ORIGINAL ARTICLE

Durvalumab Plus Chemotherapy in Patients With *EGFR*-Mutated Advanced NSCLC Whose Disease Progressed on First-Line Osimertinib: ORCHARD

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Received 28 April 2025; revised 14 November 2025; accepted 15 November 2025
Available online - 23 March 2026

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Cite this article as: Cho BC, Nishio M, Ahn MJ, et al. Durvalumab plus chemotherapy in patients with *EGFR*-mutated advanced NSCLC whose disease progressed on first-line osimertinib: ORCHARD. *JTO Clin Res Rep* 2026;7:100937

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2025.100937

ABSTRACT

Introduction: ORCHARD (NCT03944772) was a phase II, biomarker-directed platform study designed to characterize resistance mechanisms and evaluate novel therapy combinations after progressive disease (PD) on first-line osimertinib. We report results of the module assessing durvalumab plus chemotherapy.

Methods: Patients with epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) with PD on first-line osimertinib whose tumors did not harbor a prespecified alteration by next-generation sequencing of a post-osimertinib biopsy, or for whom a biomarker-matched treatment was not available, were eligible. Patients received 4 to 6 cycles of durvalumab 1500 mg plus carboplatin target area under the curve 5 and pemetrexed 500 mg/m^2. After platinum-based chemotherapy, patients without PD could continue to receive durvalumab plus pemetrexed maintenance. Primary end point was objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 by investigator assessment.

Results: Overall, 25 patients received more than or equal to 1 dose of durvalumab plus chemotherapy; all had discontinued treatment at the primary analysis data cutoff. Confirmed ORR was 16% (80% confidence interval [CI]: 7–30); response was maintained for more than 6 months in the four patients with confirmed response. Furthermore, 22 patients (88%) had PD and median progression-free survival was 4.8 months (95% CI: 2.6–7.6). Ten patients (40%) had died, and median overall survival was 23.4 months (95% CI: 8.8–not calculable). Nine patients (36%) had grade 3 or higher adverse events, most often neutrophil count decreased (20%).

Conclusions: Durvalumab plus chemotherapy demonstrated limited clinical benefit for *EGFR*-mutated NSCLC after PD on first-line osimertinib. Although the combination was well tolerated, the overall risk-benefit profile did not warrant further evaluation.

Keywords: Epidermal growth factor receptor mutated; Non–small cell lung cancer; Durvalumab; Chemotherapy; Osimertinib

Introduction

Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), with demonstrated efficacy in *EGFR*-mutated non-small cell lung cancer (NSCLC), including central nervous system (CNS) metastases.[1–7] Based on results from the phase III FLAURA trial (NCT02296125), which demonstrated improved progression-free survival (PFS) and overall survival (OS) with osimertinib versus comparator EGFR-TKIs,[1,2] osimertinib is considered the preferred first-line treatment for *EGFR*-mutated advanced NSCLC.[8,9]

Despite the demonstrated efficacy of osimertinib in *EGFR*-mutated advanced NSCLC, most patients will have disease progression.[10] Currently, platinum-based chemotherapy is recommended for most patients after progressive disease (PD) on first-line osimertinib.[8,9] Improved understanding of acquired mechanisms of resistance to osimertinib may help to inform optimal treatment for these patients. Common mechanisms of resistance to osimertinib include bypass-tract activation, such as MET amplification or overexpression, on-target resistance such as *EGFR* C797S mutation, and histologic transformation.[11–14] Patients with targetable mechanisms of resistance may benefit from targeted therapy against the identified resistance alteration,[15,16] and this approach—through enrollment in an appropriate clinical trial where feasible—is recommended in treatment guidelines.[8,17] However, for other patients, it may not be possible to identify a resistance mechanism, or they may have a resistance alteration for which targeted therapy is not available.

Agents targeting the programmed cell death protein 1 (PD-1) pathway, given in combination with chemotherapy, are a standard first-line treatment for patients with advanced NSCLC without driver mutations.[18,19] However, the efficacy of immunotherapy in patients with *EGFR*-mutated NSCLC is not well characterized. Several studies evaluating anti–PD-1/programmed death-ligand 1 (PD-L1) monotherapy revealed efficacy was not improved in patients with previously treated *EGFR*-mutated advanced NSCLC versus standard chemotherapy.[20–22] However, preliminary data suggest that this resistance among patients with *EGFR*-mutated NSCLC who have progressed on an EGFR-TKI may be overcome by combining immunotherapy with additional agents, such as platinum-based chemotherapy with/without bevacizumab (or bevacizumab biosimilar).[23–25]

ORCHARD (NCT03944772) was a phase II, biomarker-directed platform study that enrolled patients with *EGFR*-mutated advanced NSCLC who had PD on first-line osimertinib.[26] ORCHARD aimed to characterize resistance mechanisms and evaluate novel therapy combinations, based on identified mechanisms of resistance, in this patient population. The modular study design allowed multiple study treatments to be assessed

and enabled the addition of new treatment modules as the study progressed, depending on the identification of further biomarkers and treatments. Here, we describe results from the ORCHARD module 4 within group B, assessing the efficacy and safety of the anti–PD-L1 antibody, durvalumab, in combination with platinum-based chemotherapy in patients with *EGFR*-mutated NSCLC adenocarcinoma who had progressed on first-line osimertinib and had no detectable resistance biomarkers, or for whom biomarker-matched study treatments were not available (Supplementary Fig. 1).

