BRIEF REPORT

Osimertinib Plus Durvalumab versus Osimertinib Monotherapy in EGFR T790M–Positive NSCLC following Previous EGFR TKI Therapy: CAURAL Brief Report

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ABSTRACT

Introduction: Osimertinib is a third-generation EGFR-tyrosine kinase inhibitor (TKI). Durvalumab is an anti–programmed death ligand 1 monoclonal antibody. The phase III open-label CAURAL trial (NCT02454933) investigated osimertinib plus durvalumab versus osimertinib monotherapy in patients with EGFR-TKI sensitizing and EGFR T790M mutation–positive advanced NSCLC and disease progression after EGFR-TKI therapy.

Methods: Patients were randomly assigned 1:1 to receive orally administered osimertinib (80 mg once daily) with or without durvalumab (10 mg/kg administered intravenously every 2 weeks) until progression. Treatment could continue beyond progression, providing clinical benefit continued (judged by the investigator). The amended primary objective was to assess the safety and tolerability of osimertinib plus durvalumab; efficacy was an exploratory objective.

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Results: CAURAL recruitment was terminated early because of increased incidence of interstitial lung disease–like events in the osimertinib plus durvalumab arm from the separate phase Ib TATTON trial (NCT02143466). At termination of CAURAL recruitment, 15 patients had been randomly assigned to treatment with osimertinib and 14 to treatment with osimertinib plus durvalumab. The most common AEs were diarrhea (53% [grade ≥3 in 6% of patients]) in the osimertinib arm and rash (67% [grade ≥3 in 0 patients]) in the combination arm. One patient who had been randomized to the combination arm reported grade 2 interstitial lung disease while receiving osimertinib monotherapy (after discontinuing durvalumab therapy after one dose). The objective response rates were 80% in the osimertinib arm and 64% in the combination arm.

Conclusion: Limited patient numbers preclude formal safety and efficacy comparisons between the two treatment arms. The combination of programmed cell death 1/programmed death ligand 1 inhibitors and EGFR-TKIs as therapy for NSCLC is not well understood, but it requires a careful approach if considered in the future.

Keywords: Osimertinib; Durvalumab; Combination; Non–small cell lung cancer; EGFR

Introduction

Mutations in the *EGFR* gene are observed in approximately 40% and 20% of patients with NSCLC in Asian and non-Asian populations, respectively.[1] Osimertinib, a third-generation, central nervous system–active, irreversible EGFR-tyrosine kinase inhibitor (TKI), is selective for both EGFR-TKI sensitizing mutations (EGFRm) and EGFR T790M resistance mutations.[2,3] Osimertinib is a treatment option for patients with advanced NSCLC harboring EGFRm in the first-line setting and the treatment of choice for patients with T790M-positive NSCLC after disease progression during treatment with a first-line EGFR-TKI.[2,3]

Durvalumab, a selective, high-affinity, engineered human immunoglobulin G1 monoclonal antibody, blocks binding of programmed cell death 1 ligand 1 (PD-L1) to programmed cell death protein 1 (PD-1) and CD80 molecule.[4] Murine models have demonstrated significant response to anti–PD-1 antibody treatment in EGFR-mutant tumors.[5] EGFR activation has been shown to induce PD-L1 expression; therefore, EGFR-TKIs may enhance antitumor immunity through downregulation of PD-L1.[5,6] The phase III, open-label, randomized CAURAL trial (NCT02454933) was planned to investigate osimertinib plus durvalumab versus osimertinib monotherapy in patients with T790M-positive advanced NSCLC and disease progression after EGFR-TKI therapy.

CAURAL recruitment terminated early after the interim safety results from a phase 1b study of osimertinib plus durvalumab for EGFRm NSCLC (TATTON [NCT02143466]), which observed a higher than expected incidence of interstitial lung disease (ILD)-like events (13 of 34 patients [38%]), none of which were fatal.[7]

We present CAURAL safety and efficacy results.

