Tepotinib + osimertinib for *EGFR* mutant (*EGFR*m) NSCLC with *MET* amplification (*MET*amp) after first-line (1L) osimertinib

Daniel Shao-Weng Tan[1] (daniel.tan.s.w@singhealth.com.sg; @danieltanmd / Twitter), Tae Min Kim[2], Valentina Guarneri[3], Pei Jye Voon[4], Boon Khaw Lim[5], Marie Wislez[6], Cheng Huang[7], Chong Kin Liam[5], Julien Mazieres[8], Lye Mun Tho[9], Hidetoshi Hayashi[10], Nhung Nguyen[11], Puey Ling Chia[12], Filippo de Marinis[13], Xiuning Le[14], Pongwut Danchaivijitr[15], Niki Karachaliou[16], Sabine Brutlach[17], Svenja Adrian[16], Barbara Ellers-Lenz[18], Yi-Long Wu[19]

[1]Division of Medical Oncology, National Cancer Centre, Singapore; [2]Seoul National University Cancer Research Institute, Seoul, Republic of Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [3]Department of Surgery, Oncology and Gastroenterology, University of Padova, Oncology 2, IOV - Istituto Oncologico Veneto IRCCS -IOV, Padova, Italy; [4]Hospital Umum Sarawak, Kuching, Sarawak, Malaysia; [5]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [6]Thoracic Oncology Unit, Service de Pneumologie, Hôpital Cochin, APHP, Université Paris Cité, France; [7]Department of Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China; [8]CHU de Toulouse, Pneumology Departement, Paul Sabatier University, Toulouse, France; [9]Department of Oncology, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [10]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan; [11]National Lung Hospital, Hanoi, Viet Nam; [12]Department of Medical Oncology, Tan Tock Seng Hospital, Singapore; [13]Thoracic Oncology Division, European Institute of Oncology (IEO), IRCCS, Milan, Italy; [14]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [16]Global Clinical Development, the healthcare business of Merck KGaA, Darmstadt, Germany; [17]Global Development Operations, the healthcare business of Merck KGaA, Darmstadt, Germany; [18]Department of Biostatistics, the healthcare business of Merck KGaA, Darmstadt, Germany; [19]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China

POSTER PDF

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

CONCLUSIONS

- **Tepotinib + osimertinib was highly active in patients with *EGFR*m NSCLC with acquired resistance to 1L osimertinib and *MET*amp**
- **The combination treatment was well tolerated with no new safety signals observed**
- **Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted therapy option in this population with a high unmet need, regardless of the method used for detecting *MET*amp**

INTRODUCTION

- *MET*amp is a common resistance mechanism in patients with *EGFR*m NSCLC following treatment with 1L osimertinib[1]
- Clinical studies suggest that tepotinib, an oral, once daily, highly selective MET inhibitor, when combined with EGFR TKIs in *EGFR*m *MET*amp NSCLC may be an effective treatment following osimertinib resistance[2–4]
- Here we report new interim data from the INSIGHT 2 study evaluating the efficacy and safety of tepotinib + osimertinib in patients with *EGFR*m NSCLC harboring *MET*amp and resistance to 1L osimertinib with ≥3 months' follow-up by September 26, 2022 (data cut-off)

METHODS

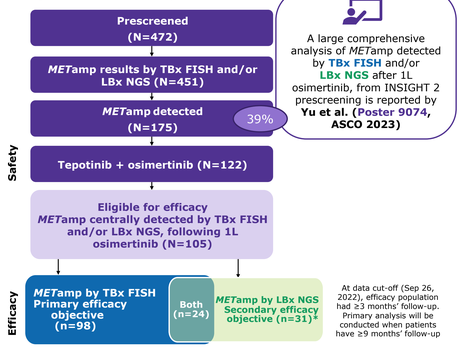
- Enrolled patients received tepotinib 500 mg (450 mg active moiety) + osimertinib 80 mg once daily (**Supplementary Figure 1**)
- *MET*amp was detected centrally by **TBx FISH** (*MET* GCN ≥5 and/or *MET*/*CEP7* ≥2) and/or by **LBx NGS** (*MET* GCN ≥2.3; Archer®)
- The primary endpoint was objective response by IRC for patients with centrally detected *MET*amp by **TBx FISH**, treated with tepotinib + osimertinib
- Secondary endpoints included objective response for patients with *MET*amp detected by **LBx NGS**, DOR, PFS, OS, and safety

RESULTS

Patients

- Efficacy data are reported for patients with ≥3 months' follow-up, and safety data for all patients who received at least one dose of tepotinib + osimertinib
- *MET*amp is commonly detected by NGS or by FISH, but FISH has been shown to be the most sensitive diagnostic tool of the two[4]

Figure 1. Patient disposition



*Seven patients had *MET*amp detected by central LBx NGS only (TBx FISH was not evaluable in five patients; TBx FISH was negative in two patients).

