Tepotinib + osimertinib for *EGFR*-mutant NSCLC with resistance to first-line osimertinib due to *MET* amplification: INSIGHT 2

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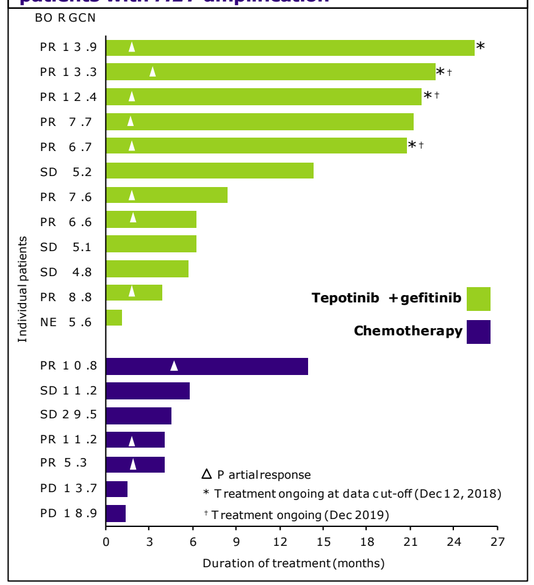
TEPOTINIB and INSIGHT study

- Tepotinib is an orally available, once daily, highly selective, potent MET TKI[1,2]
- Tepotinib blocks MET-mediated signaling pathways involved in tumorigenesis[1,2]
- In preclinical models, tepotinib overcame acquired resistance to first-, second-, and third-generation EGFR TKIs that was mediated by *MET* amplification[3]

INSIGHT study results

- INSIGHT was an open-label, Phase Ib/II, multicenter, randomized trial that compared tepotinib + gefitinib with chemotherapy in patients with relapsed *EGFR*-mutant NSCLC with MET overexpression (IHC2+ or IHC3+) and/or *MET* amplification (NCT01982955)[2]
- In patients with relapsed *EGFR*-mutant NSCLC and *MET* amplification, tepotinib + gefitinib showed improved outcomes versus chemotherapy (**Figure 1**)[2]:
  - Median PFS: 16.6 vs 4.2 months (HR=0.13; 90% CI: 0.04, 0.43)[2]
  - Median OS: 37.3 vs 13.1 months (HR=0.08; 90% CI: 0.01, 0.51)[2]
  - ORR: 67% vs 43% (OR=2.67; 90% CI: 0.37, 19.56)[2]
  - Median DOR: 19.9 months (90% CI: 7.0, NE) vs 2.8 months (90% CI: 2.8, 9.7)[2]

Figure 1. INSIGHT study (Phase II): Time on treatment and BOR (investigator-assessed) in patients with *MET* amplification[2]



INSIGHT 2 resources

- 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 Healthcare KGaA, Darmstadt, Germany (Tel: +49 6151720; www.merck kgroup.com)

GET INSIGHT 2 TRIAL CARD

GET INSIGHT 2 TRIAL ANIMATION

GET INSIGHT 2 PATIENT BROCHURE

GET INSIGHT 2 PHYSICIAN BROCHURE

INTRODUCTION

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

Figure 2. 1L osimertinib resistance mechanisms[4]

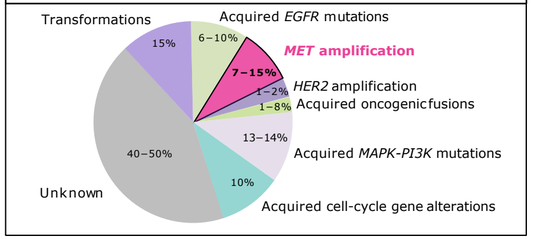
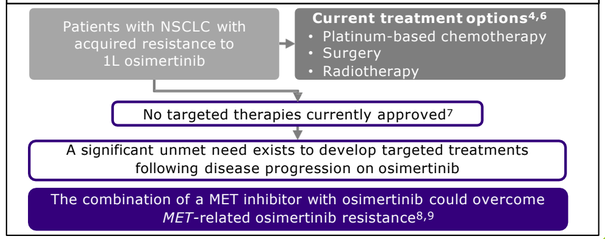


