SAFFRON: Ph3 savolitinib + osimertinib vs chemotherapy in EGFRm NSCLC with MET overexpression/amplification post-osimertinib

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Plain language summary

Why are we going to perform this research?

- Patients with advanced lung cancer who have a mutation in their epidermal growth factor receptor (EGFR) gene that drives tumour growth, are often treated with a type of drug known as an EGFR-tyrosine kinase inhibitor (TKI) - Osimertinib.
- Osimertinib works by blocking the activity of the EGFR protein on cancer cells to reduce their growth and spread.
- Osimertinib is effective in EGFR-mutant NSCLC and is a preferred treatment for these patients. Unfortunately, patients may subsequently develop other alterations within their cancer leading to osimertinib treatment no longer working.
- The emergence of secondary tumour resistant mutations results in increased levels of another receptor, called MET, which drives tumour growth.
- Early clinical studies showed that combining osimertinib with savolitinib treatment (a drug that blocks the activity of MET protein) might benefit these patients by reducing the growth and spread of cancer.

How will we perform this research?

- The SAFFRON study is ongoing and recruiting patients. We expect to include approximately 324 patients from 27 countries.
- The SAFFRON study is a global, multicentre, randomised, open-label Phase III study designed to assess the efficacy and safety of savolitinib plus osimertinib in combination with chemotherapy in patients with EGFRm, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC post EGFR-TKI treatment, with acceptable tolerability in the selected patient population.
- Documentation of MET exon 14 skipping in tumour cells as detected by fluorescence in situ hybridisation.
- Tumour assessments using computed tomography or magnetic resonance imaging will be collected every 6 weeks ± 7 days, up to 54 weeks, and then every 18 weeks ±7 days until disease progression.

Key inclusion criteria

- Adults ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC not amenable to curative therapy
- Documented EGFRm (Ex19del/L858R) and/or T790M and MET overexpression and/or amplification as determined prospectively by clinical laboratory testing
- Disease progression on 1L or 2L treatment with osimertinib as the most recent anti-cancer therapy
- Eastern Cooperative Oncology Group performance status ≤1

Key exclusion criteria

- Prior chemotherapy in the metastatic setting
- NSCLC with predominant squamous cell histology
- Major surgery, radiation or brain or primary or in the tumour
- History or active leptomeningeal carcinomatosis
- Active gastrointestinal disease, recent uncontrolled disease, severe or uncontrolled systemic disease, active hepatitis B or C infection, active infections (HIV or tuberculosis) and liver disease

Study endpoints

- Progression-free survival
- By Response Evaluation Criteria in Solid Tumors version 1.1 and assessed by blinded independent central review

- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Time to discontinuation of treatment or death
- Tumour shrinkage
- Time to deterioration in pulmonary core systems (pleuropulmonary, coughed and chest pain)

Safety will be evaluated in terms of:
- Adverse events, serious adverse events, discontinuation due to adverse events and deaths, clinical chemistry and hematology, electrocardiograms/multigated acquisition (KUGRA) scans, electrocardiograms, vital signs and ECG, haematology, and safety
- Disease-relevant, response, or resistance markers in tumour specimens and blood samples
- Adverse events, serious adverse events, discontinuation due to adverse events and deaths, clinical chemistry and hematology, electrocardiograms/multigated acquisition (KUGRA) scans, electrocardiograms, vital signs and ECG, haematology, and safety
- Disease-relevant, response, or resistance markers in tumour specimens and blood samples

Rationale

- Savolitinib is a third-generation, irreversible, oral EGFR/EGFR that potently and selectively inhibits both EGFR-TKI acquired resistance (activating T790M and EGFR759M resistance mutations), with demonstrated efficacy in EGFRm non-small-cell lung cancer (NSCLC), including central nervous system metastases.

- Savolitinib is the preferred first-line (1L) treatment in EGFRm NSCLC. However, tumours can develop resistance to osimertinib.

- MET overexpression and/or amplification is the most common resistance mechanism to osimertinib. Despite this, there is no approved targeted therapy for these patients, with platinum-based chemotherapy remaining the standard of care with limited efficacy.

- Savolitinib is conditionally approved in China for the treatment of metastatic NSCLC with MET exon 14 skipping in tumour cells as detected by fluorescence in situ hybridisation. 10th and 11th amendment criteria include unacceptable toxicity or patient withdrawal, crossing over from chemotherapy to the combination treatment, and crossing over from savolitinib to osimertinib.

- Co-primary end points are defined as a composite of 1L or 2L treatment with osimertinib as the most recent anti-cancer therapy, as reported by radiology review (BICR) or oncologists.

- The study is planned to recruit across 27 countries, globally, with an estimated 324 patients to be randomised.

- The primary endpoint is expected by July 2025.

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References


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