INSIGHT 2: Tepotinib + osimertinib in patients with *EGFR*-mutant NSCLC having acquired resistance to 1st-line osimertinib due to *MET* amplification

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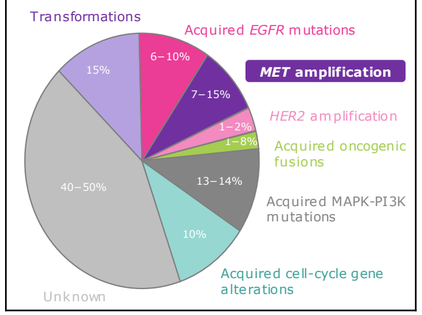
INTRODUCTION

- *MET* amplification is a resistance mechanism to EGFR TKIs occurring via the over-activation of downstream signaling pathways, such as PI3K and MAPK[1]
- *MET* amplification is a common cause of acquired resistance to EGFR TKI therapy and occurs in 7–15% of patients whose disease became resistant to osimertinib as a first-line 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]

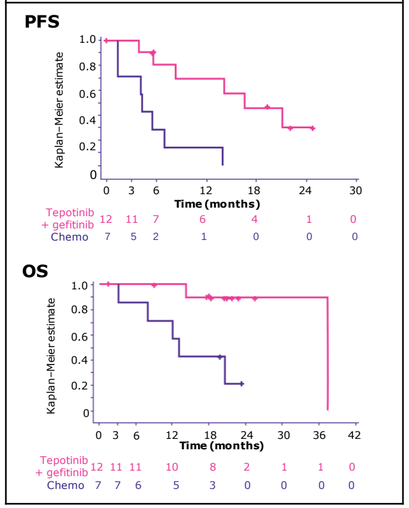
Figure 1. Resistance mechanisms to first-line osimertinib[2]



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 a Phase Ib/II randomized trial that compared tepotinib plus 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, treatment with tepotinib plus gefitinib improved investigator-reported PFS and OS (**Figure 2**)[8]
  - The PFS was 16.6 vs 4.2 months (HR = 0.13; 90% CI: 0.04, 0.43) compared with chemotherapy[8]
  - The OS was 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51) compared with chemotherapy[8]

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

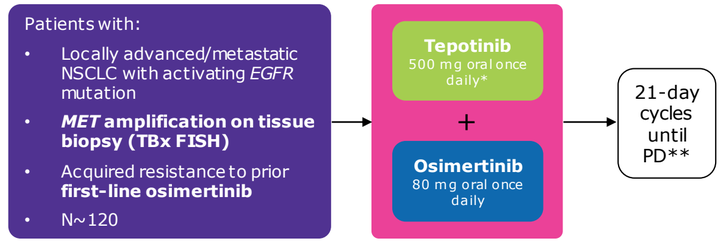


INSIGHT 2

Study design and methods

- INSIGHT 2 (NCT03940703) is a global, open-label, Phase II study that was opened in September 2019 (**Figure 3**)
- Following a protocol amendment in April 2020, the study is enrolling patients with *MET*-amplified advanced/metastatic NSCLC with acquired resistance to first-line osimertinib; patients will receive treatment with tepotinib plus osimertinib
- Enrollment is allowed based on local FISH testing while awaiting central confirmation of *MET* amplification
- An initial safety run-in period will confirm the safety and tolerability of tepotinib 500 mg once daily plus osimertinib 80 mg once daily
- The study is anticipated to enroll 120 patients overall

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 the 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.

- INSIGHT 2 aims to assess the efficacy of tepotinib in combination with osimertinib in patients with *MET*-amplified advanced/metastatic NSCLC with activating *EGFR* mutations
- Study endpoints are shown in **Table 1**
- Safety and efficacy 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

Table 1. Study endpoints

Primary endpoint	OR by independent review committee per RECIST v1.1
Secondary endpoints	PFS, OS, and duration of response
	ORR by investigator assessment
	Tolerability and safety
	Health-related quality of life
	Pharmacokinetics

Eligibility criteria

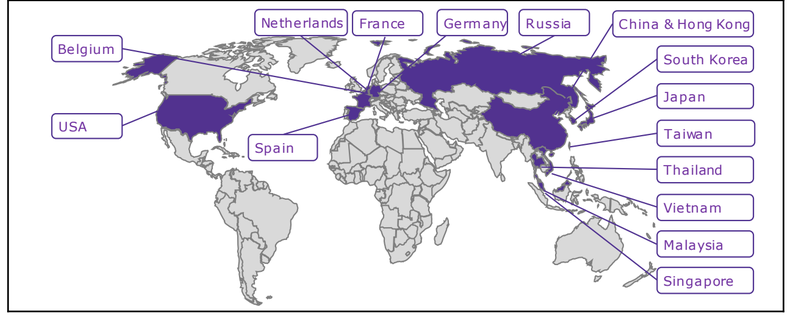
- INSIGHT 2 will be conducted in patients with *MET*-amplified advanced/metastatic NSCLC with activating *EGFR* mutations and acquired resistance to prior first-line osimertinib (**Table 2**)

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 • Received only first-line therapy with osimertinib for advanced or metastatic NSCLC and acquired resistance on previous first-line osimertinib • 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 first-line of therapy

- Recruitment is ongoing with >300 patients pre-screened, and approximately 103 sites in 15 countries in Europe, Asia, and North America are expected to participate (**Figure 4**)

Figure 4. Study sites



Study contacts

- 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)

GET INSIGHT2 TRIAL CARD

Colorectal cancer: Trial in progress

- Tepotinib is also being investigated in a Phase II study that will assess the efficacy and safety of tepotinib plus cetuximab in patients with *RAS/BRAF* WT left-sided metastatic CRC with acquired resistance to anti-EGFR therapy due to *MET* amplification (NCT04515394)

GET CRC TRIAL CARD

Abbreviations: BRAF, proto-oncogene B-Raf; CI, confidence interval; CRC, colorectal cancer; 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; IHC, immunohistochemistry; MAPK, mitogen-activated protein kinase; MET, mesenchymal–epithelial transition factor; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma viral oncogene homolog; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TBx, tissue biopsy; WT, wild-type.

References: 1. Wu YL, et al. Cancer Treat Rev. 2017;61:70–81; 2. Leonetti A, et al. Br J Cancer. 2019; 121(9):725–37; 3. Soria JC, et al. N Engl J Med. 2018;378:113–25; 4. Ahn M, et al. J Thorac Oncol. 2017;12(suppl. 2):S1768; 5. Sequist LV, et al. Lancet Oncol. 2020;21(3):373–86.; 6. Bladt F, et al. Clin Cancer Res. 2013;19:2941–51; 7. Friese-Hamim M, et al. Am J Cancer Res. 2017;7:962–72; 8. Wu Y-L, et al. Lancet Respir Med. 2020. doi:10.1016/S2213-2600(20)30154-5.

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