Tepotinib efficacy and safety in patients with *MET* exon 14 skipping NSCLC

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

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CONCLUSIONS

- **Tepotinib demonstrated robust and durable clinical activity across treatment lines in patients with *MET*ex14 skipping NSCLC, with particularly durable efficacy in treatment-naïve patients**
- **Tepotinib was generally well tolerated, with a low proportion of TRAEs leading to discontinuation**

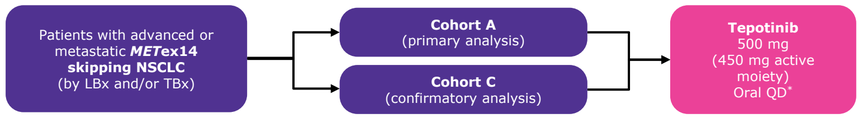
INTRODUCTION

- *MET*ex14 skipping is reported in 3–4% of patients with NSCLC, can be detected using liquid and/or tissue biopsy, and is sensitive to MET inhibition[1–4]
- Tepotinib is an oral, once daily, highly selective, potent MET TKI,[5] and is recommended by treatment guidelines for the treatment of metastatic NSCLC harboring *MET*ex14 skipping alterations[6–8]
- In VISION Cohort A (median age 73.1 years [range 41–94]), tepotinib showed robust and durable clinical activity in patients with *MET*ex14 skipping NSCLC (data cut off: July 2020)[9]
- Here, we report updated outcomes, with interim analyses from a confirmatory cohort

METHODS

- VISION (NCT02864992) is a single-arm, Phase II trial of tepotinib in patients with NSCLC harboring *MET*ex14 skipping (Cohorts A and C)

Figure 1. VISION study design, endpoints, and eligibility criteria



Endpoints† (data cut off: Feb 2021)

Primary endpoint	• Objective response by IRC according to RECIST v1.1
Key secondary endpoints	• DOR, PFS, OS • Safety (AEs‡ assessed using NCI-CTCAE v4.03)

Key inclusion criteria

- ≥18 years of age
- Histologically or cytologically confirmed NSCLC with *MET*ex14 skipping detected by TBx and/or LBx
- 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

*Treatment continues until disease progression, intolerable toxicity, or withdrawal of consent.
†Efficacy was assessed in patients with more than 3 months' follow-up, and safety was analyzed in all patients having received at least one dose of tepotinib by the data cut-off.
‡AEs were defined as events that started within the day of first dose of trial treatment until 30 days after last dose of treatment or that started before first dose but worsened during the treatment period.

RESULTS

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

- Overall, most of the patients in Cohorts A and C that were assessed for efficacy (N=275) were elderly (median 72.4 years [range 41–94]), half were male, half had smoking history, and most had adenocarcinoma (**Table 1**)
- Of 275 patients, 174 had *MET*ex14 skipping detected by TBx, 159 by LBx, and 59 had *MET*ex14 skipping detected by both methods; baseline characteristics were broadly consistent in patients with *MET*ex14 skipping detected by TBx and LBx, although patients enrolled based on LBx had characteristics associated with a worse prognosis, such as higher tumor load (**Table 1**)

Table 1. Baseline characteristics

Baseline characteristics		Overall (N=275)	Treatment-naïve (n=137)	Previously treated (n=138)
Median age, years (range)		72.4 (41–94)	74.6 (47–94)	70.9 (41–89)
Sex, %	Male/Female	49.1/50.9	49.6/50.4	48.6/51.4
Smoking history,* %	Yes	46.5	53.3	39.8
Adenocarcinoma histology, %		80.0	79.6	80.4
Brain metastases,† %		18.5	17.5	19.6
Median tumor load,‡ mm (range)	Overall	57.4 (10.2–227.8)	62.1 (10.2–227.8)	53.8 (11.6–178.3)
	L+	*n=159* 68.0 (11.6–227.8)	*n=81* 66.4 (11.7–227.8)	*n=78* 70.7 (11.6–178.3)
	T+	*n=174* 52.9 (10.2–227.8)	*n=86* 56.9 (10.2–227.8)	*n=88* 52.2 (11.6–178.3)

*Smoking history was missing in ten patients. †Baseline brain metastases identified by IRC or investigator. ‡Tumor load of target lesions by IRC.

