Patients with *EGFR*-mutant *MET*-altered NSCLC receiving tepotinib with an EGFR tyrosine kinase inhibitor (TKI): A case series

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CONCLUSIONS

- **In this case series, the combination of tepotinib plus EGFR-TKIs showed promising clinical activity in patients with *MET*-altered NSCLC treated outside of clinical trials and who have progressed on previous EGFR-TKIs, including those with several lines of prior treatment**
- **Clinical benefit was observed irrespective of *MET* alteration type with a large proportion of patients continuing to benefit from ongoing treatment. These results further support the benefit of MET inhibition in the post-EGFR-TKI setting, as previously reported in INSIGHT and INSIGHT 2**

INTRODUCTION

- Oncogenic activation of MET is a common mechanism of acquired resistance to EGFR-TKIs in patients with *EGFR*-mutant NSCLC, with *MET* amplification (*MET*amp) constituting the most frequent cause of bypass pathway activation[1,2]
- Tepotinib, a once-daily and highly selective MET-TKI, approved in multiple countries for the treatment of *MET*ex14 skipping NSCLC, has been investigated in combination with the EGFR-TKI gefitinib in patients with *EGFR*-mutant NSCLC in the Phase Ib/II INSIGHT study (NCT01982955)[3]
  - 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) with a progression-free survival of 16.6 versus 4.2 months, and overall survival 37.3 versus 13.1 months[3]
- Tepotinib is also being investigated in combination with osimertinib in the Phase II INSIGHT 2 study (NCT03940703) in patients with *EGFR*-mutant *MET*amp NSCLC with acquired resistance to first-line osimertinib[4]
  - In the interim analysis of INSIGHT 2, ORR (95% CI) was 43.9% (33.9, 54.3) in patients with ≥3 months' follow-up (n=98) (**Poster 9021**, ASCO 2023)
- Tepotinib combined with an EGFR-TKI may therefore overcome MET-related EGFR-TKI resistance
- Outside of clinical trials, patients with *EGFR*-mutant *MET*-altered 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 unsolicited compassionate use requests
- Cases reported herein include patients with *EGFR*-mutant *MET*-altered NSCLC and resistance to EGFR-TKIs, who received tepotinib through early access (500 mg [450 mg active moiety] once daily; first dose by October 2022) 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 participating physicians up to April 2023

RESULTS

Patient characteristics

- Of 28 patients included in the case series, age ranged from 41–86 years, 19 patients were female, eight had smoking history, and all had adenocarcinoma histology (**Table 1**)

