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

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Disclosure

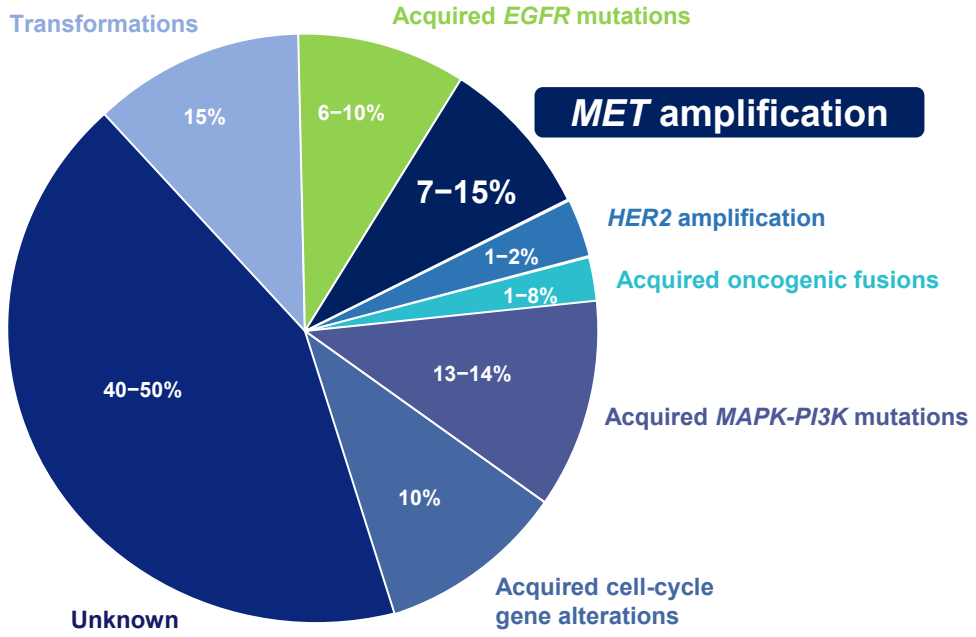
Christophe Dooms does not have any financial relationships to disclose.

Content

Background

- *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 with NSCLC whose disease has become resistant to osimertinib as 1L therapy[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]
- While osimertinib can provide effective disease control in patients with NSCLC, most patients develop resistance and tumor progression, with a median PFS ranging from 9–19 months[3,4]

Resistance mechanisms to 1L osimertinib[2]



1L, first-line; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; TKI, tyrosine kinase inhibitor.

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. Mok TS, et al. *N Engl J Med*. 2017;376(7):629–640.

High unmet need for effective treatments post-osimertinib in patients with NSCLC

Patients with NSCLC with acquired resistance to 1L osimertinib

Current options[1,2]

- Surgery
- Radiotherapy
- Platinum-based chemotherapy

No targeted therapies currently approved[3]

A significant unmet need exists to develop targeted treatments following disease progression on osimertinib

1L, first-line; NSCLC, non-small cell lung cancer.

1. Planchard D, et al. *Ann Oncol.* 2018;29(Suppl. 4):iv192–237; 2. Leonetti A, et al. *Br J Cancer.* 2019;121(9):725–737; 3. Mu Y, et al. *Target Oncol.* 2019;14:335–342.