Tepotinib demonstrated robust clinical activity irrespective of therapy line or method of *MET*ex14 skipping detection

- Overall, ORR was 49.1%, DCR was 74.9%, mDOR was 13.8 months, mPFS was 10.8 months, and mOS was 19.7 months (**Table S1, Figure S1A**)
- Treatment-naïve patients (n=137) had an ORR of 54.0%, DCR was 74.5%, mDOR was 32.7 months, mPFS was 10.4 months, and mOS was 17.6 months (**Table 2, Figure S1B**), and previously treated patients (n=138) had an ORR of 44.2%, DCR was 75.4%, mDOR was 11.1 months, mPFS was 11.0 months, and mOS was 19.9 months (**Table 2, Figure S1B**)
- >90% of patients had tumor shrinkage, irrespective of therapy line (**Figure S2**)
- In patients with *MET*ex14 skipping identified by TBx, treatment-naïve patients (n=86) had an ORR of 54.7%, mDOR was 32.7 months, mPFS was 15.3 months, and mOS was 29.7 months (**Table 2, Figure 2**), and previously treated patients (n=88) had an ORR of 47.7%, mDOR was 10.1 months, mPFS was 11.1 months, and mOS was 22.3 months (**Table 2, Figure 3**)
- Efficacy in patients with *MET*ex14 skipping identified by TBx across therapy lines is shown in **Table S2** and **Figure S3**; efficacy in patients with *MET*ex14 skipping identified by LBx is shown in **Table S3** and **Figure S4**

Table 2. Efficacy of tepotinib

Efficacy (IRC)	Treatment-naïve		Previously treated	
	Either detection method (n=137)	T+ (n=86)*	Either detection method (n=138)	T+ (n=88)*
ORR, % (95% CI)	**54.0** (45.3, 62.6)	**54.7** (43.5, 65.4)	**44.2** (35.8, 52.9)	**47.7** (37.0, 58.6)
DCR, % (95% CI)	74.5 (66.3, 81.5)	80.2 (70.2, 88.0)	75.4 (67.3, 82.3)	79.5 (69.6, 87.4)

*Patients with *MET*ex14 skipping identified by both LBx and TBx are included in both analysis sets (overall, n=59; treatment-naïve, n=30; previously treated, n=29); testing by both methods was not required for enrollment.

Figure 2. DOR, PFS, and OS in treatment-naïve T+ patients

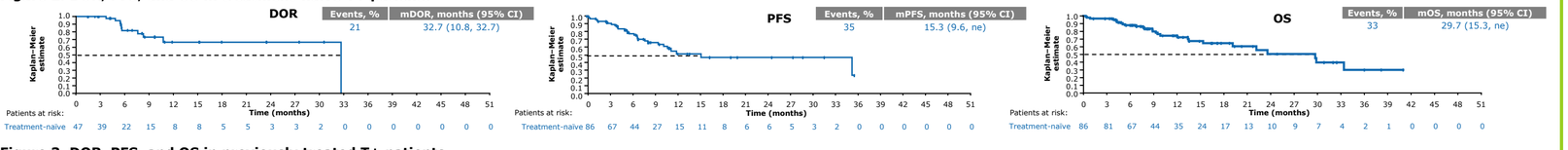
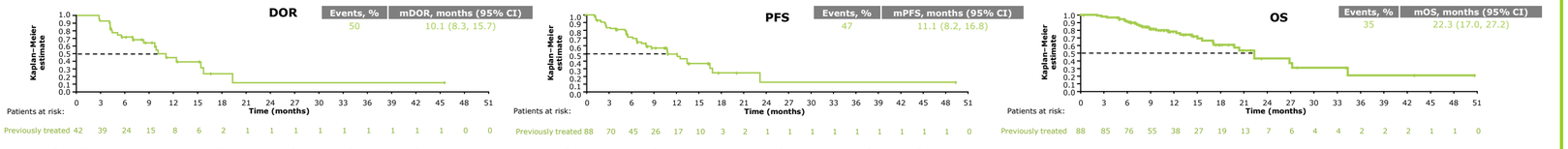