Materials and Methods

Study Design

ORCHARD (NCT03944772) was a global, phase II, open-label, multicenter, biomarker-directed platform study designed to assess the efficacy and safety of multiple treatments in patients with *EGFR*-mutated advanced NSCLC who had progressed on first-line osimertinib treatment. Details of the trial design have been published previously.[26] Briefly, patients were allocated to three groups (A, B, and C) based on molecular analysis of a post-progression tumor biopsy (Supplementary Fig. 1). Tissue samples were analyzed by next-generation sequencing (NGS; FoundationOne CDx [F1CDx], Foundation Medicine Inc., Boston, MA). Results of local NGS analysis were accepted, but tissue for retrospective central NGS confirmation was required. In group B, patients without a predefined biomarker of resistance were assigned to non-biomarker–matched treatment in one of the applicable three modules, with three different treatment regimens.

For group B, patients were eligible if they were above or equal to 18 years of age (Japan, $\geq$20 years old), had locally advanced or metastatic NSCLC harboring an *EGFR* mutation known to be associated with EGFR-TKI sensitivity at diagnosis, had evidence of PD on first-line osimertinib (80 mg once daily), and were suitable for a mandatory biopsy. Patients must have had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v.) 1.1 and a World Health Organization performance status (WHO PS) of 0 or 1. Key exclusion criteria for group B included the following: patients whose disease had progressed within the first 3 months of osimertinib; those who had experienced toxicity that led to permanent discontinuation or dose reduction of prior osimertinib; and patients with any unresolved toxicities from prior osimertinib (>grade 1). Patients with spinal cord compression, symptomatic and unstable brain metastases, except for those who had completed definitive therapy and had a stable neurologic status for more than or equal to 2 weeks after completion of definitive therapy and steroids, were also excluded. Patients must not have discontinued osimertinib more than 60 days before the first dose of study treatment.

To be eligible for treatment with durvalumab plus chemotherapy (module 4 within group B [patients without an available biomarker match]), patients must also have had body weight more than 30 kg. Patients with neuroendocrine-transformed cancers or predominant squamous cell carcinoma were excluded from this module. Patients must also not have had active or prior documented autoimmune or inflammatory disorders or active infection (including tuberculosis). Patients were allocated to study treatment based on cohorts that were open at the site at that time. As such, patients with an identified resistance marker could be enrolled to a non-matched cohort, such as module 4, if the matched cohort was not open at their site. For example, those with MET alterations were allowed in module 4 after closure of module 1. Retrospective NGS tissue testing per F1CDx was performed for patients allocated to treatment cohorts based on local NGS testing results. Retrospective testing may have identified biomarker-matched alterations which were not reported in local results.

ORCHARD was approved by the institutional review board or independent ethics committee at each study center. The study was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference for Harmonization), applicable regulatory requirements, and the policy of the trial sponsor, AstraZeneca, on bioethics and human biologic samples. All patients provided written informed consent.

Treatments

Patients received intravenous infusions of durvalumab (1500 mg) plus carboplatin (target area under the curve 5) and pemetrexed (500 mg/m^2 body surface area) administered on day 1 of every 21-day cycle for 4 to 6 cycles. After platinum-based chemotherapy, patients without disease progression could continue to receive durvalumab 1500 mg plus pemetrexed 500 mg/m^2 maintenance therapy on day 1 of every 28-day cycle. Durvalumab was administered every 3 weeks in the platinum-doublet chemotherapy phase to conform to the chemotherapy schedule and was administered every 4 weeks thereafter as maintenance therapy. Pemetrexed was administered every 4 weeks in the maintenance phase to align with the schedule for durvalumab. Treatment continued until PD per RECIST v.1.1, unacceptable toxicity, or another discontinuation criterion was met. Treatment could continue beyond RECIST v.1.1–defined PD if the investigator concluded that the patient was obtaining clinical benefit, in the absence of another discontinuation criterion.

End Points and Assessments

The primary end point was objective response rate (ORR) assessed by investigator assessment per RECIST v.1.1; secondary end points included duration of response, PFS and OS. Safety was assessed based on adverse events (AEs)/serious AEs (SAEs), physical examinations, laboratory findings, vital signs, electrocardiogram parameters, and left ventricular ejection fraction. Exploratory end points included assessment of tumor mutational burden (TMB) and molecular alterations by NGS of baseline tumor tissue samples and their correlation with response. Detection of common sensitizing *EGFR* mutation circulating tumor DNA (ctDNA) in the plasma before treatment and on day 1 of cycle 3 was also conducted. NGS of ctDNA from matched baseline and PD plasma samples was performed to assess potential mechanisms of acquired resistance.