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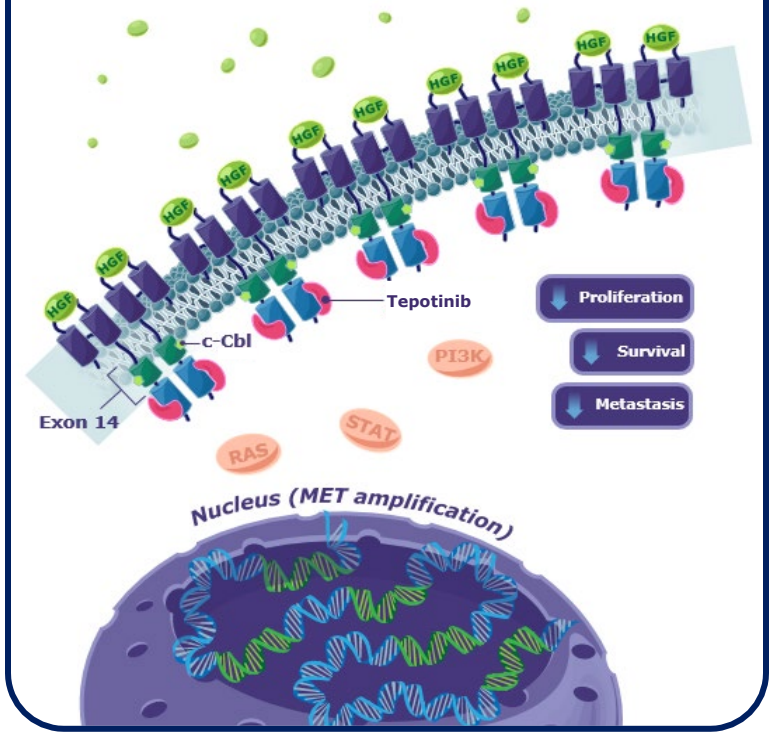
Rationale for tepotinib and osimertinib combination

- Tepotinib is an orally available, once daily, highly selective, potent MET TKI that blocks MET-mediated signaling pathways involved in tumorigenesis[1]
- In preclinical models, tepotinib overcame acquired resistance to first-, second-, and third-generation EGFR TKIs that were mediated by *MET* amplification[2]
- The **INSIGHT study** was an open-label, Phase Ib/II, randomized trial that compared tepotinib (MET TKI) + gefitinib (EGFR TKI) with chemotherapy in patients with relapsed *EGFR*-mutant NSCLC with MET overexpression (IHC2+ and IHC3+) and/or *MET* amplification (NCT01982955)[3]

Tepotinib mechanism of action



EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Bladt F, et al. *Clin Cancer Res.* 2013;19:2941–2951; 2. Friese-Hamim M, et al. *Am J Cancer Res.* 2017;7:962–972; 3. Wu YL, et al. *Lancet Respir Med.* 2020;8(11):1132–1143.

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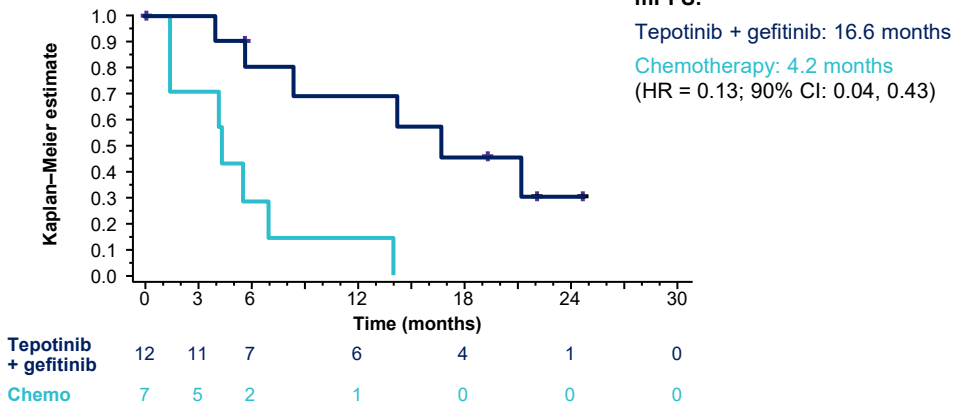
INSIGHT study results

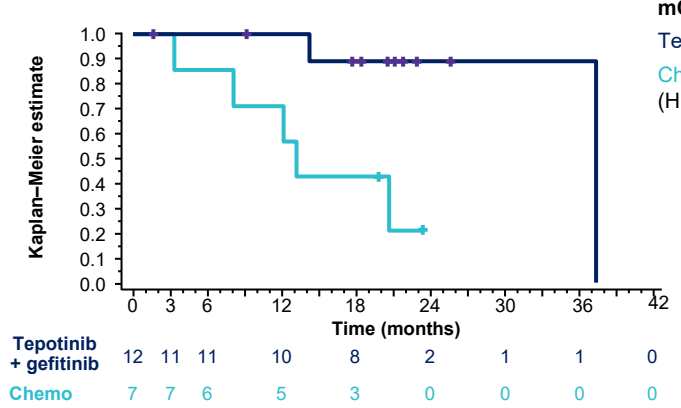
- In patients with relapsed *EGFR*-mutant NSCLC and *MET* amplification, tepotinib (MET TKI) + gefitinib (EGFR TKI) improved outcomes versus chemotherapy:[1]
  - mPFS: 16.6 vs 4.2 months (HR = 0.13; 90% CI: 0.04, 0.43)
  - ORR: 67% vs 43% (OR = 2.67; 90% CI: 0.37, 19.56)
  - mOS: 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51)
  - mDOR: 19.9 months (90% CI: 7.0, NE) vs 2.8 months (90% CI: 2.8, 9.7)

