985P – Tepotinib outcomes according to prior therapies in patients with *MET* exon 14 (*MET*ex14) skipping NSCLC

Egbert F. Smit[1], Marina C. Garassino[2], Enriqueta Felip[3], Hiroshi Sakai[4], Xiuning Le[5], Remi Veillon[6], Julien Mazieres[7], Alexis B. Cortot[8], Jo Raskin[9], Michael Thomas[10,11], Santiago Viteri[12,13], Karin Berghoff[14], Rolf Bruns[15], Gordon Otto[16], Paul K. Paik[17,18]

[1]Department of Pulmonary Diseases, Leiden University Medical Centre, Leiden, The Netherlands; [2]Department of Medicine, Section of Hematology/Oncology, Knapp Center for Biomedical Discovery, The University of Chicago, IL, USA; [3]Department of Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Department of Thoracic Oncology, Saitama Cancer Center, Kitaadachi-gun, Japan; [5]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]CHU Bordeaux, Service des Maladies Respiratoires, Bordeaux, France; [7]CHU de Toulouse, Université Paul Sabatier, Toulouse, France; [8]Univ. Lille, CHU Lille, CNRS, Inserm, Institut Pasteur de Lille, UMR9020 – UMR-S 1277 - Canther, F-59000 Lille, France; [9]Department of Pulmonology and Thoracic Oncology, Antwerp University Hospital (UZA), Edegem, Belgium; [10]Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Heidelberg, Germany; [11]Translational Lung Research Center Heidelberg (TLRC-H), member of the German Center for Lung Research (DZL); [12]Instituto Oncológico Dr. Rosell, Hospital Universitario Dexeus, Grupo Quironsalud, Barcelona, Spain; [13]UOMI cancer center, Clínica Mi NovAliança, Lleida, Spain; [14]Global Patient Safety, Merck Healthcare KGaA, Darmstadt, Germany; [15]Department of Biostatistics, Merck Healthcare KGaA, Darmstadt, Germany; [16]Global Clinical Development, Merck Healthcare KGaA, Darmstadt, Germany; [17]Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [18]Department of Medicine, Weill Cornell Medical College, New York, NY, USA

CONCLUSIONS

- **In VISION – the largest study of a MET inhibitor in patients with *MET*ex14 skipping NSCLC – tepotinib demonstrated robust and durable efficacy in treatment-naïve and previously treated patients**
  - **In previously treated patients, efficacy was observed regardless of prior therapies, including IO and/or platinum-based CT**
- **Tepotinib had a manageable safety profile irrespective of line of treatment and prior IO, consisting of mostly mild to moderate AEs, with few leading to discontinuation**
  - **Peripheral edema was the most common AE**

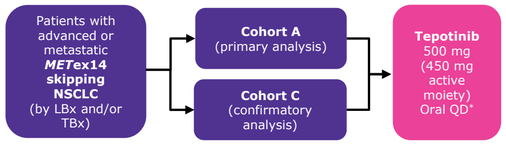
INTRODUCTION

- MET activated by exon 14 skipping alterations (*MET*ex14 skipping) is reported in 3–4% of patients with NSCLC and is sensitive to MET inhibition[1–4]
- Tepotinib is an oral, once daily, highly selective, potent MET inhibitor that has shown clinical activity in MET-driven tumors[5,6] and is approved in many countries in North America, Europe, South America and Asia, for treating advanced/metastatic *MET*ex14 skipping NSCLC
- **Here, we report the first analysis of tepotinib according to prior therapies from all patients with *MET*ex14 skipping NSCLC in VISION Cohorts A+C (data cut-off: February 20, 2022)**
- These data are relevant for clinical practice given that tepotinib was approved by the European Commission for patients with advanced NSCLC harboring *MET*ex14 skipping, previously treated with IO and/or platinum-based CT

METHODS

- VISION is a single-arm, Phase II trial of tepotinib in patients with advanced NSCLC harboring *MET*ex14 skipping
- Predefined analyses included first line (1L), second line (2L), second or later line (2L+), and patients with *MET*ex14 skipping detected by TBx (T+) – the most widely used detection method

Figure 1. Study design, endpoints, and eligibility criteria of VISION



*Treatment continues until disease progression, intolerable toxicity, or withdrawal of consent.