Figure 3. DOR, PFS, and OS in previously treated T+ patients



Tepotinib was generally well tolerated, with a low proportion of TRAEs leading to discontinuation

- Overall, Grade ≥3 TRAEs occurred in 29.6% of patients, and 14.1% of patients discontinued due to TRAEs **(Table 3)**
- In treatment-naïve patients, Grade ≥3 TRAEs occurred in 33.1% of patients, and 16.2% of patients discontinued due to TRAEs; in previously treated patients, Grade ≥3 TRAEs occurred in 25.9% of patients, and 11.9% of patients discontinued due to TRAEs **(Table 3)**
- Peripheral edema was the most reported all-cause AE, occurring in 66.2% treatment-naïve patients and 65.0% previously treated patients **(Table 4)**; Grade ≥3 peripheral edema occurred in 10.7% of patients overall

Table 3. Tepotinib safety profile by line of therapy, irrespective of detection method

TRAE, n (%)	Overall (N=291)	Treatment-naïve (n=148)	Previously treated (n=143)
Any grade	264 (90.7)	137 (92.6)	127 (88.8)
Grade ≥3	86 (29.6)	49 (33.1)	37 (25.9)
Leading to death	2 (0.7)	1 (0.7)	1 (0.7)
Leading to dose reduction	90 (30.9)	51 (34.5)	39 (27.3)
Leading to interruption	114 (39.2)	63 (42.6)	51 (35.7)
Leading to discontinuation	41 (14.1)	24 (16.2)	17 (11.9)

Table 4. All-cause AEs by line of therapy, irrespective of detection method

All-cause AEs in ≥20% of patients, n (%)	Overall (N=291)	Treatment-naïve (n=148)	Previously treated (n=143)
Peripheral edema	191 (65.6)	98 (66.2)	93 (65.0)
Nausea	88 (30.2)	51 (34.5)	37 (25.9)
Diarrhea	81 (27.8)	42 (28.4)	39 (27.3)
Hypoalbuminemia	81 (27.8)	41 (27.7)	40 (28.0)
Blood creatinine increase	76 (26.1)	34 (23.0)	42 (29.4)
Dyspnea	60 (20.6)	40 (27.0)	20 (14.0)

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IRC, independent review committee; L+, patients with *MET*ex14 skipping detected by LBx; LBx, liquid biopsy; mDOR, median duration of response; MET, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14; 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; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; T+, patients with *MET*ex14 skipping detected by TBx; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

References: 1. Reungwetwattana T, et al. *Lung Cancer*. 2017;103:27–37; 2. Rosell R, Karachaliou N. *Lancet Oncol*. 2016;387:1354–1356; 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. Hanna NH, et al. *J Clin Oncol*. 2021;39(9):1040–1091; 7. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 4.2021. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2021. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed March 1, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org; 8. Japanese Lung Cancer Society Lung Cancer Practice Guidelines 2020. Available at https://www.haigan.gr.jp; 9. Paik PK, et al. *J Thorac Oncol*. 2021;16(3):S174 [and presentation].

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Supplementary results

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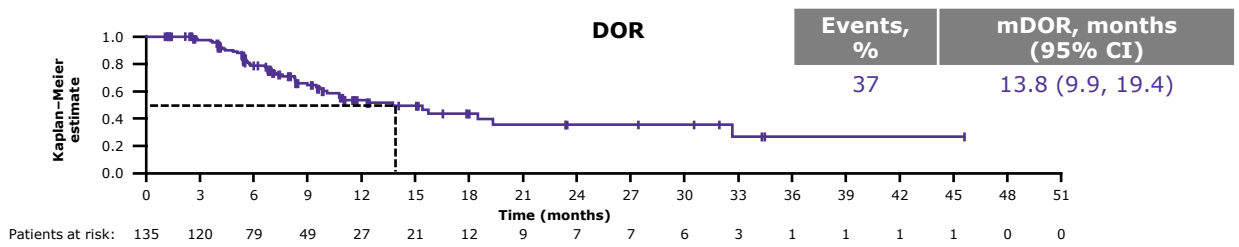
SUPPLEMENTARY RESULTS

