ORIGINAL ARTICLE

# Durvalumab, Tremelimumab, and Platinum Chemotherapy in *EGFR* Mutation–Positive NSCLC: An Open-Label Phase 2 Trial (ILLUMINATE)

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## ABSTRACT

**Introduction:** *EGFR*-mutant NSCLC is associated with low mutation burden and low levels of PD-L1 expression. We conducted a phase 2 trial to determine the efficacy of durvalumab, tremelimumab, and platinum-pemetrexed in *EGFR*-mutant NSCLC after progression with EGFR tyrosine kinase inhibitors (TKIs).

**Methods:** Participants were treated with induction durvalumab, tremelimumab, and platinum-pemetrexed, followed by durvalumab-pemetrexed maintenance. Participants were divided into two cohorts: (1) *EGFR* exon 20 T790M negative (T790M−, progressing on either first-line osimertinib, or on a single line of first/second generation TKI), and (2) T790M positive (T790M+, progressing on greater than or equal to 1 lines of TKI, including osimertinib). The primary endpoint was the confirmed objective response rate (ORR) assessed by the investigators. Progression-free survival and safety were secondary outcomes.

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**Results:** One hundred participants from Australia and Taiwan were enrolled. Median follow-up was 26 months with 88% and 96% experiencing progression events for T790M− and T790M+, respectively. The ORR for T790M− was 31% (95% confidence interval: 20–45), including two complete responses. The ORR for T790M+ was 21% (95% confidence interval: 12–34). Median durations of response were 9.5 months and 6.3 months for T790M− and T790M+, respectively; median progression-free survival rates were 6.5 months and 4.9 months, respectively. For T790M−, ORR was 27% for 50% or higher PD-L1 (n = 22) and 0% for less than 50% PD-L1 (n = 10), respectively. For T790M+, ORR was 17% for 50% or higher PD-L1 (n = 24). The safety profile was consistent with previous reports.

**Conclusions:** Durvalumab, tremelimumab, and platinum-pemetrexed had modest anti-tumor activity in *EGFR*-mutant NSCLC after progression on TKI. The T790M− cohort had higher ORR and a longer duration of response. Immune adverse events were not increased with tremelimumab. The clinical registration number of this trial is NCT03994393.



*Keywords:* Non-small cell lung cancer; EGFR mutation; Checkpoint inhibitors; Chemotherapy

## Introduction

NSCLC with activating mutations of the *EGFR* gene are characterized by a high response rate to EGFR tyrosine kinase inhibitor (TKI) therapy. Today, a third-generation TKI, such as osimertinib,[1] is the preferred therapy for newly diagnosed, advanced, *EGFR*-mutant NSCLC.[2,3] For patients treated with upfront first- or second-generation TKIs, but with an acquired *EGFR* exon 20 Thr790Met (T790M) resistance mutation, osimertinib is the preferred salvage therapy.[4] Despite excellent initial tumor responses and prolonged progression-free survival (PFS), almost all patients develop drug resistance. Platinum doublet chemotherapy is the standard treatment after progression on TKI, resulting in tumor response rates of 31% to 34% with a median PFS of 4.4 to 5.4 months, highlighting a clear unmet need for this patient population.[4,5]

Single-agent immune checkpoint inhibitors (ICIs) such as monoclonal antibodies targeting the programmed death 1 (PD-1) receptor or programmed death ligand 1 (PD-L1) have improved survival in advanced NSCLC in both the front-line[6,7] and second-line settings.[8–10] Nevertheless, we have previously demonstrated with our meta-analyses[11,12] that single-agent ICI is not superior to chemotherapy for *EGFR*-mutant NSCLC in the second-line setting. Furthermore, a phase 2 trial of pembrolizumab (PD-1 antibody) in TKI-naïve, advanced, *EGFR*-mutant NSCLC was terminated early when none of the patients with centrally confirmed *EGFR* mutations achieved a tumor response, including those with PD-L1 expression of 50% or higher.[13] A randomized phase 2 study of dual ICI comparing ipilimumab and nivolumab (cytotoxic T-lymphocyte-associated protein 4 [CTLA4] and PD-1 antibody) with nivolumab monotherapy in the second-line setting also closed early owing to futility.[14]

*EGFR*-mutant NSCLC is associated with low tumor mutation burden (TMB),[15] a high frequency of inactive tumor-infiltrating lymphocytes,[16,17] and low levels of concurrent PD-L1 expression.[17] The limited benefit of single-agent ICI in *EGFR*-mutant NSCLC has led us to investigate alternative approaches, including combination treatment strategies that target multiple immune pathways. Anti–PD-L1 and anti-CTLA4 antibodies have complementary mechanisms of action, and when combined with chemotherapy, may induce more potent immune responses in TKI-resistant, *EGFR*-mutant NSCLC. In advanced, *EGFR* wild-type NSCLC, first-line nivolumab (PD-1 antibody) plus ipilimumab (CTLA4 antibody) prolonged overall survival (OS) when compared with chemotherapy alone, and this benefit was independent of both PD-L1 expression and TMB.[18]

The ILLUMINATE trial (NCT03994393) was designed to evaluate the efficacy and tolerability of a dual ICI blockade combination of durvalumab (anti–PD-L1) and tremelimumab (anti-CTLA4) with carboplatin-pemetrexed in metastatic, *EGFR*-mutant NSCLC after progression on one or two lines of TKIs.