PFS



mPFS:
Tepotinib + gefitinib: 16.6 months
Chemotherapy: 4.2 months
(HR = 0.13; 90% CI: 0.04, 0.43)

OS



mOS:
Tepotinib + gefitinib: 37.3 months
Chemotherapy: 13.1 months
(HR = 0.08; 90% CI: 0.01, 0.51)

mPFS, mOS and ORR are according to investigator assessment.

Further details about prolonged activity observed with tepotinib + an EGFR TKI in patients with *EGFR*-mutant NSCLC and resistance to EGFR TKIs due to *MET* amplification, in clinical trials and clinical practice, are presented by Liam et al (abstract number 47).

CI, confidence interval; DOR, duration of response; EGFR, epidermal growth factor receptor; HR, hazard ratio; MET, mesenchymal–epithelial transition factor; mDOR, median DOR; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

1. Wu YL, et al. *Lancet Respir Med.* 2020;8(11):1132–1143.

Purpose of the INSIGHT 2 study

Rationale

The combination of a MET inhibitor with osimertinib has the potential to overcome *MET*-related osimertinib resistance[1,2]

Aim

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

1L, first-line; EGFR, epidermal growth factor receptor; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer.

1. Ahn M, et al. *J Thorac Oncol*. 2017;12(Suppl. 2):S1768; 2. Sequist LV, et al. *Lancet Oncol*. 2020;21(3):373–386.

Molecular testing prior to enrollment in INSIGHT 2

Locally advanced/metastatic **NSCLC** with documented ***EGFR* mutation**

Submission of **both tissue (TBx) and blood (LBx) samples** collected following progression on osimertinib

***MET* amplification** by FISH (TBx)*,†,‡ or NGS (LBx)§

Acquired resistance to 1L osimertinib (advanced or metastatic NSCLC setting)

- **Radiologic documentation of disease progression** on 1L osimertinib
- **Objective clinical benefit documented during previous osimertinib therapy** (defined by either partial or complete radiologic response, or durable stable disease [lasting <6 months after initiation])

Implementing new logistics for sample submission during prescreening reduced the turnaround time to ~7 business days, thereby expediting clinical decisions

*Gene copy number ≥5 and/or *MET/CEP7* ratio ≥2 by TBx; †The gold standard for detecting *MET* amplification is via tumor profiling using TBx and FISH, which more robustly detect *MET* amplification (compared with NGS or circulating tumor DNA NGS) and are more predictive markers of clinical response with MET inhibitors than *MET* amplification by NGS or MET overexpression by IHC.[1,2] 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; §Gene copy number ≥2.3 by LBx.

1L, first-line; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LBx, liquid biopsy; MET, mesenchymal–epithelial transition factor; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; TBx, tissue biopsy.

1. Hartmaier RJ, et al. *Cancer Res*. 2019;79(Suppl. 13):Abstract 4897; 2. Peng L, et al. *J Thorac Oncol*. 2021;16:S669.

Tissue or liquid biopsy for *MET* amplification testing?

