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Phase II study of durvalumab plus tremelimumab as therapy for patients with previously treated anti-PD-1/PD-L1 resistant stage IV squamous cell lung cancer (Lung-MAP substudy S1400F, NCT03373760)

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ABSTRACT

Introduction S1400F is a non-match substudy of Lung Cancer Master Protocol (Lung-MAP) evaluating the immunotherapy combination of durvalumab and tremelimumab to overcome resistance to anti-programmed death ligand 1 (PD-(L)1) therapy in patients with advanced squamous lung carcinoma (sq non-small-cell lung cancer (NSCLC)).

Methods Patients with previously treated sqNSCLC with disease progression after anti-PD-(L)1 monotherapy, who did not qualify for any active molecularly targeted Lung-MAP substudies, were eligible. Patients received tremelimumab 75 mg plus durvalumab 1500 mg once every 28 days for four cycles then durvalumab alone every 28 days until disease progression. The primary endpoint was the objective response rate (RECIST V.1.1). Primary and acquired resistance cohorts, defined as disease progression within 24 weeks versus ≥24 weeks of starting prior anti-PD-(L)1 therapy, were analyzed separately and an interim analysis for futility was planned after 20 patients in each cohort were evaluable for response.

Results A total of 58 eligible patients received drug, 28 with primary resistance and 30 with acquired resistance to anti-PD-(L)1 monotherapy. Grade ≥3 adverse events at least possibly related to treatment were seen in 20 (34%) patients. The response rate in the primary resistance cohort was 7% (95% CI 0% to 17%), with one complete and one partial response. No responses were seen in the acquired resistance cohort. In the primary and resistance cohorts the median progression-free survival was 2.0 months (95% CI 1.6 to 3.0) and 2.1 months (95% CI 1.6 to 3.2), respectively, and overall survival was 7.7 months (95% CI 4.0 to 12.0) and 7.6 months (95% CI 5.3 to 10.2), respectively.

Conclusion Durvalumab plus tremelimumab had minimal activity in patients with advanced sqNSCLC progressing on prior anti-PD-1 therapy.

Trial registration number
NCT03373760.

INTRODUCTION

The Lung Cancer Master Protocol (Lung-MAP) was designed to employ tumor screening with broad-based next generation sequencing (NGS) in order to simultaneously evaluate multiple novel targeted therapies in patients with advanced, previously treated squamous lung carcinoma (sq non-small-cell lung cancer (NSCLC)).[1 2] This platform facilitates screening large numbers of patients to identify rare, actionable mutations or other unique molecular features and then matching the patient to a biomarker-driven Lung-MAP substudy. Those without a biomarker match, or otherwise not qualified for a targeted substudy, could be enrolled into a 'non-match' substudy. After Lung-MAP was developed and began accrual, the standard of care for platinum-treated advanced sqNSCLC patients evolved from docetaxel chemotherapy to Programmed cell death protein 1 (PD-1)/programmed death -ligand 1 (PD-L1)-directed checkpoint inhibitor therapy. With response rates in the range of 20%, a significant number of patients do not derive long-term benefit from second-line therapy with single agent PD-1 or PD-L1 inhibitors, and the majority of those with initial response subsequently progress.[3–5] A similar pattern has emerged as PD-1 or PD-L1

inhibitors have moved to the first-line setting, with or without chemotherapy. Greater understanding of the scientific basis underlying primary and acquired resistance to PD-1 checkpoint inhibitors, and options to overcome this resistance, are urgently needed.