## Materials and Methods

ILLUMINATE was a multicentre phase 2 trial conducted in two cohorts at 10 sites in Australia and six in Taiwan.

### *Participants*

Eligible participants were adults (age ≥ 18 years in Australia and ≥ 20 years in Taiwan) with histologically or cytologically confirmed non-squamous NSCLC with an *EGFR* exon 19 deletion or an exon 21 Leu858Arg (L858R) point mutation. Participants were assigned to one of two cohorts: (1) T790M negative (T790M−), if they were *EGFR* exon 20 T790M mutation negative on both tissue and plasma and had disease progression on a single line of a first or second generation TKI, and (2) T790M positive (T790M+), if they were T790M mutation positive either on tissue or plasma after progression on at least one line of TKI including osimertinib. All participants who received first-line osimertinib were assigned to the T790M− cohort.

Other key eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, at least one target lesion on the basis of Response Evaluation Criteria in Solid Tumors version 1.1, and adequate end-organ function. Participants were excluded if they had a history of interstitial lung disease or active autoimmune or inflammatory disorders. Participants with central nervous system metastases were allowed if they were asymptomatic or treated. A contemporary biopsy was recommended at the time of TKI progression before study entry for the exclusion of small cell transformation. The full eligibility criteria are available in the study protocol (Supplementary Materials).

### Study Treatment

During the induction phase, participants received up to four cycles of durvalumab 1500 mg (fixed dose), tremelimumab 75 mg (fixed dose), pemetrexed 500 mg/m$^2$, and physician's choice of cisplatin 75 mg/m$^2$ or carboplatin at an area under the concentration-time curve 5 mg/mL/min, all administered once every 21 days. During the maintenance phase, participants received durvalumab 1500 mg and pemetrexed 500 mg/m$^2$ once every 28 days. Treatment continued until disease progression or unmanageable toxicity.

ILLUMINATE was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, the Declaration of Helsinki, relevant laws, and institutional guidelines. Institutional review boards or independent ethics committees (Reference # 2019/ETH07510) approved the study protocol, participation information, and consent forms at each participating site. All participants provided signed, written, informed consent.

This investigator-initiated study was led by the Thoracic Oncology Group of Australasia, in collaboration with the Taiwan Cooperative Oncology Group, the National Health Research Institutes (Taiwan), and the National Health and Medical Research Council Clinical Trials Centre, University of Sydney.

### Endpoints and Assessments

The primary endpoint was the investigator-assessed objective response rate (ORR) defined as the percentage of confirmed complete responses (CR) and partial responses (PR) with confirmation by repeat imaging at least four weeks after initial observation of CR/PR according to Response Evaluation Criteria in Solid Tumors version 1.1. Tumor assessments were performed using computed tomography or magnetic resonance imaging at baseline before study enrolment, at the end of weeks 6 and 12, then every eight weeks for 12 months, and then every 12 weeks until disease progression.

Key secondary endpoints included disease control rate, PFS time, PFS rate at 12 months (PFS12), OS, and safety. Adverse events (AEs) were graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Exploratory biomarker analysis on tissue and blood was performed to identify emerging biomarkers associated with treatment resistance and prognosis. Evaluable plasma samples were analyzed for circulating tumor DNA (ctDNA) by next-generation sequencing using the AVENIO expanded kit V2 (Roche Diagnostics).

### Statistical Analysis

We used a Simon minimax two-stage design with a null hypothesis of 15% ORR and an alternative hypothesis of 30% for the primary endpoint (ORR) with 80% power and 5% one-sided type I error. If four or more responses were observed in the first 23 participants enrolled during the first stage, 25 additional participants would be recruited in the second stage. A total of 50 evaluable participants were to be recruited into each of the two cohorts (T790M− and T790M+) to allow for up to 4% drop-out.

All participants who received at least one cycle of therapy and had their disease re-evaluated beyond baseline were considered evaluable for response. All participants who received at least one dose of therapy were considered evaluable for safety.

Objective response rates and corresponding 95% exact two-sided confidence intervals (CIs) were calculated using the method of Wilson. Duration of response curves were estimated using the Kaplan-Meier product-limit method for participants with CR or PR. PFS, PFS12, and OS were also estimated using the Kaplan-Meier method, and the associated two-sided 95% CIs were calculated for medians and survival rates. Post hoc and exploratory biomarker analyses for additional subgroups were also performed; analyses were considered descriptive and not adjusted for multiplicity. Safety results are presented for each study cohort.

## Results

### Participants and Treatment

From April 2019 to November 2022, 100 participants were enrolled, including 50 participants in each study cohort. Ninety-nine participants received at least one dose of study treatment. Three participants found to be ineligible were excluded from the efficacy analysis (Fig. 1). The median follow-up time was 26 months (interquartile range: 20–32 months).