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

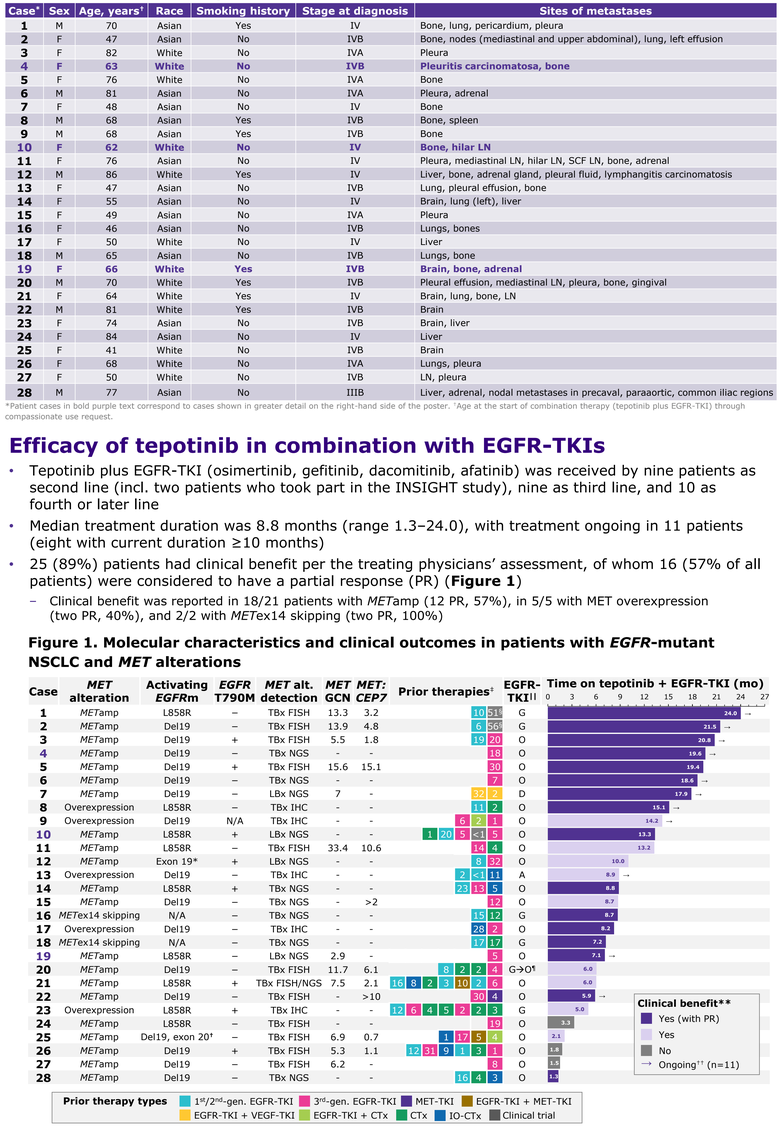
Case*	Sex	Age, years†	Race	Smoking history	Stage at diagnosis	Sites of metastases
1	M	70	Asian	Yes	IV	Bone, lung, pericardium, pleura
2	F	47	Asian	No	IVB	Bone, nodes (mediastinal and upper abdominal), lung, left effusion
3	F	82	White	No	IVA	Pleura
4	F	63	White	No	IVB	Pleuritis carcinomatosa, bone
5	F	76	White	No	IVA	Bone
6	M	81	Asian	No	IVA	Pleura, adrenal
7	F	48	Asian	No	IV	Bone
8	M	68	Asian	Yes	IVB	Bone, spleen
9	M	68	Asian	Yes	IVB	Bone
10	F	62	White	No	IV	Bone, hilar LN
11	F	76	Asian	No	IV	Pleura, mediastinal LN, hilar LN, SCF LN, bone, adrenal
12	M	86	White	Yes	IV	Liver, bone, adrenal gland, pleural fluid, lymphangitis carcinomatosis
13	F	47	Asian	No	IVB	Lung, pleural effusion, bone
14	F	55	Asian	No	IV	Brain, lung (left), liver
15	F	49	Asian	No	IVA	Pleura
16	F	46	Asian	No	IVB	Lungs, bones
17	F	50	White	No	IV	Liver
18	M	65	Asian	No	IVB	Lungs, bone
19	F	66	White	Yes	IVB	Brain, bone, adrenal
20	M	70	White	Yes	IVB	Pleural effusion, mediastinal LN, pleura, bone, gingival
21	F	64	White	Yes	IV	Brain, lung, bone, LN
22	M	81	White	Yes	IVB	Brain
23	F	74	Asian	No	IVB	Brain, liver
24	F	84	Asian	No	IV	Liver
25	F	41	White	No	IVB	Brain
26	F	68	White	No	IVA	Lungs, pleura
27	F	50	White	No	IVB	LN, pleura
28	M	77	Asian	No	IIIB	Liver, adrenal, nodal metastases 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

- Tepotinib plus EGFR-TKI (osimertinib, gefitinib, dacomitinib, afatinib) was received by nine patients as second line (incl. two patients who took part in the INSIGHT study), nine as third line, and 10 as fourth or later line
- Median treatment duration was 8.8 months (range 1.3–24.0), with treatment ongoing in 11 patients (eight with current duration ≥10 months)
- 25 (89%) patients had clinical benefit per the treating physicians' assessment, of whom 16 (57% of all patients) were considered to have a partial response (PR) (**Figure 1**)
  - Clinical benefit was reported in 18/21 patients with *MET*amp (12 PR, 57%), in 5/5 with MET overexpression (two PR, 40%), and 2/2 with *MET*ex14 skipping (two PR, 100%)

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



*Activating mutation in exon 19. †Exon 20 A787G mutation. ‡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, D = dacomitinib, A = afatinib. ¶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 April 2023.

