ORIGINAL ARTICLE

Randomized open-label controlled study of cancer vaccine OSE2101 versus chemotherapy in HLA-A2-positive patients with advanced non-small-cell lung cancer with resistance to immunotherapy: ATALANTE-1 ☆

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Background: Patients with advanced non-small-cell lung cancer (NSCLC) treated with immune checkpoint blockers (ICBs) ultimately progress either rapidly (primary resistance) or after durable benefit (secondary resistance). The cancer vaccine OSE2101 may invigorate antitumor-specific immune responses after ICB failure. The objective of ATALANTE-1 was to evaluate its efficacy and safety in these patients.

Patients and methods: ATALANTE-1 was a two-step open-label study to evaluate the efficacy and safety of OSE2101 compared to standard-of-care (SoC) chemotherapy (CT). Patients with human leukocyte antigen (HLA)-A2-positive advanced NSCLC without actionable alterations, failing sequential or concurrent CT and ICB were randomized (2 : 1) to OSE2101 or SoC (docetaxel or pemetrexed). Primary endpoint was overall survival (OS). Interim OS futility analysis was planned as per Fleming design. In April 2020 at the time of interim analysis, a decision was taken to prematurely stop the accrual due to coronavirus disease 2019 (COVID-19). Final analysis was carried out in all patients and in the subgroup of patients with ICB secondary resistance defined as failure after ICB monotherapy second line ≥12 weeks.

Results: Two hundred and nineteen patients were randomized (139 OSE2101, 80 SoC); 118 had secondary resistance to sequential ICB. Overall, median OS non-significantly favored OSE2101 over SoC {hazard ratio (HR) [95% confidence interval (CI)] 0.86 [0.62-1.19], $P = 0.36$}. In the secondary resistance subgroup, OSE2101 significantly improved median OS versus SoC [11.1 versus 7.5 months; HR (95% CI) 0.59 (0.38-0.91), $P = 0.017$], and significantly improved

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post-progression survival (HR 0.46, $P = 0.004$), time to Eastern Cooperative Oncology Group (ECOG) performance status deterioration (HR 0.43, $P = 0.006$) and Quality of Life Questionnaire Core 30 (QLQ-C30) global health status compared to SoC ($P = 0.045$). Six-month disease control rates and progression-free survival were similar between groups. Grade ≥ 3 adverse effects occurred in 11.4% of patients with OSE2101 and 35.1% in SoC ($P = 0.002$).

Conclusions: In HLA-A2-positive patients with advanced NSCLC and secondary resistance to immunotherapy, OSE2101 increased survival with better safety compared to CT. Further evaluation in this population is warranted.

Key words: cancer vaccine, advanced NSCLC, immunotherapy resistance, quality of life

INTRODUCTION

Over the last decade, the therapeutic strategy of treatment-naïve patients with advanced non-small-cell lung cancer (NSCLC) lacking oncogenic drivers has been revolutionized by the approval of immune checkpoint blockers (ICBs), administered as monotherapy or in combination, including dual-immunotherapy approaches.[1] However, ultimately, the majority of patients will relapse, and this resistance to chemotherapy (CT)-ICB represents an unmet medical need in the absence of any registered treatments and with only limited data from randomized studies. CT remains the standard of care (SoC) in this setting, with options being those CTs not administered in the first line.[2,3] In Europe, after ICB failure, docetaxel is the preferred choice and usually administered as monotherapy.[4-6] Alternatives to single CT (generally docetaxel) could be doublets of CT in combination with antiangiogenic agents such as nintedanib,[7] ramucirumab[8] and bevacizumab,[9] but these strategies compared to docetaxel monotherapy in the pre-ICB era did not improve overall survival (OS) or lead to a modest improvement in OS.

Multiple clinical trials are evaluating novel strategies based on immune stimulatory agents other than anti-programmed death (ligand)-1 [PD(L)-1], or immunotherapies acting on T-cell priming such as vaccines, or other drugs including antiangiogenic treatments or antibody drug conjugates generally compared to single-agent CT.[10-14]

Biologically, secondary resistance to ICB can occur through different mechanisms, such as an insufficiently immunogenic tumor, alterations in antigen presentation, inefficient activation and infiltration of T cells in the tumor microenvironment, exhausted tumor-specific CD8+ T cells with a lack of effector function, such as interferon-γ (IFN-γ) production,[15] or increased immunosuppressive cellular subsets in the tumor microenvironment, including T-regulatory cells, myeloid-derived suppressor cells and M2 macrophages.[16-19]

OSE2101 is a T-specific immunotherapy designed to induce cytotoxic T lymphocytes (CTLs) against five tumor-associated antigens (TAAs) frequently overexpressed in NSCLC (HER-2/neu, CEA, MAGE 2, MAGE 3 and p53). This therapeutic vaccine is composed of nine synthetic peptides from these TAAs that are presented in lung cancer cells by the human leukocyte antigen (HLA)-A2 phenotype, which occurs in up to 45% of the population.[20] A 10th pan-DR peptide has been added to elicit the T helper lymphocyte immune response. These multi-chemically modified epitopes from the five TAAs in the OSE2101 cancer vaccine represent an ideal target to break immune tolerance in resistant tumors. They generate a novel and specific activation of CTLs that attack recognized tumor cells, as measured by increased IFN-γ production.[21] The vaccine promotes an increase in TAA presentation, the priming and activation of T cells and the recognition of cancer cells expressing the TAA, thereby invigorating antitumor-specific immune responses (specific CD8+ T cells) and possibly the overall T response through CD4+ activation. In the pre-ICB era, among 64 heavily pretreated patients with HLA-A2-positive platinum-refractory advanced NSCLC, OSE2101 gave a median OS of 17.3 months and a 1-year OS of 60%. Along with the clinical activity, OSE2101 induced a CTL immune response to at least one epitope after vaccination in 91% of patients. Overall, in advanced NSCLC, longer survival was significantly associated with a higher number of immune responses induced by OSE2101 vaccine.[22,23] Based on these promising data and the potential capability of OSE2101 to be synergistic or complementary to ICB in inducing strong CTL responses, the therapeutic benefit of OSE2101 merited further evaluation in patients with HLA-A2-positive advanced NSCLC who are resistant to ICB. The phase III ATALANTE-1 trial assessed the efficacy and safety of OSE2101 versus standard CT in patients with progressive disease (PD) after ICB.

PATIENTS AND METHODS

Patients

Eligible patients had received one line of ICB therapy for locally advanced or metastatic *EGFR/ALK*-negative NSCLC, given sequentially (second line) or combined with platinum-based CT (first line) with disease progression (measurable and non-measurable disease), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 and central confirmation of HLA-A2 positivity in total blood. Patients with baseline brain metastases were eligible if asymptomatic.

Key exclusion criteria were small-cell lung cancer or mixed NSCLC histology, spinal cord compression, leptomeningeal carcinomatosis, interstitial lung disease, autoimmune disease, immunodeficiency, previous cancer within 5 years, severe acute or chronic medical or psychiatric conditions or active type B or C hepatitis. Patients were not eligible if ICB was stopped due to toxicity.