ORR was defined as the percentage of patients with a confirmed investigator-assessed response of complete response or partial response (PR). Duration of response was defined as the time from the first documented response until documented objective PD or death in the absence of progression. PFS was defined as the time from the first dose until the date of objective PD or death by any cause in the absence of progression. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of their last evaluable RECIST v.1.1 assessment. OS was defined as the time from the first dose of study treatment until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

Tumor assessments were performed using computed tomography or magnetic resonance imaging at baseline and every 6 weeks (±1 wk) for the first 24 weeks and every 9 weeks (±1 wk) thereafter until PD per RECIST v.1.1 or the end of study treatment. AEs were monitored throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Plasma samples were collected at baseline, on day 1 of each treatment cycle, and at treatment discontinuation and PD. Plasma ctDNA *EGFR* mutation analysis (Ex19del and L858R only) was conducted by droplet digital polymerase chain reaction (ddPCR; Biodesix, Boulder, CO) as reported previously.[27] NGS of ctDNA in the plasma was evaluated by Guardant360 CDx (Guardant Health, Redwood City, CA). PD-L1 expression was detected by immunohistochemistry (CellCarta, Montreal, Quebec, Canada). TMB was evaluated by F1CDx and therefore was only available when the primary sample was analyzed centrally or if central retrospective confirmatory testing was successful.

Statistical Methods

Safety was analyzed in all patients who received at least one dose of the study treatment (safety set). Efficacy was analyzed in all patients from the safety set who had measurable disease at baseline (evaluable for efficacy set).

Planned recruitment was up to 40 patients. The sample size for the primary analysis was based on a decision framework that used confidence intervals (CIs) for ORR to categorize efficacy using prespecified target and lower reference values.[28] An interim analysis could be performed after approximately 16 evaluable patients had the opportunity for two post-baseline RECIST assessments. Recruitment could be stopped if efficacy was below the predefined futility threshold (a $<$10% predicted probability that the ORR would be $>$45%, chosen as a clinically relevant improvement to current observed standard-of-care ORRs). For example, with a sample size of 16, an ORR of 25% (80% CI: 11–44) or below would be deemed futile. At the primary analysis, the same criteria could apply for not continuing further development (e.g., a sample size of 30 with an ORR of 30% [80% CI: 19–43] or a sample size of 40 with an ORR of 33% [80% CI: 23–44]). Conversely, an observed more than 80% probability for the ORR to be more than 30% would be considered a good signal (e.g., a sample size of 30 with an ORR of $\geq$40% or a sample size of 40 with an ORR of $\geq$38%).

Analyses of efficacy and safety were descriptive. For the primary end point, ORR was summarized with two-sided exact binomial 80% CIs. PFS, duration of response, and OS were assessed using Kaplan–Meier methodology. The data cutoff date for the primary analysis was June 25, 2022.

Results

Patients

Between October 10, 2019, and December 14, 2020, 25 patients from four countries (Japan, Republic of Korea, Spain, and the USA) initiated treatment. In an interim analysis of 18 evaluable patients (data cutoff November 10, 2020), two patients had confirmed responses and the ORR of 11% (80% CI: 3–27) was below the predefined futility threshold. Recruitment was therefore paused, at which time 25 patients had received treatment, and subsequently, the decision was made to close recruitment to this module.

All 25 patients received at least one dose of durvalumab plus chemotherapy (Supplementary Fig. 2). At data cutoff, all patients had discontinued the study treatment. Five patients (20%) completed six cycles, 20 patients completed more than or equal to four cycles,

Table 1. Patient Demographics and Disease Characteristics

Characteristic	Durvalumab Plus Chemotherapy (N = 25)
Median age, y (minimum-maximum)	61 (39-77)
Age group, n (%)	
≥18-<65 y	17 (68)
≥65 y	8 (32)
Sex, n (%)	
Male	6 (24)
Female	19 (76)
Race, n (%)	
Asian	19 (76)
White	6 (24)
Country, n (%)	
Japan	9 (36)
Republic of Korea	7 (28)
Spain	3 (12)
United States	6 (24)
Smoking status, n (%)	
Never	15 (60)
Current	1 (4)
Former	9 (36)
Presence of CNS metastases at baseline, n (%)	
Yes	6 (24)
No	19 (76)
WHO performance status, n (%)	
0	10 (40)
1	15 (60)
Sites of disease[a], n (%)	
Sites of locally extensive disease	19 (76)
Sites of metastasis	24 (96)
EGFR mutation at baseline, n (%)	
Exon 19 deletion	12 (48)
L858R	8 (32)
Other *EGFR* alterations[b]	5 (20)
PD-L1 status at baseline, n (%)	
>50%	0
1%-50%	3 (12)
<1%	3 (12)
Unknown	19 (76)
Time to progression on first-line osimertinib, n (%)	
<12 mo	8 (32)
≥12 mo	17 (68)

CNS, central nervous system; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TNM, tumor-node-metastasis; WHO, World Health Organization.
[a]Sites of disease classification did not denote TNM staging but were based on evaluation of individual disease sites in individual patients. For example, an individual patient could have both locally extensive sites of disease (such as bulky lymph nodal or primary disease) and metastatic sites of disease.
[b]Other *EGFR* alterations detected at baseline included amplification, exon 21 L861Q, and exon 18 G719S.

and five patients completed fewer than four cycles of therapy. The most common reason for treatment discontinuation was physician decision for carboplatin per protocol (12/20 discontinued patients) and PD for pemetrexed and durvalumab (23/25 patients). Furthermore, 14 patients discontinued the study (10 due to death and four withdrew consent) and 11 patients completed the study.

Patient demographics are summarized in Table 1. Most patients were female (76%) and Asian (76%); median age was 61 (range 39–77) years, with 68% aged less than 65 years old, and all had WHO PS of 0 or 1. Six patients (24%) had CNS metastases at baseline. Eight patients (32%) had progressed within 12 months on first-line osimertinib.

