# 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


**Viola W. Zhu**[1] (zhuvw@hs.uci.edu), Christine Bestvina[2], Gilberto de Lima Lopes[3], John Hamm[4], Melissa Johnson[5], Philip Lammers[6], Xiuning Le[7], Luis Raez[8], Suman Rao[9], Joshua Sabari[10], Ronald Scheff[11], Umit Tapan[12], Jonathan Thompson[13], Niki Karachaliou[14], Barbara Ellers-Lenz[15], Sabine Brutlach[14], Egbert Smit[16], Yi-Long Wu[17]

[1]University of California Irvine, Chao Family Comprehensive Cancer Center, California, USA; [2]University of Chicago Medical Center, Chicago, Illinois, USA; [3]University of Miami Miller School of Medicine, Florida, USA; [4]Norton Cancer Institute, Louisville, USA; [5]Tennessee Oncology – Skyline Satellite, Nashville, USA; [6]Baptist Cancer Center, Memphis, USA; [7]University of Texas MD Anderson Cancer Center, Houston, USA; [8]Memorial Healthcare System, Hollywood, USA; [9]Medstar Franklin Square Clinical Research Center, Baltimore, USA; [10]NYU Langone Clinical Cancer Center, New York, USA; [11]Weill Cornell Medical College, New York, USA; [12]Boston Medical Center, Boston, USA; [13]Medical College of Wisconsin, Milwaukee, USA; [14]Global Clinical Development, Merck KGaA, Darmstadt, Germany; [15]Department of Biostatistics, Merck KGaA, Darmstadt, Germany; [16]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [17]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

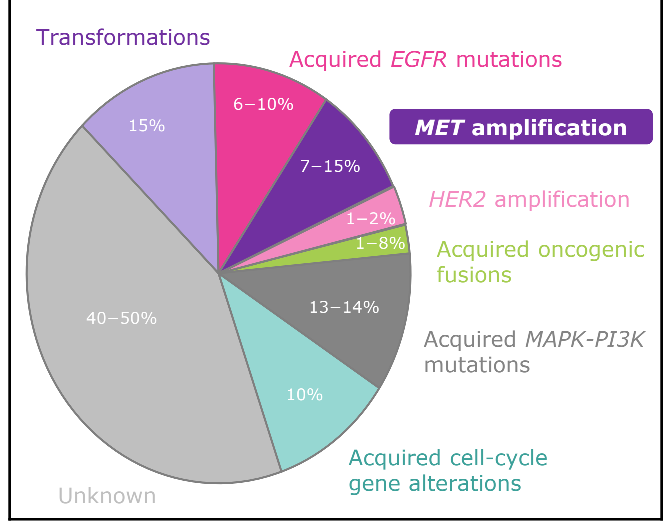


Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the author of this poster


## 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]

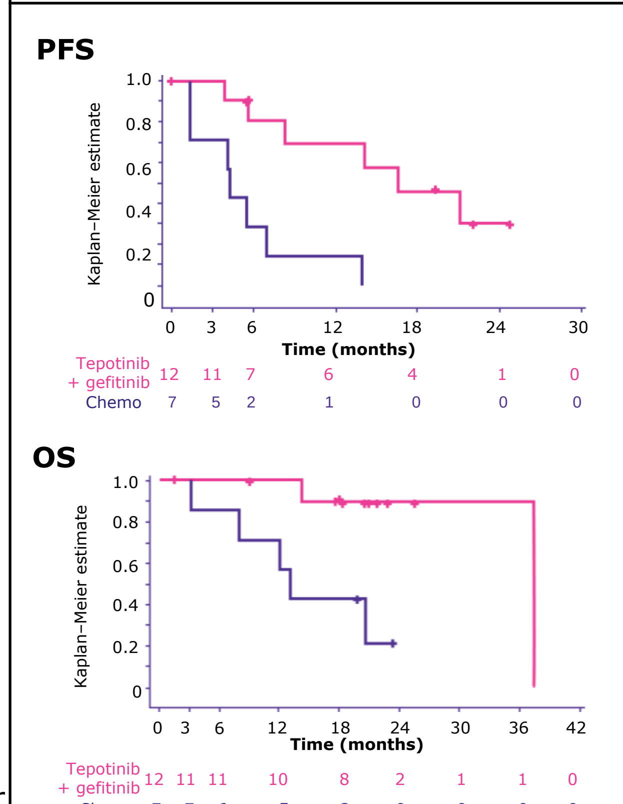
**Figure 1. Resistance mechanisms to 1L osimertinib[2]**