The study was approved by an independent ethics committee for each site, and all patients provided written informed consent.

Trial design and treatment

In this open-label, international ATALANTE-1 trial (NCT02654587), patients were centrally randomized (initially 1 : 1, and then 2 : 1 after protocol amendment 4 in December 2017) to OSE2101 or investigator's choice of SoC CT with pemetrexed or docetaxel. OSE2101 was administered at 5 mg, 1 ml subcutaneously on day 1 every 3 weeks for six cycles, then every 8 weeks until 1 year of treatment and thereafter every 12 weeks. Pemetrexed was administered at 500 mg/m^2 intravenously over 10 min, and docetaxel at 75 mg/m^2 intravenously over 1 h, both every 3 weeks with premedication, according to international guidelines. Patients were stratified by histology (non-squamous versus squamous), best response to first-line treatment [complete response (CR) or partial response (PR) versus stable disease (SD) or PD] and line of treatment with prior ICB (first-line ICB when combined with platinum-based CT versus second-line ICB when administered as sequential treatment).

Treatment was continued until unequivocal PD by RECIST 1.1, unacceptable toxicity or consent withdrawal. Crossover to OSE2101 from the SoC arm at the time of PD was not allowed as per protocol. In the event of toxicity, dose reduction of pemetrexed or docetaxel was recommended according to the manufacturer's guidelines. Dose reduction of OSE2101 was not permitted. OSE2102 and CT administration could be delayed until recovery to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) grade ≤1 or baseline levels. If pseudo-progression, delayed response or disease progression occurred, OSE2101 could be continued if the patient experienced clinical benefit. Tumor imaging (computed tomography scan or magnetic resonance imaging) was carried out at baseline and every 6 weeks until PD. Tumor response by RECIST 1.1 was assessed by the investigator. Quality of life (QoL) questionnaires [European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and lung cancer (LC)-13], adverse events (AEs, assessed according to NCI CTCAE v5.0) and laboratory tests were collected before each treatment administration until PD. Survival and treatments administered after investigational treatment discontinuation were recorded. Patient follow-up was discontinued on 15 January 2021 when the last patient had at least 9 months' follow-up.

Statistical analysis

Sample size. The study was carried out according to a two-step adaptive design. Step 1 was a futility analysis (Fleming design) with a primary objective to evaluate the 12-month OS rate in the OSE2101 arm with H0 <25% and H1 >40% in patients having been followed up for survival for at least 12 months. The primary objective of step 2 was to demonstrate the superiority of OSE2101 over SoC in terms of median OS. A total of 278 events among 363 patients was initially required to reach a power of 80% for the log-rank test at the 5% significance level with a two-sided test, assuming a median OS of 7 months for SoC and 10 months for OSE2101 [hazard ratio (HR) 0.7].

At the time of the planned interim analysis (cut-off of February 2020) when the first 103 patients reached 12 months of follow-up, decision was taken by the sponsor to prematurely stop the accrual due to the coronavirus disease 2019 (COVID-19) pandemic which was rapidly expanding with a strong concern about its impact on patient safety and data integrity. Thereafter, treatment and follow-up continued for the ongoing 219 patients already randomized.

Due to this early accrual discontinuation, the data were unblinded and analyzed in the first 103 patients. A subgroup of interest from a stratification factor was identified based on a clinical and biological rationale: patients who received sequential CT-ICB and showed secondary resistance to ICB, defined as PD after second-line ICB monotherapy of at least 12 weeks.

Considering the final sample size lower than expected (219 of 363 patients) and the identification of this subgroup of interest, the statistical hypotheses and the analysis plan were revised before the final database lock, proposing patients with secondary resistance as the primary population (main analysis), assuming a median OS of 7 months in the SoC group and of 11 months in the OSE2101 group, an HR of 0.55 and a total of 90 events, for a power of 80%, and a two-sided log-rank test at a 5% two-sided level. The intention-to-treat (ITT) population (219 randomized patients) was considered for sensitivity analysis with a decrease of the power from 80% to 62% due to the reduction of the sample size.

Endpoints. The primary endpoint was OS, defined as the time from randomization to death from any cause. OS was estimated using the Kaplan—Meier method and compared between arms using a two-sided log-rank test (primary) and then a Cox regression model (secondary), stratified for the randomization factors. The impact of COVID-19 on OS was evaluated by a time-dependent analysis testing the heterogeneity of randomization periods with or without COVID-19. Patients included before February 2019 and followed up for 12 months were attributed to the 'pre-COVID-19 pandemic' period (same cut-off as for step 1 interim analysis), and patients included after February 2019 and followed up until January 2021 were attributed to the 'during-COVID-19 pandemic' period.[24,25]

Secondary endpoints included post-progression survival (PPS) (defined as the time from the earliest date of progression according to RECIST 1.1 until death), time to worsening of ECOG PS (defined as the time from randomization to the earliest date when ECOG PS was >1), QLQ-C30 global health status, QLQ-C30 functional scores, QLQ-C30 symptom scores, QLQ-LC13 symptom scores, disease control rate (DCR) at 6 months, with DCR defined as the number of patients with CR, PR or SD at 6 months, and

progression-free survival (PFS) defined as the time from randomization to the earliest date of progression according to RECIST 1.1. Secondary efficacy endpoints were tested at a 5% significance level using the above hierarchical order to control the overall type I error. Investigator-assessed objective response rate (ORR) was an exploratory endpoint. Time to event endpoints were analyzed as for OS.

For QoL, scores were derived from the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaire items according to the respective scoring manuals. For each domain or symptom, mean changes from baseline to the last cycle with >25% of the total number of included patients were reported. Changes in scores from baseline until treatment discontinuation were assessed using a mixed-effects model for repeated measures analysis with the patient as the random effect, treatment, visit and treatment-by-visit interaction as explanatory variables and baseline score as covariates. Least squares mean differences were reported and plotted with corresponding 95% confidence intervals (CIs).

RESULTS

Between February 2016 and April 2020, 219 patients from 9 countries were randomly assigned to receive OSE2101 ($n = 139$) or SoC ($n = 80$), representing the ITT population. Of them, 53.8% (118/219) met the secondary resistance

criterion (80 patients with OSE2101; 38 patients with SoC) and were considered the primary population (Figure 1).

Patient characteristics were well balanced between treatment arms in the ITT population (Table A1) and the primary population (Table 1), with no major differences. In the primary population, median age was 65 years and 74% were male. One-third of patients had squamous NSCLC and 9% were never smokers (all tobacco); 19% presented with ≥3 metastatic sites, and 16% and 19% of patients had brain and/or liver metastases, respectively. Prior ICB treatment lasting 12-24 weeks was reported in 42% of patients, and >24 weeks in 58% of patients. In the SoC arm, 81% of patients received docetaxel, and 19% received pemetrexed.

