Poster Number 13P

Durvalumab plus chemotherapy in patients with advanced EGFR mutation-positive NSCLC whose disease progressed on first-line osimertinib: an ORCHARD study interim analysis

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Objective

- To report data from an ORCHARD interim analysis concerning treatment with the anti-PD-L1 antibody durvalumab in combination with chemotherapy in patients with advanced epidermal growth factor receptor mutation-positive (EGFRm) non-small cell lung cancer (NSCLC) that had progressed on first-line (1L) osimertinib without detectable resistance mechanisms, or those patients for whom biomarker-directed study treatments were not available

Conclusions

- In this population, which comprised patients with advanced EGFRm NSCLC that progressed on 1L osimertinib with no biomarker-detected resistance mechanisms, or for whom biomarker-directed study treatments were not available, study stop criteria (<10% chance that objective response rate [ORR] is ≥45%) were met following treatment with durvalumab and chemotherapy. On account of this, recruitment was closed for this specific ORCHARD study arm
- Durvalumab plus chemotherapy was well tolerated with no new or unexpected safety signals
- Further biomarker analyses are ongoing to better understand the efficacy data concerning use of immune checkpoint inhibitors (ICIs) plus chemotherapy in this particular patient population
- The ORCHARD study continues to evaluate other novel therapy combinations in biomarker-matched and non-biomarker matched patients with advanced EGFRm NSCLC that progressed on 1L osimertinib

Plain language summary

What is the purpose of the ORCHARD study?

- ORCHARD is a study with different treatment arms designed to find possible treatments for patients with advanced NSCLC who have a change (or mutation) in the EGFR gene, and whose disease gets worse on osimertinib
- There are many treatment arms in the ORCHARD study. Patients are assigned to treatment arms that may benefit them

What are we reporting in this poster?

- Here we report data from one of the treatment arms: the durvalumab and chemotherapy treatment arm

How do we perform this research?

- Patients whose disease initially responded but then got worse on osimertinib were treated with durvalumab and chemotherapy until their disease got worse again, or until the patients and their doctors decided to stop treatment for other reasons

What did we find and what are the next steps?

- Although patients tolerated the combination of durvalumab and chemotherapy, it did not benefit patients enough and the treatment arm was stopped
- The other treatment arms in the ORCHARD study will continue

Where can I access more information?

- More information on the ORCHARD study can be found on ClinicalTrials.gov (NCT03944772): https://clinicaltrials.gov/ct2/show/NCT03944772

Poster

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials and the overall ORCHARD study design
Alternatively, please click on the following link: https://bit.ly/3hQi51U

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Introduction

- Osimertinib is a third-generation, irreversible, oral EGFR-tyrosine kinase inhibitor (TKI) that potently and selectively inhibits EGFR TKI-sensitising mutations and EGFR T790M resistance mutations, with efficacy in EGFRm NSCLC, including central nervous system metastases[1–5]
- Osimertinib is the preferred 1L treatment in patients with advanced EGFRm NSCLC;[6,7] however, tumours treated with osimertinib may eventually develop treatment resistance[8]
- The ongoing phase II ORCHARD platform study (NCT03944772) aims to characterise resistance mechanisms and evaluate novel therapy combinations in patients with advanced EGFRm NSCLC that progressed on 1L osimertinib[9]
- Treatment with ICIs (e.g., anti-PD1/ anti-PD-L1) in pre-treated patients with EGFRm NSCLC results in limited clinical benefit versus chemotherapy[10]
  - The anti-PD-1 antibody pembrolizumab was assessed previously in combination with platinum-doublet chemotherapy in 12 patients with EGFRm NSCLC that had progressed on osimertinib. This combination did not improve outcomes compared with chemotherapy alone[11]
- Further research is needed to confirm if ICIs in combination with other anticancer therapies can overcome the limited efficacy of ICIs alone in patients with pre-treated EGFRm NSCLC

Methods

- ORCHARD is a global, phase II, open-label, multicentre, multi-drug, biomarker-directed platform study in patients aged ≥18 years old (Japan, ≥20 years old) with locally advanced/metastatic EGFRm NSCLC that progressed on 1L osimertinib 80 mg once daily (QD) monotherapy (NCT03944772; please access the ORCHARD study design via the QR code)[9]
- Patients with stable and asymptomatic brain metastases were permitted
- Key exclusion criteria: EGFRm NSCLC that progressed in the first three months of osimertinib treatment; toxicity leading to permanent osimertinib discontinuation or dose reduction; unresolved toxicity from osimertinib. Patients must not have discontinued osimertinib >60 days prior to first study dose
- Patients were allocated to treatment after disease progression on 1L osimertinib based on post-progression tumour rebiopsy and molecular profiling by NGS using standard reported variants from the Foundation Medicine CDx platform
- Patients without detectable resistance mechanisms, or for whom biomarker-directed study treatments were not available, were allocated to non-biomarker matched treatment cohorts