Limited data are available on mechanisms of resistance to PD-1 checkpoint inhibitor therapy in lung cancer. There is growing interest in genomic correlates of PD-1 checkpoint inhibitor response, including increased tumor mutational burden (TMB) and DNA damage response and repair (DDR) gene alterations.[6–8] Failure of engagement of tumor-infiltrating T cells by tumor antigens, an immunosuppressive tumor microenvironment, impaired T-cell effector function, and signaling via alternate immune inhibitory checkpoints are all potential mechanisms of resistance. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1 checkpoints are both negative regulators of T cell activation and function, and use distinct mechanisms to block T cell activity. CTLA-4 decreases signaling via CD28, leading to impaired T-cell activation, while PD-1 inhibition results in T cell effector dysfunction. Preclinical and clinical studies demonstrate synergy when CTLA-4 and PD-1 axis inhibitors are combined, which has led to superior outcomes with combination immunotherapy in melanoma and renal cell carcinoma.[9–12] The combination of CTLA-4 and PD-1 axis inhibitors has also emerged as a standard option in the treatment of advanced pleural mesothelioma and one of several first-line options for patients with advanced NSCLC.[13 14]

We explored adding tremelimumab, a fully humanized IgG_2 monoclonal antibody that binds CTLA-4 on activated T cells, to ongoing PD-L1 inhibition with durvalumab, a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody, in patients with advanced pre-treated sqNSCLC and primary or acquired resistance to PD-(L)1 inhibitors. We also explored the relationship of PD-L1 tumor expression with patient outcomes, and post-hoc exploration of outcomes by TMB and somatic mutations in DDR genes, potential correlates of checkpoint inhibitor response.

MATERIALS AND METHODS

Study design

This multicenter, open-label, phase II trial and substudy of Lung-MAP (S1400), was conducted through the National Clinical Trials Network and led by the SWOG Cancer Research Network as described previously.[1 2] Patients were stratified into two cohorts based on prior response to checkpoint inhibitor monotherapy. Primary PD-(L)1 resistance was defined as disease progression within 24 weeks of initiation of single agent anti-PD-1/PD-L1 therapy. Acquired PD-(L)1 resistance was defined as 24 weeks or more of disease control (complete response, partial response, or stable disease) after initiation of single agent anti-PD-1/PD-L1 therapy that had subsequently progressed after 24 weeks. The trial assessed outcomes of durvalumab plus tremelimumab-treated patients with primary vs acquired resistance to anti-PD(L)1 therapy.

Eligibility

Patients must have been eligible for the Lung-MAP (S1400) screening study and not eligible for any of the actively accruing biomarker-driven sub-studies.[2 15–18] Other eligibility criteria included: histologically confirmed stage IV or recurrent sqNSCLC with measurable disease per RECIST V.1.1, prior platinum-based chemotherapy, and progression during or after anti-PD-1 or anti-PD-L1 antibody monotherapy as their most recent line of treatment, no prior treatment with CTLA-4 inhibitors, no immunosuppressive medication nor attenuated vaccinations within 28 days, and no systemic corticosteroids within 24 hours prior to registration. Patients with a history of organ transplant requiring immunosuppressive therapy were excluded. Patients could not have active, known, or suspected tuberculosis, HIV, AIDS, hepatitis B, hepatitis C, or autoimmune or inflammatory disease within 3 years. In addition, patients could not have experienced grade 3 or greater immune-mediated toxicity, except asymptomatic rash, nor any toxicity that led to permanent discontinuation of prior anti-PD-1/PD-L1 therapy. Patients were stratified into two cohorts for analysis purposes, primary anti-PD-1/PD-L1 resistance and acquired anti-PD-1/PD-L1 resistance.

Tremelimumab 75 mg was administered intravenously over 1 hour, followed by durvalumab 1500 mg intravenous administration over 1 hour on day 1 of 28-day cycles for the first four cycles. Starting at cycle 5, only durvalumab 1500 mg was administered on day 1 of each cycle as maintenance until disease progression or unacceptable toxicity. Disease assessment occurred every two cycles, and treatment was continued until disease progression or unacceptable toxicity. Only dose interruptions or discontinuations were allowed to manage toxicity and were discussed with the study chairs as specified in the protocol.

Biomarker screening and analysis

All Lung-MAP (S1400) patients had tumor tissue biomarker screening by NGS by Foundation Medicine, as previously described. PD-L1 immunohistochemistry (IHC) staining and scoring was performed by Clarient, using the technically validated IHC-based SP263 assay developed by AstraZeneca for PD-L1 determination in partnership with Ventana Medical Systems, a College of American Pathologists (CAP)-accredited/Clinical Laboratory Improvement Amendments-certified laboratory (Tucson, AZ).