Interim analysis and efficacy in the ITT population

The planned interim analysis (cut-off 26 February 2020) in the 103 patients for 80 (78%) events with at least 1-year follow-up showed a 12-month OS rate of 46.0% (95% CI 33.4% to 59.1%) in the OSE2101 arm, rejecting the null hypothesis of 25%. In the SoC arm, the 12-month OS rate was 36% (95% CI 21% to 54%).

In the final analysis (cut-off 15 January 2021) in the 219 patients for 181 events (83%), median OS was 8.8 months (95% CI 7.6-10.8 months) with OSE2101 versus 8.3 months (95% CI 6.5-9.8 months) in the SoC arm (HR 0.86, 95% CI
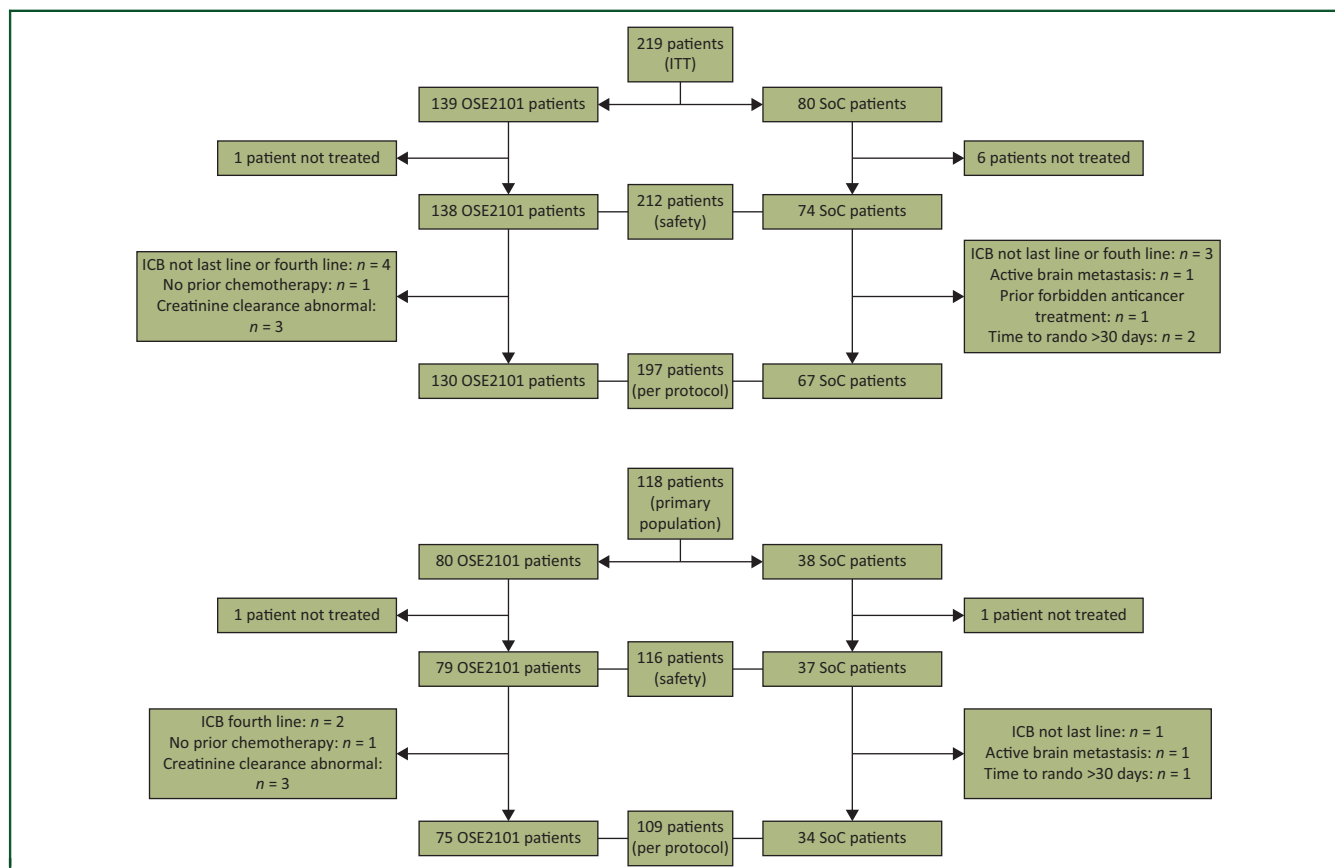
Figure 1. CONSORT diagram of patient disposition, showing the total population randomized to OSE2101 or standard of care (SoC) (upper panel), and the primary population of secondary resistance to ICB (lower panel).
ICB, immune checkpoint blocker; ITT, intention-to-treat; rando, randomization; SoC, standard of care (docetaxel or pemetrexed).

Table 1. Baseline demographics and patient and disease characteristics for NSCLC patients with secondary resistance to ICB

		OSE2101 (n = 80)	SoC (n = 38)	Total (n = 118)
Age (years)	Mean (SD)	65.4 (8.57)	64.6 (8.38)	65.2 (8.49)
	Median	65.0	64.0	64.5
	Min-max	44-82	48-81	44-82
Gender	Male	60 (75.0%)	27 (71.1%)	87 (73.7%)
	Female	20 (25.0%)	11 (28.9%)	31 (26.3%)
Race	White	70 (93.3%)	37 (100.0%)	107 (95.5%)
	Black or African American	3 (4.0%)	0	3 (2.7%)
	Asian	2 (2.7%)	0	2 (1.8%)
Ethnicity	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	78 (100.0%)	37 (100.0%)	115 (100.0%)
Smoking status	Never smoker	7 (8.8%)	4 (10.5%)	11 (9.3%)
	Ex-smoker	59 (73.8%)	22 (57.9%)	81 (68.6%)
	Current smoker	14 (17.5%)	12 (31.6%)	26 (22.0%)
Line of prior ICB treatment	First-line ICB	0	0	0
	Second-line ICB	79 (98.8%)	38 (100.0%)	117 (99.2%)
	Third-line ICB	1 (1.3%)	0	1 (0.8%)
Histology	Squamous	28 (35.0%)	11 (29.7%)	39 (33.3%)
	Non-squamous	52 (65.0%)	26 (70.3%)	78 (66.7%)
Previous pemetrexed treatment	Yes	40 (50.0%)	21 (55.3%)	61 (51.7%)
Best response to ICB	Complete response	1 (1.3%)	1 (2.8%)	2 (1.8%)
	Partial response	21 (26.9%)	7 (19.4%)	28 (24.6%)
	Stable disease	26 (33.3%)	14 (38.9%)	40 (35.1%)
	Progressive disease	30 (38.5%)	14 (38.9%)	44 (38.6%)
Time since end of previous ICB (weeks)	Mean (SD)	6.69 (4.32)	7.00 (3.95)	6.79 (4.19)
	Median	5.57	6.00	5.71
	Min-max	2.4-22.1	2.1-19.7	2.1-22.1
Duration of ICB	>12-24 weeks	35 (43.8%)	14 (36.8%)	49 (41.5%)
	>24 weeks	45 (56.3%)	24 (63.2%)	69 (58.5%)
Disease stage at entry	III	8 (10.0%)	3 (7.9%)	11 (9.3%)
	IV	72 (90.0%)	35 (92.1%)	107 (90.7%)
Brain metastases at entry	Yes	14 (17.5%)	5 (13.2%)	19 (16.1%)
Liver metastases at entry	Yes	16 (20.0%)	6 (15.8%)	22 (18.6%)
Number of different metastasis locations	n	78	38	116
	0	8 (10.3%)	5 (13.2%)	13 (11.2%)
	1	31 (39.7%)	16 (42.1%)	47 (40.5%)
	2	25 (32.1%)	9 (23.7%)	34 (29.3%)
	3	14 (17.9%)	8 (21.1%)	22 (19.0%)
ECOG PS at baseline	0	32 (40.0%)	11 (28.9%)	43 (36.4%)
	1	48 (60.0%)	27 (71.1%)	75 (63.6%)
PD-L1	Positive	25 (31.3%)	7 (18.4%)	32 (27.1%)
	Negative	32 (40.0%)	16 (42.1%)	48 (40.7%)
	Unknown	23 (28.8%)	15 (39.5%)	38 (32.2%)
Baseline LDH classification	>ULN	23 (32.4%)	14 (43.8%)	37 (35.9%)
dNLR at baseline	≥3	25 (32.1%)	16 (42.1%)	41 (35.3%)