Table 1. Demographics and characteristics of patients receiving tepotinib + osimertinib

Baseline characteristics		Tepotinib + osimertinib (N=122)
Median age, years (range)		61 (20–84)
Sex, n (%)	Female	73 (59.8)
	Male	49 (40.2)
Race, n (%)	Asian	73 (59.8)
	White	43 (35.2)
	Others/Not collected	6 (4.9)
Smoking status, n (%)	Never	83 (68.0)
	Former/Current	39 (32.0)
ECOG PS, n (%)	0	34 (27.9)
	1	88 (72.1)
Brain metastases by IRC, n (%)	Yes	21 (17.2)
***EGFR* mutation, n (%)**	Del19	72 (59.0)
	L858R	44 (36.1)
	Other exon 21 mut.	5 (4.1)
	Other	1 (0.8)
Mean SOLD, mm ± SD		72.1 ± 43.8
Time on 1L osimertinib*, n (%)	<12 months	35 (28.7)
	≥12 months	79 (64.8)

*Eight patients did not receive 1L osimertinib.

Efficacy

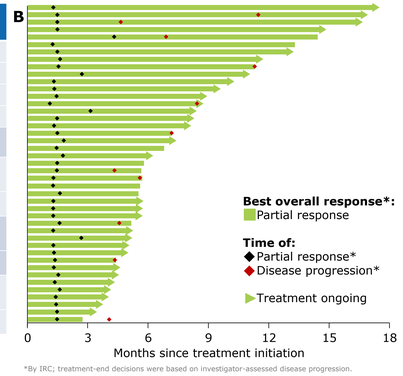
- Of 98 patients with **TBx FISH⁺** *MET*amp (primary analyses set), median *MET* GCN was 11 (range 5.0–50.6) and baseline tumor load (mean SOLD ± SD) was 73.2 ± 47.1 mm
- BOR was PR in 43 patients, for an ORR of 43.9% (95% CI: 33.9, 54.3); as the data matures, six additional PRs have been confirmed. Treatment was still ongoing in 42 patients

Figure 2. Efficacy outcomes in patients with *MET*amp detected centrally by TBx FISH receiving tepotinib + osimertinib (primary analysis set). A. Summary, **B.** Time on treatment in patients with objective response, **C.** Tumor shrinkage, **D.** DOR, and **E.** PFS.

A

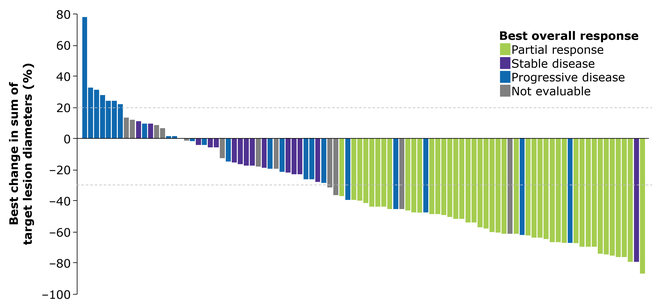
		TBx FISH⁺ (n=98)
BOR, n (%)	PR	43 (43.9)
	SD	15 (15.3)
	PD	23 (23.5)
	NE	17 (17.3)
ORR	% (95% CI)	**43.9** (33.9, 54.3)
DOR	Median, months (95% CI)	**9.7** (5.6, ne)
	Events, n (%)	11 (25.6)
PFS	Median, months (95% CI)	**5.4** (4.2, 7.1)
	Events, n (%)	51 (52.0)
OS	Median, months (95% CI)	**ne** (11.1, ne)
	Events, n (%)	23 (23.5)

B



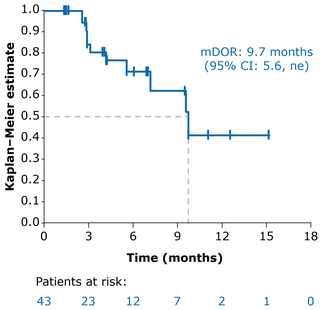
*By IRC; treatment-end decisions were based on investigator-assessed disease progression.

C

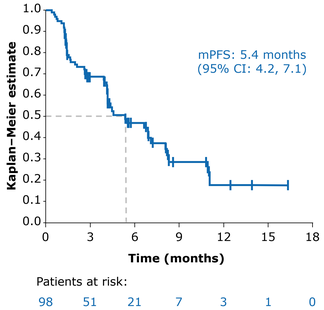


*Four patients were excluded due to baseline/post-baseline measurement not being available.

D



E



*Only patients with a response (n=43) were included in Kaplan–Meier analyses.

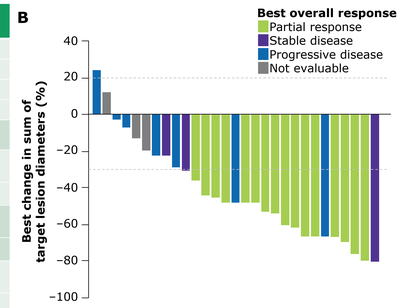
- Of 31 patients with **LBx NGS⁺** *MET*amp, including 24 who were also **TBx FISH⁺**, median *MET* GCN was 16.4 (range 2.1–45.3) and mean SOLD ± SD was 93.9 ± 51.4 mm

Figure 3. Efficacy outcomes in patients with *MET*amp detected centrally by LBx NGS receiving tepotinib + osimertinib. A. Summary and **B.** Tumor shrinkage.