Methods

Patients

Eligible patients were aged 18 years or older (in Japan, ≥20 years) and had a WHO performance status of 0 or 1 and EGFRm locally advanced/metastatic NSCLC (stage IIIB–IV). Radiological documentation of disease progression after EGFR-TKI therapy was mandatory; other lines of therapy also may have been given. Centrally confirmed T790M-positive tumor status from a biopsy sample taken after disease progression during the most recent therapy was required. Patients with stable, asymptomatic, central nervous system metastases were eligible. Patients with a history or evidence of clinically active ILD or radiation pneumonitis were ineligible.

Trial Design and Treatment

Patients were randomized centrally (1:1) to receive orally administered osimertinib (80 mg once daily) with or without durvalumab (10 mg/kg administered intravenously every 2 weeks). The stratification factors were previous lines of treatment (one versus two or more), and ethnicity (Asian versus non-Asian). Treatment could continue beyond disease progression, provided clinical benefit continued (judged by the investigator).

Objectives

The amended primary objective was assessment of safety and tolerability of osimertinib plus durvalumab. Exploratory objectives included the safety of osimertinib and efficacy of osimertinib monotherapy and combination therapy.

Outcome Measures

Safety and tolerability outcome measures included adverse events (AEs) graded by the Common Terminology Criteria for Adverse Events, version 4. The efficacy outcome measures included investigator-assessed (according to the Response Evaluation Criteria in Solid Tumors, version 1.1) objective response rate (ORR), duration of response (DoR), progression-free survival

(PFS), tumor shrinkage, disease control rate, and overall survival (OS).

Statistical Analysis

Safety data were summarized according to randomized treatment received in the safety analysis set (patients who received at least one dose). Efficacy data were summarized according to randomized treatment in the full analysis set (all randomized patients regardless of treatment received). At time of recruitment termination, the sample size was too small for formal statistical comparisons between arms; summaries are descriptive. PFS, DoR, and OS were summarized by using Kaplan-Meier estimates. ORR was summarized with associated 95% confidence intervals (CIs) by using the Clopper-Pearson method. The data cutoff (DCO) date was March 21, 2018. These are the final data to be reported from this study.

Trial Oversight

The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, applicable regulatory requirements, and policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. The trial was funded by the sponsor and designed by the principal investigators and sponsor.

Results

Patients and Treatment

A total of 29 patients from nine centers in South Korea, Canada, and the Republic of China (Taiwan) were randomized: 15 to osimertinib monotherapy and 14 to osimertinib plus durvalumab combination therapy (Table 1 and Fig. 1). Two patients were incorrectly randomized to combination therapy, switched to osimertinib therapy, and never received durvalumab.

All 12 patients who received durvalumab stopped taking it during the study owing to disease progression (n = 5), AE (n = 3 [with two of these cases possibly causally related]), patient withdrawal (n = 3), or investigator decision (n = 1). The median duration of durvalumab treatment was 10.0 months (range 0–27 months). In all, 22 patients (76%) (12 of whom received osimertinib alone and 10 of whom received combination therapy) discontinued osimertinib during the study because of disease progression (n = 17), an AE (n = 2), or patient withdrawal (n = 3). Seven patients (24%) (five who were receiving osimertinib and two who were receiving combination therapy) were still receiving osimertinib at DCO. The median duration of osimertinib treatment was 21.1 months overall (range 2–30 months), and the median durations of treatment were 23.9 and 17.1 months in the osimertinib and combination arms, respectively (Fig. 2).

Table 1. Baseline Demographics and Clinical Characteristics (Safety Analysis Set)

Characteristic	Osimertinib (n = 17)	Osimertinib + Durvalumab (n = 12)
Age, y		
Median	65.0	56.0
Range	41-80	41-78
Sex, n (%)		
Male	4 (24)	6 (50)
Female	13 (76)	6 (50)
Race, n (%)		
White	2 (12)	1 (8)
Asian	15 (88)	11 (92)
Smoking history, n (%)		
Smoker	0	1 (8)
Nonsmoker	13 (77)	8 (67)
Ex-smoker	4 (24)	3 (25)
Disease classification, n (%)		
Metastatic	9 (53)	6 (50)
Locally advanced	0	0
Both	8 (47)	6 (50)
Stage, n (%)		
IIIA	3 (18)	1 (8)
IIIB	0	1 (8)
IV	13 (77)	10 (83)
Missing	1 (6)	0
Previous anticancer therapy regimens, n (%)		
1	10 (59)	8 (67)
2	5 (29)	2 (17)
3	2 (12)	0
≥4	0	2 (17)