Data are shown for number of patients (%) unless otherwise stated.
ALK, anaplastic lymphoma kinase; dNLR, derived neutrophil-to-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ICB, immune checkpoint blocker; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PS, performance status; SD, standard deviation; SoC, standard of care (docetaxel or pemetrexed); ULN, upper limit of normal.

0.62-1.19, $P = 0.36$). Median OS in the subgroup analyses for the overall population is shown in Figure A1.

The impact of COVID-19 pandemic on OS was assessed. Median OS in the pre-COVID-19 period ($n = 103$) was 9.4 months (95% CI 8.0-12.2 months), and significantly decreased to 8.1 months (95% CI 6.5-9.1 months) (HR 1.36, 95% CI 1.00-1.86, $P = 0.048$) in the during-COVID-19 period ($n = 116$), with 12-month OS rates of 44.4% (95% CI 31.0% to 57.0%) and 33.2% (95% CI 21.5% to 45.2%), respectively (Figure A2).

Efficacy in patients with secondary resistance to ICB

At the final analysis (cut-off 15 January 2021), after a median follow-up of 24.8 months (95% CI 15.7-30.3 months), 95 (80.5%) deaths were observed in the primary population. Median OS was 11.1 months (95% CI 8.6-13.5 months) in the OSE2101 arm and 7.5 months (95% CI 4.7-10.3 months) in the SoC arm (HR 0.59, 95% CI 0.38-0.91, $P = 0.017$) (Figure 2). The 12-month OS rate was 44.4% (95% CI 32.8% to 54.6%) in the OSE2101 arm versus 27.5% (95% CI 14.3% to 42.4%) in the SoC arm. A consistent survival benefit of OSE2101 over SoC was shown across all predefined subgroups (Figure 3).

Post-progression treatment was administered to 69% of patients ($n = 55$) in the OSE2101 arm and 42% ($n = 16$) in the SoC arm in the primary population (Table A2, including a description of therapy types). Median PPS was 7.7 months (95% CI 5.6-9.7 months) in the OSE2101 arm and 4.6 months (95% CI 3.1-5.8 months) in the SoC arm (HR 0.46, 95% CI 0.27-0.79, $P = 0.004$) (Figure 4).

To address a possible bias on OS due to a higher proportion of patients who received a post-progression treatment in the OSE2101 arm, OS was estimated by Kaplan—Meier and compared between treatment arms in the subgroups of patients with and without post-progression treatment. Median OS was 13.5 months in the OSE2101 arm versus 10.6 months in the SoC arm (HR 0.71, 95% CI 0.38-1.30) in patients who received a post-progression treatment, and was 6.3 months in the OSE2101 arm versus 4.6 months in the SoC arm (HR 0.76, 95% CI 0.41-1.41), for those who did not receive a post-progression treatment. The difference in OS favored the OSE2101 arm irrespective of post-progression treatment (Figure A3).

The time to worsening of ECOG PS was markedly prolonged in the OSE2101 arm compared to the SoC arm (9.0 versus 3.3 months; HR 0.43, 95% CI 0.23-0.80, $P = 0.006$) (Figure 5).

At the time of analysis, 113 (95.8%) PFS events had been observed. Median PFS was similar in the OSE2101 and SoC arms (HR 1.28, 95% CI 0.82-2.0, $P = 0.29$), at 2.7 months (95% CI 1.61-2.79 months) and 3.0 months (95% CI 2.6-4.5 months), respectively (Figure A4).

