Tepotinib with an EGFR-tyrosine kinase inhibitor in patients with *EGFR*-mutant *MET*-amplified NSCLC: A case series

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CONCLUSIONS

- **In this case series, the combination of tepotinib plus EGFR-TKIs showed promising clinical activity for patients with *MET*amp NSCLC who have progressed on previous EGFR-TKIs, including those with several lines of prior treatment**
- **Tepotinib plus osimertinib is being investigated in the INSIGHT 2 study (NCT03940703) in patients with *EGFR*-mutant *MET*amp NSCLC with acquired resistance to first-line osimertinib[1]**

INTRODUCTION

- *MET* amplification (*MET*amp) is a mechanism of resistance to EGFR-TKIs, occurring in 15–30% of patients with *EGFR*-mutant NSCLC who develop osimertinib resistance[2,3]
- Tepotinib, a once-daily and highly selective MET-TKI, is approved in multiple countries for the treatment of *MET* exon 14 skipping NSCLC, and has been investigated in combination with the EGFR-TKI gefitinib in patients with *EGFR*-mutant NSCLC in the Phase Ib/II INSIGHT study (NCT01982955)[4]
- The combination of tepotinib and gefitinib (n=12) improved outcomes compared with chemotherapy (n=7) in patients with *EGFR*-mutant *MET*amp NSCLC and EGFR-TKI resistance (data cut-off: September 3, 2021)[4]
  - Progression-free survival: 16.6 vs 4.2 months (HR=0.13, 90% CI: 0.04, 0.43)
  - Overall survival: 37.3 vs 13.1 months (HR=0.10, 90% CI: 0.02, 0.36)
- Tepotinib combined with an EGFR-TKI may therefore overcome MET-related EGFR-TKI resistance
- Outside of clinical trials, patients with *EGFR*-mutant *MET*amp NSCLC have received tepotinib through compassionate use requests, taken in combination with EGFR-TKIs; a series of these cases is presented here

METHODS

- Early access to tepotinib outside of clinical trials has been provided through compassionate use requests
- Cases reported herein include patients with NSCLC and acquired resistance to EGFR-TKIs due to *MET*amp, who received tepotinib outside of a clinical trial (500 mg [450 mg active moiety] once daily; first dose before October 2021) plus an EGFR-TKI
- All patients were treated in routine clinical practice and treatment decisions were made by the treating physicians and/or treatment centers; two patients initially received tepotinib in the INSIGHT study and continued to receive tepotinib through compassionate use after study completion
- Efficacy and safety outcomes are reported per the physicians' assessments, and standardization criteria were not applied
- Data for this case series were provided by the treating physicians up to June 2022

RESULTS

Patient characteristics

- Of 12 patients included in the case series, age ranged from 47–86 years, eight patients were female, three had smoking history, and all had adenocarcinoma histology (**Table 1**)

Table 1. Characteristics of patients with *EGFR*-mutant *MET*amp NSCLC

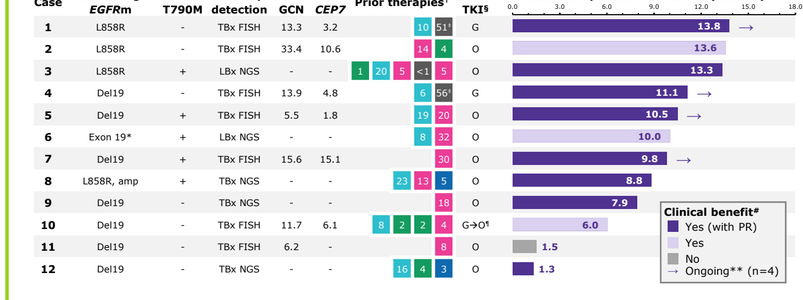
Case*	Sex	Age,† years	Race	Smoking history	Stage at diagnosis	Sites of metastases
1	M	70	Asian	Yes	IV	Bone, lung, pericardium, pleura
2	F	76	Asian	No	IV	Pleura, mediastinal LN, hilar LN, SCF LN, bone, adrenal
3	F	62	White	No	IV	Bone, hilar LN
4	F	47	Asian	No	IVB	Bone, nodes (mediastinal and upper abdominal), lung, left effusion
5	F	82	White	No	IVA	Pleura
6	M	86	White	Yes	IV	Liver, bone, adrenal, pleural fluid, lymphangitis carcinomatosis
7	F	76	White	No	IVA	Bone
8	F	55	Asian	No	IV	Brain, lung (left), liver
9	F	63	White	No	IVB	Pleuritis carcinomatosa, bone
10	M	70	White	Yes	IVB	Pleural effusion, mediastinal LN, pleural, bone, gingival
11	F	50	White	No	IVB	LN, pleura
12	M	77	Asian	No	IIIB	Liver, adrenal, nodal mets in precaval, paraaortic, common iliac regions

*Patient cases in bold purple text correspond to cases shown in greater detail on the right-hand side of the poster. †Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request.