Safety

Overall, all patients in the safety analysis set (17 patients who received osimertinib monotherapy and 12 who received combination therapy) had at least one AE (mostly grade 1 or 2) (Tables 2 and 3). The most commonly reported AEs, regardless of causality and severity, were diarrhea (n = 9 [53%]), rash (n = 9 [53%]), and paronychia (n = 7 [41%]) in the osimertinib arm and rash (n = 8 [67%]), diarrhea (n = 6 [50%]), and decreased appetite (n = 6 [50%]) in the combination arm.

Only one patient (3%) (who was randomized to combination therapy) had ILD reported (grade 2). The patient discontinued durvalumab therapy (consent withdrawal) on day 1 after one dose; the event was reported on day 63 while the patient was receiving osimertinib. The investigator reported it as a serious AE (because of hospitalization) that was possibly causally related to osimertinib and unrelated to durvalumab. The study treatment was discontinued permanently in

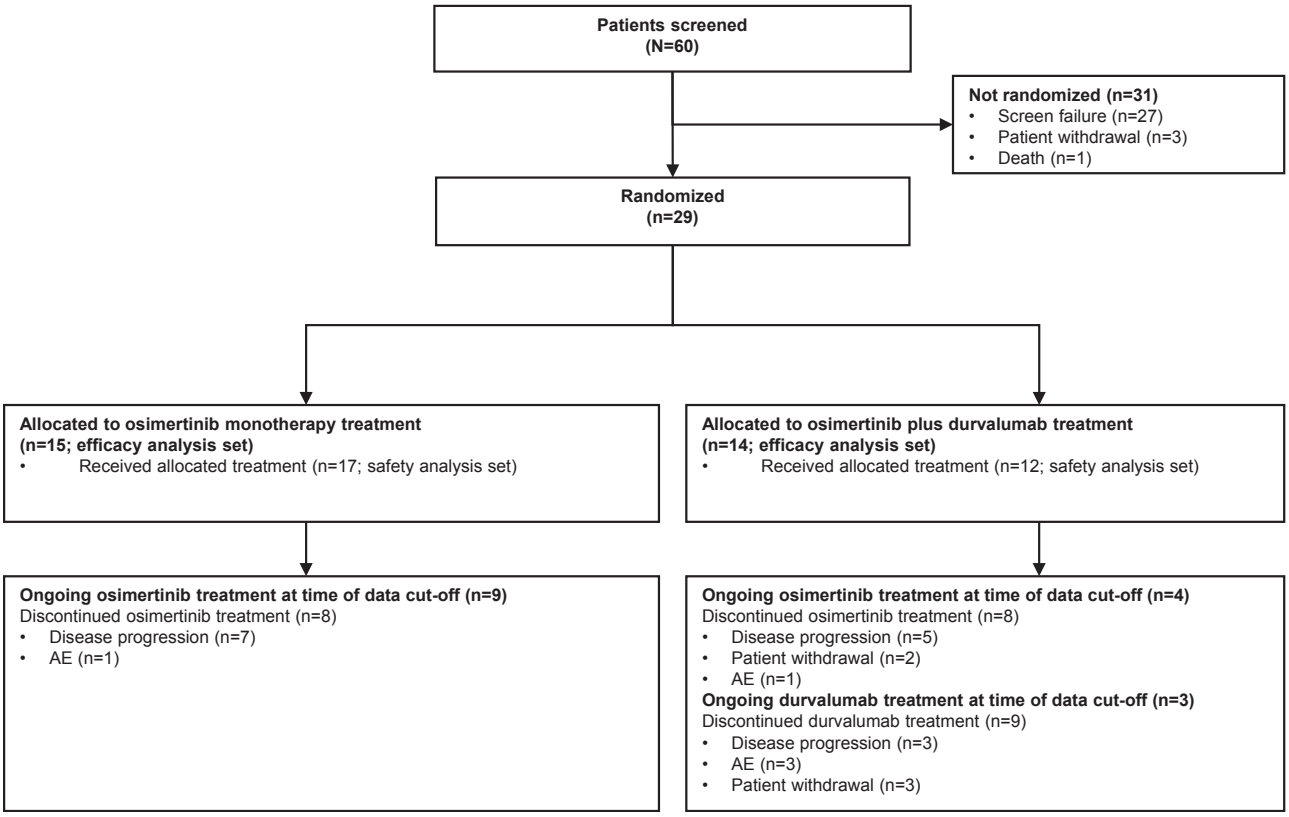

Figure 1. Patient disposition. DCO, data cutoff.

response. The event was reported as resolving at time of death due to disease progression (113 days after the last osimertinib dose).

In all, 10 patients had an AE of grade 3 or higher (nine [53%] in the osimertinib arm and one [8%] in the combination arm), with four of the 10

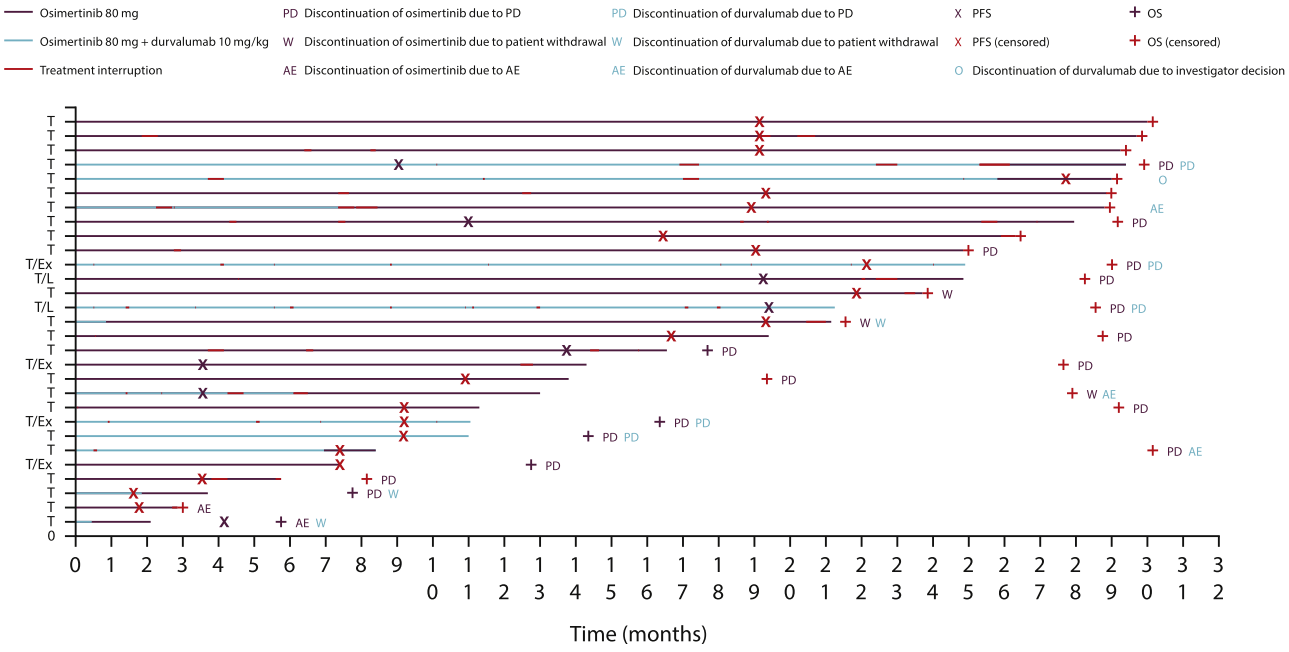

Figure 2. Total duration of treatment (safety analysis set). *Y* axis shows mutation status for each patient, where T stands for T790M-positive, L stands for L858R-positive, and Ex stands for exon 19 deletion-positive. AE, adverse event; OS, overall survival; PD, progressive disease; PFS, progression-free survival; W, patient withdrawal.