Endpoints (data cut-off: Feb 20, 2022)	
Primary endpoint	• Objective response by IRC per RECIST v1.1
Key secondary endpoints	• DOR, PFS, OS • Safety (per NCI-CTCAE v4.03)

Key inclusion criteria

- ≥18 years of age
- Histologically or cytologically confirmed NSCLC with *MET*ex14 skipping detected by LBx and/or TBx
- Measurable disease
- ECOG PS 0/1
- Prior immunotherapy allowed

Key exclusion criteria

- Tumors harboring *EGFR* mutations or *ALK* rearrangements
- >2 lines of prior therapy
- Prior use of MET inhibitors

PLAIN LANGUAGE SUMMARY

What is the purpose of this VISION study analysis?

- Tepotinib is a type of drug called a MET inhibitor and is currently approved for treating adult patients with advanced NSCLC with a genetic alteration causing *MET* exon 14 skipping
- Here we assessed how effective tepotinib is in patients who have previously been treated with other anticancer therapies

Who was included in this analysis?

- This analysis included 313 patients with *MET* exon 14 skipping NSCLC who participated in the VISION study; on average, patients were around 72 years old
- Of these, 149 patients were previously treated with other anticancer therapies, including chemotherapy and immunotherapy, and 164 patients had never been treated before for their NSCLC

What were the main findings of this analysis?

- Of 149 previously treated patients, tumors disappeared or shrunk in 45% of patients after treatment with tepotinib
- Of these, patients who had previously been treated with either chemotherapy alone, immunotherapy, or had combined treatment with chemotherapy and immunotherapy showed similar responses to treatment with tepotinib
- Of 164 patients who were not treated before, tumors disappeared or shrunk in 56% of patients after treatment with tepotinib

What side effects did patients have during VISION study?

- Most side effects related to tepotinib treatment were mild to moderate
- Low numbers of previously treated patients (14.1%) and patients who were not treated before (15.2%) discontinued due to side effects
- Peripheral edema (swelling of the hands and/or lower legs) was the most common side effect

RESULTS

VISION comprises a large population of elderly patients with NSCLC harboring *MET*ex14 skipping

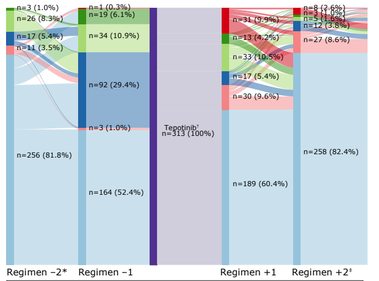
- Of 313 patients enrolled, 149 patients were previously treated (median age 70.8 years [range: 41–89]) (**Table 1**); 61.7% of previously treated patients received tepotinib as 2L and 38.3% as 3L+
  - Of these prior treatments, 84.6% of patients had received platinum-based CT, 54.4% had prior IO, and 14.8% had prior combined IO + CT, in any line; scan the QR code below to view patient outcomes with prior therapies (**Table S1**)
  - The most common therapy immediately prior to tepotinib was CT without concurrent IO received by 29.4% of patients; IO (monotherapy or IO + CT) was received by 17.0% of patients (**Figure 2**)
- 164 patients were treatment-naïve with median age 74.0 years [range: 47–94]

Table 1. Baseline characteristics

Baseline characteristics		Treatment-naïve (n=164)	Previously treated (n=149)
Median age, years (range)		74.0 (47–94)	70.8 (41–89)
Sex, %	Male	50.6	47.7
	Female	49.4	52.3
Race*, %	White	68.3	55.7
	Asian	30.5	37.6
ECOG PS, %	0	27.4	24.2
	1	72.0	75.8
Smoking history†, %	Yes	53.7	40.9
	No	45.7	53.0
Histology, adenocarcinoma, %		79.9	81.2
Enrolled in Europe, %		53.7	43.0
*MET*ex14 skipping detection	TBx	67.7	65.1
	LBx	57.9	55.7

*Race was missing/not collected at the study site for eight patients, three patients were Black/African American, and one patient was recorded as 'other'. †Smoking history was missing in ten patients.

Figure 2. Prior and subsequent therapies



*One patient received CT alone and two patients received other therapy prior to Regimen −2. †48 patients (15.3%) were still receiving tepotinib treatment. ‡Five patients received MET inhibitors, four received IO monotherapy, two received CT alone, and eight received other therapy in Regimen +3.

