Poster 3222

# ORCHARD osimertinib + savolitinib interim analysis: A biomarker-directed phase II platform study in patients with advanced non-small cell lung cancer (NSCLC) whose disease has progressed on first-line (1L) osimertinib

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## Objective

- ORCHARD (NCT03944772) is a phase II study designed to characterize 1L osimertinib resistance mechanisms and identify optimal post-progression therapies
- Herein, we present efficacy and safety data regarding osimertinib + savolitinib in adult patients with epidermal growth factor receptor (EGFR)-mutated (EGFRm) advanced NSCLC and *MET* alterations (*MET* amplification / *MET* exon 14 skipping) whose disease progressed on 1L osimertinib

## Conclusions

- In this interim analysis, osimertinib + savolitinib demonstrated preliminary activity in patients with EGFRm advanced NSCLC and *MET* alterations, after disease progression on 1L osimertinib
- The safety profile was acceptable and consistent with the known profiles of osimertinib and savolitinib
- Enrolment in this treatment arm will continue up to approximately 30 patients as pre-specified per the protocol
- Further exploration of this combination is also ongoing in the SAVANNAH study (NCT03778229)

## Plain language summary

**Why are we performing this research?**
Osimertinib is a medication used to treat a type of NSCLC with a change (mutation) in the EGFR gene; this type of NSCLC is known as EGFR-mutated NSCLC. However, while osimertinib treatment can improve patient outcomes, many patients' tumours eventually acquire resistance to osimertinib because of another mutation which can develop in some cases, called a MET amplification. In an effort to overcome this problem, the ORCHARD clinical study aims to assess osimertinib combined with savolitinib (a medication which can target changes in MET) in patients whose cancer has become resistant to osimertinib

**How do we perform this research?**
Patients with EGFR-mutated NSCLC with MET alterations and osimertinib resistance are given a combination of osimertinib and savolitinib treatment. The treatment is planned to continue until disease progression, or the if patient and their doctor decide to stop treatment for other reasons

**What are the findings of this research and what are the implications?**
To date, this study has shown some initial benefit for patients who took osimertinib combined with savolitinib, after their cancer had become resistant to osimertinib. For example, some tumours shrank in size or did not grow further. The side effects observed were consistent with what we already know about osimertinib and savolitinib. The ORCHARD study is still ongoing and more results are expected to be released in the future.

**Where can I access more information?**
ORCHARD (NCT03944772): https://clinicaltrials.gov/ct2/show/NCT03944772

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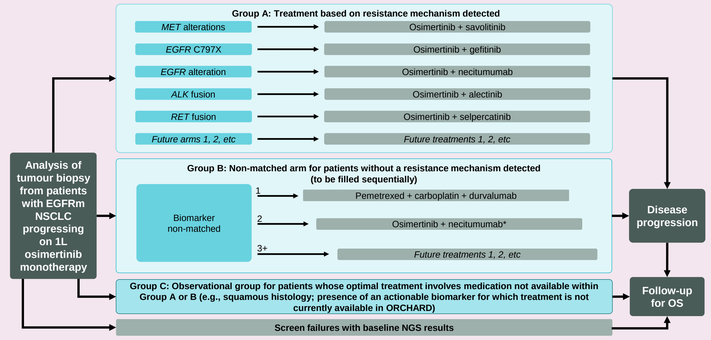
## Introduction

- Osimertinib is a third-generation, irreversible oral EGFR-tyrosine kinase inhibitor (TKI) that potently and selectively inhibits EGFR-TKI sensitising mutations (EGFRm; Ex19del/L858R) and the resistance mutation EGFR T790M, and has demonstrated efficacy in EGFRm NSCLC, including central nervous system metastases[1–4]. Osimertinib is the preferred first-line treatment in EGFRm advanced NSCLC[5,6]
- The tumours of patients with EGFRm NSCLC who are treated with EGFR-TKIs, including osimertinib, eventually acquire resistance. *MET* amplifications are one of the most common resistance mechanisms to osimertinib[7,8]
- The phase II ORCHARD platform study aims to characterise resistance mechanisms to 1L osimertinib and identify optimal post-progression therapies (**Figure 1**)
- This interim analysis builds on findings from the TATTON study (NCT02143466)[9] and reports on the use of osimertinib + savolitinib, an oral, potent and highly selective MET-TKI,[10–12] in adult patients with EGFRm advanced NSCLC and *MET* alterations, whose disease has progressed on 1L osimertinib

