Phase II, two-arm study of tepotinib + osimertinib in patients with *EGFR*-mutant NSCLC and acquired resistance to first-line osimertinib due to *MET* amplification: INSIGHT 2

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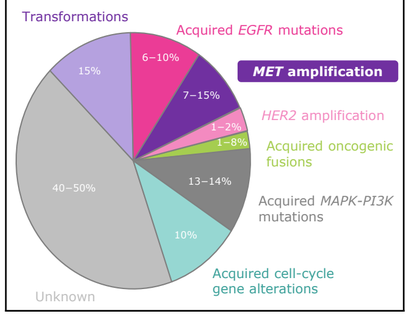
INTRODUCTION

- *MET* amplification is a resistance mechanism to EGFR TKIs[1]
- *MET* amplification is a common cause of acquired resistance to EGFR TKI therapy and occurs in 7–15% of patients whose disease has become resistant to osimertinib as a 1L therapy (**Figure 1**)[2]
- Osimertinib is a third-generation EGFR TKI that has demonstrated efficacy in patients with NSCLC with activating *EGFR* mutations, irrespective of T790M resistance mutation[3]
- The combination of a MET inhibitor with osimertinib has the potential to overcome MET-related osimertinib resistance[4,5]

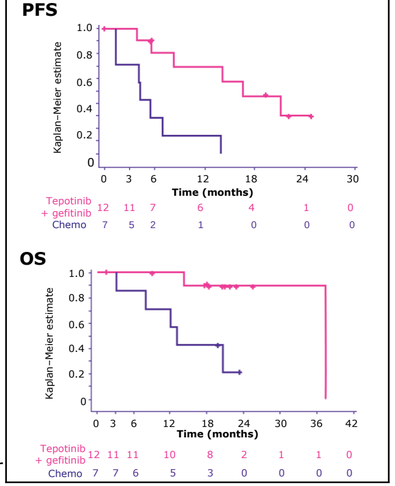
Figure 1. Resistance mechanisms to 1L osimertinib[2]



TEPOTINIB

- Tepotinib is an orally available, highly selective MET TKI that blocks MET-mediated signaling pathways involved in tumorigenesis[6]
- In preclinical models, tepotinib overcame acquired resistance to first-, second-, or third-generation EGFR TKIs that was mediated by *MET* amplification[7]
- The INSIGHT study was an open-label, Phase I/II randomized trial that compared tepotinib + gefitinib with chemotherapy in relapsed *EGFR*-mutant NSCLC with MET overexpression (IHC2+ and IHC3+) and/or *MET* amplification (NCT01982955)[8]
- In patients with *MET* amplification tepotinib + gefitinib improved:
  - Investigator-reported PFS and OS (**Figure 2**)[8]
    - Median PFS was 16.6 vs 4.2 months (HR = 0.13; 90% CI: 0.04, 0.43) compared with chemotherapy[8]
    - Median OS was 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51) compared with chemotherapy[8]
  - Investigator-reported objective response rates were 67% for tepotinib + gefitinib vs 43% for chemotherapy (OR = 2.67; 90% CI: 0.37, 19.56)[8]
  - Median DOR was 19.9 months (90% CI: 7.0, NE) for tepotinib + gefitinib vs 2.8 months (90% CI: 2.8, 9.7) for chemotherapy[8]

Figure 2. INSIGHT study: PFS and OS of patients with *MET* amplification[8]

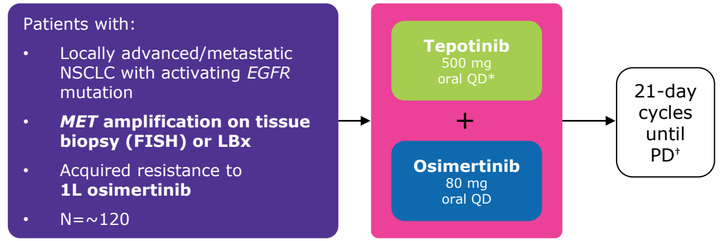


INSIGHT 2

Study design and methods

- INSIGHT 2 (NCT03940703) is a global, open-label, Phase II trial of tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC; the study opened in September 2019 (**Figure 3**)
- Following a protocol amendment in April 2020, the study is now enrolling patients with *MET*-amplified advanced/metastatic NSCLC with acquired resistance to 1L osimertinib
- An initial safety run-in period was completed in August 2020; the safety and tolerability of tepotinib 500 mg QD (450 mg active moiety) + osimertinib 80 mg QD was confirmed
- The study is estimated to enroll 120 patients

Figure 3. INSIGHT 2 study design



*Initially, eligible patients who are detected to be positive for *MET* amplification will be randomly assigned in a ratio of 2:1 to either the combination of tepotinib and osimertinib or tepotinib alone, until 12 are enrolled in the monotherapy arm. After this, all patients will be assigned to the combination. Patients who are randomized to tepotinib monotherapy will have the opportunity to switch over to the combination at the time of disease progression.