Efficacy of tepotinib in combination with EGFR-TKIs

- Five patients received tepotinib with an EGFR-TKI in second line (includes two patients who took part in the INSIGHT study), three in third line, and four in fourth-or-later line (**Figure 1**)
- 11 patients had clinical benefit per the treating physicians' assessment, of whom eight (66.7% of all patients) were considered to have a partial response (**Figure 1**)
- Four cases are shown in greater detail on the right-hand side of the poster (**Case 1, 2, 3, 6**)

Figure 1. Molecular characteristics and clinical outcomes in patients with *EGFR*-mutant *MET*amp NSCLC

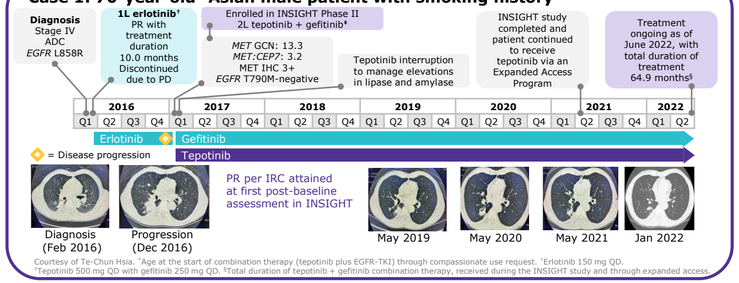


*Activating mutation in exon 19. †Values indicate time on treatment (months). ‡Two patients received tepotinib plus gefitinib in the INSIGHT study (NCT01982955) for 51 and 56 months each, and subsequently continued to receive tepotinib via compassionate use request following study completion. §EGFR-TKI received in combination with tepotinib, O = osimertinib, G = gefitinib. ¶Patient received tepotinib plus gefitinib for 5 months, followed by tepotinib plus osimertinib for 1 month. #As determined by the treating physician. **Treatment ongoing as of June 17, 2022.

Safety

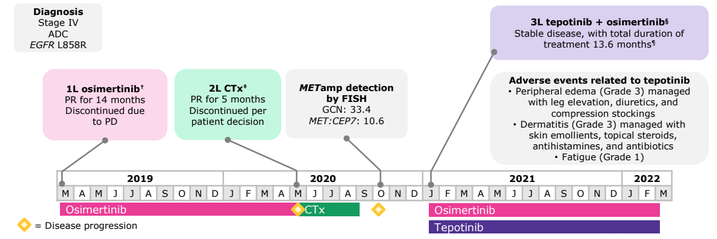
- Of 12 patients with AEs considered related to tepotinib, seven had peripheral edema
  - Four patients had Grade 1 peripheral edema, two patients had Grade 2, and one patient had Grade 3
  - Management strategies reported by the treating physicians included leg elevation, compression stockings, physiotherapy, lymph drainage, and diuretics
- Three patients had Grade 3 tepotinib-related AEs; no Grade 4 or 5 tepotinib-related AEs were reported
  - One patient had Grade 3 peripheral edema and Grade 3 dermatitis
  - One patient had Grade 3 elevated amylase and Grade 3 elevated lipase
  - One patient had Grade 3 pneumonia and Grade 3 pneumonitis; pneumonia was managed with treatment interruption for 8 days and antibiotics, and pneumonitis was managed with treatment discontinuation and steroids
- Two patients discontinued treatment due to AEs
  - One patient stopped treatment due to Grade 3 pneumonitis (described above), and one patient stopped treatment due to Grade 2 pneumonitis

Case 1: 70-year-old* Asian male patient with smoking history



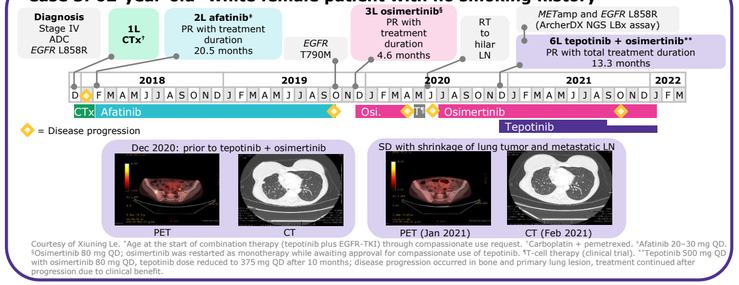
Courtesy of Te-Chun Hsia. *Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request. †Erlotinib 150 mg QD. ‡Tepotinib 500 mg QD with gefitinib 250 mg QD. §Total duration of tepotinib + gefitinib combination therapy, received during the INSIGHT study and through expanded access.

Case 2: 76-year-old* Asian female patient with no smoking history



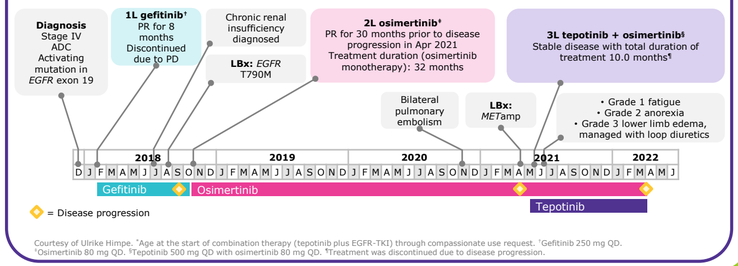
Courtesy of Lye Mun Tho. *Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request. †Osimertinib 80 mg QD. ‡Carboplatin AUC 4, pemetrexed 500 mg/m², every 3 weeks for 6 cycles. §Tepotinib 500 mg QD with osimertinib 80 mg QD. ¶Treatment was discontinued due to pneumonia which led to death, considered unrelated to malignancy.