Baseline demographics and disease characteristics are summarized in Table 1. The proportions of

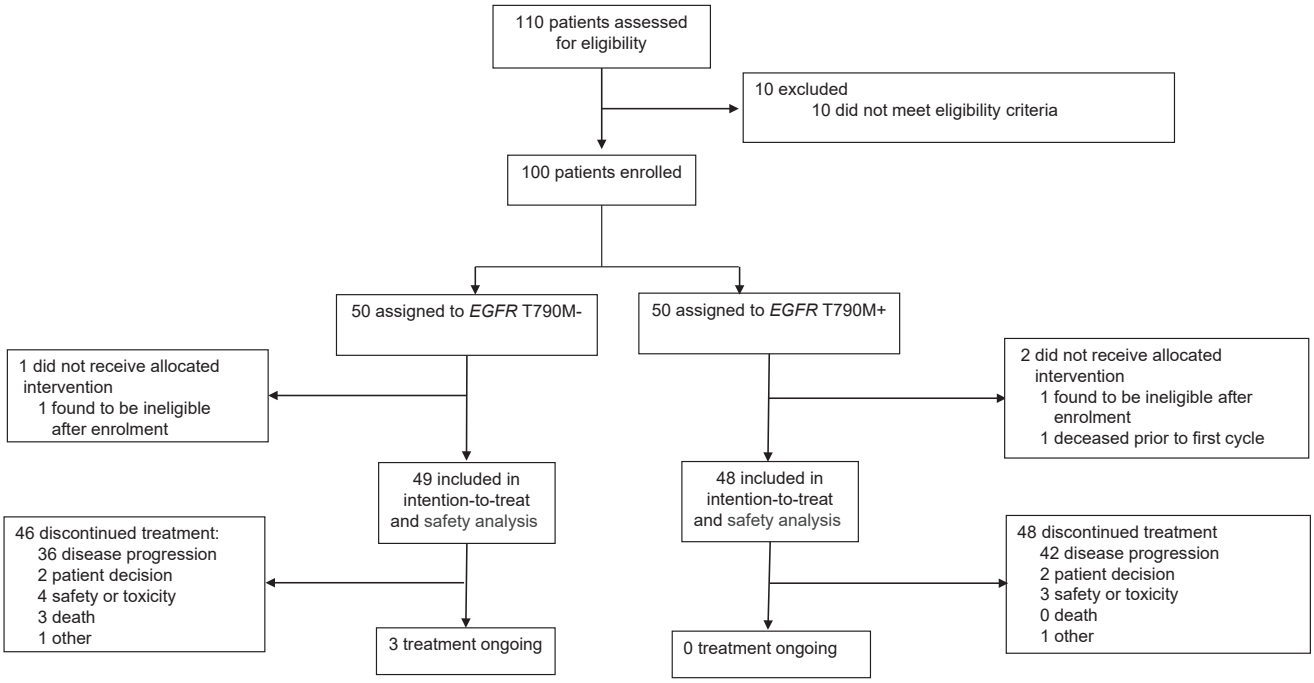


**Figure 1.** CONSORT Diagram.

participants aged 65 years and above were 33% and 40% in the T790M− and T790M+ cohorts, respectively. The majority of participants were female individuals, 53% and 73%, respectively. Non-Asian ethnicity accounted for 16% and 25%, respectively. There was a higher prevalence of exon 19 deletion than exon 21 L858R in the T790M+ cohort (71% versus 27%). In contrast, the prevalences of exon 19 deletion and exon 21 L858R were similar in the T790M− cohort (45% versus 57%). In the T790M− cohort, 31% had received upfront osimertinib as first-line treatment. All participants in the T790M+ cohort had received osimertinib. A total of 48/49 (98%) of T790M− and 44/48 (92%) of T790M+ participants had biopsies after recent TKI progression and excluded small cell transformation.

The median number (range) of cycles of study treatment were seven(1–42) and six(1–18) for T790M− and T790M+ cohorts, respectively. All four planned induction cycles were received by 86% and 77%, respectively. The median number of treatment cycles (interquartile range) in both induction and maintenance phases were 7(5–11) and 6 (4–9) respectively. At the time of data cut-off, 3 patients (6%) in the T790M− cohort were continuing maintenance treatment. All patients in the T790M+ cohort had discontinued treatment.

## *Clinical Efficacy*

There was a total of 48 participants evaluable for investigator-assessed tumor response in each of the T790M− and T790M+ cohorts. The confirmed ORR was 31% (95% CI: 20%–45%) for the T790M− cohort, including two participants with CR (Table 2, Fig. 2). In the T790M+ cohort, ORR was 21% (95% CI: 12%–35%) with no CR (Fig. 2). The unconfirmed ORR in the T790M− and T790M+ cohorts were 42% (95% CI: 29%–56%) and 35% (95% CI: 23%–50%), respectively, with the majority of PR re-classified as stable disease (SD) on confirmatory scans. There were 54% and 58% of participants with confirmed SD in the T790M− and T790M+ cohorts, respectively. Thus, the confirmed disease control rate (CR + PR + SD) was 85% (95% CI: 73%–93%) for the T790M− cohort and 79% (95% CI: 66%–88%) for the T790M+ cohort.

The median duration of response (Fig. 3*A*) was 9.5 months (95% CI: 5.3–23.8) for the T790M− cohort and 6.3 months (95% CI: 3.3–not estimable [NE]) for the T790M+ cohort. Figure 3*B* shows the spider plot illustrating changes from baseline in the sum of diameters of target lesions.

In T790M− and T790M+ cohorts, 88% and 96% of participants had progressed or died respectively. The median PFS times were 6.5 months (95% CI: 5.0–10.4) and 4.9 months (95% CI: 4.4–6.8), respectively (Fig. 4*A*). Progression-free survival rate at 12 months rates were 30% (95% CI: 19%–46%) and 11% (95% CI: 4.8%–25%), respectively.

