ORIGINAL ARTICLE

Eftilagimod Alpha (a Soluble LAG-3 Protein) Combined With Pembrolizumab in Second-Line Metastatic NSCLC Refractory to Anti–Programmed Cell Death Protein 1/Programmed Death-Ligand 1-Based Therapy: Final Results from a Phase 2 Study

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ABSTRACT

Introduction: Eftilagimod alpha (efti), a soluble lymphocyte activation gene-3 protein, triggers antigen-presenting cell and T-cell ($CD4^+$ and $CD8^+$) activation and helps overcome resistance to programmed cell death protein 1 or programmed cell death-ligand 1 (PD-(L)1) inhibitors. We assessed efti plus pembrolizumab in second-line anti–PD-(L)1-refractory metastatic patients with NSCLC.

Methods: After confirmed progression on anti-PD-(L)1-based first-line therapy, patients received efti (30 mg subcutaneously every 2 weeks for eight 3-week cycles and then every 3 weeks for up to 54 weeks) plus pembrolizumab (200 mg intravenously every 3 weeks for up to 105 weeks). The primary endpoint was the objective response rate by modified Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapies. Secondary endpoints included disease control rate, progression-free survival, overall survival (OS), and tolerability. Exploratory endpoints included tumor growth kinetics and predefined subgroup analyses. Programmed cell death-ligand 1 tumor proportion score was assessed centrally.

Results: Thirty-six patients were enrolled from April 2019 to August 2021 using Simon's two-stage design. Most patients (81.8%) had low or negative (<50%) PD-(L)1 tumor proportion score. First-line therapy was anti–PD-(L)1-based for all patients, combined with chemotherapy for 66.7%. The confirmed objective response and disease control rates

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were 8.3% and 33.3%. The median progression-free survival was 2.1 months and the median OS was 9.9 months. Patients exhibiting high PD-(L)1 expression or acquired resistance to PD-(L)1 inhibitors revealed superior response and survival outcomes, and OS was closely correlated with disease control. No treatment-emergent adverse event led to permanent discontinuation of study treatment.

Conclusions: Efti plus pembrolizumab was well-tolerated and revealed signs of antitumor activity in patients with NSCLC resistant to PD-(L)1 inhibitors, warranting further investigation. Trial registration number: NCT03625323.

Keywords: Non–small cell lung cancer; Anti-PD-(L)1 Refractory; Eftilagimod alpha; Immune checkpoint inhibitor; Pembrolizumab

Introduction

Despite recent progress in diagnosis and treatment, lung cancer remains the leading cause of cancer-related deaths worldwide[1]; NSCLC accounts for approximately 85% of all lung cancers and almost 800,000 new cases are reported globally each year.[2]

Within the past decade, immunotherapy (IO) has become a key component in the standard-of-care treatment for metastatic NSCLC. First-line therapy now routinely includes the use of immune checkpoint inhibitors (ICIs) such as programmed cell death protein 1 or programmed cell death-ligand 1 (PD-(L)1) inhibitors, either alone or in combination with chemotherapy or another ICI.[3] Clinical benefit has been revealed for anti–PD-(L)1 monotherapy in patients with high (≥50%) programmed death-ligand 1 (PD-L1) tumor proportion score (TPS); treatment with pembrolizumab, an anti–programmed cell death protein 1 (anti–PD-1) antibody, in the KEYNOTE-024 trial resulted in an objective response rate (ORR) of 46% and median overall survival (OS) of 26 months.[4] Trials assessing monotherapy with other PD-(L)1 inhibitors in PD-L1-selected populations have shown comparable results.[5–7] In PD-L1 unselected patient with NSCLC populations with either nonsquamous or squamous tumors, pembrolizumab plus chemotherapy led to ORRs of 48% and 63% and median OS of 22 months and 17 months in the KEYNOTE-189 and KEYNOTE-407 studies, respectively.[8,9]

Unfortunately, a important proportion of patients develop resistance to PD-(L)1 inhibitors over time. Some patients exhibit primary resistance (typically defined as progression within the first three months of starting IO treatment[10]), while the majority will develop secondary resistance after a period of stability or response.[11] Very few treatment options are available in the second-line setting (mainly single-agent chemotherapy, such as taxanes), and finding new strategies to overcome immune resistance represents a major unmet clinical need.[3] The current second-line standard of care, docetaxel (± nintedanib) in nonsquamous NSCLC, results in more than half of patients experiencing grade 3–4 treatment-related adverse events (TRAEs) and a median OS of 8.1 months.[12–14] As such, its use is diminishing in routine care and the definition of meaningful clinical benefit in this setting should be considered long-term stabilization of the disease (>6 mo), leading to improved OS, together with a favorable safety profile.