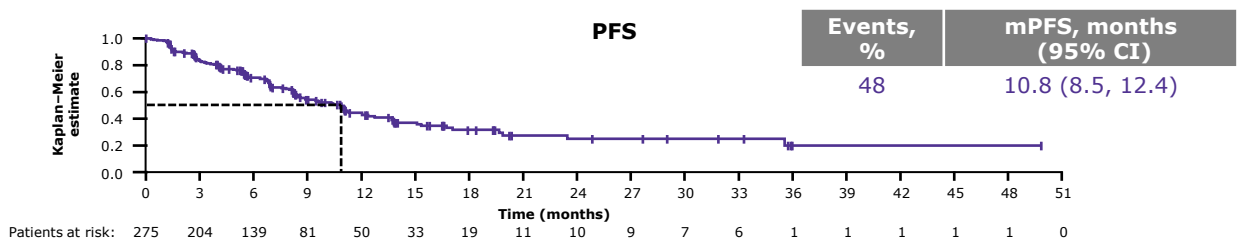
Table S1. Overall efficacy of tepotinib, across lines of therapy

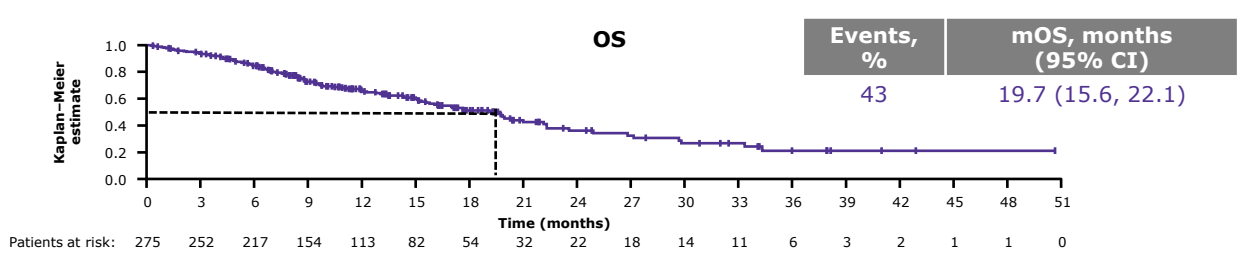
Efficacy (IRC)	Overall (N=275)
ORR, % (95% CI)	**49.1** (43.0, 55.2)
DCR, % (95% CI)	74.9 (69.4, 79.9)