Tepotinib demonstrated robust clinical activity irrespective of prior treatment

- ORR, DOR, PFS, and OS were meaningful in treatment-naïve and previously treated patients, including those who received prior platinum-based chemotherapy and/or immunotherapy (**Table 2, Figures 3–4**)
- In treatment-naïve patients, ORR was 56.1%, mDOR was 46.4 months, mPFS was 12.6 months, and mOS was 19.1 months; in previously treated patients, ORR was 45.0%, mDOR was 12.4 months, mPFS was 11.0 months, and mOS was 19.6 months
- Efficacy was also clinically meaningful and robust in T+ patients (**Table 2, Figure 3**)
- ORR for 2L patients who received CT alone as 1L was 50.0% (95% CI: 36.1, 63.9) and 60.5% (43.4, 76.0) in T+ patients (**Figure 3**)
- ORR in 2L patients with prior IO + CT was 62.5% (35.4, 84.8) and 63.6% (30.8, 89.1) in T+ patients (**Figure 3**)

Figure 3. Objective response rate according to line of therapy

Tepotinib efficacy		Overall (N=313) n	Overall (N=313) ORR, % (95% CI)	T+ patients (N=208) n	T+ patients (N=208) ORR, % (95% CI)
Overall		313	50.8 (45.1, 56.5)	208	53.4 (46.3, 60.3)
Treatment-naïve		164	56.1 (48.1, 63.8)	111	56.8 (47.0, 66.1)
Previously treated: 2L+		149	45.0 (36.8, 53.3)	97	49.5 (39.2, 59.8)
Prior therapy	IO*	79	39.2 (28.4, 50.9)	47	38.3 (24.5, 53.6)
	IO + CT	22	54.5 (32.2, 75.6)	16	56.3 (29.9, 80.2)
	CT	104	48.1 (38.2, 58.1)	64	53.1 (40.2, 65.7)
Previously treated: 2L only		92	45.7 (35.2, 56.4)	65	53.8 (41.0, 66.3)
Prior therapy	IO*	36	38.9 (23.1, 56.5)	25	44.0 (24.4, 65.1)
	IO + CT	16	62.5 (35.4, 84.8)	11	63.6 (30.8, 89.1)
	CT	54	50.0 (36.1, 63.9)	38	60.5 (43.4, 76.0)

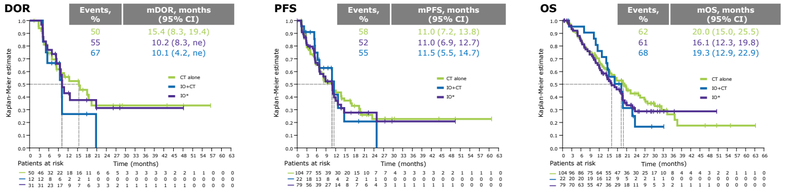
*Patients received IO monotherapy or IO + platinum-based CT.

Table 2. Efficacy according to line of therapy

Efficacy (IRC)	Overall (N=313) 1L (n=164)	Overall (N=313) 2L (n=92)	Overall (N=313) 2L+ (n=149)	T+ (N=208) 1L (n=111)	T+ (N=208) 2L (n=65)	T+ (N=208) 2L+ (n=97)
ORR, % (95% CI)	56.1 (48.1, 63.8)	45.7 (35.2, 56.4)	45.0 (36.8, 53.3)	56.8 (47.0, 66.1)	53.8 (41.0, 66.3)	49.5 (39.2, 59.8)
mDOR, months (95% CI)	46.4 (13.8, ne)	12.6 (8.3, 20.8)	12.4 (9.5, 18.5)	46.4 (13.4, ne)	12.4 (7.0, 20.8)	10.2 (8.3, 18.0)
mPFS, months (95% CI)	12.6 (9.6, 17.7)	10.9 (8.2, 13.8)	11.0 (8.2, 13.7)	15.3 (11.3, ne)	13.7 (8.2, 19.4)	11.5 (8.2, 16.8)
mOS, months (95% CI)	19.1 (13.7, 23.7)	20.0 (15.8, 23.7)	19.6 (15.2, 22.3)	25.9 (17.5, 36.6)	20.9 (17.7, 32.5)	20.4 (17.0, 26.8)

- In patients with prior CT alone, mDOR was 15.4 months, mPFS was 11.0 months, and mOS was 20.0 months; in patients with prior IO + CT, mDOR was 10.1 months, mPFS was 11.5 months, and mOS was 19.3 months (**Figure 4**)
- In T+ patients with prior CT alone, mDOR was 15.4 months, mPFS was 13.7 months, and mOS was 22.3 months; in T+ patients with prior IO + CT, mDOR was 10.1 months, mPFS was 11.5 months, and mOS was 17.1 months
- Scan the QR code below to view efficacy according to line of therapy in L+ patients (**Table S2**)

Figure 4. Overall efficacy according to prior therapies in all previously treated patients



*Patients received IO monotherapy or IO + platinum-based CT.