Statistical considerations

The primary objective was to evaluate the objective response rate (ORR; confirmed and unconfirmed, complete and partial) by RECIST version 1.1 in each cohort, the primary PD-(L)1 resistant cohort, and the acquired PD-(L)1 resistant cohort. The sample size for

each cohort was based on a design with 82% power to rule out an ORR of 15% at the 5% level if the true rate was 35%. The accrual goal for each cohort was 66 patients to achieve 60 evaluable patients per cohort. The design included two interim analyses for each cohort separately at 20 and 40 patients evaluable for response, and the cohorts would continue accrual independently; at least one response was needed to accrue past the first interim analysis, and at least four responses were needed to accrue past the second interim analysis. If a study cohort reached full accrual, 6 or more responses were needed to rule out a 15% ORR. Other key secondary objectives to be analyzed by cohort included overall survival (OS), progression-free survival (PFS), and the relationship of PD-L1 expression status to response and PFS. Post hoc exploratory analysis of PFS by TMB and somatic mutations in DNA DDR genes, potential correlates of checkpoint inhibitor response and treatment outcomes, was also performed.[7 8]

RESULTS

Patient characteristics and treatment

Between October 2 2017 and March 24 2020, 1388 patients were genomically screened in Lung-MAP using NGS; 211 patients (15% of those screened on S1400 while S1400F was actively accruing) were assigned to S1400F and 67 patients were enrolled. Seven patients were ineligible for study; six did not receive anti-PD-L1 monotherapy as their most recent line of treatment and one had inadequate documentation of measurable disease. Another two patients were ineligible for analysis, as one expired prior to receiving any treatment and one withdrew consent prior to treatment. In all, 58 eligible patients received protocol therapy, 28 in the primary resistance cohort and 30 in the acquired resistance cohort (online supplemental figure 1). Baseline characteristics were similar in the two cohorts and are described in table 1. Genomic alterations in tumor tissue are listed in online supplemental table 1. The acquired and the primary resistance cohorts were permanently closed to accrual by the data and safety monitoring committee on November 6 2019 due to futility and on March 24 2020 due to poor accrual, respectively. Of note, the primary resistance cohort met the criterion to continue accrual past the first interim analysis.

Table 1 Patient demographics and characteristics

	Primary PD-(L)1 resistance (N=28)	Acquired PD-(L)1 resistance (N=30)
Age median (range), years	67.6 (49.7–89.8)	67.8 (46.6–84.0)
Male	18 (64)	18 (60)
Race		
White	24 (86)	26 (87)
Black	3 (11)	3 (10)
Native American	1 (3)	0 (0)
Not reported	0 (0)	1 (3)
Hispanic ethnicity	1 (4)	3 (10)
No of prior lines of therapy for stage IV disease		
<2	9 (32)	12 (40)
≥2 (max 4)	19 (68)	18 (60)
Median (range) PFS on prior anti-PD-(L)1 therapy, months	3.0 (1.4–5.5)	10.0 (5.6–30.4)
Best response to prior anti-PD-(L)1 therapy		
Complete response*	0 (0)	3 (10)
Partial response*	2 (7)	7 (23)
Stable disease	11 (39)	20 (67)
Progressive disease	15 (54)	0 (0)
Performance status		
0	7 (25)	10 (33)
1	21 (75)	20 (67)
Smoking status		
Current smoker	10 (36)	10 (33)
Former smoker	17 (61)	19 (63)
Never smoker	1 (4)	1 (3)
Weight loss ≥10%	2 (8)	2 (7)
PD-L1 expression† (TPS (%))		
<1%	10 (36)	3 (10)
1%–49%	5 (18)	9 (30)
50%	5 (18)	2 (7)
Unknown	8 (28)	16 (53)
Tumor mutational burden		
<10 mt/Mb	8 (28)	11 (37)
≥10 mt/Mb	17 (61)	17 (57)
Not evaluable	3 (11)	2 (6)

Values are shown as n (%) unless otherwise stated.
*Includes confirmed and unconfirmed responses per investigator assessment.
†PD-L1 expression was assessed by immunohistochemistry on tumor samples using 22C3 pharmDx assay (Agilent Technologies, Santa Clara, California, USA).
PD-L1, programmed death ligand 1; TPS, Tumor Proportion Score.