The exploratory endpoint of investigator-assessed ORR was 7.7% (95% CI 2.9% to 16.0%) with OSE2101 and 18.4% (95% CI 7.7% to 34.3%) with SoC [odds ratio (OR) 0.33, 95% CI 0.10-1.11, $P = 0.07$] (Table A3). DCR at 6 months showed no difference between arms: 25% (95% CI 15.6% to 35.8%)
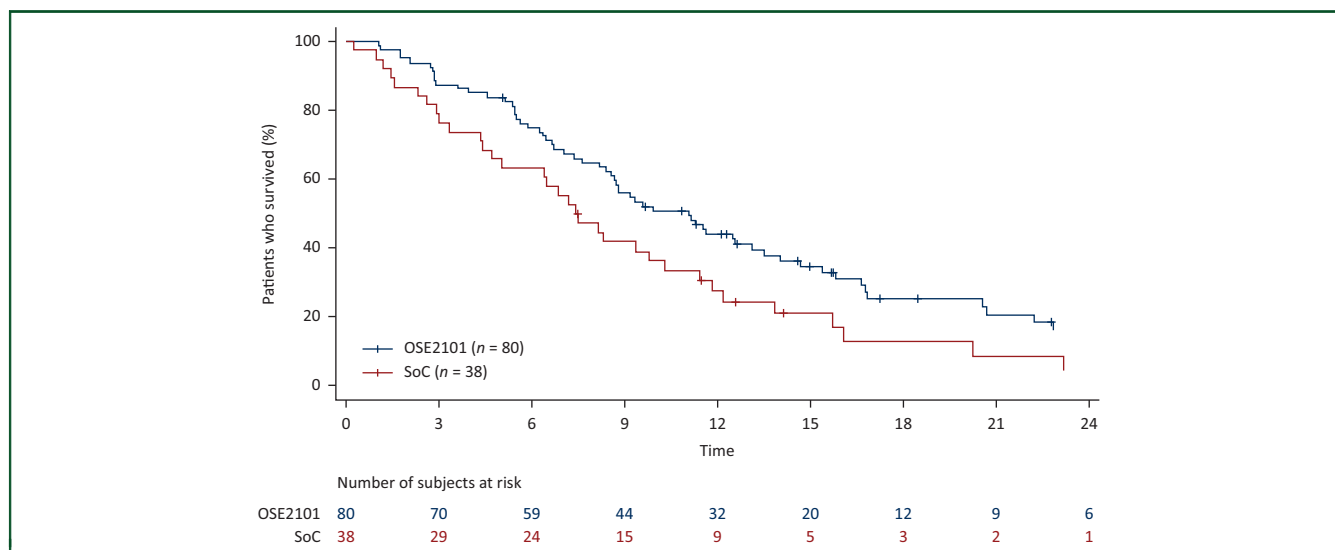
Figure 2. Overall survival estimates (Kaplan–Meier) of NSCLC patients with secondary resistance to ICB.
ICB, immune checkpoint blocker; NSCLC, non-small-cell lung cancer; SoC, standard of care.
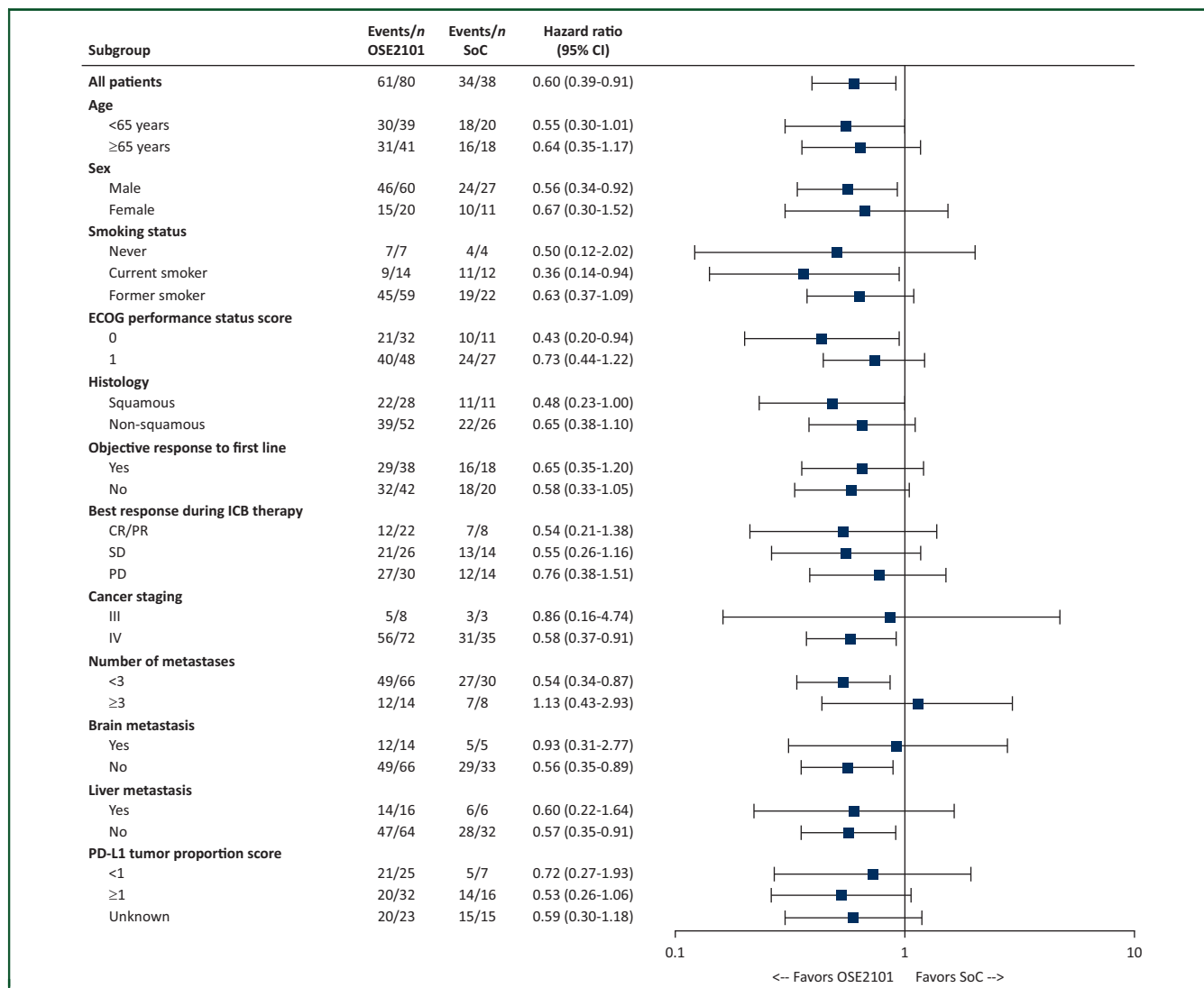
Figure 3. Subgroup analysis of overall survival in NSCLC patients with secondary resistance to ICB, using a two-sided log-rank test and a Cox regression model.
CR, complete response; ECOG, Eastern Cooperative Oncology Group; ICB, immune checkpoint blocker; NSCLC, non-small-cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; SoC, standard of care (docetaxel or pemetrexed).
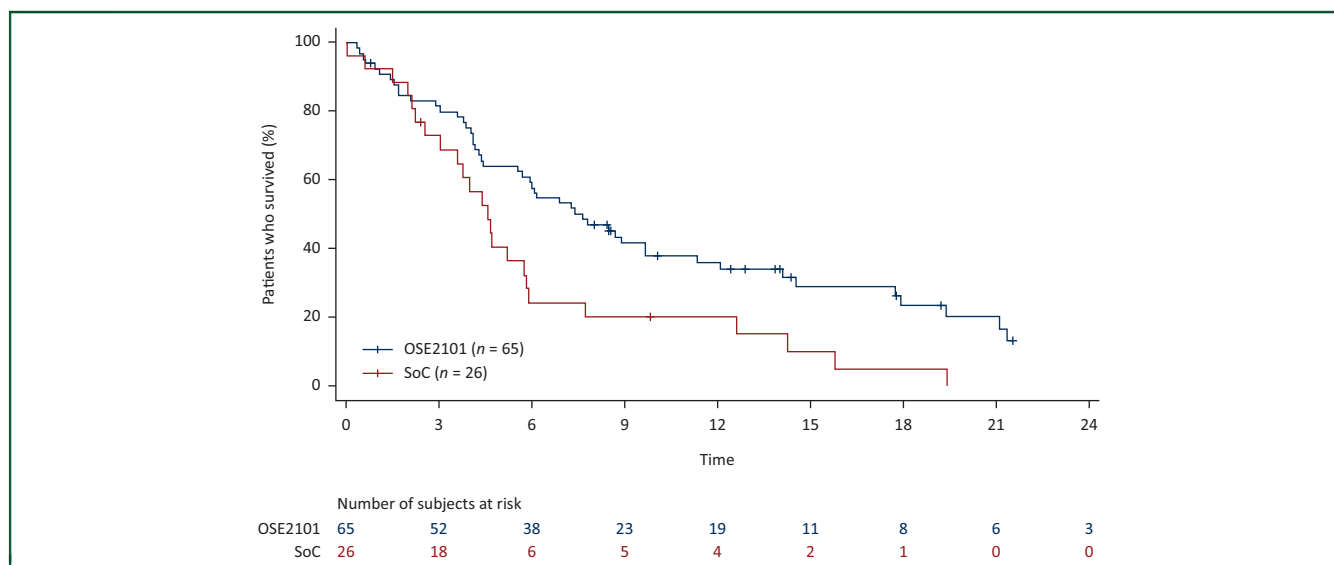
Figure 4. Post-progression survival estimates (Kaplan—Meier) in NSCLC patients with secondary resistance to ICB.
ICB, immune checkpoint blocker; NSCLC, non-small-cell lung cancer; SoC, standard of care (docetaxel or pemetrexed).

with OSE2101 versus 24% (95% CI 11.4% to 40.2%) with SoC (OR 1.09, 95% CI 0.43-2.75, $P = 0.87$).