For OS, 55% and 71% of participants had died in the T790M− and T790M+ cohorts, respectively. The median OS was 19.4 months (95% CI: 16.7–NE) and 13.2 months (95% CI: 11.7–17.9), respectively (Fig. 4*B*).

**Table 1.** Demographic and Baseline Characteristics

| Baseline Characteristics | *EGFR* T790M−, N = 49 | *EGFR* T790M+, N = 48 |
|---|---|---|
| Age, y | | |
| Median (IQR) | 60 (51-67) | 62 (56-68) |
| ECOG performance status | | |
| 0 | 24 (49) | 24 (50) |
| 1 | 25 (51) | 24 (50) |
| Ethnicity, n (%) | | |
| Asian | 38 (81) | 36 (75) |
| Other/unknown | 9 (19) | 12 (25) |
| Sex, n (%) | | |
| Female | 26 (53) | 35 (73) |
| Male | 23 (47) | 13 (27) |
| *EGFR* mutation | | |
| Exon 19 deletion | 21 (43) | 34 (71) |
| Exon 21 L858R | 27 (55) | 13 (27) |
| Exon 19 deletion & Exon 21 L858R | 1 (2) | 1 (2) |
| PD-L1 status | | |
| 0%-49% | 10 (20) | 2 (4) |
| ≥50% | 22 (45) | 24 (50) |
| Unknown | 17 (35) | 22 (46) |
| Smoking, n (%) | | |
| Current/former smoker | 4 (8) | 6 (12) |
| Never smoked | 11 (23) | 21 (44) |
| Unknown | 34 (69) | 21 (44) |
| Prior TKI therapy, n (%)[a] | | |
| Osimertinib | 15 (31) | 48 (100) |
| Gefitinib | 7 (14) | 15 (31) |
| Erlotinib | 15 (31) | 29 (60) |
| Afatinib | 18 (31) | 8 (17) |
| No of prior TKI, n (%) | | |
| 1 line | 45 (92) | 2 (4) |
| ≥2 line | 4 (8) | 46 (96) |
| Time on TKI, mo | | |
| Median (IQR) | 13 (2-96) | 30 (1-64) |

[a]Total percentage exceeds 100 as participants may have had exposure to more than one type of TKI due to toxicity or progression.
ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death ligand 1; T790M, *EGFR* exon 20 T790M mutation; T790M+, T790M positive; T790M−, T790M negative; TKI, tyrosine kinase inhibitors.

### *Subgroup Analysis*

At the time of data cutoff, tumor PD-L1 expression was known in 65% and 54% of the T790M− and T790M+ cohorts, respectively, with ongoing analysis of the remaining tumor samples. In the T790M− cohort, the ORR for 50% or higher PD-L1 was 27% (6/22, 95% CI: 13%–48%) but 0% for less than 50% PD-L1 (0/10) (Supplementary Fig. 1). The median PFS was 9.8 months (95% CI: 5.7–25.4) and 4.8 months (95% CI: 2.4–NE) for 50% or higher PD-L1 and less than 50% PD-L1, respectively (Supplementary Fig. 2). In the T790M+ cohort, the ORR for 50% or higher PD-L1 was 17% (4/24, 95% CI: 7%–36%) and median PFS was 4.8 months (95% CI: 4.4–6.8). There were only two participants whose tumor had less than 50% PD-L1 in the T790M+ cohort.

In the T790M− cohort, the ORR for exon 19 deletion and 21 L858R was 18% (4/22, 95% CI: 7%–39%) and 41% (11/27, 95% CI: 25%–59%), respectively. The median PFS was 5.0 months (95% CI: 4.6–10.4) and 6.6 months (95% CI: 5.0–13.1), respectively. In the T790M+ cohort, the ORR for exon 19 deletion and exon 21 L858R were 18% (6/34, 95% CI: 8%–34%) and 21% (3/13, 95% CI: 8%–50%), respectively. The median PFS was 4.9 months (95% CI: 4.4–7.2) and 4.6 months (95% CI: 2.6–NE), respectively. Objective response rate did not differ significantly between subgroups (Supplementary Fig. 1).

### *Safety*

In total, 49 and 48 participants were evaluated for safety in the T790M− and T790M+ cohorts, respectively. Adverse events of any grade and cause, irrespective of attribution to study treatment, occurred in 98% of participants. Adverse events reported as grade 3 or higher occurred in 61% and 67% in the T790M− and T790M+ cohorts, respectively.

Immune-related AE (irAE) of any grade occurred in 53% and 50% in the T790M− and T790M+ cohorts, respectively (Supplementary Table 1). Grade 3 or higher irAE were reported in 16% and 25% of participants, respectively. There was no grade 5 irAE in either cohort. The most frequent irAEs were colitis (8%), hepatitis (4%), adrenal insufficiency (2%), and pneumonitis (1%). Discontinuation of immunotherapy for irAEs occurred in 8% of participants (T790M−, 6%; T790M+, 10%).

### *Exploratory Biomarker Analysis*

Next-generation sequencing was performed on 22 participants (T790M−, N = 13; T790M+, N = 9) with paired plasma ctDNA samples available at baseline and radiological progression. *TP53* co-mutation was the most commonly present before the commencement of study treatment (54%) (Supplementary Fig. 3). *EGFR* amplification was another alteration common at baseline (55%) and at disease progression (14%). The number of baseline genomic alterations (excluding exon 19 deletion, exon 21 L858R, and exon 20 T790M) was higher in the T790M+ cohort (mean 4, range 0-8) than the T790M− cohort (mean = 1.7, range: 1–4).

