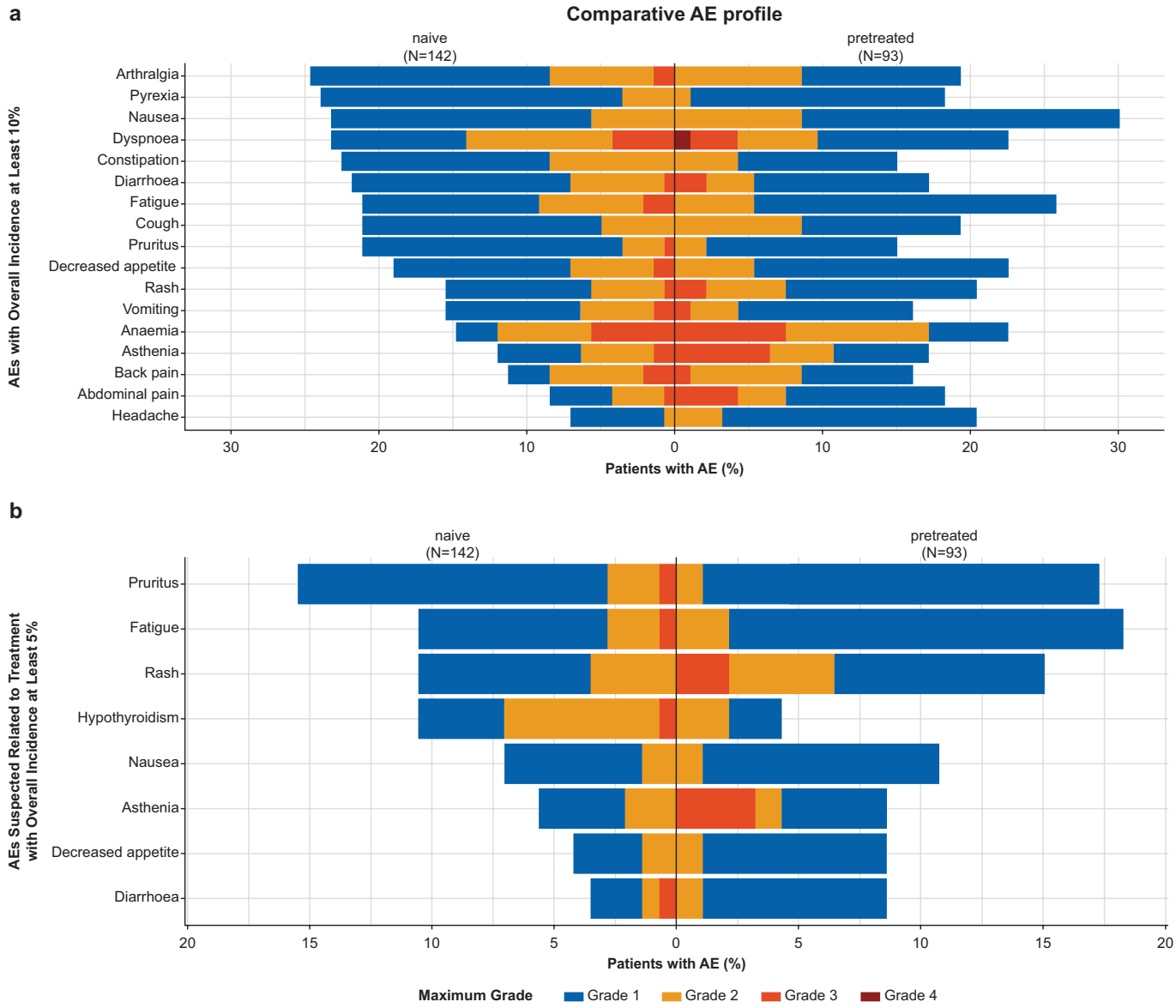
In the anti-PD-1/L1 naive and pretreated cohorts, 9.9% and 5.4% of patients, respectively, discontinued study treatment due to AEs regardless of study drug relationship (Supplementary Table S4). Details related to reasons for patient discontinuation are provided in Supplementary Table S1 and Supplementary Table S3. SAEs suspected to be treatment related were 8.5% (one case each of autoimmune hepatitis, cardiac tamponade, eyelid ptosis, hypophysitis, and pyrexia) and 2.2% (one case of adrenal insufficiency) in the anti-PD-1/L1 naive and pretreated cohorts, respectively (Supplementary Table S5).