## Methods

- ORCHARD is a global, phase II, open-label, multicentre, multi-drug, biomarker-directed platform study in adult patients with locally advanced/metastatic EGFRm NSCLC whose disease has progressed on 1L osimertinib monotherapy (NCT03944772). Patients with stable and asymptomatic brain metastases were permitted
- Patients were allocated to treatment cohorts after disease progression on 1L osimertinib, based on tumour biopsy molecular profiling by next generation sequencing, using standard reported variants from the Foundation Medicine CDx platform
- Patients with *MET* alterations (*MET* amplification or *MET* exon 14 skipping) were allocated to receive osimertinib 80 mg orally (PO) once-daily (QD) + savolitinib 300 or 600 mg PO QD
  - After initial enrolment at savolitinib 600 mg QD, a protocol amendment introduced weight-based savolitinib dosing. Patients ≤55 kg received 300 mg QD, and those >55 kg received 600 mg QD. The protocol was later amended to a 300 mg QD dose, regardless of weight. Japanese patients received savolitinib 300 mg QD throughout the study
- Primary endpoint: objective response rate (ORR) confirmed by investigator assessment using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1
- Secondary endpoints include: duration of response (DoR) and safety/tolerability

### Figure 1. ORCHARD study design




Group A: Patients who are positive for protocol-determined biomarker; Group B: patients without an available protocol-determined biomarker match, allocated sequentially, once first cohort cap has been reached, the next cohort allocation will begin; Group C: observational cohort, treated in accordance with local practice.
*Recruitment dependent on the outcome of planned interim analyses of the osimertinib + necitumumab combination arm in the biomarker matched cohort.
1L; first-line; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NGS, next generation sequencing; ORR, objective response rate; OS, overall survival

## Results and interpretation

### Patients

- Patient demographics and clinical characteristics are summarised in **Table 1** (data cut-off: 21 January 2021)
- All enrolled patients had *MET* amplification. Of those with available central confirmation of *MET* amplification, *MET* gene copy numbers ranged from 7–68

### Table 1. Patient characteristics

| Characteristic | Osimertinib + savolitinib N=20 |
|---|---|
| **Age groups, years, n (%)** | |
| 18–65 | 14 (70) |
| Over 65 | 6 (30) |
| **Gender, female, n (%)** | 13 (65) |
| **Race, n (%)** | |
| White | 10 (50) |
| Asian | 8 (40) |
| American Indian / Alaska Native | 1 (5) |
| Other | 1 (5) |
| **Smoking history, n (%)** | |
| No | 11 (55) |
| Yes (previously) | 8 (40) |
| Yes (currently) | 1 (5) |
| **WHO performance status, n (%)** | |
| 0 | 8 (40) |
| 1 | 12 (60) |
| **Histology type, n (%)** | |
| Adenocarcinoma | 20 (100) |
| **CNS involvement at study entry, n (%)** | |
| Yes | 7 (35) |
| No | 13 (65) |
| **Liver involvement at study entry, n (%)** | |
| Yes | 4 (20) |
| No | 16 (80) |

CNS, central nervous system; WHO, World Health Organization

### Efficacy

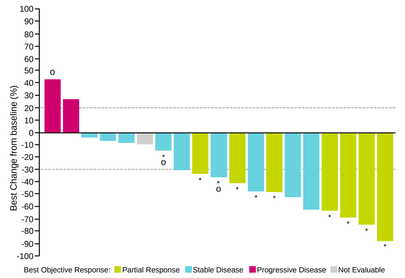
- Of the 20 patients who received osimertinib + savolitinib, 17 were evaluable for confirmed response analysis at DCO and had been followed-up for 13 weeks (**Table 2**)
- ORR was 41% (7/17; confirmed partial response); 7 (41%) had stable disease, including 3 patients with unconfirmed partial responses, 1 (6%) had disease progression and 2 (12%) were not evaluable (**Figure 2**)
- All patients who had a confirmed partial response were receiving treatment at data cut-off (**Figure 3**)
- As futility criteria based on confirmed ORR were not met, enrolment to this treatment arm will continue up to approximately 30 patients as pre-specified per the protocol
- Final efficacy data are anticipated in Q4 2022