Figure S1. Overall DOR, PFS, and OS

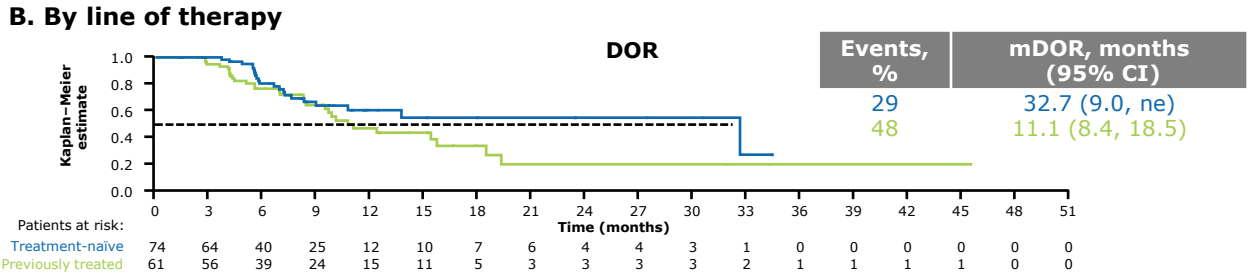
A. Irrespective of line of therapy

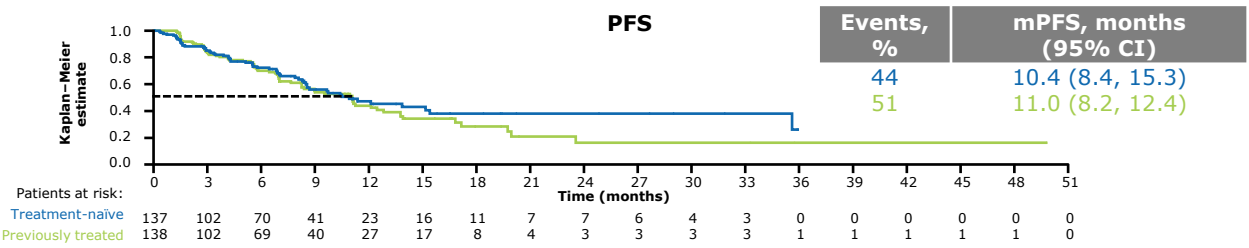


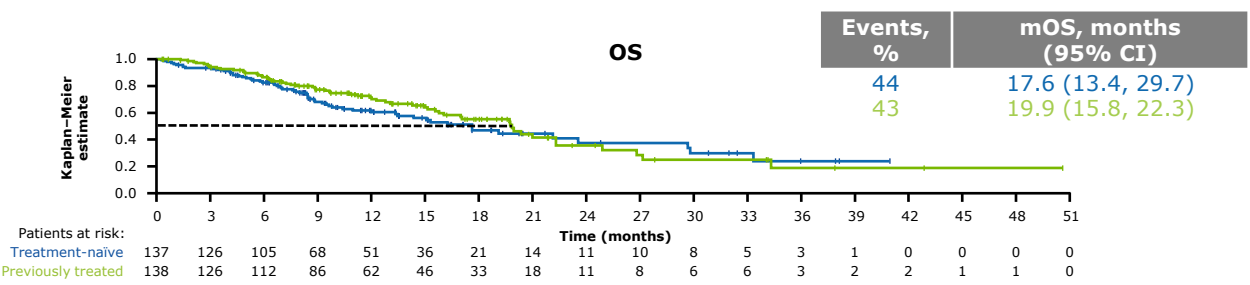




B. By line of therapy







Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ne, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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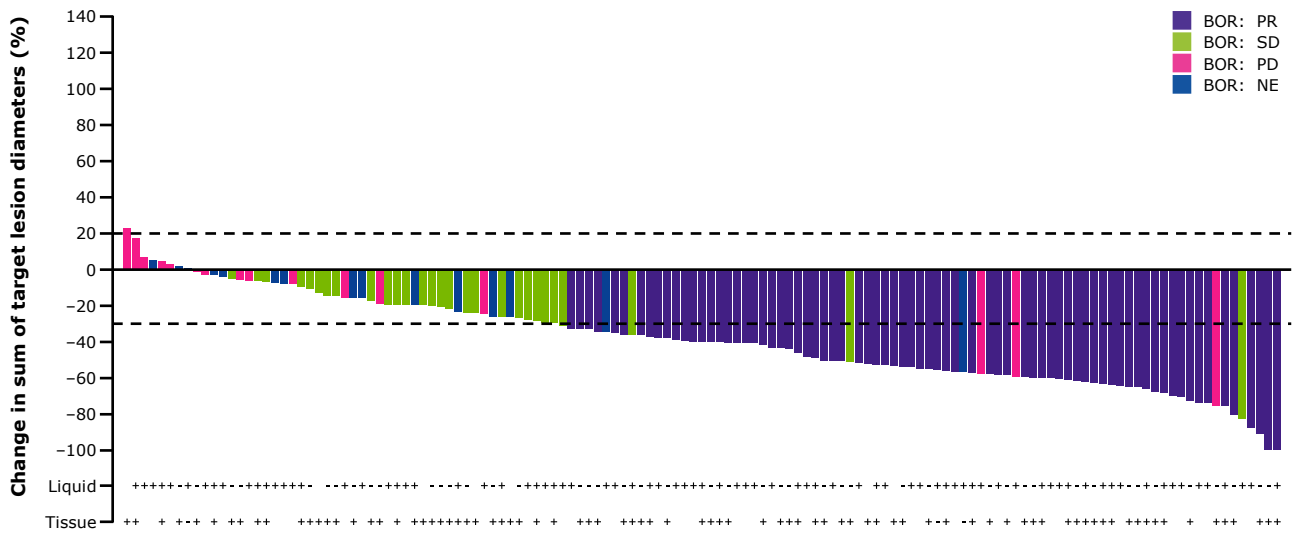
SUPPLEMENTARY RESULTS