Antigen-presenting cell (APC) activators are a type of IO that leverages APCs and reactivate the dendritic cell network. Eftilagimod alpha (efti), a soluble LAG-3 protein, acts as a major histocompatibility complex class II agonist. Efti triggers the activation of APCs leading to the reactivation and proliferation of memory T-cell subsets, which results in a sustained immune response in preclinical and clinical studies.[15–20] Stimulating APCs and subsequent T-cell recruitment with efti may revert anti–PD-(L)1 resistance. Initial clinical data with efti support this notion. In the Two ACTive Immunotherapies (TACTI)-mel study, patients with melanoma and suboptimal response to pembrolizumab were treated with the addition of efti to pembrolizumab; pooled ORR was 54%.[19] In the INSIGHT platform study (Stratum D), patients with different solid tumors (partially IO-insensitive diseases) were treated with avelumab (anti–PD-L1) plus efti; ORR was 42%.[21] Lastly, treatment with efti plus pembrolizumab in first-line patients with NSCLC who were expected to exhibit absence of benefit because of their negative PD-L1 status revealed an ORR of 31% and median OS of 15.5 months.[22]

Here we report the final results from part B of the TACTI-002 study (NCT03625323; EudraCT: 2018-001994-25), a nonrandomized, open-label, single-arm, phase 2 study designed to investigate the efficacy and safety of efti plus pembrolizumab in second-line metastatic patients with NSCLC resistant to PD-(L)1 inhibitors. Interim and final analyses of Part B have been previously reported at various congresses.[23–25]

Materials and Methods

Patients

We performed a multicenter, open-label, single-arm, phase 2 study of efti plus pembrolizumab in multiple indications (part A: first-line NSCLC; part B: second-line

NSCLC refractory to anti–PD-(L)1-based therapy; part C: second-line head and neck squamous cell cancer; Supplementary Fig. 1).

Patients eligible for part B of the study were adults with advanced or metastatic NSCLC who progressed (confirmed progressive disease [PD] per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1] on two consecutive scans) on the prior treatment of at least two cycles of any anti–PD-(L)1-based therapy (alone or combined with other immune- or chemotherapeutics). An Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease per RECIST 1.1, and a tumor specimen evaluable for PD-L1 expression were required. Patients were not preselected on the basis of their PD-L1 expression and gene testing was not compulsory. Individuals with neuroendocrine or sarcomatoid NSCLC tumor types, radiotherapy of higher than 30 Gy within the 6 months before study treatment started, or prior anti–LAG-3 therapy were excluded. Full inclusion and exclusion criteria are reported in the study protocol.

The study protocol was approved by independent ethics committees at all participating institutions; all patients provided written informed consent. The study was conducted according to the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice standards.

Treatment

Patients received intravenous pembrolizumab (200 mg as a 30-minute infusion every 3 weeks [q3w]) plus subcutaneous efti (30 mg every 2 weeks [q3w from start of cycle 9]) for 54 weeks, followed by another 51 weeks of pembrolizumab alone q3w (Supplementary Fig. 1). Patients were to stay on treatment until confirmed PD, unacceptable toxicity, completion of study treatment, or discontinuation for any other reason.

Measures

Tumor response was assessed radiologically, mainly on the basis of contrast-enhanced computed tomography scans. Magnetic resonance imaging was permissible if iodinated computed tomography contrast was contraindicated. Radiological assessment was done at intervals of 9 weeks until week 36 and every 12 weeks thereafter. Scans were investigator-assessed for measurability and response to treatment, and treatment decisions were made according to modified RECIST 1.1 for immune-based therapies (iRECIST). Patients were followed up for OS every 12 weeks until death, withdrawal of consent, loss to follow-up, or until the end of the study. The safety of study treatments was monitored for up to 120 days after the last treatment. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5.0.

Retrospective immunohistochemical assessment of tumor PD-L1 expression was performed centrally in a Clinical Laboratory Improvement Amendments-certified, accredited laboratory (Labcorp Central Laboratory Services, Meyrin, Switzerland) and was tested using the Dako PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent, Carpinteria, California). The assay was performed according to the package insert, with appropriate controls. Scoring of TPS was performed by certified pathologists specifically trained in PD-L1 22C3 CDx scoring for NSCLC. Local assessment of tumor PD-L1 expression was performed according to site protocols. Central results always prevailed over local results, if available (central PD-L1 results for 27 patients; local results for six patients).