Efficacy

All 25 patients were evaluable for efficacy; of these, confirmed ORR with durvalumab plus chemotherapy was 16% (80% CI: 7–30), with all four confirmed responses being PRs (Table 2). Five patients had unconfirmed PRs among 16 patients with a best objective response of stable disease. Duration of response for the four patients with confirmed PRs is found in Supplementary Figure 3. Response was maintained for more than 6 months in all four patients with confirmed response (range 6.2–12.2 mo; two of whom had progressed at data cutoff). Tumor shrinkage was observed in most patients, most often at the first RECIST assessment. Initial response was achieved at the first RECIST assessment in three of the four patients with confirmed response (data not shown).

At data cutoff, 22 patients (88%) had progressed. Median PFS was 4.8 (95% CI: 2.6–7.6) months (Fig. 1*A*). Ten patients (40%) had died; median OS was 23.4 (95% CI: 8.8–not calculable) months (Fig. 1*B*).

Safety

Patients received a median of four cycles of carboplatin (20 patients [80%] received ≥4 cycles) and seven cycles of pemetrexed and durvalumab. The median total treatment duration (range) was 2.9 (0.7–5.1) months for carboplatin and 5.3 (0.9–20.0) months for pemetrexed and durvalumab. All patients had more than or equal to 75% relative dose intensity for pemetrexed and durvalumab, and 24 patients (96%) had more than or equal to 75% relative dose intensity for carboplatin.

Of the 25 patients who received treatment, 24 (96%) experienced at least 1 treatment-emergent AE (TEAE) and nine patients (36%) had at least one grade 3 or higher TEAE (Supplementary Table 1). There were no TEAEs with outcome of death. The most common TEAEs (occurring in >25% of patients) were constipation (52%), nausea (40%), alanine aminotransferase (ALT) increase (28%), and neutrophil count decrease (28%). The most common grade 3 or higher TEAEs were neutrophil count decrease (20%) and anemia (12%; Table 3).

Table 2. Efficacy Outcomes

Efficacy End Point	Durvalumab Plus Chemotherapy (N = 25)
ORR, % (80% CI)	16 (7-30)
Best objective response, n (%)	
CR[a]	0
PR[a]	4 (16)
Stable disease ≥6 wk[b]	16 (64)
Unconfirmed CR or PR[c]	5 (20)
Stable disease	11 (44)
Progression	4 (16)
RECIST progression	4 (16)
Death	0
Not evaluable (incomplete post-baseline assessments)	1 (4)

CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Response required confirmation after more than or equal to 4 weeks.
[b]Stable disease could be recorded at 6 weeks minus 1 week to allow for an early assessment within the assessment window.
[c]PR or CR achieved but either no confirmation assessment performed, or a confirmation assessment performed but response not confirmed.

AEs considered possibly related to any treatment were reported in 23 patients (92%), with seven patients (28%) experiencing grade 3 or higher related TEAEs (Supplementary Table 1). The most common AEs considered possibly related to any treatment (occurring in >25% of patients) were nausea (32%), ALT increase (28%), and neutrophil count decrease (28%).

SAEs were reported in three patients (12%). One patient had SAEs of neutrophil count decreased (grade 3; considered possibly related to carboplatin and pemetrexed) and ischemic cerebral infarction (grade 3; considered not related to treatment). One patient had an SAE of dyspnea (grade 4; considered not related to treatment), and another had an SAE of nausea (grade 3 [later downgraded to grade 2] considered possibly related to carboplatin and pemetrexed).

One patient (4%) had a TEAE leading to discontinuation of any treatment (grade 1 nausea leading to discontinuation of carboplatin). Four patients (16%) had TEAEs leading to dose reduction: one patient had TEAEs leading to dose reduction of carboplatin and four had AEs leading to dose reduction of pemetrexed.

AEs of special interest (AESIs) for durvalumab (as defined by the sponsor) were reported in 11 patients (44%) and comprised dermatitis/rash (28%), diarrhea/colitis (8%), hypothyroid events (4%), and infusion/hypersensitivity reactions (4%). All AESIs were grade 1 or 2 in severity. There were no reports of pneumonitis/interstitial lung disease (ILD).

Correlation of TMB and Molecular Alterations in Baseline Tissue With Response

TMB was generally low across all tumor tissue samples at baseline; there was no association between TMB level and response to chemoimmunotherapy (Fig. 2). After osimertinib progression, alterations that are known to confer resistance were identified in multiple baseline tissue samples, reflecting inclusion of patients for whom matched biomarker cohorts were not available at the time of enrollment or identification of alterations based on retrospective central testing. *EGFR*-independent resistance alterations, including *MET* amplification, *ERBB2* amplification, *PIK3CA/PTEN* alterations, and *BRAF/KRAS* alterations, were frequently observed in patients without an objective response; however, none of the four patients with confirmed PR had any of these alterations (Fig. 2). *CDKN2A/B* deletions and *STK11* mutations were only observed in patients without objective response. Conversely, loss-of-function alterations of *RBM10* were detected in two of four patients with confirmed PR who also had the deepest responses to the study treatment. Only six patients had sufficient tissue for PD-L1 testing after NGS; of these, none had PD-L1 expression more than 50% (Fig. 2).