Table 2. Safety Summary (Safety Analysis Set): Summary of AEs

AE Category[a]	Osimertinib, n (%) (n = 17)	Osimertinib + Durvalumab, n (%) (n = 12)
Any AE	17 (100.0)	12 (100.0)
Any AE possibly causally related to treatment, as assessed by the investigator	14 (82)	8 (67)
Any AE possibly causally related to osimertinib only, as assessed by the investigator	14 (82)	8 (67)
Any AE possibly causally related to durvalumab only, as assessed by the investigator	0	4 (33)
Any AE possibly causally related to osimertinib and durvalumab, as assessed by the investigator	0	3 (25)
Any AE of CTCAE grade ≥3	9 (53)	1 (8)
Any AE of CTCAE grade ≥3, possibly causally related to treatment, as assessed by the investigator	4 (24)	0
Any AE of CTCAE grade ≥3, possibly causally related to osimertinib only, as assessed by the investigator	4 (24)	0
Any AE of CTCAE grade ≥3, possibly causally related to durvalumab only, as assessed by the investigator	0	0
Any AE of CTCAE grade ≥3, possibly causally related to osimertinib and durvalumab, as assessed by the investigator	0	0
Any AE with death as the outcome	0	0
Any SAE (including events with death as the outcome)	6 (35)	3 (25)
Any SAE (including events with death as the outcome), possibly causally related to treatment, as assessed by the investigator	0	1 (8)

[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes adverse events with an onset date on or after the date of first dose of study treatment and up to and including 30 days after the date of last dose of osimertinib or 90 days after the last dose of durvalumab, whichever is later.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

grade 3 or higher AEs considered possibly causally related to treatment (all in the osimertinib arm). No AEs led to death. One patient in each arm had an AE resulting in discontinuation of osimertinib. Three patients had an AE resulting in discontinuation of durvalumab.

Table 3. Safety Summary (Safety Analysis Set): AEs Reported in Three or More Patients in Either Arm (Regardless of Causality)

	Osimertinib, n (%) (n = 17)		Osimertinib + Durvalumab, n (%) (n = 12)	
AEs reported in ≥3 patients in either arm (regardless of causality)	Any grade, n (%)	CTCAE grade ≥3, n (%)	Any grade, n (%)	CTCAE grade ≥3, n (%)
Diarrhea	9 (53)	1 (6)	6 (50)	0
Rash[a]	9 (53)	0	8 (67)	0
Paronychia[a]	7 (41)	0	2 (17)	0
Arthralgia	5 (29)	0	2 (17)	0
Stomatitis	5 (29)	0	0	0
Neutropenia	4 (24)	2 (12)	0	0
Pruritus	4 (24)	0	5 (42)	0
Cough	4 (24)	0	4 (33)	0
Viral upper respiratory tract infection	4 (24)	0	1 (8)	0
Dyspnea	4 (24)	0	0	0
Back pain	3 (18)	0	3 (25)	0
Constipation	3 (18)	0	4 (33)	0
Dry skin[a]	3 (18)	0	4 (33)	0
Nausea	3 (18)	0	1 (8)	0
Neutrophil count decreased	3 (18)	0	0	0
Productive cough	3 (18)	0	1 (8)	0
Rhinorrhea	3 (18)	0	3 (25)	0
Pneumonia	3 (18)	2 (12)	2 (17)	0
Upper respiratory tract infection	3 (18)	0	1 (8)	0
Aspartate transaminase level increased	2 (12)	0	3 (25)	0
Decreased appetite	2 (12)	0	6 (50)	0
Hypoesthesia	1 (6)	0	3 (25)	0

[a]Reported as grouped terms.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

Efficacy

In the osimertinib arm, 12 of 15 patients had a confirmed partial response (ORR 80% [95% CI: 52–96]); in the combination arm, nine of 14 patients had a confirmed partial response (ORR 64% [95% CI: 35–87]). The median DoR was 17.5 months (95% CI: 9.1–not calculable) in the osimertinib arm versus 21.4 months (95% CI: 6.4–not calculable) in the combination arm. The disease control rate was 100% (95% CI: 78–100) in the osimertinib arm versus 93% (95% CI: 66–100) in the combination arm. All patients had a reduction in target lesion size compared with baseline (Fig. 3).