The pattern of activity of OSE2101 was explored by describing OS in patients according to their best response with OSE2101 and with SoC CT. In patients with ORR during study treatments ($n = 13$), median OS was 11.2 months with OSE2101 and 13.8 months with SoC (HR 0.75, 95% CI 0.18-3.23); in patients with SD ($n = 45$), median OS was 13.1 months with OSE2101 and 9.4 months with SoC (HR 0.61, 95% CI 0.33-1.14); and in patients with disease progression ($n = 39$), median OS was 8.0 months with OSE2101 and 5.0 months with SoC (HR 0.45, 95% CI 0.19-1.04).

Deterioration in QLQ-C30 global health status relative to baseline was significantly higher with SoC compared to OSE2101 ($P = 0.045$), remaining stable for the first three cycles in the OSE2101 arm. All QLQ-C30 sub-scores were also better with OSE2101 than with SoC. Mean differences between OSE2101 and SoC were significant for the role

function ($P = 0.025$) and marginally significant for physical function ($P = 0.069$) (Figure 6). In terms of symptoms, patients had less mouth soreness ($P = 0.01$), dysphagia ($P = 0.01$), peripheral neuropathy ($P = 0.03$) and alopecia ($P < 0.001$) with OSE2101 than with SoC. The absolute change from baseline of dyspnea, cough, hemoptysis and pain (chest, arm/shoulder and other parts) was not significantly different between the study arms (Figure A5).

Of note, in the remaining ITT population ($n = 101$ out of 219 patients) of non-secondary resistance, median OS with OSE2101 was 7.3 months (95% CI 6.0-9.2 months), and 8.7 months (95% CI 6.3-11.7 months) in the SoC arm (HR 1.26, 95% CI 0.81-1.96, $P = 0.30$).

Safety in the primary population

Safety was evaluated in the 79 patients who received at least one dose of OSE2101 and 37 patients who received
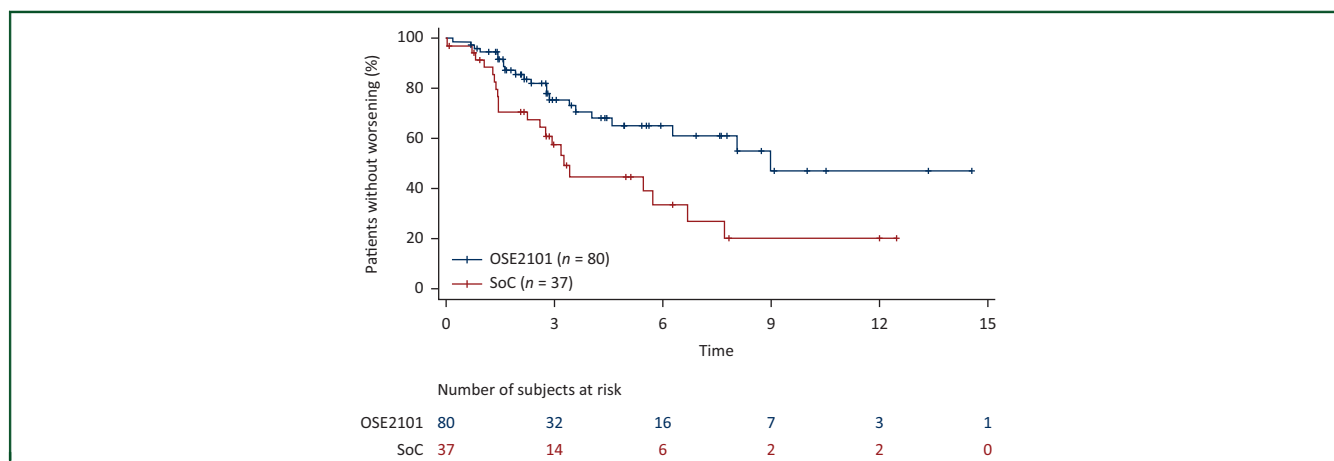
Figure 5. Time to worsening ECOG PS (Kaplan—Meier) in NSCLC patients with secondary resistance to ICB.
ECOG, Eastern Cooperative Oncology Group; ICB, immune checkpoint blocker; NSCLC, non-small-cell lung cancer; PS, performance status; SoC, standard of care (docetaxel or pemetrexed).
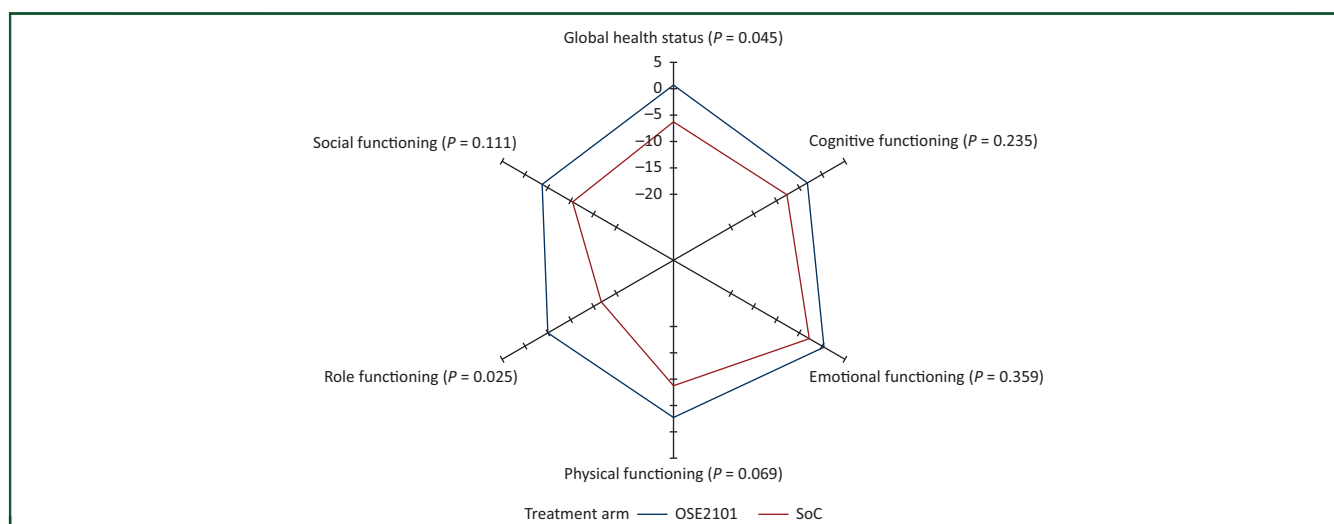
Figure 6. Absolute changes from baseline in the QoL scores of global health status, physical, role, emotional, social and cognitive functioning from the QLQ-C30 in the OSE2101 arm (blue line) and the standard-of-care arm (SoC; docetaxel or pemetrexed; red line) in NSCLC patients with secondary resistance to ICB.
ICB, immune checkpoint blocker; NSCLC, non-small-cell lung cancer; QoL, quality of life.