## Discussion

In this study, the addition of durvalumab and tremelimumab to chemotherapy had modest anti-tumor activity in advanced EGFR-mutant NSCLC after progression from TKI. In the T790M− cohort, the ORR was 31% and we observed meaningful prolongation of PFS (median = 6.5 months) and OS (19.4 months). Nevertheless, in the

**Table 2.** Tumor Response and Survival Outcomes

| Efficacy Evaluable Patients | *EGFR* T790M−, N = 49 | *EGFR* T790M+, N = 48 |
|---|---|---|
| Confirmed ORR, No. (%, 95% CI) | 15 (31, 20-45) | 10 (21, 12-35) |
| DCR, No. (%, 95% CI) | 41 (85, 73-93) | 38 (79, 66-88) |
| Best overall response | | |
| CR | 2 (4) | 0 (0) |
| Confirmed CR | 2 (4) | 0 (0) |
| PR | 18 (37) | 17 (35) |
| Confirmed PR | 13 (27) | 10 (21) |
| SD | 26 (53) | 28 (58) |
| PD | 7 (14) | 10 (21) |
| NE | 1 (2) | 0 (0) |
| Median duration of response, mo (95 % CI) | 9.5 (5.3-23.8) | 6.3 (3.3-NE) |
| No. of PFS events (%) | 43 (88) | 46 (96) |
| Median PFS, mo (95% CI) | 6.5 (5.0-10.4) | 4.9 (4.4-6.8) |
| PFS rate at 12-mo, % (95% CI) | 30 (19-46) | 11 (4.8-25) |
| No. of OS events (%) | 27 (55) | 34 (71) |
| Median OS, mo (95% CI) | 19.4 (16.7-NE) | 13.2 (11.7-17.9) |
| OS rate at 12-mo, % (95% CI) | 74 (63-88) | 57 (44-73) |

CI, confidence interval; CR, complete response; DCR, disease control rate; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T790M, *EGFR* exon 20 T790M mutation.

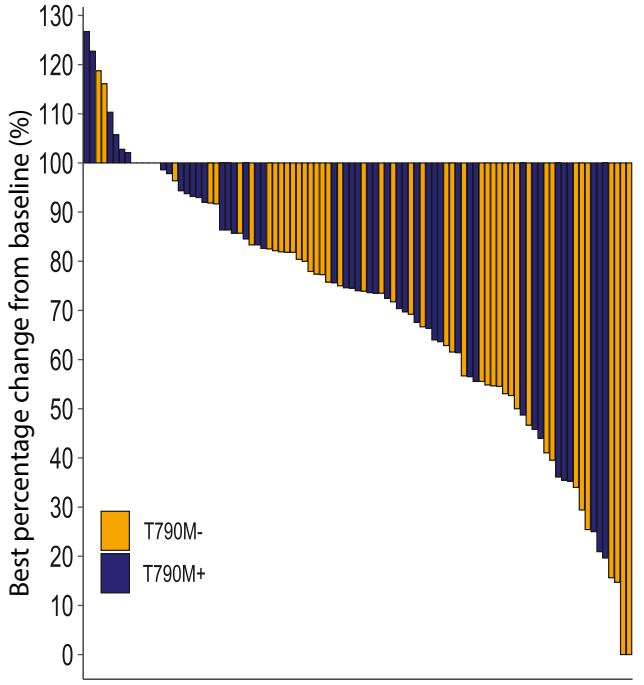


**Figure 2.** Waterfall plot of maximum percentage change in target lesion size from baseline. T790M, *EGFR* exon 20 T790M mutation.

T790M+ cohort, the ORR was only 21%, with shorter PFS (4.9 months) and OS (13.2 months). There were no new safety concerns identified, no grade 5 irAE, and only 8% discontinued treatment owing to irAE. The safety profile of durvalumab and tremelimumab plus chemotherapy was consistent with previous studies in *EGFR* wild-type NSCLC.[19,20]

Multiple randomized trials of chemoimmunotherapy in advanced, *EGFR*-mutant NSCLC after progression on TKI have reported conflicting results. The CheckMate-722 phase 3 trial compared nivolumab plus platinum doublet chemotherapy versus platinum-doublet chemotherapy alone and did not demonstrate a significant benefit in either PFS or OS.[21] In that study of a predominantly T790M− population, nivolumab plus chemotherapy had an ORR of 31% and median PFS of 5.6 months, similar to our study. The KEYNOTE-789 phase 3 trial compared pembrolizumab plus chemotherapy versus chemotherapy alone and reported trends toward improved PFS and OS that were not statistically significant.[22]