Outcomes

The study's primary objective was to determine the ORR according to iRECIST. There was no formal hypothesis testing nor p value to be generated. The primary endpoint was the ORR according to iRECIST. The ORR according to RECIST 1.1 was a secondary endpoint. Other secondary end points included: safety profile (AEs, events of clinical interest, abnormalities in standard safety assessments); time to and duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), all according to iRECIST and RECIST 1.1; and OS. Exploratory endpoints included tumor growth kinetics (TGKs) using local response assessment and predefined subgroup analyses.

Statistical Analysis

Patients were recruited according to Simon's optimal two-stage design.[26] For part B of the study, the sample size was calculated using R V3.3.3[27]: the null hypothesis that the true response rate was 7% was tested against a one-sided alternative that the true response rate was 19%. In the first stage, 23 patients were to be accrued. If there was one or no response in these patients, the study was to be stopped. Otherwise, 13 additional patients were to be accrued for a total of 36 patients. The study was designed to have a one-sided type I error rate of 5% significance and power of 70% to reject the null hypothesis.

Both the intent-to-treat population and the safety population consisted of all assigned patients who received at least 1 dose of either study treatment. The intent-to-treat population was the primary population for analyses of efficacy endpoints.

The ORR (primary endpoint) and DCR were summarized by binomial response rate with 95% exact confidence intervals (CIs) using the Clopper-Pearson method. Parameters related to DoR, PFS, and OS, including landmark analyses, were estimated using the Kaplan-Meier analysis method. The ORR, DCR, DoR, and PFS were reassessed per RECIST 1.1 as sensitivity analyses. Subgroup analyses were planned for response and survival parameters considering PD-L1 expression, first-line therapy for NSCLC, and resistance to first-line therapy. Tumor dynamics were explored using TGK, a comparative ratio of the difference of the sum of the largest diameters of target lesions pre and postbaseline.[28]

To assess the correlation between treatment response and OS, as a posthoc analysis, we employed the log-rank test to compare the survival distributions of patients categorized by their response to treatment (best overall response of complete response, partial response [PR], or stable disease versus PD or nonevaluable). This analysis was performed using GraphPad V9.5.0 (GraphPad Software Inc.).

Safety data were analyzed descriptively. All preplanned data analyses were performed with SAS V9.4 (SAS Institute Inc.) or higher.

Patient and Public Involvement

Patients were not involved in the design or conduct of this study aside from their kind participation.

Results

Patients

Between April 2019 and August 2021, TACTI-002 part B screened 54 patients at 10 sites in Australia, Spain, the United Kingdom, and the United States of America. A total of 36 patients met the eligibility criteria and were enrolled; all received at least one dose of efti plus pembrolizumab (Supplementary Fig. 2).

The median age was 67 years (range: 46–84), and 61.1% of patients were male (Table 1). Patients had both squamous (19.4%) and nonsquamous (77.8%) tumor histologic diagnosis (Table1). Patients were unselected for PD-L1 expression at study entry; of patients with evaluable tumor samples (n = 33), 81.8% had low or negative PD-L1 TPS (TPS < 50%) (Table 1). All patients who underwent gene testing were negative for *EGFR* (n = 29) and *ROS1* (n = 18) mutations. First-line therapy was anti-PD-(L)1-based for all patients, and for most also included chemotherapy (66.7%) (Table 1). Per the inclusion criterion, all patients had confirmed disease progression while on their previous anti–PD-(L)1-based therapy; 25.0% and 69.4% of patients met the criteria for primary and secondary resistance, respectively (Table 1)

Efficacy

Exposure. Among the 36 treated patients, three completed 1 year of combined treatment; one completed the maximum treatment duration of 35 pembrolizumab cycles (Supplementary Fig. 2). At the cutoff date of 15 August 2023, the median (range) follow-up time was 39.3 months (1.2–49.7). Median (range) treatment duration was 2.8 months (0.5–12.5) for efti and 2.8 months (0.7–23.6) for pembrolizumab; patients received a median (range) of seven (2–22) efti doses and 5 (2–35) pembrolizumab doses. A total of 18 patients (50.0%) went on to have poststudy anticancer therapy: all had chemotherapy-based therapy, except two patients, one treated with KRAS inhibitor-based therapy, and one treated with protein kinase inhibitor-based therapy.

Primary and Secondary Analyses. Three of the 36 patients had confirmed PR by iRECIST leading to an ORR of 8.3% (95% CI: 1.8–22.5) (Table 2). The median DoR for the three evaluable responses was 10.3 months (95% CI: 4.3–not calculable); treatment duration ranged from 16.9 to 20.8 months in these three patients.

The DCR, defined as the proportion of patients with disease stabilization (best objective response of complete response, PR, or stable disease per iRECIST), was 33.3% (95% CI: 18.6–51.0) (Table 2). Median PFS was 2.1 months (95% CI: 1.9–2.1) and the proportion of progression-free patients at 6 months was 25.0% according to iRECIST (Table 2 and Fig. 1*A*).