QLQ-C30 domain Least squares mean (95% CI)	OSE2101 (n = 70)	SoC (n = 25)	P value
Global health status	0.77 (−2.92 to 4.47)	−6.19 (−11.83 to −0.55)	0.045
Physical functioning	−2.74 (−6.21 to 0.73)	−8.75 (−14.17 to −3.33)	0.07
Role functioning	−5.09 (−10.60 to 0.43)	−16.78 (−25.29 to −8.28)	0.03
Emotional functioning	0.50 (−3.29 to 4.28)	−2.75 (−8.63 to 3.12)	0.36
Cognitive functioning	−3.20 (−7.18 to 0.78)	−7.64 (−13.86 to −1.43)	0.24
Social functioning	−3.82 (−8.30 to 0.66)	−10.43 (−17.23 to −3.64)	0.11

After the scoring process, scores range from 0 to 100. Highest scores correspond to a better quality of life for global health status (GHS) and functional scales; lowest scores correspond to a better quality of life for symptom scales. Least squares mean change estimates in each treatment group [and their 95% confidence interval (CI)] and P value of the overall treatment effect were assessed using mixed-effects model for repeated measures analysis with patient, treatment, visit and treatment-by-visit interaction as explanatory variables and baseline score as covariate.

SoC. The median duration of treatment was the same in the two arms at 63 days, with a range of 0-746 days with OSE2101 and 0-332 days with SoC. The median number of doses was the same in the two treatment arms: 4.0 (range 1-15) with OSE2101 versus 4.0 (range 1-16) with SoC.

Overall, 97% of patients (96% OSE2101, 100% SoC) experienced at least one AE, and the most frequent related AEs are presented in Table 2. Grade ≥3 drug AEs were observed in 35.4% (drug-related 11.4%) of patients with OSE2101, and 64.9% (drug-related 35.1%) in SoC (P = 0.002 and P = 0.003 for drug-related). The most frequent severe drug-related AEs were grade 3 pyrexia (n = 2, 2.5%) with OSE2101 and grade 3-4 neutropenia and asthenia (n = 6 each, 16.2%) with SoC (Table A4). There were no fatal AEs in either treatment arm and no grade 4 AEs in the OSE2101 arm. AEs led to study drug withdrawal for two patients (2.5%) treated with OSE2101 and four patients (10.8%) treated with docetaxel, none of which were related to study treatment.

The safety profile in the randomized population was consistent with that in patients with secondary resistance to ICB (Table A5). At least one AE was observed in 95% of patients with OSE2101 and 100% with SoC (P = 0.049). Grade ≥3 AEs (P < 0.0001), grade ≥3 drug-related AEs (P < 0.0001) and AEs leading to withdrawal from the study

(P = 0.017) were significantly less frequent in the OSE2101 arm than in the SoC arm (docetaxel in 86% of patients).

DISCUSSION

Despite the unprecedented outcomes achieved with ICB, almost half of these patients do not initially respond to this strategy (primary resistance), and furthermore, a subset of patients who initially respond later relapse developing secondary resistance.[26,27] The ATALANTE-1 study was designed to address an unmet medical need in patients with HLA-A2-positive advanced NSCLC without actionable alterations who have developed secondary resistance after a sequential CT-ICB approach, representing a highly challenging population. The novel cancer vaccine OSE2101 demonstrated improved OS over standard CT (docetaxel or pemetrexed), with a 3.6-month increase in median OS, without negatively impacting QoL. These data support that sparing CT strategies are feasible and safe in ICB secondary resistance population. The combination of docetaxel with nintedanib, ramucirumab or bevacizumab was not an option in the control arm as these drugs are not refunded in all the countries. Of note, most of ongoing or completed trials in the same setting use docetaxel single agent as the control arm (as an example LEAP-008—NCT03976375:

Table 2. Drug-related adverse events in >5% of NSCLC patients with secondary resistance to ICB

	OSE2101 (n = 79)		SoC (n = 37)		Total (n = 116)	
	n	(%)	n	(%)	n	(%)
Any adverse event	60	(75.9)	29	(78.4)	89	(76.7)
Pyrexia	15	(19.0)	3	(8.1)	18	(15.5)
Asthenia	13	(16.5)	15	(40.5)	28	(24.1)
Injection site induration	11	(13.9)	0		11	(9.5)
Arthralgia	9	(11.4)	1	(2.7)	10	(8.6)
Injection site reaction	9	(11.4)	0		9	(7.8)
Chills	7	(8.9)	0		7	(6.0)
Cytokine release syndrome	6	(7.6)	0		6	(5.2)
Fatigue	6	(7.6)	5	(13.5)	11	(9.5)
Injection site pain	5	(6.3)	0		5	(4.3)
Nausea	5	(6.3)	5	(13.5)	10	(8.6)
Vomiting	5	(6.3)	5	(13.5)	10	(8.6)
Myalgia	5	(6.3)	1	(2.7)	6	(5.2)
Injection site pruritus	4	(5.1)	0		4	(3.4)
Decreased appetite	4	(5.1)	4	(10.8)	8	(6.9)
Diarrhea	3	(3.8)	8	(21.6)	11	(9.5)
Peripheral edema	2	(2.5)	2	(5.4)	4	(3.4)
Pain	2	(2.5)	2	(5.4)	4	(3.4)
Anemia	1	(1.3)	5	(13.5)	6	(5.2)
Stomatitis	1	(1.3)	2	(5.4)	3	(2.6)
Edema	1	(1.3)	2	(5.4)	3	(2.6)
Alopecia	0		8	(21.6)	8	(6.9)
Neutropenia	0		6	(16.2)	6	(5.2)
Peripheral neuropathy	0		3	(8.1)	3	(2.6)
Paresthesia	0		2	(5.4)	2	(1.7)
Leukopenia	0		2	(5.4)	2	(1.7)
Thrombocytopenia	0		2	(5.4)	2	(1.7)
Neurotoxicity	0		2	(5.4)	2	(1.7)
Weight decreased	0		2	(5.4)	2	(1.7)

ICB, immune checkpoint blocker; NSCLC, non-small-cell lung cancer; SoC, standard of care (docetaxel or pemetrexed).

pembrolizumab + lenvatinib versus docetaxel; CONTACT-01—NCT04471428: atezolizumab + cabozantinib versus docetaxel; SAPPHIRE—NCT03906071: nivolumab + sitravatinib versus docetaxel).