Efficacy

There was one confirmed complete and one partial response, both in the primary resistance cohort for an ORR of 7% (95% CI 0% to 17%); there were no responses in the acquired resistance cohort (table 2). The median duration of response for the two responding patients in the primary resistance cohort was 8.5 months and 5.9 months, respectively. The patient with partial response had a tumor PD-L1 score <1%, both responders had a tumor TMB of 15 mutations/Mb and multiple somatic alterations including in TP53, PTEN, and PIK3 genes. Ten and 14 patients had stable disease in the primary and acquired resistance cohorts, respectively, with disease control rates at 12 weeks of 43% (95% CI 25% to 61%) and 40% (95% CI 23% to 58%). Figure 1 depicts the waterfall plot for individual responses color coded by cohort.

OS and investigator-assessed PFS (IA-PFS) were similar in both cohorts (figure 2). In those with primary resistance, the median IA-PFS was 2.0 months (95% CI 1.6 to 3.0) and

Table 2 Patient tumor responses

	Total (N=58)	Primary PD-(L)1 Resistance (N=28)	Acquired PD-(L)1 Resistance (N=30)
Complete response	1 (2)*	1 (4)	0
Partial response	1 (2)*	1 (4)	0
Stable disease/no response	24 (41)	10 (36)	14 (47)
Increasing disease	27 (47)	12 (43)	15 (50)
Symptomatic deterioration	4 (7)	3 (11)	1 (3)
Assessment inadequate	1 (2)	1 (4)	0
Objective response rate	2 (3 (95% CI 0 to 8))	2 (7 (95% CI 0 to 17))	0
Disease control rate	26 (45 (95% CI 32 to 58))	12 (43 (95% CI 25 to 61))	14 (47 (95% CI 29 to 65))

Values are shown as n (%) unless otherwise stated.
*Includes confirmed and unconfirmed responses per investigator assessment.
PD-L1, programmed death ligand 1.

the median OS was 7.7 months (95% CI 4.0 to 12.0). In the cohort with acquired resistance to anti-PD-(L)-1 inhibitor therapy, the median IA-PFS was 2.1 months (95% CI 1.6 to 3.2) and the median OS was 7.6 months (95% CI 5.3 to 10.2). Subgroup analysis did not identify any clinical or pathological characteristics associated with benefit, including age, performance status, sex, smoking status, PD-L1 tumor expression, nor tissue TMB, shown in figure 3. In post hoc analysis, patients with tumors harboring at least one or more alterations in DDR genes had similar IA-PFS and OS compared with patients with no tumor DDR genomic alterations (figure 3, online supplemental figure 2).

Safety

Patients in both the primary and acquired resistance cohorts received a median of 3 cycles of durvalumab (range 1–14 in primary resistance, 1–16 in acquired resistance), and a median of 4 planned cycles of tremelimumab (range 1–4). There were two treatment-related deaths in the acquired resistance cohort (one pneumonitis, one death not otherwise specified possibly related to pneumonitis). The patient with fatal pneumonitis also experienced grade 4 dyspnea. Additionally, two patients experienced grade 4 adverse events due to lymphopenia