A

		LBx NGS⁺ (n=31)
BOR, n (%)	PR	16 (51.6)
	SD	3 (9.7)
	PD	7 (22.6)
	NE	5 (16.1)
ORR	% (95% CI)	**51.6** (33.1, 69.8)
DOR	Median, months (95% CI)	**5.6** (2.9, ne)
	Events, n (%)	7 (43.8)
PFS	Median, months (95% CI)	**4.6** (2.7, 6.9)
	Events, n (%)	19 (61.3)
OS	Median, months (95% CI)	ne (6.8, ne)
	Events, n (%)	9 (29.0)

B



*Two patients were excluded due to baseline/post-baseline measurement not being available.

Safety

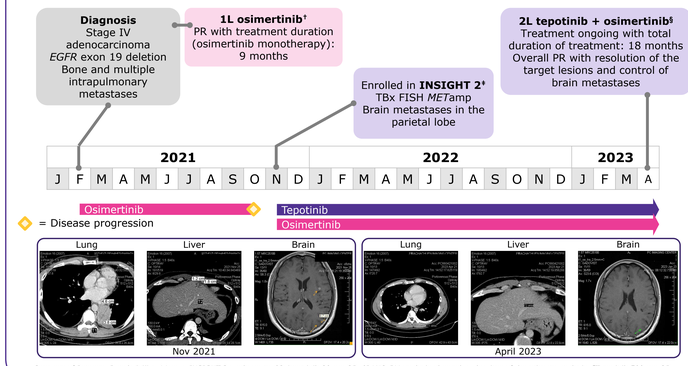
- Tepotinib + osimertinib was well tolerated
- Treatment-related adverse events led to dose reduction in 21 (17.2%) patients
  - Tepotinib dose was reduced in 19 patients
  - Osimertinib dose was reduced in four patients
- Seven patients (5.7%) discontinued treatment due to treatment-related adverse events

Table 2. Most common TRAEs in patients treated with tepotinib + osimertinib

TRAEs, n (%)	Tepotinib + osimertinib (N=122)	
Any grade	99 (81.1)	
Grade ≥3	34 (27.9)	
Leading to dose reduction	21 (17.2)	
Leading to treatment discontinuation	7 (5.7)	
Leading to death	2 (1.6)*	
TRAEs in >15% of patients, n (%)	**All grades**	**Grade ≥3**
Diarrhea	57 (46.7)	0
Peripheral edema	42 (34.4)	5 (4.1)
Paronychia	25 (20.5)	1 (0.8)
Decreased appetite	22 (18.0)	4 (3.3)
Nausea	20 (16.4)	2 (1.6)

*Two patients had AEs leading to death that were considered potentially related to either trial drug by the investigator (pneumonia/pneumonitis and dyspnea/pneumonitis).

Case study: Control of brain metastases in a 33-year-old* Asian male with a durable response to tepotinib + osimertinib



Courtesy of Pongwut Danchaivijitr. *Age at INSIGHT 2 study entry. †Osimertinib 80 mg QD. ‡RANO-BM analysis planned at the time of the primary analysis. §Tepotinib 500 mg QD plus osimertinib 80 mg QD.

Abbreviations: 1L, first line; AE, adverse event; BOR, best overall response; CEP7, centromere 7; CI, confidence interval; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; GCN, gene copy number; IRC, independent review committee; LBx, liquid biopsy; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; ne, not evaluable; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; SD, standard deviation; SOLD, sum of longest diameters of target lesion; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

References: 1. Ríos-Hoyo A, et al. *Cancers* (Basel) 2022;14(8):1931; 2. Friese-Hamim M, et al. *Am J Cancer Res* 2017;7(4):962–72; 3. Wu YL, et al. *Lancet Respir Med* 2020;8(11):1132–43; 4. Peng L, et al. J Thorac *Oncol* 2021;16(3):S669.

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

Disclosures: Daniel Shao-Weng Tan - Consulting or Advisory for: Novartis, the healthcare business of Merck KGaA, Darmstadt, Germany, Loxo, AstraZeneca, Roche, Pfizer, C4 Therapeutics; Travel, Accommodations, Expenses received from: Pfizer, Boehringer Ingelheim, Roche; Honoraria from: Bristol-Myers Squibb, Takeda, Novartis, Roche, Pfizer. Research Funding: Novartis, GlaxoSmithKline, AstraZeneca.

Supplementary materials

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

Abstract 9021| Presented at the American Society of Clinical Oncology Annual Meeting (ASCO) | June 2–6, 2023 | Chicago, Illinois, USA and virtual