Similar results were obtained according to RECIST 1.1 (Supplementary Table 1).

Median OS was 9.9 months (95% CI: 6.5–22.4) and the proportion of patients alive at 12 months was 44.4%; 27.6% were alive at 24 months (Table 2 and Fig. 1*B*).

Exploratory Analyses. Preplanned subgroup analyses by PD-L1 expression indicated that ORR and DCR were numerically higher, and median PFS and OS numerically longer, in patients with high PD-L1 expression (TPS ≥50%; n = 6) when compared with patients with low or negative PD-L1 expression (TPS <50%; n = 27) (ORR: 33.3% versus 0.0%; DCR: 83.3% versus 22.2%; median PFS: 10.3 versus 2.0 mo; median OS: 21.2 versus 9.6 mo; Table 2 and Fig. 2*A* and *B*). Additional subgroup analyses of OS by first-line therapy for NSCLC and by resistance to first-line therapy indicated that median OS was numerically longer in patients who had previously received anti–PD-(L)1 therapy without chemotherapy versus those who had received anti-PD-(L)1 therapy with chemotherapy

Table 1. Patient Characteristics

Characteristics	ITT Population, N = 36, n (%)	
Age, median (range) y	67 (46-84)	
Sex		
Female	14 (38.9)	
Male	22 (61.1)	
ECOG performance status		
0	12 (33.3)	
1	24 (66.7)	
Smoking status		
Current	8 (22.2)	
Ex-smoker	23 (63.9)	
Nonsmoker	5 (13.9)	
Histologic findings		
Squamous	7 (19.4)	
Nonsquamous	28 (77.8)	
Unknown	1 (2.8)	
PD-L1 expression TPS	Central[a] (n = 27)	Central + local[b] (n = 33)
<1%	11 (40.7)	13 (39.4)
1%-49%	12 (44.4)	14 (42.4)
≥50%	4 (14.8)	6 (18.2)
First-line therapy for NSCLC[c]		
Anti-PD-(L)1 without chemotherapy	12 (33.3)	
Anti-PD-(L)1 with chemotherapy	24 (66.7)[d]	
Resistance to first-line therapy[e]		
Primary	9 (25.0)	
Secondary	25 (69.4)	
Not specified	2 (5.6)	

[a]Central PD-L1 assessed with Dako IHC 22C3 pharmDx for 27 patients.
[b]Central PD-L1 assessed with Dako IHC 22C3 pharmDx for 27 patients. Local results of six patients were included due to nonevaluable central assessment results, which were obtained according to site protocols.
[c]First-line therapy for NSCLC included anti-PD-(L)1 (pembrolizumab, durvalumab, nivolumab, atezolizumab, and avelumab); other ICIs (ipilimumab); targeted therapy (cabozantinib); other therapy (stem cells); and chemotherapy (carboplatin, cisplatin, pemetrexed, gemcitabine, and paclitaxel).
[d]Chemotherapy was platinum-based for the majority who had received it (87.5%; 21 of 24); the remaining patients were treated with pemetrexed (12.5%; three of 24).
[e]Defined according to Society for Immunotherapy of Cancer Immunotherapy Resistance Taskforce Consensus[10]: Primary: drug exposure at six weeks or higher with the best response of PD or SD lasting less than 6 months. Secondary: drug exposure at six months or higher with the best response as CR, PR, or SD for over six months. Not specified: not meeting primary or secondary definitions.
CR, complete response; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ITT, intent-to-treat; PD, progressive disease; PD-(L)1, programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1); PR, partial response; SD, stable disease; TPS, tumor proportion score.

(16.5 versus 8.1 mo; Supplementary Fig. 3) and in patients with secondary versus primary resistance (11.4 versus 7.5 mo; Supplementary Fig. 3). Posthoc subgroup analysis of OS by treatment response indicated that median OS was numerically longer in patients with controlled disease versus no disease control (24.6 versus 7.0 mo; Fig. 3).

Analysis of TGK in patients with data available on the same lesions pre and postbaseline (n = 24) indicated that the vast majority (75.0%) of patients revealed either a reduction in the rate of target lesion growth (50.0%) or shrinkage (29.2%) compared with prestudy levels (Supplementary Fig. 4).

Safety

Treatment with efti plus pembrolizumab was well tolerated. No treatment-emergent AE (TEAE) led to the permanent discontinuation of either study treatment. Serious TEAEs were reported in 25.0% of patients and were considered related to study treatment in 8.3% of patients. TEAEs leading to death occurred in 5.6% of patients: these events were associated with the progression of the underlying disease and none were related to the study treatment.