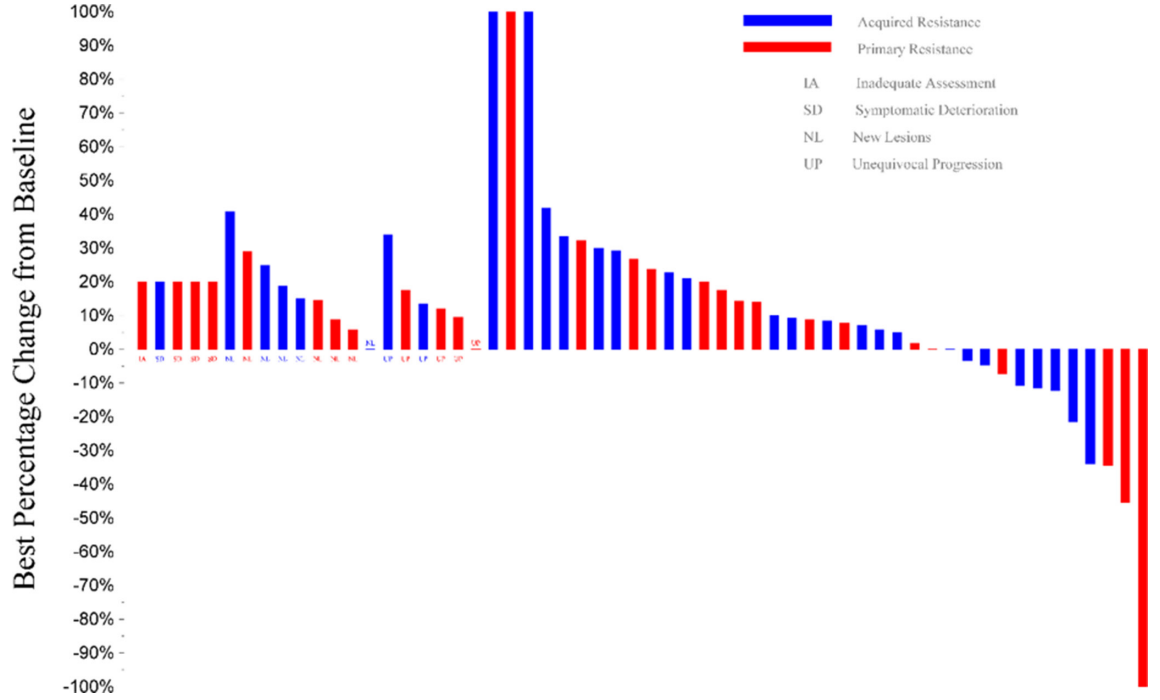

Figure 1 Waterfall plot of response to durvalumab plus tremelimumab. Of four patients with more than 30% reduction in tumor measurements, two had documented responses in the primary resistance cohort (1 partial and one complete response). One patient in the primary resistance cohort was found to have stable disease on independent radiology review. One patient in the acquired resistance cohort stopped treatment before disease progression (best response of stable disease) and started a new treatment prior to subsequent tumor measurements (included above).

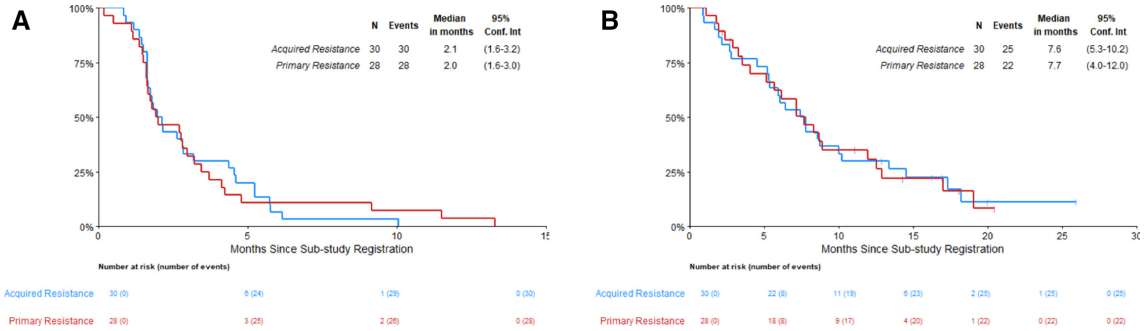

Figure 2 Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) in the primary and acquired PD-(L)1 resistant cohorts. (A) PFS. (B) OS. PD-(L)1, programmed death ligand 1.

(1) and leukopenia (1). In the primary resistance cohort, one patient experienced treatment-related grade 4 thrombocytopenia. Overall, 33% of patients in the primary resistance and 36% of patients in the acquired resistance cohorts experienced grade three or higher treatment-related adverse events (table 3). Four patients in each cohort discontinued protocol therapy for toxicity. Further details of patient disposition are listed in online supplemental figure 1.