The INSIGHT 2 protocol amendment, which requires ***MET* amplification determined by FISH TBx**, is based on:

- The scientific evidence of **FISH as the gold standard for the detection of *MET* amplification**[1]
- **NGS** (TBx or LBx) can **miss detection of *MET* amplification** and thereby **reduce enrollment**[2-4]

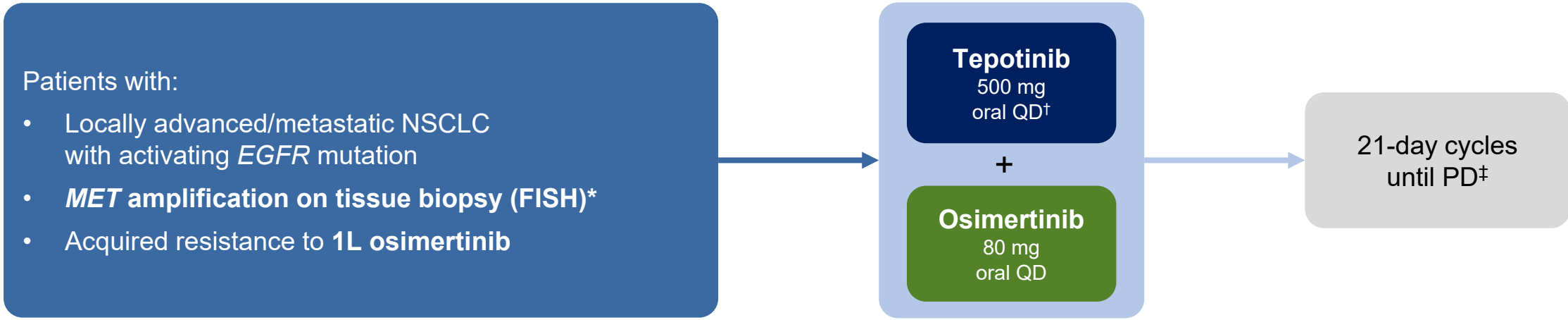
Detection strategy	*MET* amplification detection rate
NGS testing (LBx)	~5%*
FISH testing (TBx)	>45%†

*Detection of *MET* amplification according to protocol v1.0; †Detection of *MET* amplification according to protocol v2.0.
FISH, fluorescence in situ hybridization; MET, mesenchymal–epithelial transition factor; NGS, next-generation sequencing; LBx, liquid biopsy; TBx, tissue biopsy.
1. Mondelo-Macía P, et al. *Cells*. 2020(2):522; 2. Peng L, et al. *J Thorac Oncol.* 2021;16(3):S669; 3. Hartmaier RJ, et al. *Cancer Res.* 2019;79(Suppl. 13):Abstract 4897; 4. Schmid S, et al. *Lung Cancer.* 2020;147:123–129.

INSIGHT 2 study design

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, and the expected total number of patients is ~120

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



*Gene copy number ≥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 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.
1L, first-line; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer; PD, progressive disease; QD, once daily.

INSIGHT 2 eligibility criteria

Key inclusion 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 radiologic documentation of disease progression and objective clinical benefit during previous 1L osimertinib therapy
- ECOG performance status 0–1
- 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

1L, first-line; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HGF, hepatocyte growth factor; LBx, liquid biopsy; MET, mesenchymal–epithelial transition factor; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer.

INSIGHT 2 study endpoints

Efficacy and safety analyses will be based on all patients who received treatment with any study medication

Primary endpoint*

- Objective response, including confirmed complete response or partial response, by independent review committee per RECIST v1.1

*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

Secondary endpoints

- Objective response by investigator assessment
- DOR by IRC and investigator assessment
- PFS
- OS
- HRQoL
- Pharmacokinetics
- Resistance markers
- Safety and tolerability

DOR, duration of response; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HRQoL, health-related quality of life; IRC, independent review committee; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors.