Most patients (97.2%) experienced TEAEs, the majority were mild or moderate in intensity (grade 1–2), and TEAEs of grade 3 or higher were reported in 36.1% of patients. The most frequent TEAEs (incidence ≥15% by the preferred term [PT]) and the most frequent TRAEs (incidence ≥10% by PT) are reported in Table 3. In total, 69.4% of patients experienced TRAEs; most were mild or moderate in intensity (grade 1–2), and TRAEs of grade 3 were reported in 11.1% of patients. No grade 4 or 5 TRAEs were reported. The most frequent TRAEs by PT were asthenia (in 13.9% of patients, grade 1–2 only), injection site erythema (in 13.9% of patients, grade 1 only), injection site pain (in 13.9% of patients, of grade 1–2 only), pruritus (in 13.9% of patients, of grade 3 in one instance), arthralgia (in 11.1% of patients, grade 1–2 only), and injection site reaction (in 11.1% of patients, grade 1 only).

Local injection site reactions (a typical efti-related AE) were reported in 38.9% of patients: events were mild in intensity (grade 1) in most patients, lasting for a median of 2.0 days, and none were serious. Immune-related AEs were reported in 27.8% of patients: events were mild or moderate in intensity (grade 1–2) in most patients, with grade 3 events of pruritus and rash reported in the same, single patient.

Discussion

After confirmed progression (by means of 2 consecutive scans) on first-line anti-PD-(L)1-based therapy, second-line patients with NSCLC, with predominantly low or negative PD-L1 expression (PD-L1 TPS <50%: 81.8%), revealed signs of efficacy after treatment with efti plus pembrolizumab. Of note, less than 20% of patients had high PD-L1 expression, a well-known predictive marker for anti–PD-(L)1-based therapy,[29] and 67% received doublet chemotherapy plus anti–PD-(L)1-based therapy as first-line treatment for NSCLC (prior chemotherapy was mostly platinum-based [87.5%]). Interestingly, only a minority of patients had a high PD-L1 TPS, which may be due to the small sample size. The observed treatment effects were durable, with all responders on

Table 2. Efficacy Overview Overall, by PD-L1 Expression, by First-Line Therapy for NSCLC, and by Resistance to First-Line Therapy

		Subgroups					
		By PD-L1 Expression (TPS)[a]		By First-Line Therapy for NSCLC		By Resistance to First-Line Therapy	
	ITT Population Overall	<50%	≥50%	Anti-PD-(L)1 With Chemotherapy	Anti-PD-(L)1 Without Chemotherapy	Primary	Secondary
	N = 36	n = 27	n = 6	n = 24	n = 12	n = 9	n = 25
ORR,[b] n (%) [95% CI]	3 (8.3) [1.8-22.5]	0	2 (33.3) [4.3-77.8]	2 (8.3) [1.0-27.0]	1 (8.3) [0.2-38.5]	0	2 (8.0) [1.0-26.0]
DCR,[b] n (%) [95% CI]	12 (33.3) [18.6-51.0]	6 (22.2) [8.6-42.3]	5 (83.3) [35.8-99.6]	6 (25.0) [9.8-46.7]	6 (50.0) [21.1-78.9]	2 (22.2) [2.8-60.0]	9 (36.0) [18.0-57.5]
PFS[b]							
Median [95% CI], mo	2.1 [1.9-2.1]	2.0 [1.7-2.1]	10.3 [2.1-NR]	2.1 [1.8-2.1]	2.6 [1.6-6.2]	1.8 [0.9-10.0]	2.1 [1.9-4.2]
6-mo rate, %	25.0	18.5	50.0	20.8	33.3	22.2	28.0
OS							
Median [95% CI], mo	9.9 [6.5-22.4]	9.6 [5.1-23.0]	21.2 [8.7-NR]	8.1 [4.4-23.0]	16.5 [8.7-26.1]	7.5 [1.2-24.6]	11.4 [6.3-22.4]
12-mo rate, %	44.4	40.7	66.7	33.3	66.7	33.3	48.0
18-mo rate, %	38.7	32.9	66.7	33.3	50.0	33.3	39.6
24-mo rate, %	27.6	27.4	25.0	25.0	33.3	22.2	28.9
DOR[b]							
Median [95% CI], mo	10.3 [4.3-NR]	-					

[a]Central PD-L1 assessed with Dako IHC 22C3 pharmDx for 27 patients. Local results of six patients were included due to nonevaluable central assessment results.
[b]Per iRECIST.
CI, confidence interval; DCR, disease control rate; IHC, immunohistochemistry; iRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapies; ITT, intent-to-treat; NR, not reached; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1); PFS, progression-free survival; TPS, tumor proportion score.