### Table 2. Objective response rate

| ORR according to RECIST v1.1 (evaluable for confirmed response set*) | Osimertinib + savolitinib N=17 |
|---|---|
| **Number of patients with confirmed response, n (%)** | 7 (41) |
| 80% CI | 25, 59 |
| **Objective response n (%)** | 7 (41) |
| Complete response | 0 |
| Partial response | 7 (41) |
| **Stable disease ≥6 weeks** | 7 (41) |
| Unconfirmed partial response (that will never be confirmed) | 3 (18) |
| **Disease progression** | 1 (6) |
| **Death** | 0 |
| **Not evaluable** | 2 (12) |
| Stable disease <6 weeks | 1 (6) |
| Incomplete post baseline assessments | 1 (6) |

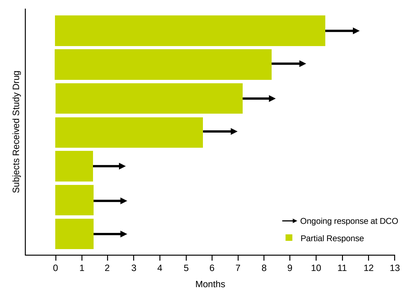
*Defined as all patients who received at least one dose of study treatment who had measurable disease at baseline, and had the opportunity to be followed up for 13 weeks.
CI, confidence interval; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1

### Figure 2. Best percentage change from baseline (efficacy analysis set†)




Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of reduction. Based on investigator's assessment of response (RECIST v1.1). N=19; one patient was not plotted as they had incomplete post-baseline assessments (discontinued due to a serious adverse event). 17/20 patients were included in the evaluable for the confirmed response analysis set.
*Patient ongoing treatment at time of data cut-off
†Patients who received at least one dose of study treatment who had measurable disease at baseline
‡Patient not included in confirmed response set due to having less than 13 weeks of follow up
RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1

### Figure 3. Duration of response




Start of responses were considered the time of the first scan showing a response (expressed as 0 months); responses were confirmed by a subsequent scan. Based on investigator's assessment of response (RECIST v1.1)
DCO, data cut-off (21 January 2021); DoR, duration of response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1

### Table 3. Incidence of AEs

| Incidence, n (%) | Osimertinib + savolitinib N=20 |
|---|---|
| **Any AE** | 20 (100) |
| **Any AE causally related to any study treatment** | 18 (90) |
| **CTCAE grade ≥3** | 6 (30) |
| **CTCAE grade ≥3, casually related to any study treatment** | 5 (25) |
| **Any SAE** | 6 (30) |
| **Any AE with outcome of death** | 0 |
| **Any AE leading to discontinuation of study treatment** | 3 (15) |
| Osimertinib | 2 (10) |
| Savolitinib | 3 (15) |

All patients who received at least one dose of study treatment.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event

### Table 4. Incidence of grade ≥3 AEs

| Most common AEs*, n (%) | Osimertinib + savolitinib N=20 |
|---|---|
| Neutrophil count decrease | 2 (10) |
| Pneumonia | 2 (10) |
| Pneumonitis | 1 (5) |
| Influenza | 1 (5) |
| Hypersensitivity | 1 (5) |
| Ischaemic stroke | 1 (5) |
| Deep vein thrombosis | 1 (5) |
| Pulmonary embolism | 1 (5) |
| Alanine aminotransferase increase | 1 (5) |
| Aspartate aminotransferase increase | 1 (5) |
| Amylase increase | 1 (5) |
| Blood fibrinogen decrease | 1 (5) |
| Lymphocyte count decrease | 1 (5) |
| White blood cell count decrease | 1 (5) |

All patients who received at least one dose of study treatment.
*AEs of any causality are included, using CTCAE
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events

### Safety

- Adverse events (AEs; of any grade) were reported by all 20 patients (100%)
- However, the majority were not serious and were mild to moderate in severity (**Table 3**)
- The most common Grade ≥3 AEs were two cases of decreased neutrophil count and two cases of pneumonia (**Table 4**). 5/20 patients (25%) reported a grade ≥3 AE that was causally related to study treatment
- 3/20 patients (15%) experienced a treatment emergent AE that resulted in discontinuation of a study treatment. These included: hypersensitivity, n=2; pneumonia, n=1; pneumonitis, n=1; aspartate aminotransferase increase, n=1; and nausea, n=1
- No deaths due to AEs were reported
- Overall, the safety profile was consistent with the known profiles of osimertinib and savolitinib, and no new safety signals were identified

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## Disclosures

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