Figure 3. High unmet need for post-osimertinib therapy

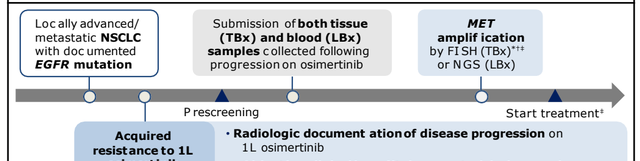


INSIGHT 2

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
- Molecular testing was conducted prior to study enrolment (**Figure 4**)

Figure 4. Molecular testing prior to enrolment in INSIGHT 2



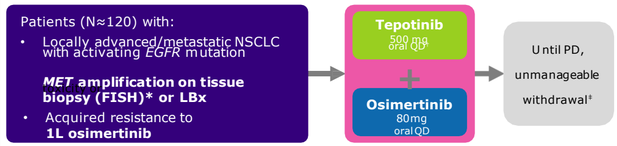
Implementing new logistics for sample submission during prescreening reduced the turnaround time

‡Gene copy number ≥5 and/or MET/CEP7 ratio ≥2; †The current gold standard for detecting *MET* amplification is using TBx and FISH, which more robustly detect *MET* amplification (compared with NGS or circulating tumor DNA NGS) and is a more predictive marker of clinical response with MET inhibitors than *MET* amplification by NGS or MET overexpression by IHC.*‡§Local biomarker testing is not required at the time of progression to 1L osimertinib; and if done, inclusion should not be based on negative local NGS results (TBx or LBx) due to low *MET* amplification detection sensitivity; §If local FISH positive results are available, treatment can start without waiting for central confirmation.

- 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 (**Figure 5**)

Figure 5. INSIGHT 2 study design

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



INSIGHT 2 protocol amendment, which requires *MET* amplification determined by FISH TBx, is based on: the scientific evidence that FISH is the current gold standard for the detection of *MET* amplification;[12] and NGS (TBx or LBx) can miss detection of *MET* amplification and lead to reduced enrolment[10,11,13]

‡GCN ≥5 or MET/CEP7 ratio ≥2; †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 + osimertinib or tepotinib alone until 12 patients with *MET* amplification centrally confirmed by FISH (TBx) 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.

Key inclusion criteria

- ≥18 years of age
- ECOG performance status 0–1
- Locally advanced/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 radiologic documentation of disease progression and objective clinical benefit during previous 1L osimertinib therapy
- Life expectancy ≥12 weeks
- Normal organ function

Key exclusion criteria

- 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 1L therapy

Study primary objective and endpoints

- To assess the efficacy and safety of tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC with acquired resistance to 1L osimertinib due to *MET* amplification
- The primary endpoint is objective response by IRC (RECIST v1.1) in patients with *MET* amplification centrally confirmed by FISH (**Table 1**)
- Efficacy and safety analyses will be based on all patients who received treatment with any study medication

Table 1. Study endpoints

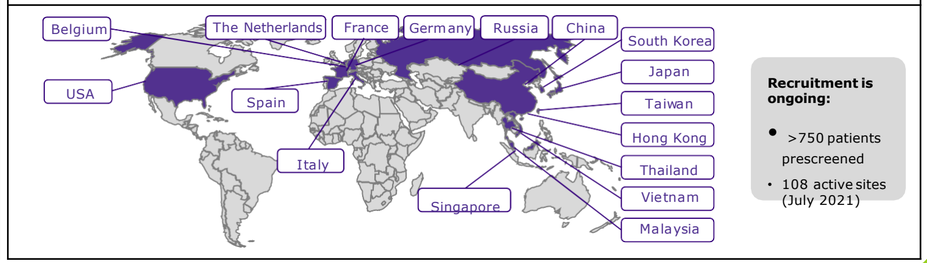
1º endpoint	Objective response by IRC per RECIST v1.1*
2º endpoints	Objective response by investigator assessment
	DOR by IRC and investigator assessment
	PFS by by IRC and investigator assessment
	OS
	PK
	HRQoL
	Safety and tolerability

*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

Study sites

- The study is estimated to enroll 120 patients (**Figure 6**)

Figure 6. Countries involved in the INSIGHT2 study



Recruitment is ongoing:

- >750 patients prescreened
- 108 active sites (July 2021)

Abbreviations: 1L, primary; 2L, secondary; 1L, first-line; BOR, best overall response; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; GCN, gene copy number; 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, liquid biopsy; MAPK, mitogen-activated protein kinase; MET, mesenchymal–epithelial transition factor; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not estimable; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetics; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor; USA, United States of America.