## 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]**

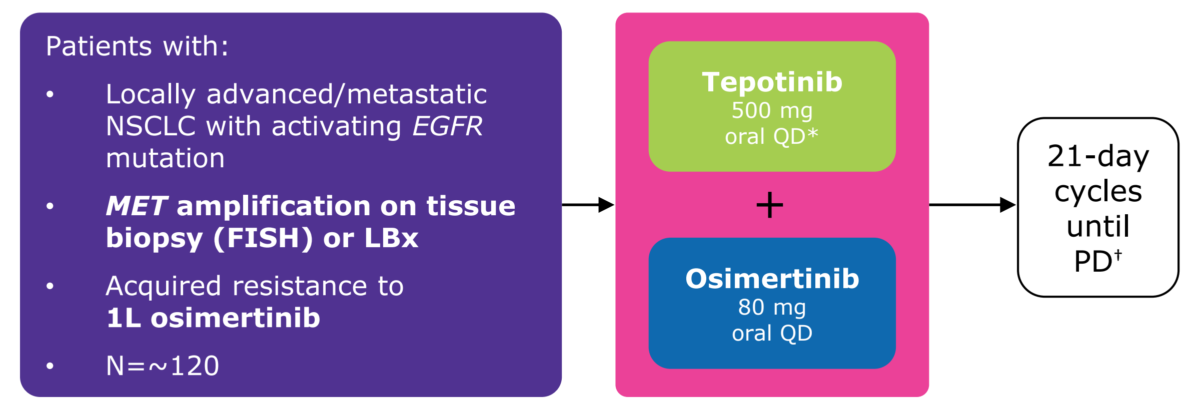



## INSIGHT 2

### 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

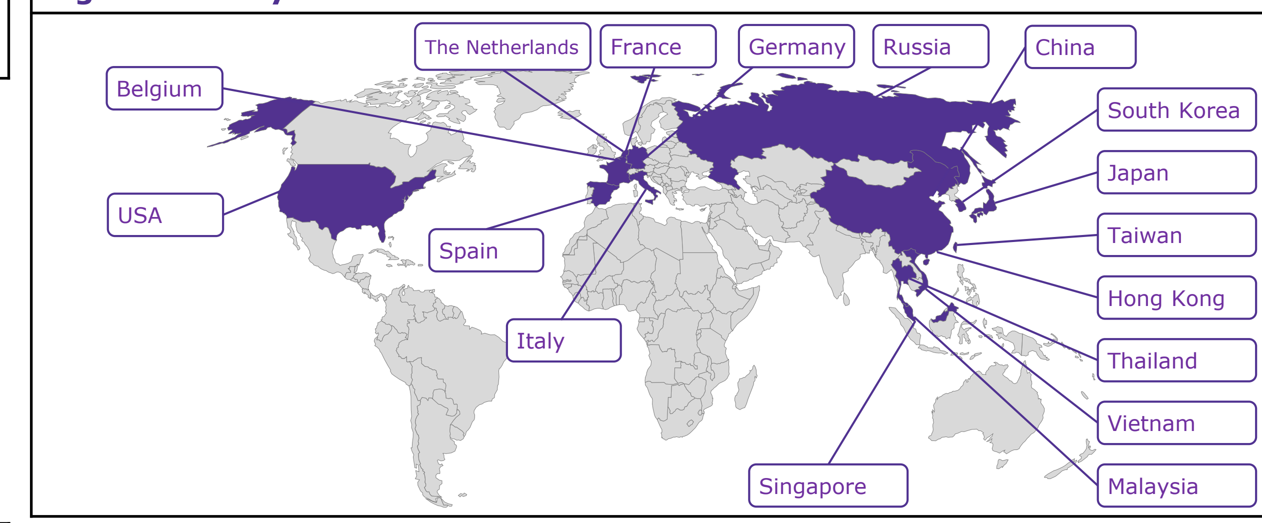
**Table 2. Key inclusion and exclusion criteria**