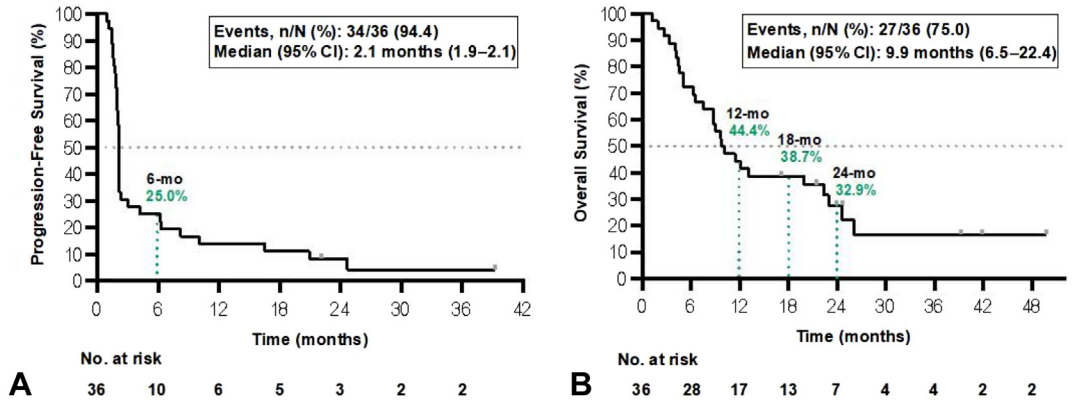

Figure 1. (*A*) PFS and (*B*) OS in the ITT population. CI, confidence interval; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

treatment for more than 16 months. The confirmed ORR was low at 8.3% but compared with the ORR of 11.2% with docetaxel as a traditional standard-of-care treatment in the second-line setting.[12] Notably, DCR was 33.3%, which is promising for the particular patient group in this study. In an exploratory analysis, DCR seemed to correlate with OS in this study, in line with previous systematic reviews[30,31]: median OS was 24.6 versus 7.0 months in patients with controlled disease versus no disease control as the best objective response. Thus, DCR may be a more informative end point for this therapy in this challenging anti–PD-(L)1-refractory setting.

The combination of efti plus pembrolizumab was well tolerated, with grade 3 TRAEs reported in 11.1% of patients and no TEAEs or TRAEs leading to permanent discontinuation of study treatment. No new safety signals were identified. Local injection site reactions were reported in 38.9% of patients, most of which were mild in intensity, an incidence in line with clinical experience with efti.[19,20]

Taken together, the findings of this study compare favorably with historical data regarding standard-of-care chemotherapy in a comparable patient population, namely second-line chemotherapy with docetaxel. Pooled median OS in patients who received docetaxel in the CheckMate 017 and 057 trials was 8.1 months,[12] whereas median OS with efti plus pembrolizumab was 9.9 months; this difference represents a relative survival benefit of 22% with the combination, above the 20% threshold generally agreed by the American Society of Clinical Oncology Cancer Research Committee to define a clinically meaningful improvement in median OS.[32] Of note, the proportion of patients alive at 24 months after treatment with efti plus