DISCUSSION

In patients with advanced pretreated sqNSCLC and acquired resistance to anti-PD-1/PD-L1 monoclonal antibody therapy, no activity was seen with the addition of CTLA-4 inhibition to ongoing PD-1 axis inhibition with durvalumab plus tremelimumab. In patients with primary resistance, the ORR was 7%. Both responders had higher TMB (15 mutations/Mb) including alterations in *TP53* and other genes, while one had tumor PD-L1 <1% and the other had PD-L1 positive tumor expression. While this cohort was closed due to poor accrual, it is unlikely that a larger sample size would have yielded clinically different results. Toxicity was as expected for the combination and there were no characteristics associated with greater benefit from therapy, including PD-L1 tumor expression, tissue TMB, nor the presence of DDR mutations.

At the time this study was designed, second-line single agent anti-PD-(L)1 therapy was a new standard for patients with advanced NSCLC, and upfront combinations of chemotherapy plus checkpoint inhibitors first-line had not yet been approved. Similarly, the use of combination nivolumab plus ipilimumab had not been approved in the first-line setting. The clinical benefit of adding CTLA-4 inhibition to PD-(L)1 checkpoint inhibition remains

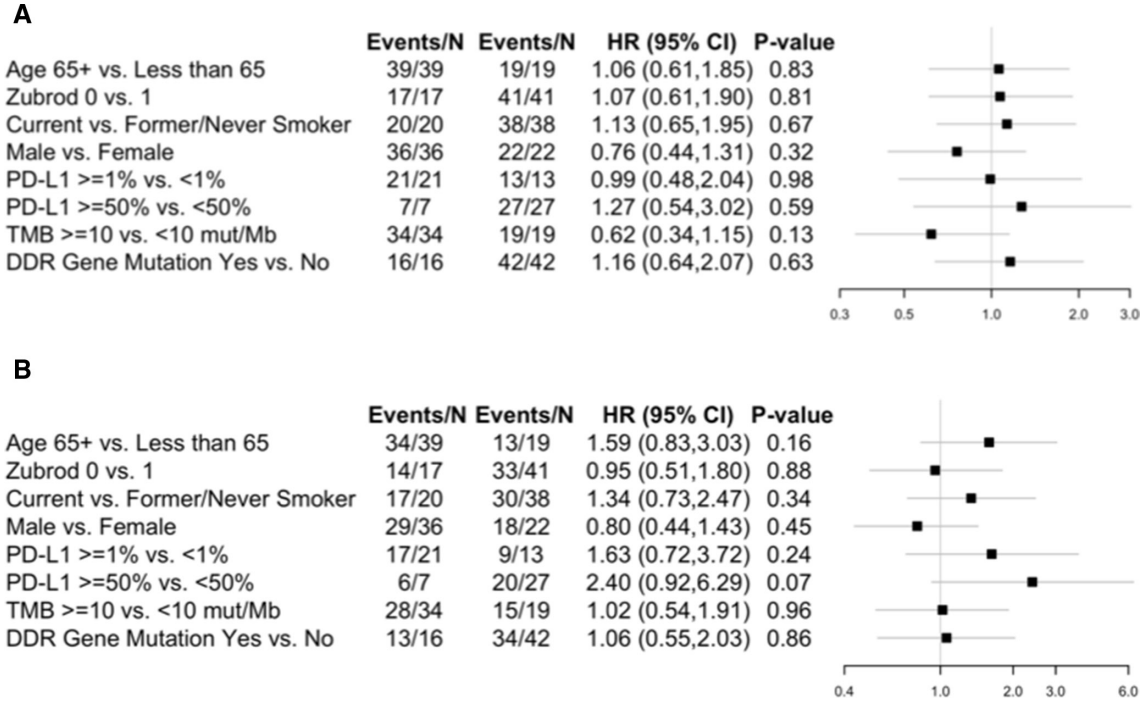

Figure 3 Forest plot comparisons of patient characteristics and progression-free survival (PFS) and overall survival (OS) in the full eligible population. (A) Forest plot for PFS. (B) Forest plot for OS. DDR, DNA damage response and repair; MB, megabase; mut, mutation; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.