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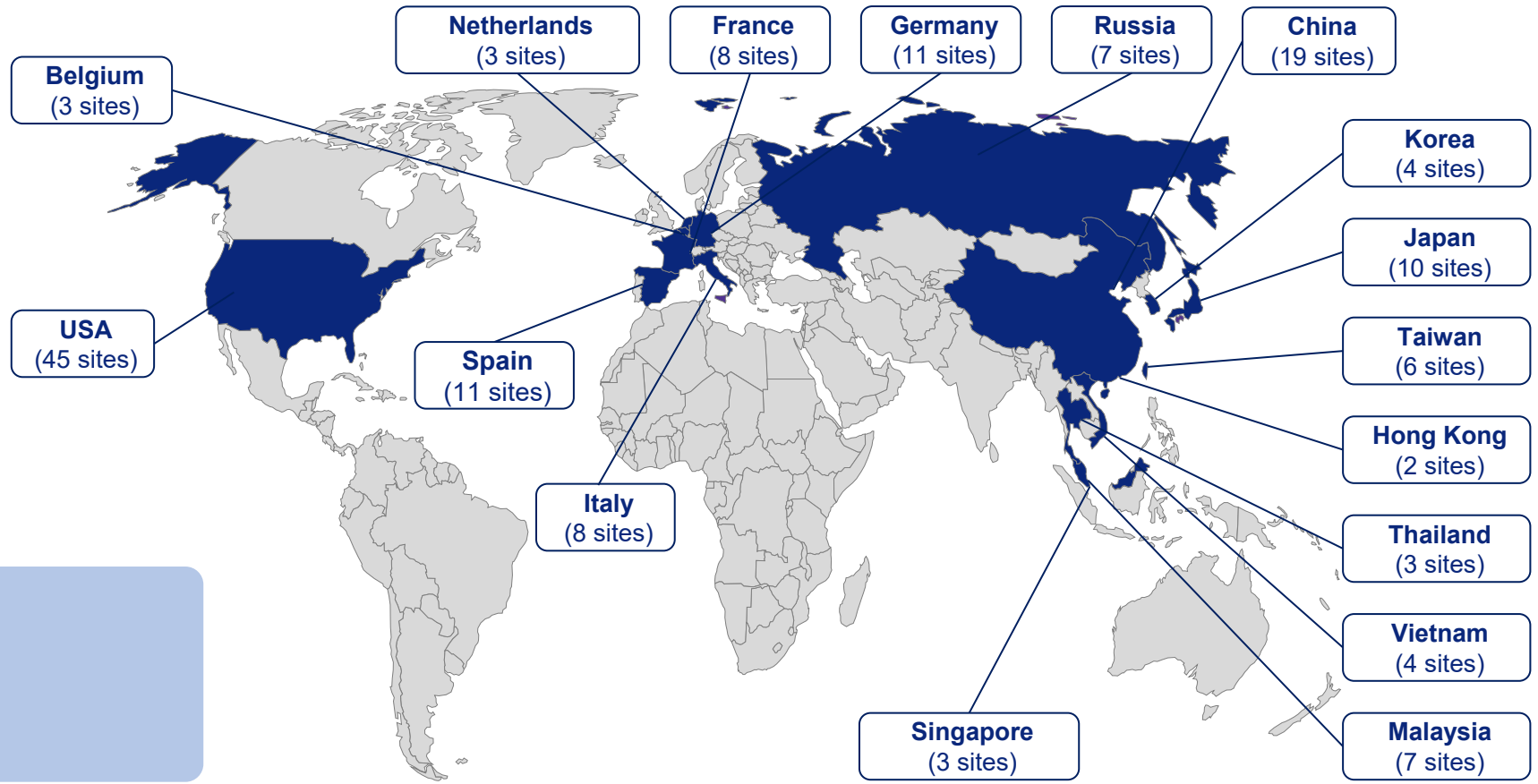
INSIGHT 2 study sites



Recruitment is ongoing:

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

INSIGHT 2 take-home messages

- INSIGHT 2 is a global, open-label, Phase II trial of tepotinib + osimertinib in patients with *MET*-amplified, advanced *EGFR*-mutant NSCLC
- Data from this study will enable a robust characterization of the benefit-to-risk ratio of tepotinib + osimertinib combination therapy, and assess the potential to fulfil an unmet need by providing a targeted therapy option for patients with *EGFR*-mutant NSCLC who progress on first-line osimertinib

EGFR, epidermal growth factor receptor; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer.

INSIGHT 2 study contacts and resources

- The Coordinating Investigator for this study is Prof Yi-Long Wu (syylwu@live.cn)
- For further information, please visit www.ClinicalTrials.gov/ct2/show/NCT03940703 or contact the healthcare business of Merck KGaA, Darmstadt, Germany (Tel: +49 6151720; www.emdgroup.com)

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GET INSIGHT 2 TRIAL ANIMATION

GET INSIGHT 2 PATIENT BROCHURE

GET INSIGHT 2 PHYSICIAN BROCHURE

Acknowledgments

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