Durvalumab + pemetrexed + carboplatin treatment arm

- In this treatment arm, patients with no biomarker-detected resistance mechanisms, or for whom biomarker-directed study treatments were not available were treated as described below (**Figure 1**)

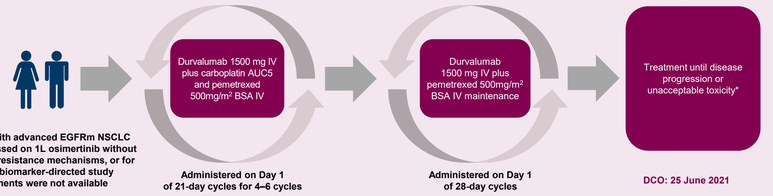


Figure 1: Durvalumab + pemetrexed + carboplatin treatment regimen
Recruitment was to be paused if study stop criteria (<10% chance that ORR is ≥45%) were met
*Treatment may continue beyond RECIST 1.1-defined progression if the investigator concluded that the patient was receiving clinical benefit, in the absence of another discontinuation criteria
AUC5, target area under the curve 5; BSA, body surface area; DCO, data cut off; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation-positive; IV, intravenous; 1L, first line

Endpoints

- **Primary endpoint:** ORR confirmed by the investigator using RECIST v1.1
- **Secondary endpoints** included progression-free survival (PFS) and duration of response (DoR)
- **Safety endpoints** included adverse events (AEs) assessed per Common terminology criteria for adverse events (CTCAE) v5
- **Exploratory endpoints** included tumour mutational burden (TMB) and molecular aberrations on next-generation sequencing (NGS) of tumour samples, and their respective correlation with clinical response

- Analyses are ongoing and data are subject to change

Results and interpretation

Baseline demographics and disease characteristics

- Between 10 October 2019 and DCO (25 June 2021), 25 patients received ≥1 dose of study treatment in this treatment cohort (**Table 1**)

Table 1. Baseline demographics and disease characteristics

Baseline demographics and disease characteristics	Durvalumab plus chemotherapy (N=25)
Age	
Median age, years (range)	61 (39–77)
≥18–<65 years / ≥65 years, n (%)	17 (68) / 8 (32)
Sex, n (%)	
Male / Female	6 (24) / 19 (76)
Race, n (%)	
Asian / White	19 (76) / 6 (24)
Smoking status, n (%)	
Current / Former / Never	1 (4) / 9 (36) / 15 (60)
WHO performance status, n (%)	
0 / 1	10 (40) / 15 (60)
Histology, n (%)	
Adenocarcinoma	25 (100)
No. of disease sites, n (%)	
1–2 / ≥3	5 (20) / 20 (80)
Mutations, n (%)	
Ex19del / L858R / T790M / other*	10 (40) / 9 (36) / 0 (0) / 4 (16)
CNS involvement at study entry, n (%)	
No / Yes	19 (76) / 6 (24)
Liver involvement at study entry, n (%)	
No / Yes	21 (84) / 4 (16)
Time to progression on first-line osimertinib therapy, n (%)	
<12 months† / ≥12 months	8 (32) / 17 (68)

*L861Q (n=2), G719S (n=2); †>3months and <12 months
CNS, central nervous system; WHO, World Health Organization

Relative dose intensity and treatment duration

- At data cut off, all patients received ≥75% relative dose intensity (percentage of actual dose delivered relative to intended dose through to treatment discontinuation or DCO) for each study drug, and 22 patients (88%) had discontinued all treatments
- Median treatment duration was 5.3 months (range, 0.9–14.3) for durvalumab and pemetrexed, and 2.9 months (range, 0.7–5.1) for carboplatin
- The median follow-up period was 9.7 months (range, 1.3–18.5) in overall survival censored patients

Objective response rate

- All 25 patients had measurable disease at baseline
- Confirmed ORR was 3/25 (12%; all confirmed partial responses); 17/25 (68%) patients had stable disease (≥six weeks) including six (24%) with unconfirmed partial responses. Four (16%) patients had disease progression and one (4%) was not evaluable (**Table 2**)

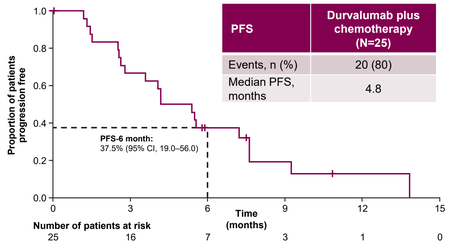
Table 2. ORR and best objective response