Plasma ctDNA Analyses

A total of 14 patients had a valid baseline plasma ddPCR result: 10 had detected and four had undetected baseline plasma *EGFR* mutations (Ex19del/L858R only). Atypical *EGFR* mutations are not detected using ddPCR, and patients with atypical *EGFR* mutations only, per tissue NGS, were considered "unknown" for ctDNA status. Among the 10 patients with detected plasma *EGFR* mutations at baseline, four patients had ctDNA clearance (plasma *EGFR* mutations not detected) at cycle 3, day 1. Two of the four patients with ctDNA clearance had a confirmed PR, but none of the six patients without ctDNA clearance had a confirmed PR (Fig. 2). NGS of ctDNA from matched plasma samples from baseline and PD (n = 18) did not reveal any consistent acquired alterations at PD (Supplementary Fig. 4).

Discussion

This module of ORCHARD evaluated patients with *EGFR*-mutated NSCLC that had progressed on first-line osimertinib and had no identified mechanism of resistance or for whom biomarker-matched study treatments were not available. Based on an interim analysis of data from 18 evaluable patients, recruitment was stopped and subsequently closed due to predefined futility criteria being met. This primary analysis of all 25 patients who were treated in this module confirmed the results of the interim analysis, with durvalumab plus

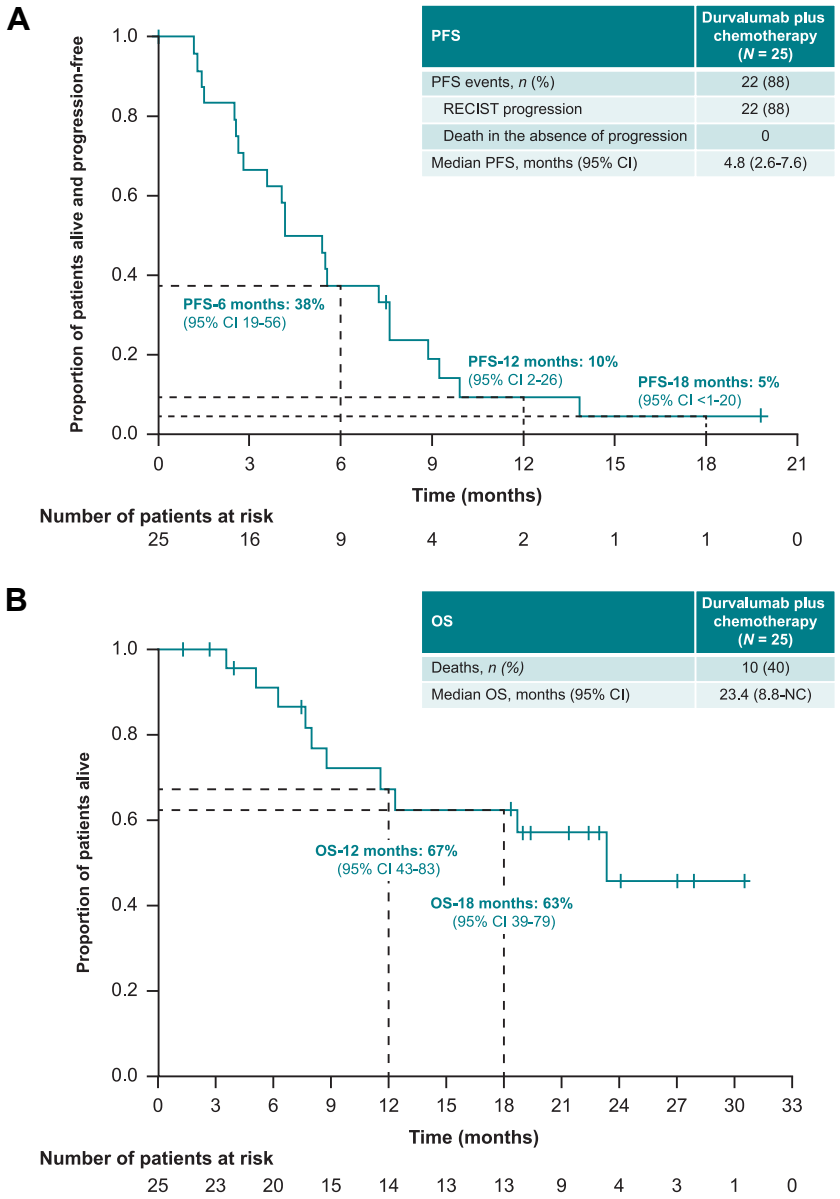

Figure 1. Kaplan-Meier analyses of (*A*) PFS and (*B*) OS. + indicates a censored observation. CI, confidence interval; NC, not calculable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

chemotherapy demonstrating limited clinical benefit in this patient population, with a confirmed ORR of 16% (80% CI: 7–30) and median PFS of 4.8 months (95% CI: 2.6–7.6). Four patients had a confirmed response (all PR), all lasting for more than 6 months. Reduction in tumor size was observed in most patients, most often at the first RECIST assessment.