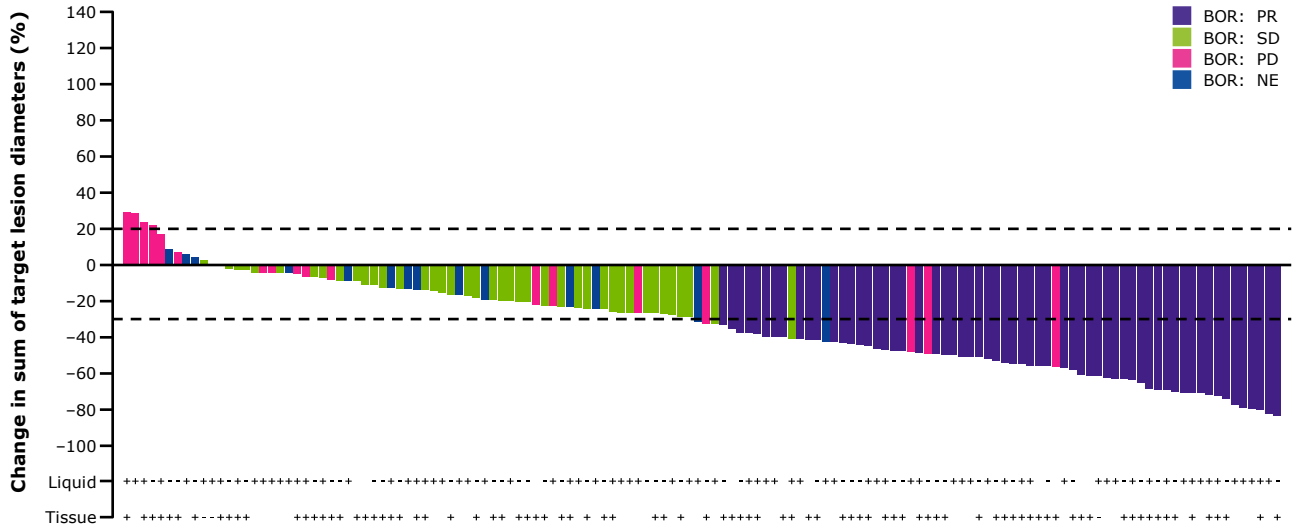
Figure S2. Tumor shrinkage according to line of therapy

A. Treatment-naïve



Four patients excluded due to unavailable baseline/on-treatment measurement.

B. Previously treated



Two patients excluded due to unavailable baseline/on-treatment measurement.

Abbreviations: BOR, best overall response; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

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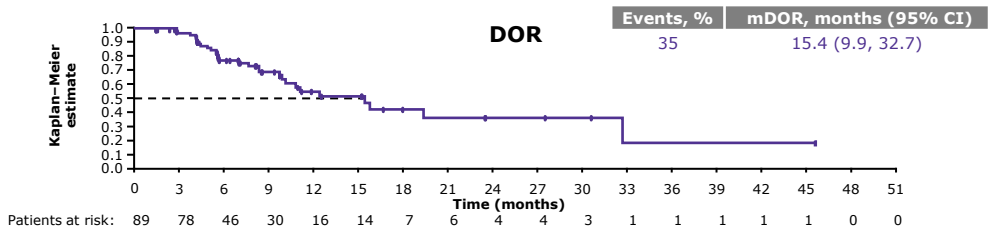
SUPPLEMENTARY RESULTS

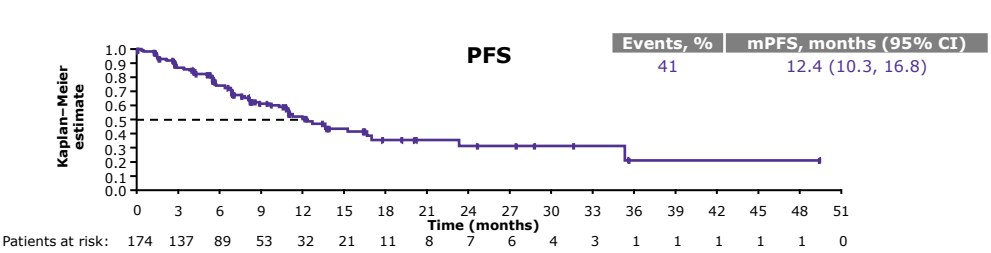
Table S2. Efficacy of tepotinib in T+ patients, across lines of therapy

