Safety of tepotinib + EGFR TKI (osimertinib or gefitinib) in patients with *EGFR*m NSCLC

Ernest Nadal[1], Tae Min Kim[2,3], Valentina Guarneri[4], Pei Jye Voon[5], Boon Khaw Lim[6], Marie Wislez[7], Cheng Huang[8], Chong Kin Liam[9], Julien Mazieres[10], Lye Mun Tho[11], Hidetoshi Hayashi[12], Nhung Nguyen[13], Puey Ling Chia[14], Filippo de Marinis[15], Sabine Brutlach[16], Svenja Adrian[16], Barbara Ellers-Lenz[17], Karin Berghoff[18], Niki Karachaliou[16], Yi-Long Wu[19]

[1]Department of Medical Oncology, Catalan Institute of Oncology, L'Hospitalet, Barcelona, Spain; [2]Seoul National University Cancer Research Institute, Seoul, Republic of Korea; [3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [4]Department of Surgery, Oncology and Gastroenterology, University of Padova, Oncology 2, IOV – Istituto Oncologico Veneto IRCCS -IOV, Padova, Italy; [5]Hospital Umum Sarawak, Kuching, Sarawak, Malaysia; [6]Department of Internal and Respiratory Medicine, Sunway Medical Centre, Selangor, Malaysia; [7]Service de Pneumologie, Hopital Cohin, Assistance Publique – Hôpitaux de Paris, Paris, France; [8]Department of Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China; [9]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [10]CHU de Toulouse, Université Paul Sabatier, Toulouse, France; [11]Department of Oncology, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [12]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan; [13]National Lung Hospital, Hanoi, Vietnam; [14]Department of Medical Oncology, Tan Tock Seng Hospital, Singapore; [15]Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [16]Global Clinical Development, Merck Healthcare KGaA, Darmstadt, Germany; [17]Department of Biostatistics, Merck Healthcare KGaA, Darmstadt, Germany; [18]Global Patient Safety, Merck Healthcare KGaA, Darmstadt, Germany; [19]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China

CONCLUSIONS

- **Tepotinib in combination with an EGFR TKI was well tolerated in patients with *EGFR*m NSCLC and progressive disease following prior EGFR TKI therapy, reflecting the established safety profile of the individual drugs**
- **The lower incidence of peripheral edema in patients with *EGFR*m NSCLC (any grade: 20.7–40.7%; Grade ≥3: 3.4–4.4%) compared with those reported for *MET*ex14 skipping NSCLC (any grade: 67.1%; Grade ≥3: 11.2%)[1] may be due to younger age and/or the EGFR TKI combination**
  - **Median age: INSIGHT 2, 61.3 years; INSIGHT, 61.5 years; VISION, 72.0 years[1]**
- **These safety analyses from the INSIGHT studies, together with efficacy data from INSIGHT 2[2], suggest tepotinib + osimertinib as a potential chemotherapy-sparing oral targeted therapy option for patients with *EGFR*m NSCLC with *MET*amp that have developed resistance to prior EGFR TKI therapy**

INTRODUCTION

- *MET*amp is a common driver of secondary resistance in patients with *EGFR*m NSCLC following treatment with an EGFR TKI in 1L, and may be responsive to MET inhibition[3,4]
- **INSIGHT 2** (NCT03940703) reported promising activity for the combination of tepotinib (a highly selective and once-daily oral MET TKI) and osimertinib in patients (n=98) with *EGFR*m NSCLC and *MET*amp confirmed by central tissue biopsy, which progressed on 1L osimertinib[2]
  - ORR: 50.0% (95% CI: 39.7, 60.3)[2]
  - mDOR: 8.5 months (95% CI: 6.1, ne)[2]
- **INSIGHT** (NCT01982955) reported improved outcomes with the combination of tepotinib and gefitinib versus chemotherapy in a subgroup of patients (n=12 vs 7) with *EGFR*m NSCLC with *MET*amp and acquired resistance to EGFR TKI[5]
  - mPFS: 16.6 vs 4.2 months (HR, 0.13 [90% CI: 0.04, 0.43])[5]
  - mOS: 37.3 vs 13.1 months (HR, 0.10 [90% CI: 0.02, 0.36])[5]
- Tepotinib monotherapy has been extensively studied in patients with *MET*ex14 skipping NSCLC in the VISION study (N=313) and is generally well tolerated, with low rates of discontinuation due to TRAEs (14.7%)[1]
  - The most common TRAE in the VISION study was peripheral edema (any grade: 67.1%; Grade ≥3: 11.2%)[1]
- **INSIGHT 2** showed tepotinib + osimertinib had a manageable safety profile, consistent with the known safety profile of the individual drugs[2]
- This analysis further characterizes the safety profiles of tepotinib + EGFR TKIs in patients with *EGFR*m NSCLC which had progressed on prior therapy with an EGFR TKI