Primary resistance and secondary resistance are the key clinical barriers to improving the outcome of patients with advanced NSCLC.[12] A definition of ICB resistance has been proposed when ICB is used as monotherapy.[27,28] The definition is more challenging for patients receiving an immuno-CT combination in the first-line setting, where the regimen component contributing to efficacy and resistance is not easily discerned. However, given the evidence that anti-programmed cell death protein 1 (PD-1) receptor binding declines 2-3 months after the last administration of anti-PD-1 and anti-programmed death-ligand 1 (PD-L1) therapies,[12,29] PD within or >12 weeks after starting ICB monotherapy may be considered an optimal cut-off for defining primary versus secondary resistance. This cut-off of at least 12 weeks of ICB monotherapy after a sequential CT-ICB approach was used to define the population of secondary resistance in the ATALANTE-1 study at the time of the interim analysis in the first 103 out of 219 patients. Biologically, secondary resistance to ICB may occur through alterations in antigen presentation, and more frequently by T-cell exhaustion leading to progressive loss of effector function measured by IFN-γ production, whereby

exhausted cytotoxic CD8+ T cells fail to control late-stage tumor progression.[15] The mechanism of action of OSE2101 that enhances a new specific CD8+ T-cell effector function, and which maintains antigen presentation and avoids immune escape leading to decreased T-cell recognition of the tumor, is a mechanistically plausible explanation of the clinical benefit observed in our study and in emerging new studies with cancer vaccines.[30]

A phase I trial evaluating a TAA cancer vaccine targeting melanoma in patients who had failed previous ICB was recently reported.[31] The RNA-LPX vaccine appeared to reverse the anti-PD-1-induced CD8+ T-cell dysfunction, with a correlation between T-cell responses and favorable clinical outcomes. Another phase I/IIa trial evaluating a universal cancer peptide-based vaccine targeting telomerase (UCP-Vax) in patients with refractory advanced NSCLC also showed a high immunogenicity which correlated with survival.[30] The immune response with OSE2101 was also significantly correlated with survival in a previous phase II study in a similar NSCLC population.[22,23] Thus, efficacy of OSE2101 is due to its capacity to generate a broad CTL immune response measured by increased IFN-γ, thereby invigorating antitumor immune responses, particularly in patients with secondary resistance to ICB as key mechanisms to overcome ICB resistance involve antigen presentation, IFN-γ signaling and T-cell exhaustion.[32]

The choice of OS as primary endpoint is considered to be more reliable than PFS and ORR in immunotherapy trials, as these latter endpoints are considered neither robust nor reliable in this setting. The OS benefit with OSE2101 was achieved despite lower ORR and similar PFS with the vaccine strategy compared to SoC, confirming that in advanced NSCLC, PFS is not a good surrogate marker for OS benefit under ICB.[33-35] This discrepancy has previously been reported with other vaccines in other solid tumors such as sipuleucel-T in prostate cancer.[36,37]

This discrepancy between patients' survival and the efficacy endpoints based on tumor assessments by measurements of tumor using imaging (RECIST 1.1) in cancer vaccine is probably due to its specific mechanism of action which fundamentally differs from CT. Standard CT as docetaxel acts by a direct cytotoxic effect on tumor cells, rapidly controlling tumor growth that can result in objective response or SD. Due to mechanism of resistance to CT, tumors usually relapse more or less rapidly, especially when CT has to be stopped due to toxicity. OS analysis by best response with OSE2101 and with CT showed that OS was longer with OSE2101 in patients with SD or PD compared to SoC. These data suggest that the cancer vaccine OSE2101 may act as an antitumor brake in controlling the tumor growth regardless of the best response, while efficacy observed with CT is mainly driven by objective response.

Recently, in the same setting of ICB resistance, a phase II clinical trial demonstrated significantly improved OS with ramucirumab plus pembrolizumab compared with SoC CT (investigator's choice) in patients with advanced NSCLC who failed CT and had progressed ≥84 days after initiating ICB.[13] The survival gain with this strategy was also 3 months,

whereas ORR and PFS were lower with this combination than with SoC, as was observed with OSE2101. However, this strategy used intravenous administration for ramucirumab plus pembrolizumab compared with subcutaneous administration for OSE2101; furthermore, in daily clinical practice not all patients are eligible to receive an anti-angiogenic agent either due to the disease localization or as a consequence of comorbidities.

QoL and tolerance are critical in patients with advanced NSCLC whose survival is limited. OSE2101 was previously reported to be safe and well tolerated. ATALANTE-1 confirmed the safety of this cancer vaccine in this indication. OSE2101 delayed ECOG PS deterioration by >5 months and maintained QoL as assessed by the global health status, physical and role functions. Severe AEs regardless of causal relationship to study treatment were significantly half as common with OSE2101 than with SoC CT, and severe drug-related AEs were significantly lower (11.4% versus 35.1%).

A key limitation of the current study is its premature discontinuation due to a potential COVID-19 impact, resulting in a change in the study power to 62%. Furthermore, at the time the trial was initiated, the ICB plus CT combination was not standard in the first-line setting. Thus, the proportion of patients with failure after immunotherapy first line was low [$n = 36$ (16.4%)] with a heterogeneous population which did not allow clear identification of patients with secondary resistance. As a consequence, the small number of patients with secondary resistance after a first-line concurrent approach recruited in ATALANTE-1 did not allow exploration of the efficacy of OSE2101 in this setting. Because the duration of prior treatment with ICB as a criterion for defining secondary resistance has only recently been introduced, patients with secondary resistance to ICB monotherapy were identified during the interim analysis from stratification criteria along with a clinical and biological rationale and were therefore only partially planned at the study initiation. Patients were defined as having a primary or secondary resistance based on the duration of prior ICB calculated from the first to last dose of ICB in the stratum 'second line of treatment with prior ICB' (83.6% of patients). It should be highlighted that no bias was seen, as demonstrated by baseline values of the primary population similar to those of the randomized population. It is also of note that survival in patients with primary resistance after sequential treatment with CT and ICB was similar for OSE2101 and SoC [HR 0.99 (0.58-1.71)].

In summary, this randomized international study suggests that T-cell vaccination with OSE2101 monotherapy may improve survival in patients with HLA-A2-positive advanced NSCLC who have progressed at least 12 weeks after sequential treatment with CT and ICB. This evidence is a benchmark to explore this strategy in other clinical settings with secondary resistance to immunotherapy. To our knowledge, this is the first cancer vaccine trial in HLA-A2-positive advanced NSCLC patients with secondary resistance to ICB to demonstrate a potential survival benefit with a good safety profile compared with SoC of either

docetaxel or pemetrexed. Further evaluation is planned in this population of secondary resistance to immunotherapy in prospective phase III including correlative studies.

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