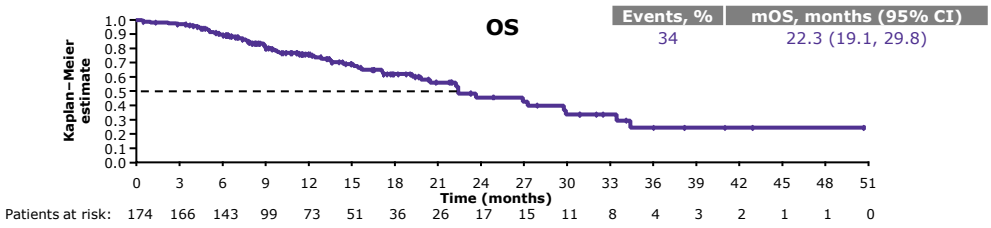
Efficacy (IRC)	T+* (n=174)
ORR, % (95% CI)	**51.1** (43.5, 58.8)
DCR, % (95% CI)	79.9 (73.2, 85.6)

*Patients with *MET*ex14 skipping identified by both liquid and tissue biopsy are included in both analysis sets (overall, n=59; treatment-naïve, n=30; previously treated, n=29); testing by both methods was not required for enrollment.

Figure S3. DOR, PFS, and OS in T+ patients, across lines of therapy







Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; mDOR, median duration of response; *MET*ex14, *MET* exon 14; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T+, patients with *MET*ex14 skipping detected by TBx; TBx, tissue biopsy.

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Tepotinib efficacy and safety in patients with *MET* exon 14 skipping NSCLC

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SUPPLEMENTARY RESULTS

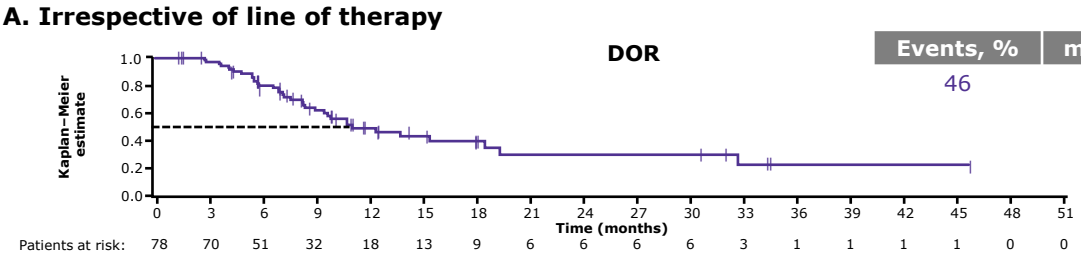
Table S3. Efficacy of tepotinib in L+ patients

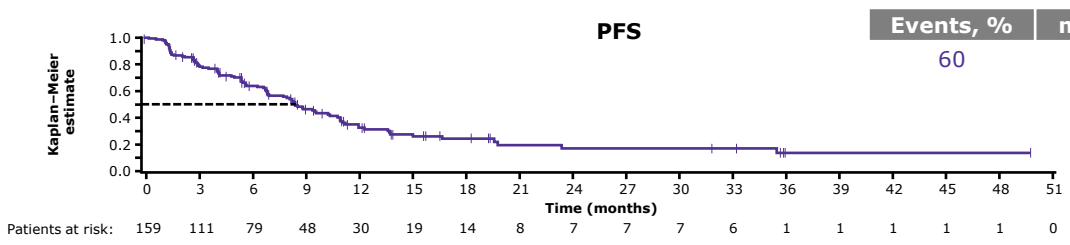
Efficacy (IRC)	Overall (N=159)	Treatment-naïve (n=81)	Previously treated (n=78)
ORR, % (95% CI)	**49.1** (41.1, 57.1)	**54.3** (42.9, 65.4)	**43.6** (32.4, 55.3)
DCR, % (95% CI)	70.4 (62.7, 77.4)	71.6 (60.5, 81.1)	69.2 (57.8, 79.2)