Preclinical studies have reported that expression of vascular endothelial growth factor was upregulated in tumor models,[23] and that vascular normalization could enhance ICI therapy,[24] suggesting that anti-angiogenic therapies might have a role in the TKI-resistant setting. In the phase 3 IMpower150 trial,[25] an underpowered subgroup analysis of participants with *EGFR*-mutant NSCLC reported higher efficacy of atezolizumab (PD-L1 antibody), bevacizumab, and chemotherapy. The Korean phase 3 ATTLAS trial[26] corroborated this finding by demonstrating significant improvements in PFS and ORR. In ATTLAS, the T790M− and T790M+ subgroups treated with atezolizumab, bevacizumab, and chemotherapy achieved median PFS times of 10.2 months and 8.3 months, respectively, longer than observed in our study. Finally, the Chinese ORIENT-31 phase 3 trial evaluating the combination of sintilimab (PD-1 inhibitor), a bevacizumab biosimilar, and chemotherapy also demonstrated significant improvement in PFS compared to chemotherapy alone.[27] Nevertheless, the phase 3 IMpower151 trial, conducted in China,[28] reported no difference in PFS when comparing atezolizumab, bevacizumab, and chemotherapy versus chemotherapy alone, contradicting the findings of ATTLAS and ORIENT-31. The Japanese Phase 3 WJOG11218L trial did not show superiority when bevacizumab was added to atezolizumab plus chemotherapy, compared with atezolizumab plus chemotherapy alone in advanced NSCLC, but did report improved survival in subgroups with driver oncogenes, including *EGFR* mutation.[29] The varying outcomes in this series of quadruplet regimen trials combining anti-VEGF and chemoimmunotherapy suggest that the choice of chemotherapy partner may matter, namely taxane in IMpower150 versus pemetrexed in IMpower151 and WJOG11218L.

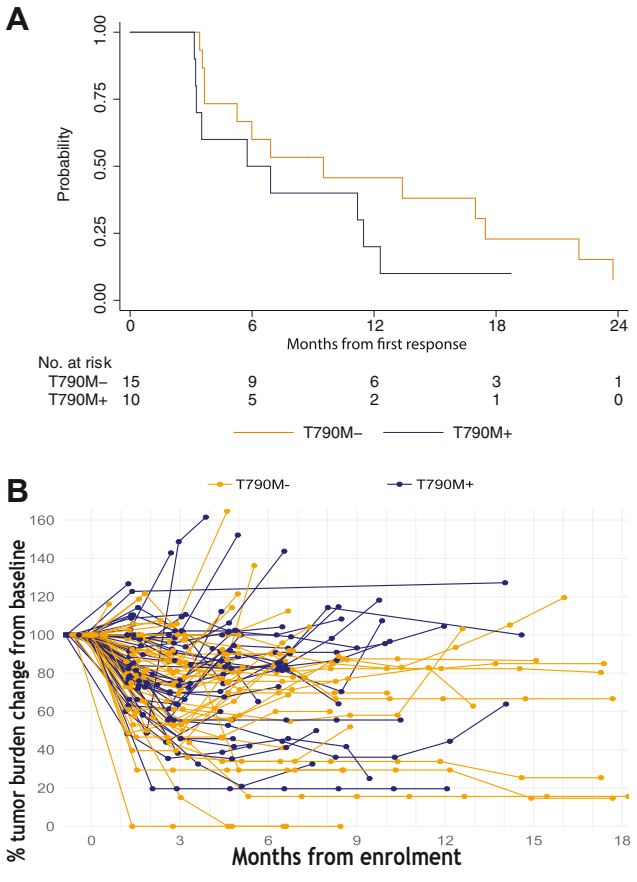


**Figure 3.** Durability of response with durvalumab, tremelimumab, and platinum-pemetrexed. *(A)* Kaplan-Meier plot of duration of response in participants with confirmed complete or partial response. *(B)* Spider plot of changes from baseline in the sum of diameters of target lesions. T790M, *EGFR* exon 20 T790M mutation.

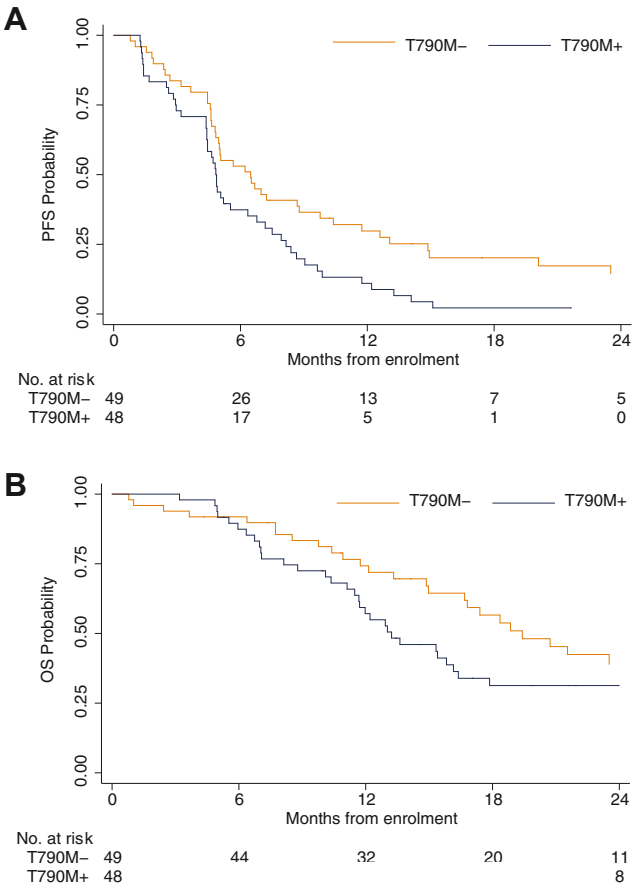


**Figure 4.** *(A)* Kaplan-Meier plot of progression-free survival in each study cohort. *(B)* Kaplan-Meier plot of overall survival in each study cohort. OS, overall survival; PFS, progression-free survival; T790M, *EGFR* exon 20 T790M mutation.