| Key inclusion criteria | Key exclusion criteria |
|---|---|
| • ≥18 years of age<br>• Locally advanced or metastatic NSCLC with activating *EGFR* mutation<br>• Presence of ≥1 independently verified measurable lesion<br>• *MET* amplification determined by FISH testing or LBx<br>• Received only 1L therapy with osimertinib for advanced or metastatic NSCLC<br>• Acquired resistance on previous 1L osimertinib with radiological documentation of disease progression and objective clinical benefit during previous 1L osimertinib therapy<br>• ECOG performance status 0−1<br>• Life expectancy ≥12 weeks | • Any unresolved NCI-CTCAE Grade ≥2 toxicity from previous therapies<br>• Inadequate hematologic, liver, renal, or cardiac function<br>• History of interstitial lung disease<br>• Contraindication to osimertinib<br>• Prior HGF/MET pathway-targeted therapy<br>• Participation in another interventional clinical study within 30 days prior to first dose<br>– 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, progressive disease; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.


**References:** 1. Wu YL, et al. *Cancer Treat Rev.* 2017;61:70–81; 2. Leonetti A, et al. *Br J Cancer.* 2019;121(9):725–737; 3. Soria JC, et al. *N Engl J Med.* 2018;378:113–125; 4. Ahn M, et al. *J Thorac Oncol.* 2017;12(Suppl. 2):S1768; 5. Sequist LV, et al. *Lancet Oncol.* 2020;21(3):373–386; 6. Bladt F, et al. *Clin Cancer Res.* 2013;19:2941–2951; 7. Friese-Hamim M, et al. *Am J Cancer Res.* 2017;7:962–972; 8. Wu YL, et al. *Lancet Respir Med.* 2020;8(11):1132–1143.



**Acknowledgments:** The authors would like to thank patients, all investigators and co-investigators, and the study teams at all participating centers and at Merck KGaA, Darmstadt, Germany. The trial was sponsored by Merck KGaA, Darmstadt, Germany. Medical writing and editorial assistance was provided by Syneos Health, UK, and funded by Merck KGaA, Darmstadt, Germany.