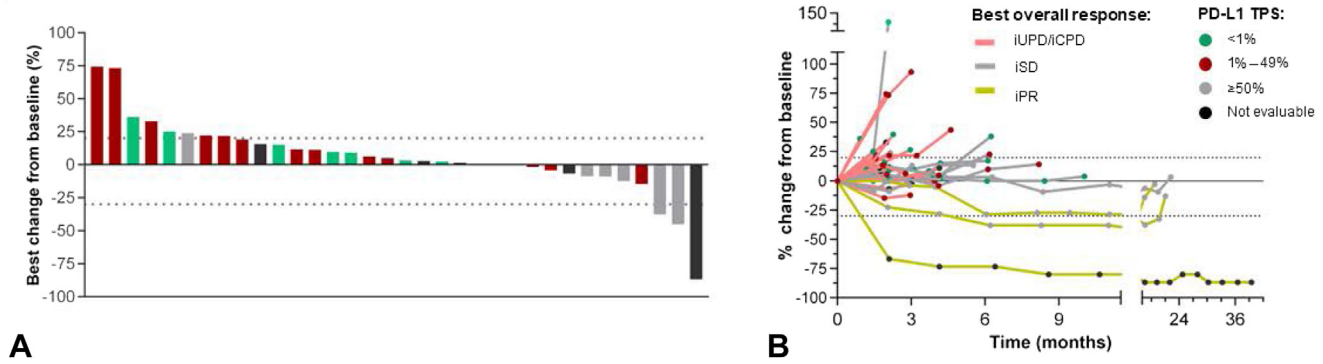

Figure 2. (*A*) Waterfall plot and (*B*) spider plot of (best) change from baseline by PD-L1 TPS in the ITT population. PD-L1 TPS is displayed using the following code: mid-gray bars or dots represent 50% or higher, red bars or dots 1% to 49%, and green bars or dots less than 1%; black bars or dots reveal patients nonevaluable for this parameter. The best overall response by iRECIST is displayed using the following code: yellow lines represent iPR, mid-gray lines iSD, and pink lines iCPD or iUPD; black lines indicate any ongoing patients. Notes: N = 34; one patient with nonevaluable postbaseline assessment, another patient died due to serious AE before any postbaseline assessment. Central PD-L1 was assessed with Dako IHC 22C3 pharmDx for 27 patients. Local results of six patients were included due to nonevaluable central assessment results. Responses were per iRECIST. AE, adverse event; iCPD, complete progression; iCPD or iUPD, confirmed or unconfirmed progressive disease according to iRECIST; IHC, immunohistochemistry; iPR, partial response according to iRECIST; iPR, partial response; iRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapies; iSD, stable disease according to iRECIST; ITT, intent-to-treat; iUPD, unconfirmed progression; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

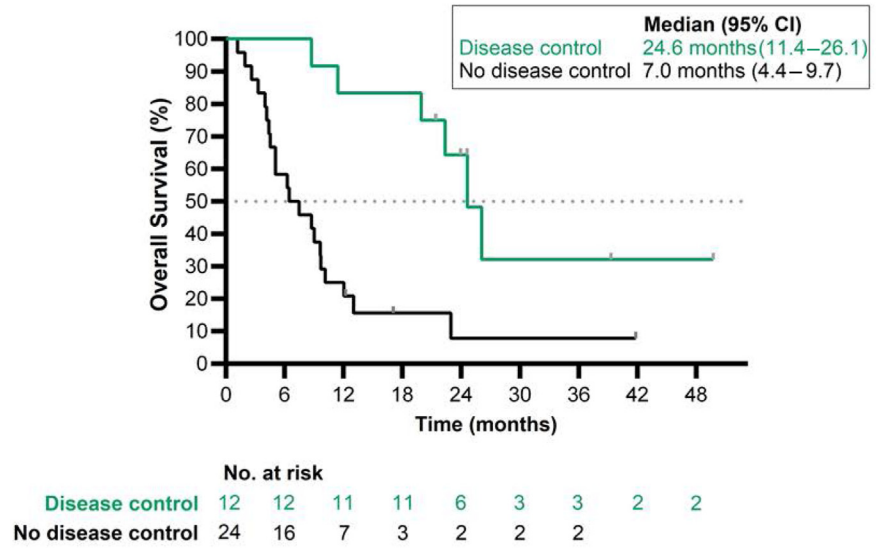

Figure 3. Observed correlation between disease control and OS. Kaplan-Meier plot of OS broken down by patients' best objective response. "Disease control" = best objective responses of CR, PR, or SD; "No disease control" = best objective response of PD or not evaluable. CI, confidence interval; CR, complete response; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

pembrolizumab was more than double that observed after treatment with docetaxel in the pooled analysis of the CheckMate 017 and 057 trials: 27.6% and 13.5%, respectively, indicating a long-lasting effect in case of disease control.[12] In terms of toxicity, in the CheckMate 017 and 057 trials, TRAEs of grade 3–4 were reported in 54–55% of patients with docetaxel, compared with just 11.1% of patients treated with efti plus pembrolizumab.[13,14]

In line with the literature,[4–7] tumor PD-L1 expression seemed to be a meaningful predictor of efficacy of anti–PD-1-based therapy; exploratory analyses indicated that ORR and DCR were numerically higher, and median PFS

Table 3. Overall Summary of AEs

	Safety Population, N = 36 n (%)			
	Any Grade	Grade 3	Grade 4	Grade 5
Frequent TEAEs (incidence ≥15%) by PT[a]				
Decreased appetite	13 (36.1)	0	0	0
Dyspnea	13 (36.1)	2 (5.6)	0	1 (2.8)[b]
Cough	11 (30.6)	0	0	0
Asthenia	8 (22.2)	1 (2.8)	0	0
Fatigue	8 (22.2)	1 (2.8)	0	0
Arthralgia	7 (19.4)	1 (2.8)	0	0
Edema peripheral	6 (16.7)	0	0	0
Nausea	6 (16.7)	0	0	0
Pruritis	6 (16.7)	1 (2.8)	0	0
Weight decreased	6 (16.7)	0	0	0
Frequent TRAEs (incidence ≥10%) by PT[c]				
Asthenia	5 (13.9)	0	0	0
Injection site erythema	5 (13.9)	0	0	0
Injection site pain	5 (13.9)	0	0	0
Pruritis	5 (13.9)	1 (2.8)	0	0
Arthralgia	4 (11.1)	0	0	0
Injection site reaction	4 (11.1)	0	0	0
Local injection site reactions (incidence ≥10%)				
Any	14 (38.9)	0	0	0