ORR	Durvalumab plus chemotherapy (N=25)
ORR, n (%; 80% CI)	3 (12; 4.5, 24.8)
Best objective response, n (%)	
Confirmed complete response	0
Confirmed partial response	3 (12)
Stable disease ≥6 weeks	17 (68)
Unconfirmed partial response	6 (24)
Stable disease	11 (44)
RECIST 1.1 disease progression	4 (16)
Death	0
Not evaluable	1 (4)
Incomplete post-baseline assessments	1 (4)

CI, confidence interval; ORR, objective response rate

Progression-free survival

- Median PFS was 4.8 months (95% confidence interval [CI]: 2.6, 7.6); PFS rate at six months was 37.5% (95% CI: 19.0, 56.0; **Figure 2**)



PFS	Durvalumab plus chemotherapy (N=25)
Events, n (%)	20 (80)
Median PFS, months	4.8

Figure 2: Progression-free survival
PFS-6 month, PFS rate at six months

Duration of response

- Median DoR in patients with a confirmed partial response (n=3) was 12.2 months
- Duration of treatment in all patients according to response type is presented in **Figure 3**
  - There was no clear correlation between length of time on prior 1L osimertinib and best response with durvalumab plus chemotherapy

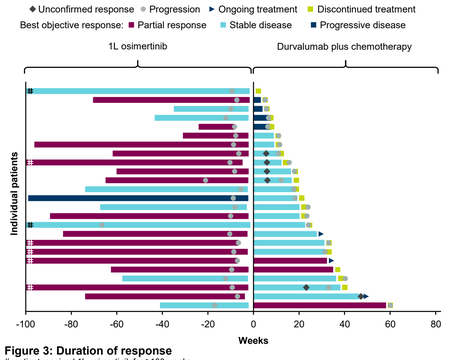


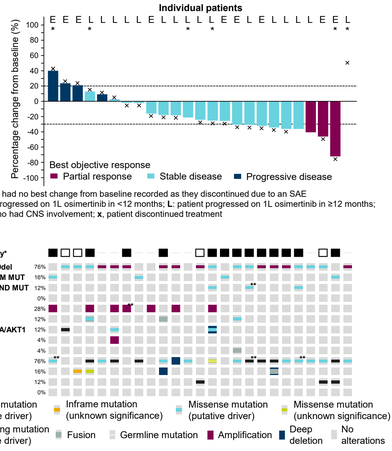
Figure 3: Duration of response
#, patient received 1L osimertinib for ≥100 weeks
1L, first line

Safety and tolerability

- Most AEs were mild or moderate in severity. There were no interstitial lung disease events
- AEs (any grade) which were considered possibly related to any study treatment were reported in 23 (92%) of patients
- The most common Grade ≥3 AEs were neutrophil count decreased (n=5, 20%) and anaemia (n=3, 12%); all of which were considered possibly related to treatment by the investigator
- SAEs were reported in three (12%) patients
  - The investigator determined that in two (8%) of these three patients, SAEs were causally related to carboplatin and pemetrexed (neutrophil count decreased and intractable nausea, each in one [4%] patient); both patients recovered from these SAEs
- One (4%) patient reported an AE (nausea) resulting in discontinuation of carboplatin
- There were no deaths due to AEs

Exploratory endpoints

- TMB was uniformly low within this particular ORCHARD study cohort **(Figure 4)**
- NGS identified that TP53 (n=19, 76%) mutations, EGFR amplifications (n=7, 28%), and EGFR secondary mutations (n=3, 12%) were the most common aberrations
- There was no association between best response and EGFR sensitising mutation type



One patient had no best change from baseline recorded as they discontinued due to an SAE
E: Patient progressed on 1L osimertinib in <12 months; **L**: patient progressed on 1L osimertinib in ≥12 months; *patients who had CNS involvement; **x**, patient discontinued treatment

*Black boxes indicate TMB was low; white boxes indicate that TMB was not evaluable; there were no other TMB categories; grey lines indicate that TMB was not tested
**Circulating tumour DNA only

Figure 4: Correlation of TMB and genomics with response type
A) Best objective response per patient; B) TMB per patient
AKT1, AKT serine/threonine kinase 1; ALK, anaplastic lymphoma kinase, serine/threonine kinase; AMP, amplification; CNS, central nervous system; EGFR, epidermal growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; MUT, mutation; PTEN, phosphatase and tensin homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RB1, retinoblastoma gene; RBM10, RNA binding motif protein 10; SAE, serious adverse event; sens, sensitive; SMARCA4, SWI/SNF related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4; uncom, uncommon; TP53, tumor protein P53; 1L, first-line

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