Table 3 AEs attributable to treatment

	Primary PD-(L)1 Resistance (N=30)			Acquired PD-(L)1 Resistance (N=28)		
	Grade			Grade		
AEs	**3**	**4**	**5**	**3**	**4**	**5**
Atrial fibrillation	1 (3)					
Atrial flutter	1 (3)					
Chills	1 (3)					
Confusion				1 (4)		
Creatinine increased				1 (4)		
Death NOS						1 (4)
Dehydration	1 (3)			2 (7)		
Diarrhea	1 (3)			3 (11)		
Dyspnea	4 (13)				1 (4)	
Encephalopathy				1 (4)		
Fatigue	1 (3)					
Febrile neutropenia				1 (4)		
Generalized muscle weakness				1 (4)		
Hyperglycemia				1 (4)		
Hypoxia	1 (3)			1 (4)		
Lung infection	1 (3)			1 (4)		
Lymphocyte count decreased	1 (3)			1 (4)	1 (4)	
Nausea				1 (4)		
Neutrophil count decreased				1 (4)		
Platelet count decreased	1 (3)	1 (3)		1 (4)		
Pneumonitis	1 (3)					1 (4)
Rash maculopapular				1 (4)		
Vomiting				1 (4)		
White blood cell decreased					1 (4)	
Maximum grade any AE	**9 (30)**	**1 (3)**		**6 (21)**	**2 (7)**	**2 (7)**

Values are n (%).
AE, adverse event; NOS, not otherwise specified; PD-L1, programmed death ligand 1.

unclear in lung cancer. The recently published Lung-MAP S1400I study demonstrated that adding ipilimumab to nivolumab did not improve outcomes compared with nivolumab alone in patients with advanced pre-treated sqNSCLC without prior checkpoint inhibitor therapy.[19] A recent report of a randomized trial of ipilimumab added to pembrolizumab also showed similar outcomes compared with pembrolizumab alone as first-line therapy in patients with advanced NSCLC and PD-L1 tumor proportion score ≥50%.[20] In the relapsed setting, a study of patients with advanced NSCLC, predominantly adenocarcinoma, that had failed up to three lines of therapy including PD-(L)1 checkpoint inhibitors demonstrated an ORR of 5% in patients with primary or acquired resistance.[21] In that study, primary resistance was defined as disease progression as the best response within 16 weeks of starting checkpoint inhibition, and acquired resistance was defined as progression after initial complete or partial response or stable disease as the best response to PD-(L)1 inhibitor therapy. The median duration of response was approximately 6 months (24 weeks).

Studies have identified upregulation of co-inhibitory receptors such as TIM-3 in tumors of patients with advanced lung cancer with acquired resistance to PD-(L)1 inhibitors as well as decreased antigen presentation and neoantigen loss, and altered metabolism to promote an immunosuppressive tumor microenvironment among other potential mechanisms of resistance.[22] The presence of mutations in KEAP1, PTEN and other genes have also been associated with checkpoint inhibitor resistance. Current strategies to overcome PD-1 inhibitor resistance include targeting the tumor immune microenvironment via a number of pathways including the vascular endothelial growth factor pathway, beta-catenin, adenosine, and

others. Novel agents targeting alternate checkpoints such as V-domain immunoglobulin suppressor of T cell activation (VISTA), Lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) are also in clinical development, as well as other approaches such as cell therapy. A number of combination approaches are also under study through the Lung-MAP Protocol, including the combination of ramucirumab plus pembrolizumab in patients with checkpoint inhibitor refractory disease (S1800A) and an upcoming study of interleukin-15 agonist N-803 with pembrolizumab in this population (S1800D).

In conclusion, the addition of a CTLA-4 checkpoint inhibitor to ongoing PD-L1 checkpoint inhibitor therapy did not yield meaningful benefit in patients with advanced sqNSCLC and resistance to PD-(L)1 inhibition, whether primary or acquired. This population of patients should be prioritized for clinical trial enrollment, including through Lung-MAP.

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