Platinum-based chemotherapy is a recommended therapy for patients with *EGFR*-mutated NSCLC that has progressed on first-line osimertinib.[8,9] The phase III AURA3 trial (NCT02151981) assessed osimertinib (n = 279) versus platinum-pemetrexed (n = 140) in patients with *EGFR* T790M-positive NSCLC with disease progression after first-line EGFR-TKI therapy.[5] Median (95% CI) PFS and OS in patients randomized to platinum-pemetrexed were 4.4 (4.2–5.6) and 22.5 (20.8–28.8) months, respectively, and ORR was 31% (95% CI: 24–40).[5,29] In this ORCHARD module, median (95% CI) PFS and OS with durvalumab plus chemotherapy were 4.8 (2.6–7.6) and 23.4 (8.8–not calculable) months, respectively. Although differences in patient populations limit direct comparisons between the studies, it suggests that durvalumab plus platinum-pemetrexed is not associated with improved PFS or ORR compared with platinum-pemetrexed alone in patients with previously treated *EGFR*-mutated NSCLC.

Our results are generally consistent with randomized studies evaluating the addition of immunotherapy to chemotherapy in patients with *EGFR*-mutated NSCLC

Table 3. Treatment-Emergent Adverse Events (Reported in ≥10% of Patients)

Preferred Term, n (%)	Durvalumab Plus Chemotherapy (N = 25)	
	Any Grade	Grade ≥3
Constipation	13 (52)	1 (4)
Nausea	10 (40)	1 (4)
ALT increased	7 (28)	1 (4)
Neutrophil count decreased	7 (28)	5 (20)
White blood cell count decreased	6 (24)	2 (8)
AST increased	6 (24)	0
Anemia	5 (20)	3 (12)
Decreased appetite	5 (20)	0
Insomnia	5 (20)	0
Vomiting	5 (20)	0
Fatigue	5 (20)	0
Malaise	5 (20)	0
Cough	4 (16)	0
Rash	4 (16)	0
Pyrexia	4 (16)	0
Platelet count decreased	4 (16)	2 (8)
Hiccups	3 (12)	0
Dyspepsia	3 (12)	0
Back pain	3 (12)	0
Asthenia	3 (12)	0

Note: Table includes TEAEs with an onset date or worsening on or after the date of first dose and up to and including 90 days after the date of last dose of study treatment or the date of start of subsequent cancer therapy, whichever occurred first.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

that had progressed on EGFR-TKI therapy. The phase III KEYNOTE-789 study (NCT03515837) evaluated pembrolizumab plus pemetrexed and platinum-based chemotherapy versus placebo plus pemetrexed and platinum-based chemotherapy in patients with EGFR-TKI–resistant, *EGFR*-mutated advanced NSCLC.[30] Addition of pembrolizumab to chemotherapy did not significantly improve PFS versus placebo plus chemotherapy (median [95% CI] 5.6 [5.5–5.8] versus 5.5 [5.4–5.6] mo; hazard ratio [HR] 0.80, 95% CI: 0.65–0.97; $p = 0.0122$ [boundary was $p = 0.0117$]). ORR (95% CI) was similar in the pembrolizumab plus chemotherapy arm (29%, 23–35) and the chemotherapy arm (27%, 22–33). Median (95% CI) OS was 15.9 (13.7–18.8) months with pembrolizumab plus chemotherapy versus 14.7 (12.7–17.1) months with placebo plus chemotherapy (HR 0.84, 95% CI: 0.69–1.02; $p = 0.0362$ [boundary was $p = 0.0118$]).[30] Similarly, the phase III CheckMate722 study (NCT02864251) revealed that nivolumab plus chemotherapy did not improve PFS versus chemotherapy (median [95% CI] 5.6 [4.5–6.8] versus 5.4 [4.4–5.6] mo; HR 0.75, 95% CI: 0.56–1.00; $p = 0.0528$) in patients with *EGFR*-mutated NSCLC who had been previously treated with EGFR-TKIs.[31] ORR (95% CI) was 31% (24–40) in the nivolumab plus chemotherapy arm versus 27% (20–35) in the chemotherapy arm; the lower ORR observed in this study may be a consequence of the much smaller sample size or differences in the study populations, including the proportions with early progression on prior EGFR-TKI therapy. Median (95% CI) OS was 19.4 (16.1–21.0) months with nivolumab plus chemotherapy versus 15.9 (14.0–18.8) months with chemotherapy alone.[31] Within the phase II, multicenter, ILLUMINATE trial (NCT03994393) the addition of durvalumab and tremelimumab (an anti–CTLA-4 antibody) to platinum pemetrexed chemotherapy had modest antitumor activity, in patients with *EGFR*-mutated NSCLC after progressing on EGFR-TKI therapy. The ORR was 31% with a median PFS of 6.5 months versus 21% and 4.9 months in patients with *EGFR* T790M-negative and T790M-positive disease, respectively. These data further add to the body of evidence that the addition of immunotherapy has only a modest effect in patients with *EGFR*-mutant disease.[32] Conversely, the addition of the anti–PD-1 antibody, sintilimab, to chemotherapy was associated with slightly prolonged PFS versus chemotherapy alone (median [95% CI] 5.5 [4.5–6.1] versus 4.3 [4.1–5.3] mo, HR 0.72, 95% CI: 0.55–0.94; $p = 0.016$) in patients with *EGFR*-mutated NSCLC who had progressed on treatment with EGFR-TKIs.[24] Data from the phase III IMpower150 (*EGFR*-mutated subset; NCT02366143) and HARMONi-A (NCT05184712) studies now suggest that combining immunotherapy and platinum-based chemotherapy with angiogenesis inhibition can improve outcomes, including PFS (both studies) and OS (IMpower150; OS data pending for HARMONi-A), compared with angiogenesis inhibition plus chemotherapy (IMpower150) or chemotherapy alone (HARMONi-A) in patients with *EGFR*-mutated NSCLC that has progressed on EGFR-TKI therapy.[23,33,34]