†Treatment continues until disease progression, death, an adverse event leading to discontinuation, study withdrawal, or consent withdrawal.

Study objectives and endpoints

- The aim of INSIGHT 2 is to assess the efficacy and safety of tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC
- The primary endpoint is objective response by IRC per RECIST v1.1. Other study endpoints are shown in **Table 1**
- Efficacy and safety analyses will be based on all patients who received treatment with any study medication
- The primary efficacy analysis for the primary endpoint will be conducted in all patients with *MET* amplification confirmed centrally by FISH, treated with tepotinib + osimertinib

Table 1. Study endpoints

Primary endpoint	Objective response by IRC per RECIST v1.1
Secondary endpoints	Objective response by investigator assessment
	DOR by IRC and investigator assessment
	OS
	HRQoL
	Pharmacokinetics
	Resistance markers
	Safety and tolerability

Eligibility criteria

- Key eligibility criteria are shown in **Table 2**
- Patients must be ≥18 years old, have an ECOG performance status of 0–1, and normal organ function

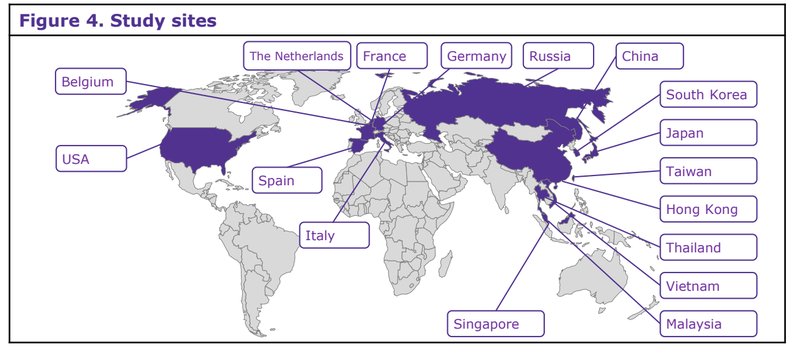
Table 2. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• ≥18 years of age • Locally advanced or metastatic NSCLC with activating *EGFR* mutation • Presence of ≥1 independently verified measurable lesion • *MET* amplification determined by FISH testing or LBx • Received only 1L therapy with osimertinib for advanced or metastatic NSCLC • Acquired resistance on previous 1L osimertinib with radiological documentation of disease progression and objective clinical benefit during previous 1L osimertinib therapy • ECOG performance status 0–1 • Life expectancy ≥12 weeks	• Any unresolved NCI-CTCAE Grade ≥2 toxicity from previous therapies • Inadequate hematologic, liver, renal, or cardiac function • History of interstitial lung disease • Contraindication to osimertinib • Prior HGF/MET pathway-targeted therapy • Participation in another interventional clinical study within 30 days prior to first dose – Except in studies where the investigational product was osimertinib as the 1L of therapy

Study sites and contacts

- Recruitment is ongoing, with >600 patients prescreened. Approximately 125 sites in 17 countries in Europe, Asia, and North America are expected to participate. Approximately 15 sites will recruit patients in the USA (**Figure 4**)

Figure 4. Study sites



- The Coordinating Investigator for this study is Prof Yi-Long Wu (syylwu@live.cn)
- For further information, please visit www.ClinicalTrials.gov (NCT03940703) or contact Merck KGaA, Darmstadt, Germany (Tel: +49 6151720; www.merckgroup.com)

INSIGHT 2 resources

GET INSIGHT 2 TRIAL CARD

GET INSIGHT 2 TRIAL ANIMATION

GET INSIGHT 2 PATIENT BROCHURE

GET INSIGHT 2 PHYSICIAN BROCHURE

Abbreviations: 1L, first-line; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; HR, hazard ratio; HRQoL, health-related quality of life; IHC, immunohistochemistry; IRC, independent review committee; LBx, central blood-based next-generation sequencing; MAPK, mitogen-activated protein kinase; MET, mesenchymal–epithelial transition factor; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not estimable; NSCLC, non-small cell lung cancer; OR, odds ratio; OS, overall survival; PD, progression-free survival; PI3K, phosphoinositide 3-kinase; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

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