Pharmacokinetic data

PK parameters for ieramilimab and spartalizumab in the phase 2 study are presented in Supplementary Tables S6 and S7. In patients naive to anti-PD-1/L1, the exposure (area under the plasma concentration time-curve over the dosing interval [AUC_{tau}] and maximum serum concentration [C_{max}]) were comparable in cycle 1 and cycle 3 across the different treatment groups. The overall variability in AUC_{tau} and C_{max} was low to moderate. The geo-mean effective half-life ($T_{1/2,eff}$; effective half-life accounting for drug accumulation) ranged from 12.2 d to 18.2 d across treatment groups at cycle 3, with drug accumulation ranging from 1.3 to 1.62.

In patients pretreated with anti-PD-1/L1, the exposures in cycle 1 and cycle 3 ($AUC_{0\text{-}504\ h}$ and C_{max}) were comparable across the different treatment groups (NSCLC, melanoma, RCC, mesothelioma, and TNBC). The overall variability in AUC_{tau} and C_{max} was low to moderate. The geo-mean $T_{1/2,eff}$ ranged from 12.7 d to 16.1 d across treatment groups at cycle 3, with drug accumulation ranging from 1.4 to 1.63.

Immunogenicity assessment in 122 evaluable patients naive to anti-PD-1/L1 revealed that the overall incidence of anti-drug antibodies (ADA) against ieramilimab was approximately 8.2%. In 80 patients with anti-PD-1/L1-pretreated disease, the ADA incidence was 6.3%.