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

Disclosures: Yi-Long Wu reports institute grants and personal fees from AstraZeneca, Roche, and Boehringer Ingelheim; and has received personal fees (speaker) from BMS, MSD, Eli Lilly, and Pfizer. Christophe Dooms has nothing to disclose. Ernest Nadal has consulted or acted in an advisory role for Merck Serono, an affiliate of Merck KGaA; and has received research grants from Merck Serono, an affiliate of Merck KGaA. Jo Raskin has acted in an advisory role for Pfizer, and Lilly; received speaker fees from Boehringer Ingelheim and BMS; and has received travel expenses from Roche. Ingel Demedts has consulted or acted in an advisory role for Astra Zeneca, BMS. Boehringer, GSK, Lilly, MSD, Novartis, Pfizer, Roche, and Takeda. Julien Mazieres has attended advisory boards for Roche, BMS, MSD, AstraZeneca, Pfizer, and Novartis. Marie Wislez reports consulting fees from AstraZeneca, Roche, and Novartis. Syadwa Abdul Shukor has nothing to disclose. Lye Mun Tho has received honoraria from Pfizer, Roche, and AstraZeneca. Chin-Chou Wang has nothing to disclose. Santiago Viteri has acted in a consulting or advisory role for AbbVie, BMS, and Roche; received speaker fees from BMS, MSD, and Roche; and received travel expenses from Roche, OSE Pharma, BMS, Merck, Merck Serono, an affiliate of Merck KGaA, Puma Biotechnology, and Janssen Cilag. Xiuning Le has consulted or acted in an advisory role for AstraZeneca, Eli Lilly, and EMD Serono, an affiliate of Merck KGaA; and received research funding from Eli Lilly and Boehringer Ingelheim. Soon Hin How has nothing to disclose. Daniel Tan reports receiving research grants, acting as an advisor for, and has received consult ancy honoraria from Novartis, Pfizer, and AstraZeneca; received research grants from consulting or acting in an advisory role f or Bayer; acted in an advisory role and received consultancy honoraria from Boehringer Ingelheim and Takeda; has received honoraria from Bristol-Myers Squibb, Takeda Pharmaceuticals, Novartis, Merck, Loxo Oncology, AstraZeneca, Roche, and Pfizer; and received research funding as part of an institution from Novartis, GlaxoSmithKline, and AstraZeneca. Masayuki Takeda has consulted or acted in an advisory role for MSD, Pfizer, and Novartis; received speaker fees for MSD, BMS, and Roche; and received research funding from Roche, Takeda, AbbVie, Merck, and BMS. Remi Veillon has consulted or acted in an advisory role for MSD, Pfizer, and Novartis; received speaker fees from MSD, BMS, and Roche; and received research funding from Roche, Takeda, AbbVie, Merck, and BMS. Niki Karachaliou and Barbara Ellers-Lenz are employees of Merck Healthcare KGaA. Darmstadt, Germany. Egbert Smit has consulted or acted in an advisory role within an institution for Lilly, AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Bristol-Myers Squibb, Merck Healthcare KGaA, Darmstadt, Germany, MSD Oncology, Takeda, Bayer, Regeneron, Novartis, Daiichi Sankyo, and Seattle Genetics; and has received research funding within an institution from Boehringer Ingelheim, Bayer, Roche/Genentech, AstraZeneca, and Bristol-Myers Squibb.

1366TiP | Presented at the European Society for Medical Oncology (ESMO) Annual Meeting | Virtual Format; 16–21 September 2021