**Disclosures:** Viola Zhu has consulted or acted in an advisory role with AstraZeneca, Takeda, TP Therapeutics, Roche/Genentech, and Xcovery, has received speaker fees from AstraZeneca, Roche/Genentech, Takeda, and Blueprint Medicines, has received travel expenses from AstraZeneca, Roche/Genentech, Takeda, and TP Therapeutics, has stock in TP Therapeutics, and has received honoraria from AstraZeneca, Roche/Genentech, Takeda, Blueprint Medicines, and Xcovery. Christine Bestvina has consulted with AbbVie, AstraZeneca, Genentech, Pfizer, Curio Science, OncLive Clinical Congress Consultants, Seattle Genetics, Creative Educational Concepts, and Takeda, has received travel expenses from EMD Serono, and has received research funding from Bristol-Myers Squibb. Gilberto de Lima Lopes has consulted with Pfizer and AstraZeneca, has received travel expenses from Boehringer Ingelheim, Pfizer, E.R Squibb Sons LLC, Janssen, has received honoraria from Boehringer Ingelheim, and has received (including his institution) research funding from Merck Sharpe and Dohme, EMD Serono, AstraZeneca, Blueprint Medicines, Tesaro, Bavarian Nordic, Novartis, G1 Therapeutics, Adaptimmune, Bristol-Myers Squibb, GlaxoSmithKline, AbbVie, Rgenix, Pfizer, Roche, Genentech, Lilly, Janssen, and Lucence. John Turner Hamm has consulted with Meda Pharmaceuticals, Pfizer, and AstraZeneca, has received honoraria from Puma Biotechnology, Exelixis, and BrightPath Biotherapeutics, and has received research funding from AbbVie, Amgen, ARMO BioSciences, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Boston Biomedical, BrightPath Biotherapeutics, Bristol-Myers Squibb, Cancer Research and Biostatistics, Celgene, Clovis Oncology, Daiichi Sankyo, Dana-Farber Cancer Institute, Deciphera, Lilly, EMD Serono, EpicentRx, Roche, Five Prime Therapeutics, G1 Therapeutics, GBG Forschungs, Genentech, Gilead Sciences, GlaxoSmithKline, Gynecologic Oncology Group, Halozyme, Immunicum, Incyte, Infinity Pharmaceuticals, Janssen, Jiangsu Hengrui Medicine, Johnson & Johnson, MedImmune, Merck, Moffitt Cancer Center, National Surgical Adjuvant Breast and Bowel Project, Nektar, Novartis, OncoMed, Pfizer, PharmaMar, Plexxikon, Pronova, Sarah Cannon Research Institute, Seattle Genetics, SWOG, and Spectrum Pharmaceuticals. Melissa Johnson has consulted or acted in an advisory role with Otsuka, Genentech/Roche, Boehringer Ingelheim, Astellas Pharma, Pfizer, Guardant Health, Ribon Therapeutics, Incyte, AbbVie, Achilles Therapeutics, Atreca, GlaxoSmithKline, Gritstone Oncology, Janssen Oncology, Lilly, Novartis, Association of Community Cancer Centers (ACCC), Amgen, Bristol-Myers Squibb, Daiichi Sankyo, EMD Serono, G1 Therapeutics, WindMIL, Checkpoint Therapeutics, and Eisai, has received travel expenses from AbbVie, AstraZeneca, Genentech, Incyte, Merck, Pfizer and Sanofi, and has received research funding from EMD Serono, Kadmon, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, Stem CentRx, Novartis, Checkpoint Therapeutics, Array BioPharma, Regeneron, Merck, Hengrui Pharmaceutical, Lycera, BeiGene, Tarveda Therapeutics, Loxo, AbbVie, Boehringer Ingelheim, Guardant Health, Daiichi Sankyo, Sanofi, CytomX Therapeutics, Dynavax Technologies, Corvus Pharmaceuticals, Incyte, Genocea Biosciences, Gritstone Oncology, Amgen, Genentech/Roche, Adaptimmune, Syndax, Neovia Oncology, Acerta Pharma, Takeda, Shattuck Labs, GlaxoSmithKline, Apexigen, Atreca, OncoMed, Lilly, Immunocore, Jounce Therapeutics, University of Michigan, WindMIL, TCR2 Therapeutics, Arcus Biosciences, Ribon Therapeutics, BerGenBio, Calithera Biosciences, Tmunity Therapeutics, Inc., Seven and Eight Biopharmaceuticals, Rubius Therapeutics, Curis, Silicon Therapeutics, Dracen, PMV Pharma, and Artios. Philip Lammers has consulted or acted in an advisory role with Pfizer, Boehringer Ingelheim, Merck, Teva, and AstraZeneca. Xiuning Le has consulted or acted in an advisory role with AstraZeneca, Lilly, EMD Serono, Spectrum Pharmaceuticals, and Daiichi Sankyo/Lilly, and has received research funding from Lilly and Boehringer Ingelheim. Luis Raez has received research funding from Genentech/Roche, Merck Serono, Boehringer Ingelheim, Novartis, Pfizer, Syndax, Loxo, Merck, Bristol-Myers Squibb, Guardant Health, Heat Biologics, and Amgen. Suman Rao has consulted or acted in an advisory role with Galvanize Therapeutics, has received speaker fees from AstraZeneca, has received travel expenses from Merck, and has received honoraria from Merck and AstraZeneca. Joshua Sabari has consulted or acted in an advisory role with AstraZeneca, Janssen Oncology, Navire, Pfizer, Regeneron, Medscape, and Takeda. Ronald Scheff has consulted or acted in an advisory role with Lilly and Boehringer Ingelheim, has received honoraria from Boehringer Ingelheim and AstraZeneca, has received speaker fees from AstraZeneca and Bristol-Myers Squibb, and has received travel expenses from AstraZeneca and Boehringer Ingelheim. Umit Tapan has nothing to disclose. Jonathan Thompson has consulted or acted in an advisory role with Pfizer, and has received speaker fees from AstraZeneca. Niki Karachaliou, Barbara Eller-Lenz, and Sabine Brutlach are employees of Merck KGaA. Egbert Smit has consulted or acted in an advisory role with Lilly, AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Bristol-Myers Squibb, Merck KGaA, MSD Oncology, Takeda, Bayer, Merck KGaA, Novartis, Daiichi Sankyo, and Seattle Genetics, and has received research funding from Boehringer Ingelheim, Bayer, Roche/Genentech, AstraZeneca, and Bristol-Myers Squibb. Yi-Long Wu has consulted or acted in an advisory role with AstraZeneca, Roche, and Boehringer Ingelheim, has received honoraria from AstraZeneca, Lilly, Roche, Pfizer, Boehringer Ingelheim, MSD Oncology, and Bristol-Myers Squibb, and has received research funding from Boehringer Ingelheim, Roche, and Pfizer.


**Poster TPS9136 presented at the American Society of Clinical Oncology Virtual Congress | June 4–8, 2021**