Confirmed (according to the Response Evaluation Criteria in Solid Tumors) progression was documented in four of 15 patients (27%) in the osimertinib arm and four of 14 (29%) in the combination arm. The median PFS was 19.3 months in the osimertinib arm versus not reached in the combination arm. The 12-month progression-free rates were 82% and 76%, respectively.

At DCO, two of 15 patients (13%) in the osimertinib arm and four of 14 patients (29%) in the combination arm had died. The median OS was not reached in either arm; the 12-month survival rate was 100% for the osimertinib arm versus 86% (95% CI: 54–96) for the combination arm.

Discussion

As limited patients were randomized, formal safety and efficacy comparisons between treatment arms were not possible. However, we observed no trends suggesting the combination therapy to be superior to osimertinib alone; the response to osimertinib monotherapy was consistent with the existing efficacy profile seen in phase II/III trials of osimertinib in patients with T790M-positive advanced NSCLC.[8,9] There were no new safety signals for osimertinib in combination with durvalumab or as monotherapy.

A meta-analysis of first-generation EGFR-TKI monotherapy (gefitinib/erlotinib) studies reported an ILD incidence at 1.2% (95% CI: 0.9–1.6%), ranging from 0% to 5%.[10] The incidence of ILD with osimertinib is in line with that for first-generation EGFR-TKIs, with rates of 2% to 4% in large phase II/III trials.[8,9,11]

An unexpectedly high incidence of ILD-like events (in 13 of 34 patients [38%]) was reported in the osimertinib plus durvalumab arm of TATTON.[7] In CAURAL, only one ILD event was reported in 12 patients who received

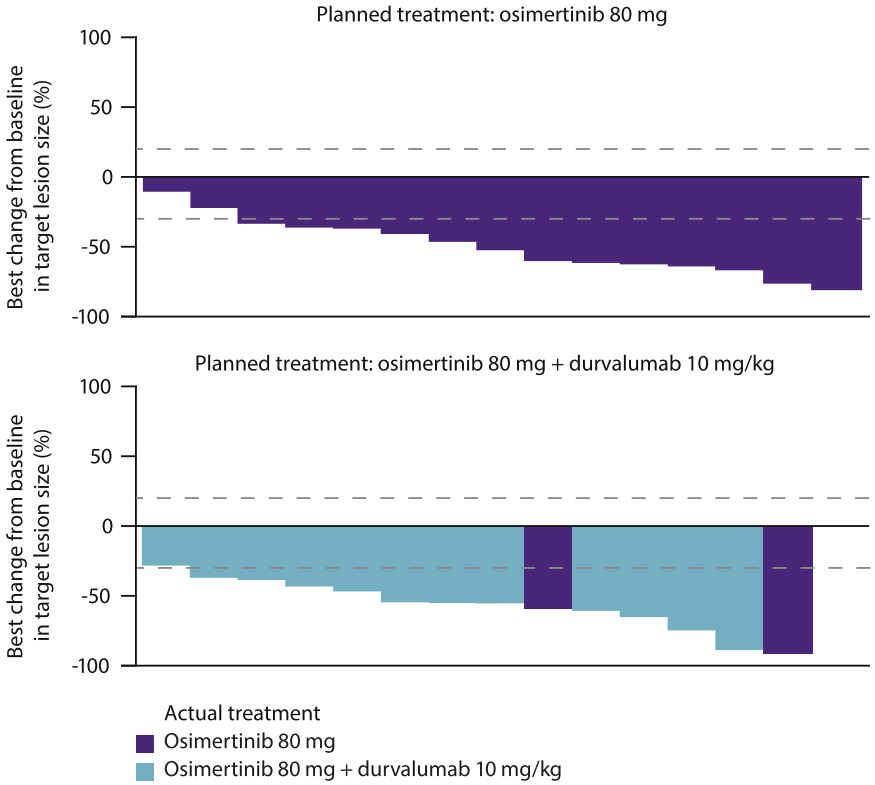

Figure 3. Best percentage change in target lesion size (full analysis set). Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Patients with at least one postbaseline Response Criteria in Solid Tumors-based target lesion assessment scan before any progression event are included. The line at 20% represents the boundary for determination of progressive disease, and the line at 30% represents the boundary for determination of partial response.