METHODS

Studies

- This analysis included patients receiving tepotinib 500 mg (450 mg active moiety) orally QD in combination with:

Osimertinib 80 mg QD (**INSIGHT 2**; including 128 patients from the combination arm, and seven patients from the tepotinib monotherapy arm who switched to the combination)[2]

or

Gefitinib 250 mg QD (**INSIGHT**; including 12 patients from Phase Ib, 31 patients from Phase II, and 15 patients from the exploratory T790M arm)[6]

- **INSIGHT 2** primary analysis safety data are based on the March 28, 2023 data cut-off[2]
- **INSIGHT** final analysis safety data are based on the September 3, 2021 data cut-off[5]
- Patients received tepotinib + EGFR TKI until disease progression, intolerable toxicity, or withdrawal for other reasons
- To manage AEs, doses of either drug in the combination could be reduced, or the administration of both drugs in combination could be discontinued

Classification of AEs

- AEs were graded according to NCI-CTCAE v5.0 in **INSIGHT 2** and NCI-CTCAE v4.0 in **INSIGHT**
- TEAEs were those noted between the first dose of tepotinib + EGFR TKI and ≤30 days after the last dose that were absent before treatment or that worsened relative to pre-treatment
- TRAEs were those considered to be related to the study treatment (tepotinib and/or osimertinib/gefitinib) by the investigator

RESULTS

Patients

- As of March 28, 2023, 193 patients with *EGFR*m NSCLC received 500 mg tepotinib QD in combination with an EGFR TKI
  - Of these, 135 patients in **INSIGHT 2** received tepotinib + osimertinib (65.9% aged <65 years, 59.3% were female, 61.5% were Asian, 69.6% were non-smokers, 71.9% had ECOG PS 1; **Table 1**)
  - A total of 58 patients in **INSIGHT** received tepotinib + gefitinib (62.1% aged <65 years, 63.8% were female, all were Asian, 70.7% were non-smokers, 84.5% had ECOG PS 1; **Table 1**)
- The median duration of treatment in patients receiving tepotinib + osimertinib or tepotinib + gefitinib was 24.1 weeks (range: 0–109) and 17.2 weeks (range: 2–246), respectively

Table 1. Patient demographics and baseline characteristics

Baseline characteristics		Tepotinib + osimertinib (INSIGHT 2; N=135)	Tepotinib + gefitinib (INSIGHT; N=58)
Age, median (range)	Years	61.3 (20–84)	61.5 (41–78)
Age, n (%)	<65 years	89 (65.9)	36 (62.1)
	≥65 years	46 (34.1)	22 (37.9)
Sex, n (%)	Female	80 (59.3)	37 (63.8)
	Male	55 (40.7)	21 (36.2)
Race, n (%)	Asian	83 (61.5)	58 (100.0)
	White	46 (34.1)	0
	Others/Unknown	6 (4.4)	0
Smoking status, n (%)	Non-smoker	94 (69.6)	41 (70.7)
	Smoker	41 (30.4)	17 (29.3)
ECOG PS, n (%)	0	38 (28.1)	9 (15.5)
	1	97 (71.9)	49 (84.5)
Geographic region, n (%)	Asia*	80 (59.3)	58 (100.0)
	Europe†	52 (38.5)	0
	North America	3 (2.2)	0

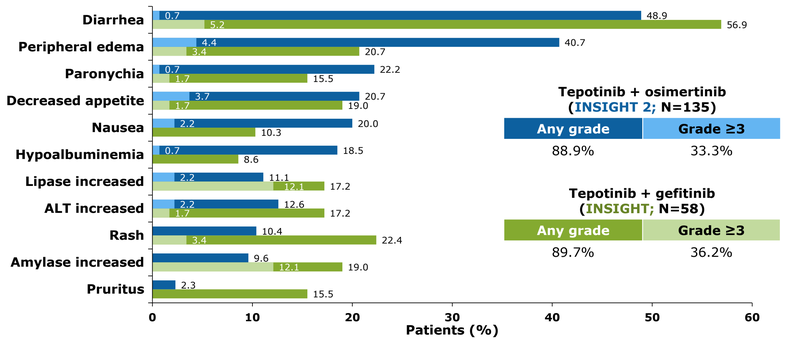
*__INSIGHT 2__: China, Hong Kong, Japan, Malaysia, Singapore, South Korea, Thailand, Vietnam; __INSIGHT__: China, Japan, Malaysia, Singapore, South Korea, Taiwan. †__INSIGHT 2__: Belgium, France, Germany, Italy, Russia, Spain, The Netherlands; __INSIGHT__: Italy, Spain, The Netherlands.