NGS of baseline tissue samples demonstrated that TMB was low across all samples, consistent with previous reports of EGFR-mutated NSCLC.[35,36] Low TMB in NSCLC has been associated with poorer responses to immunotherapy.[37] As modules within ORCHARD did not recruit concurrently, patients with *EGFR*-independent resistance alterations may have been included in this biomarker nonmatched module because the appropriate biomarker-matched module was not open at the time of enrollment. Alternatively, alterations may have been identified based on retrospective central testing of samples from patients enrolled, based on local NGS results. Overall, eight patients in this module had baseline tumors harboring known *EGFR*-independent resistance alterations, including *MET* amplification, *ERBB2* amplification, *PIK3CA/PTEN* alterations, and *BRAF/KRAS* alterations. Notably, none of the tumors from patients with objective response had any such alterations. Although our analysis is limited by small sample

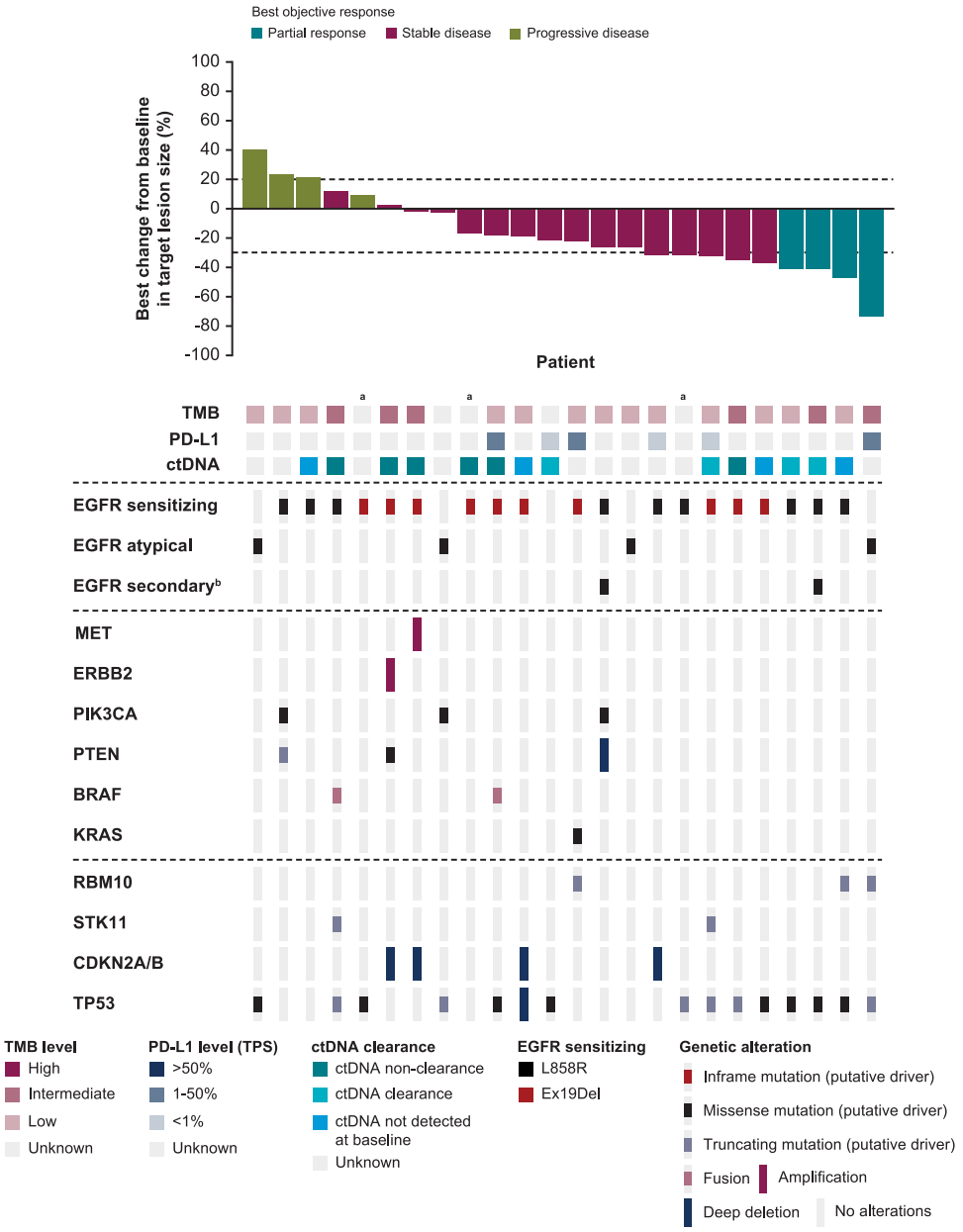

Figure 2. Correlation of TMB and molecular alterations at baseline with response type. Figure illustrates panel with TMB and molecular alterations identified in NGS of a baseline tissue biopsy, immunohistochemical staining for PD-L1, and detection of common sensitizing *EGFR* mutation (Ex19del/L858R) ctDNA from a baseline plasma sample against best objective response in patients with on-treatment target lesion measurements (n = 24). ctDNA clearance was defined as baseline plasma *EGFR* mutations that became nondetectable at day 1, cycle 3. [a]Indicates local NGS results; [b]Secondary *EGFR* mutations were L718V and C797S. ctDNA, circulating tumor DNA; Ex19del, exon 19 deletion; PD-L1, programmed death-ligand 1; NGS, next-generation sequencing; TMB, tumor mutational burden; TPS, tumor positive score.