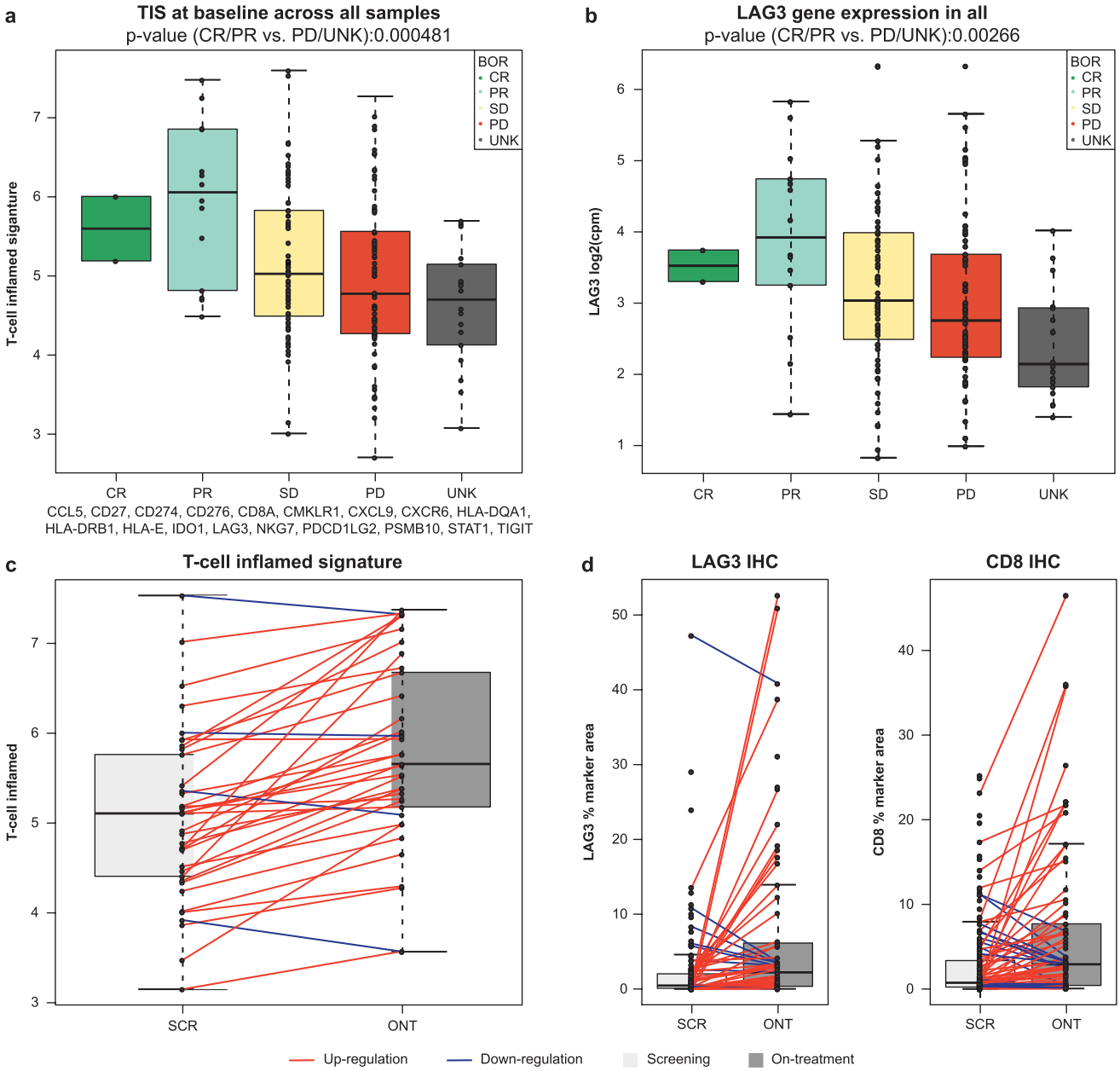


Abbreviations: AE, adverse event; PD-1, programmed cell death-1; PD-L1, programmed death ligand 1.

Figure 3. (a) AEs (=10%) regardless of study drug in patients naive to prior anti-PD-1/L1 and pretreated patients and (b) AEs (=5%) suspected to be study drug related in patients naive to prior anti-PD-1/L1 and pretreated patients.

Biomarker analysis

Bulk RNA sequencing was performed on biopsies obtained from 171 patients (33 melanoma, 45 mesothelioma, 32 NSCLC, 25 RCC, 36 TNBC) prior to initiation of study treatment, as well as from 37 patients (8 melanoma, 14 mesothelioma, 6 NSCLC, 3 RCC, 6 TNBC) between cycle 3 d 1–15. RNA sequencing was used to assess baseline tumor expression of an 18-gene T-cell-inflamed gene signature,[12] including PD-L1, whose expression correlates with response to anti-PD-1 antibodies in some cancer indications,[6] as well as LAG-3. Comparison by BOR across all indications, anti-PD-1/L1 naive and pretreated combined, revealed higher T-cell-inflamed gene signature expression among responding patients (Figure 4a). When analyzed by individual indication, this observation reached statistical significance only in melanoma (Supplementary Fig. S3). When LAG-3 gene expression was assessed separately from the other signature genes, a similar association with response was observed (Figure 4b). Comparison of RNA sequencing data from 37 paired biopsy samples obtained at baseline and during study treatment indicated that treatment with ieramilimab plus spartalizumab was generally associated with an increase in expression of T-cell-inflamed signature genes (Figure 4c). This on-treatment increase was also frequently observed for expression of LAG-3 and CD8 by immunohistochemistry (97 matched/paired samples; 34 mesothelioma, 16 NSCLC, 17 melanoma, 14 RCC, 16 TNBC) (Figure 4d). However, assessment of LAG-3 by immunohistochemistry in 219 baseline samples (39 melanoma, 52 mesothelioma, 41 NSCLC, 35 RCC, 52 TNBC) did not correlate with response.