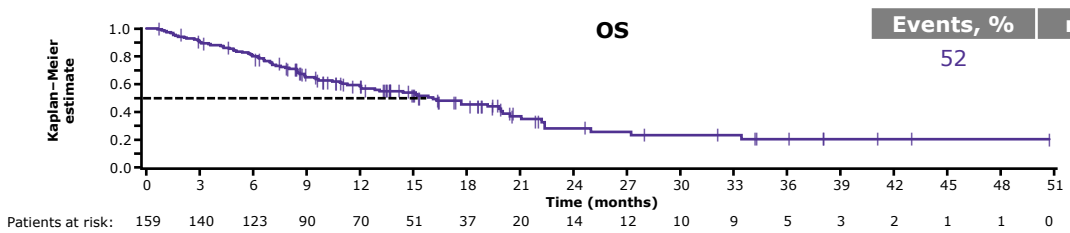
*Patients with *MET*ex14 skipping identified by both liquid and tissue biopsy are included in both analysis sets (overall, n=59; treatment-naïve, n=30; previously treated, n=29); testing by both methods was not required for enrollment.

Figure S4. DOR, PFS, and OS in L+ patients

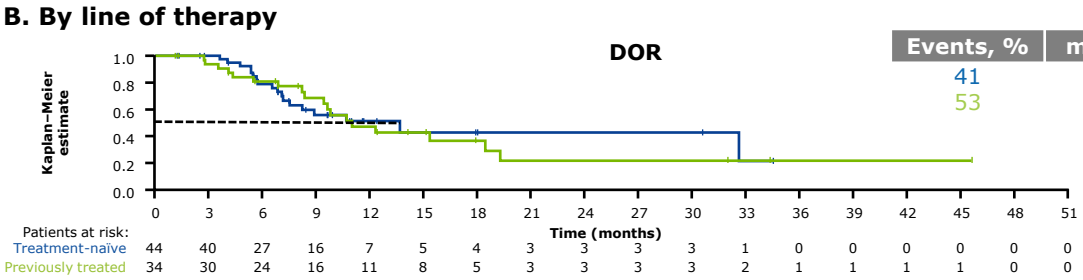
A. Irrespective of line of therapy

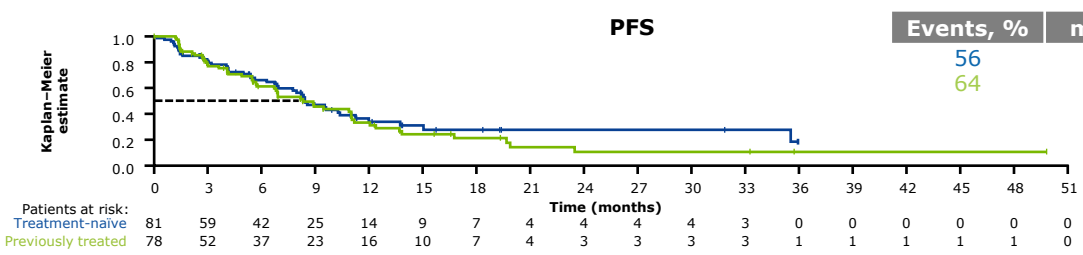


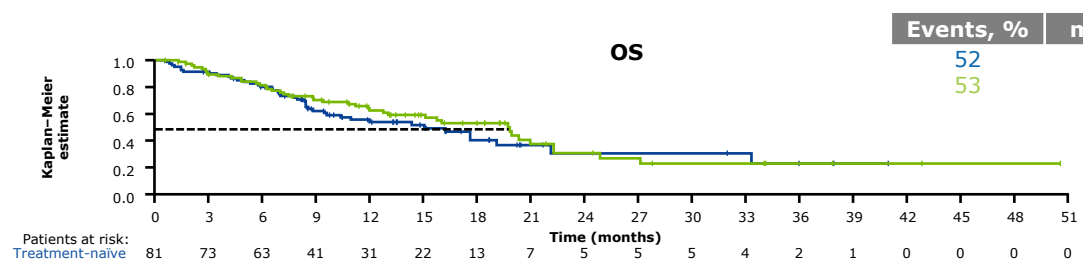




B. By line of therapy







Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; L+, patients with *MET*ex14 skipping detected by LBx; LBx, liquid biopsy; mDOR, median duration of response; *MET*ex14, *MET* exon 14; mOS, median overall survival; mPFS, median progression-free survival; ne, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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