Safety

- 22 patients had AEs considered related to tepotinib. The most frequently reported tepotinib-related AE was edema in 15 patients (most commonly peripheral edema)
  - Five patients had Grade 1 peripheral edema, four patients had Grade 2, and two patients had Grade 3
  - Peripheral edema management strategies reported by the treating physicians included leg elevation, compression stockings, physiotherapy, lymph drainage, and diuretics
- Five patients had Grade 3 tepotinib-related AEs; no Grade 4 or 5 tepotinib-related AEs were reported
  - Grade 3 tepotinib-related AEs included dermatitis, fatigue, elevated amylase, elevated lipase, pneumonia, and pneumonitis each in one patient, and peripheral edema in two patients
  - Pneumonia was managed with treatment interruption for 8 days and antibiotics, and pneumonitis was managed with treatment discontinuation and steroids in the same patient
- One patient discontinued treatment due to tepotinib-related AEs (Grade 3 pneumonitis described above)

Selected cases

- Three cases are shown in greater detail below (**Case 4, 10, and 19**)
- Scan QR code on the right to view additional cases in greater detail

Supplementary materials
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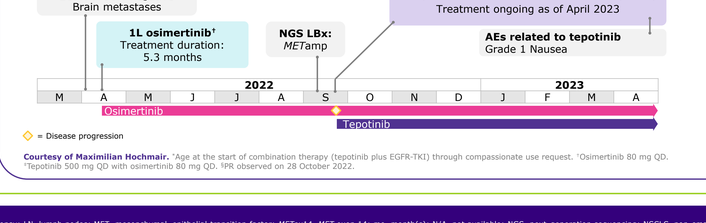
Case 4: 63-year-old* white female patient with no smoking history



Courtesy of Anthonie van der Wekken. *Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request. †Osimertinib 80 mg QD. ‡Tepotinib 500 mg QD with osimertinib 80 mg QD. Tepotinib dose reduced to 250 mg QD due to colitis. Tepotinib interrupted from 05 May 2022 to 22 July 2022 to manage pneumonitis. §PR observed on 25 October 2021.

Case 10: 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; PD occurred in bone and primary lung lesion, treatment continued after progression due to clinical benefit.

Case 19: 66-year-old* white female patient with brain metastases

Courtesy of Maximilian Hochmair. *Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request. †Osimertinib 80 mg QD. ‡Tepotinib 500 mg QD with osimertinib 80 mg QD. §PR observed on 28 October 2022.

Abbreviations: ADC, adenocarcinoma; AE, adverse event; amp, amplification; CEP7, centromere chromosome 7; CI, confidence interval; CT, computed tomography; CTx, chemotherapy; Del19, exon 19 deletion; EGFR, epidermal growth factor receptor; *EGFR*m, *EGFR* mutation; FISH, fluorescence in situ hybridization; GCN, gene copy number; gen., generation; IHC, immunohistochemistry; IO-CTx, immunotherapy-chemotherapy; L, line; LBx, liquid biopsy; LN, lymph nodes; MET, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14; mo, month(s); N/A, not available; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; 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; VEGF, vascular endothelial growth factor.
References: **1.** Ramalingam SS, et al. *Ann. Oncol.* 2018;29(suppl 8):viii740; **2.** Wang Y, et al. *Lung Cancer.* 2018;118:105–110; **3.** Liam CK, et al. *Clin Cancer Res.* 2023;29(10):1–8; **4.** Smit EF, et al. *Future Oncol.* 2022;18(9):1039–1054.
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