Case 3: 62-year-old* white female patient with no smoking history



Courtesy of Xiuning Le. *Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request. †Carboplatin + pemetrexed. ‡Afatinib 20–30 mg QD. §Osimertinib 80 mg QD; osimertinib was restarted as monotherapy while awaiting approval for compassionate use of tepotinib. ¶T-cell therapy (clinical trial). **Tepotinib 500 mg QD with osimertinib 80 mg QD, tepotinib dose reduced to 375 mg QD after 10 months; disease progression occurred in bone and primary lung lesion, treatment continued after progression due to clinical benefit.

Case 6: 86-year-old* white male patient with smoking history



Courtesy of Ulrike Himpe. *Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request. †Gefitinib 250 mg QD. ‡Osimertinib 80 mg QD. §Tepotinib 500 mg QD with osimertinib 80 mg QD. ¶Treatment was discontinued due to disease progression.

Abbreviations: ADC, adenocarcinoma; AE, adverse event; amp, amplification; AUC, area under the free carboplatin plasma concentration versus time curve; CEP7, centromere chromosome 7; CI, confidence interval; CT, computed tomography; CTx, chemotherapy; del, deletion; EGFR, epidermal growth factor receptor; *EGFRm*, *EGFR* mutation; FISH, fluorescence in situ hybridization; GCN, gene copy number; gen., generation; HR, hazard ratio; IHC, immunohistochemistry; IO-CTx, immunotherapy-chemotherapy; IRC, independent review committee; L, line; LBx, liquid biopsy; LN, lymph nodes; MET, mesenchymal–epithelial transition factor; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PD, disease progression; PET, positron emission tomography; PR, partial response; SCF, supraclavicular fossa; SD, stable disease; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor; RT, radiotherapy; QD, once daily.

References: 1. Smit EF, et al. *Future Oncol.* 2022;18(9):1039–1054; 2. Ramalingam SS, et al. *Ann. Oncol.* 2018;29(suppl 8):viii740; 3. Wang Y, et al. *Lung Cancer.* 2018;118:105–110; 4. Liam CK, et al. *Cancer Res.* 2022;82(12 suppl)[abstract CT538].

Acknowledgments: We thank all the patients and their families. Medical writing assistance was provided by Carys Davies, PhD, of Syneos Health (London, UK) and funded by Merck Healthcare KGaA, Darmstadt, Germany.

Disclosures: XL: Consulting/advisory role: AstraZeneca, Eli Lilly, EMD Serono; an affiliate of Merck KGaA, Novartis, Daiichi Sankyo, Hengrui Therapeutics; Research funding: Eli Lilly, Boehringer Ingelheim. AE: Advisory board honoraria and/or speaker fees: Amgen, Merck Healthcare KGaA, Darmstadt, Germany. UH; none to disclose. CDB; Advisory boards: Janssen. JM; Advisory boards: Roche, BMS, MSD, AstraZeneca, Pfizer, Novartis, Merck Healthcare KGaA, Darmstadt, Germany, Amgen, Takeda, Daiichi Sankyo; Research funding (institution): Roche/Genentech, AstraZeneca, Bristol Myers Squibb. IP; Consulting/advisory role: Sanofi Aventis, MSD, Takeda, Amgen, Boehringer Ingelheim. LMT; Research grants: EMD Serono, an affiliate of Merck KGaA; Honoraria: Pfizer, Roche, AstraZeneca. AA; Advisory boards: Boehringer Ingelheim, Novartis, Pfizer, MSD, Roche, Merck Healthcare KGaA, Darmstadt, Germany, Eisai, Viatris; Honoraria for speaking engagements: MSD, Novartis, Pfizer, Eisai, BMS, Roche, Amgen, Duopharma, OEP, SciGen. TCH; none to disclose. WSL; Honoraria: BMS, MSD, Roche, Pfizer, Novartis, AstraZeneca. YKJC; none to disclose. WCKL; Advisory boards: AstraZeneca, Janssen; Honoraria for speaking engagements: AstraZeneca; Employee: ACT Genomics Ltd. TYY; none to disclose. KJ; Employee of ICON plc, contracted on behalf of Merck Healthcare KGaA, Darmstadt, Germany. KB; Employee of Merck Healthcare KGaA, Darmstadt, Germany. SV; Employee of Merck N.V.-S.A., Overijse, Belgium, an affiliate of Merck KGaA. NK; Employee of Merck Healthcare KGaA, Darmstadt, Germany. AVDW; Consulting fees: AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Pfizer, Takeda; Research grant: AstraZeneca, Boehringer Ingelheim, Roche, Pfizer, Takeda.

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Poster EP08.02-162 | Presented at the World Conference on Lung Cancer (WCLC) | August 6–9, 2022 | Vienna, Austria