numbers, this suggests that presence of *EGFR*-independent resistance alterations may be associated with a poorer response to durvalumab plus chemotherapy. We also evaluated genetic alterations that might affect anti–PD-1/PD-L1 sensitivity. Notably, loss-of-function alterations of *RBM10*, a regulator of RNA splicing, were found in tumors from two of four patients with objective response. Dysregulation of the RNA-splicing machinery may increase expression of neoantigens, leading to increased antitumor immune activity.[38] Previous analyses have revealed that *RBM10* alterations may be associated with improved anti–PD-1/PD-L1 responses.[39] Conversely, *RBM10* co-mutations have been associated with poor response to *EGFR TKIs*.[40,41] *CDKN2A/B* deletions have also been reported in pre- and post-osimertinib *EGFR*-mutated NSCLC tissue biopsies.[12] In our analysis, *CDKN2A/B* deletions were only observed in patients without objective response. Type I

interferon gene cluster, located adjacent to *CDKN2A/B*, has been found to be co-deleted with *CDKN2A/B* in other solid tumors.[42,43] It has been hypothesized that this co-deletion may contribute to poor response to anti–PD-1/PD-L1 agents, owing to the crucial role of interferon signalling in eliciting effective antitumor T-cell responses (type I interferon gene cluster deletion was not assessed in ORCHARD).[42,43] Together with these considerations, chemotherapy is most likely the primary driver of treatment response in this study.

Although limited by small sample sizes, assessment of plasma *EGFR* mutations (Ex19del/L858R) by ddPCR at baseline and during treatment was consistent with previous data, which suggests that early clearance of plasma *EGFR* mutations is a predictor of more favorable outcome.[27,44] The use of ctDNA to assess or predict response is an area of active research, and ongoing studies are evaluating the utility of persisting ctDNA to guide treatment choice in *EGFR*-mutated advanced NSCLC.[45,46]

Safety data were consistent with the safety profiles of the individual drugs, and no new safety signals were observed. Most AEs were mild or moderate in severity, and no ILD events were reported.

Durvalumab plus chemotherapy was associated with an ORR of 16% (80% CI: 7–30) and median PFS of 4.8 months (95% CI: 2.6–7.6) in patients with *EGFR*-mutated NSCLC that had progressed on first-line osimertinib. As such, the overall risk–benefit profile does not support further exploration of this combination in this population. Although our study is limited by the small number of patients treated and the lack of a control arm, our results are generally aligned with other published data evaluating PD-1/PD-L1–targeted immunotherapy in combination with chemotherapy in this setting.

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Data Sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Disclosure

Dr. Cho reports having employment at Yonsei University Health System; stocks/shares with BridgeBio

Therapeutics, Cyrus Therapeutics, Gencurix Inc., Interpark Bio Convergence Corp., J INTS BIO, Kanaph Therapeutic Inc., and TheraCanVac Inc.; advisory role with BridgeBio Therapeutics, Cyrus Therapeutics, Guardant Health, J INTS BIO, Kanaph Therapeutic Inc., and Therapex Co., Ltd.; board of directors with J INTS BIO; consulting fees from Amgen, AnHeart Therapeutics, ArriVent, AstraZeneca, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, CJ, Cyrus Therapeutics, Daiichi Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Harpoon Therapeutics, Janssen, Merck Sharp & Dohme, Novartis, Ono, Pfizer, Regeneron, Roche, Sanofi, Seagen, Takeda, and Yuhan; grants/funds from AstraZeneca, Champions Oncology, CJ Bioscience, Cyrus, Dong-A ST, GI Innovation, ImmuneOncia, J INTS BIO, Janssen, Merck Sharp & Dohme, Therapex, Vertical Bio AG, and Yuhan; royalties for Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH; founder of DAAN Biotherapeutics; and invited speaker with ASCO, AstraZeneca, ESMO, Guardant, IASLC, Korean Cancer Association, Korean Cancer Study Group, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Merck Sharp & Dohme, Novartis, Pfizer, Roche, The Chinese Thoracic Oncology Society, and Zailab. 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Acknowledgments

The authors thank all the patients and their families and the staff and investigators at all study sites. The authors acknowledge Aleksandra Markovets of AstraZeneca for her contributions to the bioinformatics analysis of this study. The authors also acknowledge Michael Pluta of AstraZeneca and Riccardo Cavazzina of Fortrea Development Limited for their contributions to the statistical analyses of this study. The authors acknowledge Caroline Allinson, BSc, contracted by Ashfield MedComms, an Inizio company, for medical writing support that was funded by AstraZeneca in accordance with Good Publications Practice guidelines (https://www.ismpp.org/gpp-2022).

The ORCHARD study (NCT03944772) was funded by AstraZeneca.

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.2025.100937.

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