Abbreviations: BOR, best overall response; CR, complete response; IHC, immunohistochemistry; LAG-3, lymphocyte activation gene-3; ONT, on treatment; PD, progressive disease; PR, partial response; SCR, screening; SD, stable disease; TIS, tumor inflammation signature; UNK, unknown.

Figure 4. RNAseq and IHC biomarker assessment: (a) T-cell-inflamed signature at baseline by best overall response, (b) LAG3 gene expression at baseline by best overall response, (c) on-treatment changes in T-cell-inflamed gene signature, and (d) on-treatment changes in LAG3 and CD8 by IHC.

Discussion

This is to our knowledge the first phase 2 study to investigate the combination of anti-PD-1/LAG-3 across multiple indications in patients both naive to and after prior treatment with anti-PD-1/L1. Our study demonstrated durable clinical efficacy in different indications. In mesothelioma, the combination of spartalizumab and ieramilimab in patients naive to prior anti-PD-1/L1 treatment showed ORR of 17.1% with mPFS of 5.5 months. In comparison, the CONFIRM trial reported 11% overall response to nivolumab alone and 3.0 months median PFS[13] in a similar population of patients with malignant mesothelioma who had progressed on first-line therapy. The efficacy of nivolumab in mesothelioma may be further improved through the addition of anti-CTLA-4 ipilimumab. In the CheckMate 743 trial[14], nivolumab plus ipilimumab showed median PFS of 6.8 months (95% CI: 5.6–7.4) and objective response was reported as 40% (95% CI: 34.1–45.4). However, Grade 3–4 treatment-related adverse events (TRAEs) were reported in 91 (30%) of 300 patients with malignant pleural mesothelioma. In comparison, Grade 3–4 TRAEs were reported in 9.1% of the 121 patients who received the combination of spartalizumab plus ieramilimab in the Phase 1 study.[10] Of note, patients in the CheckMate 743 study had previously untreated disease, whereas our study enrolled patients with mesothelioma who had progressed following treatment for advanced disease.

Our data showed the highest response rate for patients with renal cell carcinoma naive to prior anti-PD-1/L1 therapy (26.3%; 90%-CI 11.0–47.6). Although similar response rates have been reported for single-agent anti-PD-1,[15] the inclusion in our study of non-clear cell RCC may affect comparisons. Our study showed durable response for >24 months in a patient with RCC who had progressed on prior anti-PD-1/L1 therapy just prior to initiating LAG525 and spartalizumab. Previous assessment of inhibitory receptor expression in tumor-infiltrating lymphocytes (TILs) isolated from patients undergoing surgery for RCC demonstrated that the most frequent inhibitory receptor combination was PD-1 and LAG-3 on both CD4-positive and CD8-positive TILs.[16] Moreover, in the same study, PD-1 blockade led to LAG-3 upregulation, and dual PD-1/LAG-3 blockade resulted in higher IFNγ release. Together, these findings may support further investigation of dual anti-PD-1/LAG-3 therapy in RCC.