osimertinib plus durvalumab. The event, which was of grade 2 severity, occurred in a 60-year-old female Asian patient, who had discontinued durvalumab after one dose; ILD was reported on day 63 while she was receiving osimertinib. There remain limited data investigating EGFR-TKI therapy in combination with immunotherapy, but no ILD events were reported from a trial of 21 patients treated with erlotinib and nivolumab (NCT01454102).[12] Similarly, preliminary results from a phase I study evaluating durvalumab and gefitinib in patients with EGFRm NSCLC (NCT02088112) demonstrated that the combination was generally tolerated.[13] However, the efficacy of PD-1/PD-L1 inhibitor monotherapy in EGFRm NSCLC has not been widely demonstrated, and potential for added benefit when combined with EGFR-TKIs of any generation is not confirmed.[14,15]

Why reported ILD frequencies differ between the osimertinib plus durvalumab arm from TATTON and that from CAURAL remains unclear. In TATTON, most ILD-like events (seven of 11 [64%]) were reported in part B (in EGFR-TKI treatment–naive patients with EGFRm NSCLC who received osimertinib [80 mg once daily] plus durvalumab [10 mg/kg administered intravenously every 2 weeks]).[7] Part A included patients with EGFRm NSCLC who had progressed after previous EGFR-TKI therapy (as in CAURAL) and received osimertinib (80 mg once daily) plus durvalumab (either 3 mg/kg administered intravenously every 2 weeks [dose 1] or 10 mg/kg administered intravenously every 2 weeks [dose 2, as in CAURAL]); ILD was reported in two of 10 patients (20%) in part A at dose 1, and four of 13 patients (31%) in part A at dose 2. The overall median time to ILD onset was 69 days in TATTON parts A and B.[7]

Although the patient numbers were limited in CAURAL, there was no obvious benefit to combining durvalumab with osimertinib in comparison with osimertinib monotherapy.

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References

1. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7:78985-78993.
2. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29:iv192-iv237.
3. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35:3484-3515.
4. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res*. 2015;3:1052-1062.
5. Akbay EA, Koyama S, Carretero J, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov*. 2013;3:1355-1363.
6. Chen N, Fang W, Zhan J, et al. Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. *J Thorac Oncol*. 2015;10:910-923.
7. Ahn MJ, Yang J, Yu H, et al. 136O: Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: results from the TATTON phase Ib trial [abstract]. *J Thorac Oncol*. 2016;11:S115.
8. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.
9. Ahn M-J, Tsai C-M, Shepherd FA, et al. Osimertinib in patients with T790M mutation-positive advanced non-small cell lung cancer: long-term follow-up from a pooled analysis of two phase 2 studies [e-pub ahead of print]. *Cancer*. https://doi.org/10.1002/cncr.31891. Accessed January 28, 2019.
10. Shi L, Tang J, Tong L, Liu Z. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials. *Lung Cancer*. 2014;83:231-239.
11. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.
12. Gettinger S, Hellmann MD, Chow LQM, et al. Nivolumab plus erlotinib in patients with EGFR-mutant advanced NSCLC. *J Thorac Oncol*. 2018;13:1363-1372.
13. Gibbons DL. 57O: Efficacy, safety and tolerability of MEDI4736 (durvalumab [D]), a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib (G): a phase I expansion in TKI-naïve patients (pts) with EGFR mutant NSCLC [abstract]. *J Thorac Oncol*. 2016;11:S79.
14. Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. *J Thorac Oncol*. 2018;13:1138-1145.
15. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer-a meta-analysis. *J Thorac Oncol*. 2017;12:403-407.