Treatment-related adverse events were mostly mild-moderate across therapy lines

- Overall (N=313), TRAEs occurred in 91.7% of patients, 34.2% had Grade ≥3 TRAEs, and 14.7% discontinued due to TRAEs
- In treatment-naïve patients (n=164), Grade ≥3 TRAEs occurred in 40.9% of patients and 15.2% of patients discontinued due to TRAEs (**Table 3**)
- In previously treated patients (n=149), Grade ≥3 TRAEs occurred in 26.8% of patients and 14.1% of patients discontinued due to TRAEs; in patients with prior IO, Grade ≥3 TRAEs occurred in 27.2% of patients and 17.3% of patients discontinued due to TRAEs
- Peripheral edema was the most common all-cause AE, occurring in 75.0% of treatment-naïve patients, 68.5% of previously treated patients, and 70.4% of patients with prior IO
- The safety profile of tepotinib was consistent in patients with prior IO (**Table 3**)

Table 3. Tepotinib safety profile

TRAEs, n (%)	Treatment-naïve (n=164)	Previously treated (n=149)	Prior IO (n=81)
Any grade	155 (94.5)	132 (88.6)	73 (90.1)
Grade ≥3	67 (40.9)	40 (26.8)	22 (27.2)
Leading to dose reduction	64 (39.0)	41 (27.5)	21 (25.9)
Leading to temporary interruption	79 (48.2)	54 (36.2)	31 (38.3)
Leading to permanent discontinuation	25 (15.2)	21 (14.1)	14 (17.3)
All-cause AEs in ≥20% of all patients, n (%)			
Peripheral edema	123 (75.0)	102 (68.5)	57 (70.4)
Nausea	55 (33.5)	41 (27.5)	21 (25.9)
Diarrhea	47 (28.7)	43 (28.9)	21 (25.9)
Hypoalbuminemia	57 (34.8)	44 (29.5)	28 (34.6)
Blood creatinine increase	46 (28.0)	45 (30.2)	27 (33.3)
Dyspnea	44 (26.8)	23 (15.4)	14 (17.3)
Decreased appetite	37 (22.6)	27 (18.1)	17 (21.0)

Abbreviations: 1L, first line; 2L, second line; 2L+, second or later line; 3L+, third or later line; AE, adverse event; ALK, anaplastic lymphoma kinase; CI, confidence interval; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IO, immunotherapy; IRC, independent review committee; L+, positive detection of *MET*ex14 skipping in liquid biopsy sample; LBx, liquid biopsy; m, median; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ne, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response evaluation criteria in solid tumors; T+, positive detection of *MET*ex14 skipping in tissue biopsy sample; TBx, tissue biopsy; TRAE, treatment-related adverse event.

References: 1. Reungwetwattana T, et al. *Lung Cancer.* 2017;103:27–37; 2. Rosell R, Karachaliou N. *Lancet.* 2016;387(10026):1354–1356; 3. Salgia R, et al. *Cancer Treat Rev.* 2020;87:102022; 4. Paik PK, et al. *Cancer Discov.* 2015;5(8):842–849; 5. Falchook GS, et al. *Clin Cancer Res.* 2020;26(6):1237–1246; 6. Paik PK, et al. *N Engl J Med.* 2020;383(10):931–943.

Acknowledgements: The authors would like to thank patients, all investigators and co-investigators, and the study teams at all participating centers and at Merck Healthcare KGaA, Darmstadt, Germany. The trial was sponsored by Merck Healthcare KGaA, Darmstadt, Germany. Medical writing and editorial assistance was provided by Pritha Bhunia of Syneos Health, UK, and funded by Merck Healthcare KGaA, Darmstadt, Germany.

Disclosures: Egbert F. Smit has received advisory/consultancy (institution) fees from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Bristol Myers Squibb, Merck Healthcare KGaA, Darmstadt, Germany, MSD Oncology, Takeda, Bayer, Regeneron, Novartis, Daiichi Sankyo and Seattle Genetics; research funding (institution) from Boehringer Ingelheim, Bayer, Roche/Genentech, AstraZeneca and Bristol Myers Squibb

Contact details: e.f.smit@lumc.nl

Supplemental results

Materials obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors

Poster 985P | Presented at the European Society for Medical Oncology (ESMO) congress | September 9–13, 2022 | Paris, France