The confirmed ORRs in patients with advanced melanoma naive to anti-PD-1/PD-L1 is lower in our study compared to reported data from other anti-LAG-3/anti-PD-1 combinations. In particular, dual blockade of LAG-3 with fianlimab and PD-1 with cemiplimab in 33 patients with advanced melanoma naive to anti-PD-1/PD-L1 reported an ORR (including unconfirmed responses) of 66.7%, while the ORR in 15 patients pretreated with anti-PD-1/L1 was 13.3%.[17] The anti-LAG-3 antibody relatlimab combined with nivolumab in patients with untreated advanced melanoma[15] or patients with melanoma who progressed on prior treatment with anti-PD-1/L1 showed ORR of 43.1%[18] and 11.5%,[19] respectively. Differences in patient and disease characteristics may explain the lower confirmed response rate in the anti-PD-1/L1-naive melanoma. For instance, 40% of patients with anti-PD-1/L1-naive melanoma in our study had non-cutaneous melanoma (including ocular/uveal or mucosal melanoma), whereas the RELATIVITY-047 study included approximately 18% mucosal or unknown subtypes of melanoma and excluded uveal melanoma.[9] The inclusion of uveal and mucosal melanomas which are less sensitive to checkpoint blockade[20–23] may have contributed to our limited response rates. Moreover, whereas only 9.3% of patients in the RELATIVITY-047 study had received prior adjuvant/neoadjuvant systemic therapy, 55% of the patients enrolled in our anti-PD-1/L1-naive melanoma cohort had refractory disease, having received 1 or 2 prior antineoplastic regimens, a setting associated with diminished sensitivity to immunotherapy.[24] Efficacy results in melanoma patients who had received prior anti-PD-1/L1 treatment seem to be more similar between our study and data from other studies. In this cohort, the proportion of patients with cutaneous melanoma was higher (82%, 18 out of 22). and the ORR was 9.1% in our study compared to 11.5% for relatlimab/nivolumab and 13.3% for fianlimab/cemiplimab, suggesting that there might be no clear differentiation between the different combinations.

In patients with NSCLC, ORR was 15% (90%-CI 4.2–34.4) in previously treated patients naive to prior anti-PD-1/L1 treatment. A phase 2 study reported a response rate of 23% (95%-CI 10–42) for the combination of pembrolizumab with the LAG-3 inhibitor favezelimab.[25] In contrast to our NSCLC cohort, this study evaluated first-line pembrolizumab-based combination therapies. This study indicated a potential impact of T-cell-inflamed gene expression profile and tumor mutational burden, a finding which seems consistent with our data showing higher T-cell-inflamed gene signature expression among responding patients.

Regarding TNBC, patients treated with pembrolizumab[26] or atezolizumab[27] monotherapy in the first-line setting showed greater benefit than in the second-line setting. Furthermore, when patients with TNBC were treated with a combination of anti-PD-1/L1 and chemotherapy, benefit was restricted to patients with tumors that were PD-L1 positive.[28,29] In our study, patients with TNBC had been previously treated and were not selected by PD-L1 status, a challenging population to demonstrate dual checkpoint blockade activity.

The safety and tolerability profile of ieramilimab combined with spartalizumab was generally acceptable across studied treatment groups with the majority of treatment-related AEs being low grade. For the combination of relatlimab and nivolumab, the rates of any-grade and grade 3/4 treatment-related AEs were 81.1% and 18.9%, respectively,[9] compared to 63.4% and 9.7% in our study. No clear new safety signals were identified in our phase 2 study compared to the phase 1 study of ieramilimab in combination with spartalizumab,[10] further supporting the previously reported assessment that the immune-mediated toxicity of the combination is comparable to that seen previously with spartalizumab alone.[10] Consistent with this, the rates of treatment-emergent AEs for fianlimab with cemiplimab suggested a safety profile as expected with cemiplimab monotherapy, with the exception of adrenal insufficiency reported in 10.4% of patients receiving combination therapy.[17] In contrast, adrenal insufficiency was uncommonly reported in our study (2.2%). The RELATIVITY-047 study showed an increase in treatment-related adverse events for relatlimab plus nivolumab compared to nivolumab alone (81.1% vs. 69.9% for any grade TRAEs; 18.9% vs. 9.7% for grade 3 TRAEs), though the safety profile was overall favorable.[9] This result highlights the need for randomized trials in order to fully inform the extent of additional toxicities incurred with the addition of anti-LAG-3 to anti-PD-1/L1 therapies.