Different patient subgroups respond differently to chemoimmunotherapy. Before the availability of ICI, patients with T790M+ tumors were known to have shorter OS when treated with chemotherapy than those with T790M− tumors after progression on first-generation TKI.[30] In our study and other recently reported chemoimmunotherapy trials,[22,26] T790M+ was associated with treatment resistance and shorter survival, thereby being the group least likely to benefit from such a regimen. Sequential therapy with a first/second generation TKI followed by a third generation TKI in T790M+ patients has remained a common treatment practice in some countries. Patients with T790M+ tumors have a poor prognosis; further studies are required to identify novel treatments and strategies for this group.

Furthermore, and supporting the hypothesis of increased clonal heterogeneity, our exploratory biomarker analysis demonstrated that the T790M+ cohort had more ctDNA genomic alterations, including multiple, concurrent, *EGFR,* on-target mutations, and bypass pathway alterations, compared with the T790M− cohort. Nevertheless, this analysis was exploratory and requires independent corroboration. Nevertheless, our analysis has shown that *EGFR* amplification, either as a resistance mechanism post-TKI or acquired after ICI, was the dominant alteration identified, particularly in the T790M+ cohort. The therapeutic implications of this finding are unclear, and additional studies are needed to investigate whether further treatment with EGFR-directed therapy might be beneficial for this subgroup.

A meta-analysis of chemoimmunotherapy trials in *EGFR* wild-type NSCLC reported that high tumor expression of PD-L1 predicted improved ORR and PFS.[31] In advanced *EGFR*-mutant NSCLC, the role of PD-L1 expression in selecting patients for chemoimmunotherapy is less clear. In our study, 50% or higher PD-L1 was associated with higher ORR and longer PFS than less than 50% PD-L1 in the T790M− cohort. In the ATTLAS trial,[26] higher PD-L1 expression was associated with greater benefit with chemoimmunotherapy over

chemotherapy alone but this finding was not replicated in other trials of chemoimmunotherapy.[21,22,28]

Across multiple randomized trials of TKI, exon 19 deletion has been associated with higher response rates and superior PFS than exon 21 L858R.[32–34] Nevertheless, there was limited data on the performance of these two subgroups when treated with chemoimmunotherapy after TKI failure. In our trial, ORR for exon 21 L858R was higher than for exon 19 deletion (41% versus 19%) in the T790M− cohort, but similar in the T790M+ cohort (23% versus 18%). Both the ATTLAS[26] and ORIENT-31[27] trials reported similar PFS for chemoimmunotherapy versus chemotherapy alone in the exon 19 deletion subgroup but improved PFS for chemoimmunotherapy in the exon 21 L858R subgroup. A possible explanation for this observation is the higher TMB associated with exon 21 L858R than with exon 19 deletion.[15]

Our study has several strengths. It is the only trial to evaluate the role of dual PD-L1 and CTLA4 blockade in combination with chemotherapy in this patient population. We did not demonstrate results as promising as seen in *EGFR* wild-type NSCLC,[18] but our findings increase knowledge about the role of ICI in *EGFR*-mutant NSCLC. We designed and powered our study to evaluate the activity of chemoimmunotherapy separately in T790M− and T790M+ populations. Follow-up is mature with 88% and 96% progression events documented for the T790M− and T790M+ cohorts, respectively. Multicenter involvement in two countries including participants from multiple ethnicities increases the generalizability of our findings. Prior osimertinib treatment was high, at 31% and 100% in the T790M− and T790M+ cohorts, respectively, reflecting preferred contemporary practice.

Our trial also has limitations. ILLUMINATE was a non-randomized study, and the lack of a chemotherapy-alone comparator precludes direct estimation of the relative treatment effect. We did not perform a central imaging review to independently assess response or progression assessments by site investigators. The moderate sample size was designed for a phase 2 evaluation of activity to guide further research. Not all patients underwent a biopsy after recent TKI progression hence we could exclude small cell transformation as the potential cause for the poorer outcomes observed in the T790M+ cohort.

In summary, durvalumab and tremelimumab plus platinum doublet chemotherapy was associated with greater ORR and longer PFS among participants with advanced *EGFR* NSCLC tumors that were T790M− than T790M+. The safety profile of using doublet immunotherapy was consistent with other chemoimmunotherapy regimens in advanced NSCLC and did not seem to be worsened by the addition of tremelimumab. With rapidly expanding treatment options, including bispecific antibody and antibody-drug conjugate therapies, the antitumor activity with durvalumab, tremelimumab, and chemotherapy is considered modest for advanced *EGFR*-mutant NSCLC after the progression of TKI.

## CRediT Authorship Contribution Statement

**Chee Khoon Lee:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

**Bin-Chi Liao:** Conceptualization, Data Curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Shalini Subramaniam:** Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing.

**Chao-Hua Chiu:** Data Curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Antony J. Mersiades:** Conceptualization, Methodology, Project administration, Resources, Validation, Writing - review & editing.

**Chao-Chi Ho:** Data curation, Investigation, Project administration, Resources, Writing - review & editing.

**Chris Brown:** Data curation, Formal analysis, Software, Validation, Visualization, Roles/Writing – original draft, Writing - review & editing.