[a]All events regardless of relationship to either study drug.
[b]Fatal acute respiratory failure considered unrelated to both efti and pembrolizumab.
[c]Any event at least possibly related to efti or pembrolizumab.
AE, adverse events; efti, eftilagimod alpha; PT, preferred term; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

and OS numerically longer, in patients with high PD-L1 expression as compared with those with low or negative PD-L1 expression. Similarly, additional exploratory analyses confirmed that the type of resistance to first-line NSCLC therapy can be indicative of response, with median OS being numerically longer in patients with secondary versus primary resistance. Primary resistant patients do not respond to initial treatment with ICIs, mainly due to a lack of recognition by T cells caused by the absence of tumor antigens. In secondary resistance, patients relapse after a period of initial response as a consequence of the appearance of tumor evasion mechanisms,[33] and those patients may be more amenable to APC activation through efti.

As an APC activator, efti acts systemically to enhance the activation of dendritic cells and monocytes, thereby facilitating optimal antigen presentation to $CD4^+$ and $CD8^+$ T cells. This boosts the capacity of immune cells to recognize tumor cells and prime an efficient effector response. As efti does not target the tumor directly, the signal observed in this study is unlikely to be indication-specific; hence, further clinical development may also consider other indications in addition to NSCLC.

Combination therapies continue to be clinically evaluated with the goal of enhancing overall antitumor activity, to provide better treatment for patients with large tumor burden. Various trials have tested ICI doublet combinations (e.g., an anti–CTLA-4, anti–LAG-3, or anti-TIGIT with an anti–PD-(L)1), exploring the hypothesis that blocking two inhibitory receptors on T cells could be better than blocking just one. Meta-analysis of such trials has indicated some efficacy benefit of ICI doublet therapy over other approaches (ICI monotherapy, chemotherapy) in advanced NSCLC, although potentially to the detriment of patient safety, with an observed higher incidence of TRAEs of grade 3 or higher.[34] Most of the studies included in the above mentioned meta-analysis assessed ICI doublet therapy in a first-line NSCLC setting. A recent study that assessed the combination of anti-TIGIT antibody, vibostolimab, with pembrolizumab in an overall patient population (similar to the present study) observed similar results[35]: an ORR of 3%, DCR of 45%, median PFS of two months, median OS of 13 months, and grade 3 or higher TRAEs in 15% of the patients in that study.

The present study had a number of limitations, namely its lack of randomization and a control group, and a small sample size. Nonrandomized controlled trials are common in phase 2 oncology research and provide valuable preliminary insights into treatment efficacy and safety.[36] A small sample size generally has limited statistical power to detect clinically meaningful effects and to allow robust subgroup analyses. These findings are hypothesis-generating, and the need for further studies is warranted to fully understand the therapeutic potential of this treatment combination in a larger population of PD-(L)1-refractory patients, particularly comparing PD-L1 high versus PD-L1 low patients or primary- versus secondary-resistance.

Conclusion

The addition of the APC activator efti administered alongside anti-PD-1 therapy after patients progressed on the first-line anti–PD-(L)1-based therapy was well tolerated and revealed promising results in terms of DCR and OS, especially in subgroups of patients with high PD-L1 expression and secondary resistance to first-line NSCLC therapy. Overall, these data support further clinical investigation in a randomized setting of this innovative combination targeting both APCs (efti) and T cells (pembrolizumab) in an anti–PD-(L)1-refractory patient population.

CRediT Authorship Contribution Statement

Matthew G. Krebs: Investigation, Validation, Writing - review & editing.

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Christian Mueller: Conceptualization, Data curation, Formal analysis, Supervision, Validation, Writing - review & editing.

Frederic Triebel: Conceptualization, Formal analysis, Funding acquisition, Supervision, Validation, Writing - review & editing

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Ethics Approval and Consent to Participate

This study was conducted according to the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, the principles of informed consent, and the requirements of the public registration of clinical trials. Written informed consent was obtained from each patient before screening. The protocol was approved by the institutional ethics committee, and the study was monitored by a data monitoring committee.

Availability of Data and Material

Most data relevant to the study are included in the article or uploaded as supplementary information. All data are available on reasonable request. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript.

Disclosure

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100725.

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