Key limitations of our study include the relatively small numbers of patients in each cohort/group, tumor subtype heterogeneity within each indication, and the lack of comparator arms in a non-randomized setting. Our data show very durable responses, exceeding 2 y in some cases across all indications for patients naive to prior anti-PD-1/L1 therapy, but also in the melanoma and RCC cohorts for anti-PD-1/L1-pretreated patients, suggesting that targeting LAG-3 may contribute to efficacy. Still, there is a need for randomized trials comparing the combination of ieramilimab plus spartalizumab to spartalizumab alone to clarify the contribution of LAG-3 blockade. The RELATIVITY-047 phase 3 study of relatlimab with nivolumab reported superior PFS benefit with the combination regimen compared to use of nivolumab alone (10.1 months vs. 4.6 months; $P = 0.006$) in patients with anti-PD-1/L1-naive unresectable or metastatic melanoma regardless of

their LAG-3 (≥1% or < 1%) expression status, providing evidence for a role of LAG-3 inhibition in improving immune checkpoint inhibitor efficacy.[9]

The role of dual LAG-3 and PD-1 blockade in other indications has not been established. In addition to the lack of comparator arms, this trial was likely limited in its ability to demonstrate signals of efficacy improvement with dual checkpoint blockade because enrolled patients had received previous standard-of-care therapy, and in most cases, multiple prior lines of therapy for refractory metastatic disease. In addition, tumors were not prospectively selected for PD-L1 status, a predictive biomarker for checkpoint blockade in some indications studied in this trial, such as NSCLC. When comparing early and metastatic stages of disease, there is a growing appreciation that the tumor immune microenvironment evolves, and that the efficacy potential for immunotherapies may be better demonstrated before the accumulation of resistance mechanisms supporting tumor growth.[30] Further study of dual LAG-3 and PD-1 blockade in solid tumors is warranted.

One of the key challenges and areas of intensive research to improve immunotherapies includes the identification of patient subsets that are more likely to experience long-term clinical benefit with immune checkpoint inhibitor combinations. Our biomarker analysis showed that patients with higher expression of T-cell-inflamed gene signature in baseline tumor samples were more likely to respond to the combination of ieramilimab plus spartalizumab. However, LAG-3 expression in baseline tumor samples by immunohistochemistry did not predict a benefit of dual LAG-3/PD-1 blockade. Data from the RELATIVITY-047 study indicated that expression of LAG-3 was not useful in predicting benefit of dual LAG-3/PD-1 treatment over anti-PD-1 alone, leading the authors to the conclusion that LAG-3 expression does not have a clear role in treatment selection.[9] Notably, LAG-3 gene expression by RNA sequencing was associated in our study with treatment response. Moreover, combination treatment increased LAG-3 gene expression and T-cell-inflamed signature genes in most patients, suggesting that combination treatment may enhance T-cell activation in the tumor microenvironment. Considering that anti-PD-1 treatment alone has been associated with an increase in T-cell-inflamed signatures,[31,32] it would be important to understand the relative additional contribution of LAG-3 blockade to this effect. However, this was not elucidated in the biomarker analysis of tumors treated with single-agent ieramilimab during this trial's phase 1 dose-escalation portion. Given the lack of single-agent anti-tumor activity associated with anti-LAG-3 in solid tumors,[10] identifying predictive biomarkers specific for anti-LAG-3 therapies may be challenging. Further investigation of the predictive value of LAG-3 gene expression and T-cell-inflamed gene signature is warranted.

In conclusion, our results suggest that dual blockade of LAG-3 and PD-1 with ieramilimab and spartalizumab is associated with clinical activity in patients across different indications. The safety and preliminary efficacy findings were in line with previously reported results and published studies exploring similar strategies in melanoma and NSCLC. In addition, our study provides new clinical insights for anti-PD-1/anti-LAG-3 immunotherapy combination in additional indications, such as RCC, TNBC and mesothelioma. Considering recent evidence on LAG-3 related tumor immunology in various malignancies, including RCC, TNBC and mesothelioma.[33] Our results support further exploration of dual LAG-3/PD-1 blockade in selected patient populations across different malignancies.

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Ethics approval and consent to participate

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