TRAEs

- In **INSIGHT 2** and **INSIGHT**, TRAEs (any grade) were reported in 120 patients (88.9%) and 52 patients (89.7%), respectively (**Figure 1**)
  - A total of 45 patients (33.3%) in **INSIGHT 2** and 21 patients (36.2%) in **INSIGHT** experienced Grade ≥3 TRAEs
- Diarrhea was the most frequently observed TRAE in both studies (**Figure 1**)
- Incidence rates of peripheral edema of any grade were 40.7% (Grade ≥3: 4.4%) in **INSIGHT 2**, and 20.7% (Grade ≥3: 3.4%) in **INSIGHT**
  - The median time of onset for peripheral edema of any grade and irrespective of causality was 9.9 weeks (range: 0.3–66.1) in **INSIGHT 2** and 12.1 weeks (range: 5.3–21.0) in **INSIGHT**

RESULTS (cont'd)

Figure 1. TRAEs occurring in ≥15% of patients receiving tepotinib + EGFR TKI



Serious TRAEs

- Serious TRAEs were reported in 16 patients (11.9%) in **INSIGHT 2** and seven patients (12.1%) in **INSIGHT**
- The most frequent serious TRAE in **INSIGHT 2** was pneumonitis (3.7%) and peripheral edema (3.4%) in **INSIGHT**

TRAEs leading to dose reduction and permanent treatment discontinuation

- TRAEs led to a dose reduction in 27 patients (20.0%) and five patients (8.6%), respectively, in **INSIGHT 2** and **INSIGHT**
  - Peripheral edema was the most frequently reported TRAE that led to dose reduction in 4.4% patients in **INSIGHT 2** and 5.2% patients in **INSIGHT** (**Table 2**)
- TRAEs leading to permanent treatment discontinuations occurred in 13 patients (9.6%) and two patients (3.4%), respectively, in **INSIGHT 2** and **INSIGHT**
  - Pneumonitis was the TRAE that most frequently led to treatment discontinuations in **INSIGHT 2** (4.4%; **Table 2**)
  - TRAEs leading to treatment discontinuation in **INSIGHT** were peripheral edema and periodontal disease in one patient (1.7%), and atypical pneumonia in one patient (1.7%)

Table 2. TRAEs leading to dose reductions or permanent treatment discontinuation in patients receiving tepotinib + EGFR TKI

TRAEs of any grade, n (%)	Tepotinib + osimertinib (INSIGHT 2; N=135)	Tepotinib + gefitinib (INSIGHT; N=58)
Leading to dose reduction	27 (20.0)	5 (8.6)
Tepotinib related	25 (18.5)	4 (6.9)
Osimertinib/gefitinib related	5 (3.7)	2 (3.4)
Leading to dose reduction in ≥3 patients		
Peripheral edema	6 (4.4)	3 (5.2)
Decreased appetite	5 (3.7)	0
Nausea	4 (3.0)	0
Asthenia	3 (2.2)	0
Leading to permanent treatment discontinuation	13 (9.6)	2 (3.4)
Tepotinib related	13 (9.6)	2 (3.4)
Osimertinib/gefitinib related	6 (4.4)	2 (3.4)
Leading to permanent treatment discontinuation in ≥2 patients		
Pneumonitis*	6 (4.4)	0
Peripheral edema	3 (2.2)	1 (1.7)

*Includes two events of pneumonitis that led to death in **INSIGHT 2**.

TRAEs leading to death

- In **INSIGHT 2**, four patients (3.0%) had TRAEs leading to death that were considered potentially related to either trial drug
  - Pneumonitis (n=2)
  - Respiratory failure after COVID-19 infection (n=1)
  - Decrease platelet count (n=1); non-hemorrhage-associated decreased platelet count – a known AE of osimertinib – worsened after treatment discontinuation, and so may have been related to the underlying disease
- No deaths due to TRAEs were reported in **INSIGHT**

Abbreviations: 1L, first line; AE, adverse event; ALT, alanine transaminase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal derived growth factor; *EGFR*m, *EGFR* mutant; HR, hazard ratio; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; *MET*ex14, *MET* exon 14; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ne, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once daily; TKI, tyrosine kinase inhibitor; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

References: 1. Mazieres J, et al. *JAMA Oncol*. 2023;9(9):1260–1266; 2. Kim TM, et al. WCLC 2023. Oral presentation OA21.05; 3. Rios-Hoyo A, et al. *Cancers (Basel)*. 2022;14(8):1931; 4. Wang Y, et al. *Lung Cancer*. 2018;118:105–110; 5. Liam CK, et al. *Clin Cancer Res*. 2023;29(10):1879–1886; 6. Wu YL, et al. *Lancet Respir. Med.* 2020;8(11):1132–1143.

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