**Chun-Liang Lai:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Brett G.M. Hughes:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Tsung-Ying Yang:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Ken O'Byrne:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Yung-Hung Luo:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Sonia Yip:** Conceptualization, Methodology, Writing - review & editing.

**Ching-Liang Ho:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Victoria Bray:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Wu-Chou Su:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Melissa Moore:** Data curation, Investigation, Project administration, Supervision, Resources, Writing - review & editing.

**Wei-Lien Feng:** Project administration, Resources, Writing - review & editing.

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**Michelle M. Cummins:** Project administration, Resources, Visualization, Writing - review & editing.

**Martin R. Stockler:** Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing - review & editing.

**Benjamin J. Solomon:** Conceptualization, Data Curation, Investigation, Methodology, Supervision, Resources, Writing - review & editing.

**Thomas John:** Conceptualization, Data Curation, Investigation, Methodology, Supervision, Resources, Writing - review & editing.

**James Chih-Hsin Yang:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing - original draft, Writing - review & editing.

## Disclosure

Dr. Lee reports receiving grants or contracts from Rche, Amgen, AstraZeneca, and Merck kGA. He reports receiving honoraria from AstraZeneca, Amgen, Janssen, GSK, Merck kGA, Merck, Roche, Gilead, Novartis, and Takeda. Dr. Liao reports honoraria/speaker fees from AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceuticals, Stone Pharmaceuticals, Eli Lilly, Merck, Merck Sharp & Dohme (MSD), Novartis, Ono Pharmaceuticals, Pfizer, Roche and Takeda. Dr. Chiu reports receiving honoraria/speaker fees from Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi-Sankyo, Eli Lilly, Janssen, Merck KGaA, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, Shionogi, and Takeda. Dr. Mersiades reports receiving support to attend conferences from Pfizer. Dr. Hughes reports being an advisory board member for AstraZeneca. Dr. O'Byrne reports receiving honoraria from Merck Sharp & Dohme, BMS, Roche, Boehringer Ingelheim, AstraZeneca, Pfizer/EMD Serano, Merck Group, Ipsen, Seagen, Diacchi, Tristar Technology Group, Takeda, Amgen, BeiGene. He has consulting/advisory roles for Merck Sharp & Dohme, Boehringer Ingelheim, Roche/Genentech, Pfizer, AstraZeneca/MedImmune, BMS, Sanofi, Amgen, BeiGene, Ipsen, Seagen and Diacchi. He has stock and other ownership interests with Carpe Vitae Pharmaceuticals, Repluca Pharmaceuticals, and DGC Diagnostics and has four active patents (two published and two provisional). He has speaking roles for Merck Sharp & Dohme, Boehringer Ingelheim, BMS, Roche, Janssen, Pfizer, Merck Group, Seagen, and Beigene and has received travel/accommodation funding from Bayer Holding and Sanofi. Dr. Luo reports receiving honoraria from AstraZeneca, Boehringer Ingelheim, Pfizer, Chugai, and Takeda Oncology. Dr. Bray reports participation on a data safety monitoring or advisory board for the SHERLOCK study and the OCEANiC study. Dr. Moore reports receiving honoraria from Roche and Gilead, participation on a data safety monitoring or advisory board for Gilead, Merck, and Takeda and Leadership or Fiduciary role as Board Director, Thoracic Oncology Group of Australasia (TOGA). Dr. Stockler reports receiving support for the present manuscript from Cancer Australia and the Australian National Health and Medical Research Council. Grants or contracts to institution from Astellas, Celgene, Bionomics, Medivation, Sanofi, Pfizer, AstraZeneca, BMS, Roche, Amgen, Merck Sharp & Dohme, Tilray. Dr. Solomon reports receiving honoraria and is an advisory board member for AstraZeneca, Pfizer, Roche/Genetech, Lilly, Merck Sharpe Dohme, Bristol Myers Squibb, Amgen, Janssen and a Leadership or fiduciary role as board of directors for International Association for the study of Lung Cancer, Thoracic Oncology Group of Australasia, Cancer Council of Victoria. Dr. John reports receiving consulting fees to institution for BMS, AstraZeneca, Amgen, Roche, Pfizer, Takeda, Boehringer Ingelheim, MSD, Merck, Puma, Specialised Therapeutics, Gilead, Seagan, Johnson and Johnson. He reports receiving travel/speaker fees from AstraZeneca and MSD and support for attending meetings/conferences from AstraZeneca. Dr. Yang reports consulting/advisory role paid to institution from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck KGaA, Darmstadt Germany, Merck Sharp and Dohme, Novartis, Ono Pharmaceuticals, Pfizer, Roche.Genentech, Takeda Oncology, Yuhan Pharmaceuticals, Janssen Pharmaceuticals. He reports personal fees for consulting/advisory roles from Amgen, AstraZeneca, Boehringer Ingelheim, and Bristol Myers Squibb. He reports grants from AstraZeneca and Roche/Genentech. He reports institutional fees for advisory services from Gilead Sciences Inc., GSK, BeiGene, Regeneron Pharmaceutical, Taiho Pharmaceutical, ArriVent, AnHeart Therapeutics. Dr. Yang reports personal fees and others from Amgen, grants, personal fees and others from AstraZeneca, personal fees and others from Bayer, personal fees and others from Boehringer Ingelheim, personal fees and others from Bristol Myers Squibb, others from Daiichi Sankyo, other from Eli Lilly,

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## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100771.

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