Supplementary Appendix: Tepotinib In Patients With *MET* Exon 14 Skipping Non-Small-Cell Lung Cancer. Paik et al.

VISION Investigators

Biomarker assay methodology

Supplemental figures

Supplemental tables

References

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Biomarker assay methodology

MET exon 14 skipping was tested centrally from either circulating tumor DNA (ctDNA) collected from plasma (liquid biopsy) using next-generation sequencing panel Guardant360® (73-gene) or from RNA collected from tumor tissue (tissue biopsy) using Oncomine™ Focus Assay (OFA; 52-gene). Target turnaround time for both assays (liquid or tissue) was 10 working days. The median time for central verification was 10 working days (range: 8 to 14) based on liquid biopsy and 9 working days (range: 7 to 11) for tumor-biopsy based detection.

Central verification of *MET* exon 14 skipping was required prior to study entry; if patients had been previously identified via local testing, they were required to have central verification prior to treatment.

The protocol allowed investigators the freedom to determine the sampling time before enrollment; hence, reflecting testing in real-world practice. Tissue- and liquid-biopsy testing could be done at any stage during the pre-screening period prior to requiring trial treatment. A fresh biopsy sample was not required. For *MET* exon 14 testing on tumor tissue, the sample could be from archival tissue or fresh tissue. Patient blood plasma for liquid biopsy (ctDNA samples) was collected for central testing as soon as the patient was identified as eligible for trial pre-screening. There was no limit on the time between when the biopsy was taken for determination of *MET* exon 14 skipping and trial entry. For tissue samples, the median (range) time from sampling to first dose of tepotinib was 137 days (15–1711).

Next-generation sequencing panel Guardant360® (73-gene)

The liquid-biopsy assay was set up to detect changes to the splice acceptor or splice donor region of *MET* exon 14. Any change to genomic DNA occurring in the two regions leads to deletion (skipping) of *MET* exon 14.

Specifically, any single-nucleotide variant or Indel variant type that overlaps any of the two splice regions of *MET* exon 14 (chromosome 7:116411902 and 116412043; mapped to the human genome [hg19]) defined as 8 bp into the intron or 3 bp into the exon was identified with the Guardant360® assay. Based on the coordinates of these exon–intron junctions, variants found that affect bases 116411894 through 116411905 and 116412040 through 116412051 would be identified as a *MET* exon 14 alteration leading to skipping and thus identified a positive testing result.

Assay sensitivity: *MET* exon 14 skipping detection has a limit of detection of 0.2% mutant allele frequency (MAF) for 30 ng input and 2% MAF for 5 ng input (Guardant Health 360). The sensitivity for other actionable mutations is 0.3% MAF.[1]

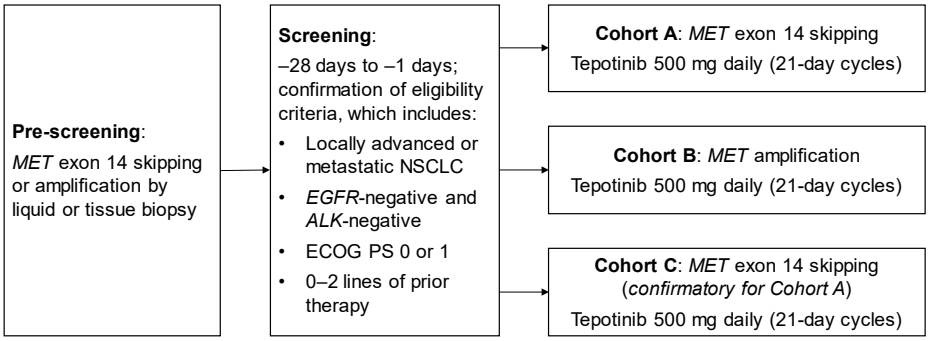
Clinical validation using orthogonal plasma- and tissue-based clinical genotyping across >750 patients demonstrated high accuracy and specificity (positive percent agreement and negative percent agreement >99% and positive predictive values 92–100%].[1]

Oncomine™ Focus Assay (OFA; 52-gene)

The tissue-biopsy assay testing was performed on RNA and demonstrates that, in practice, exon 14 was skipped/deleted. An RT-PCR assay was used, which included primers geared towards the identification of the absence of *MET* exon 14 in a next-generation sequencing read-out of the MET mRNA. This is a functional assay directly demonstrating that *MET* exon 14 skipping has occurred at the gene expression level.

Definition of tested regions are based on splice-site definitions in the literature that have shown that these intronic mutations lead to alternative splicing and deletion of *MET* exon 14.[2-6]

Figure S1. Study design



500 mg tepotinib hydrochloride hydrate (active ingredient) contains 450 mg tepotinib free base (active moiety).

ALK, anaplastic lymphoma kinase; ECOG PS, Easter Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer.

Figure S2. Screening and enrollment

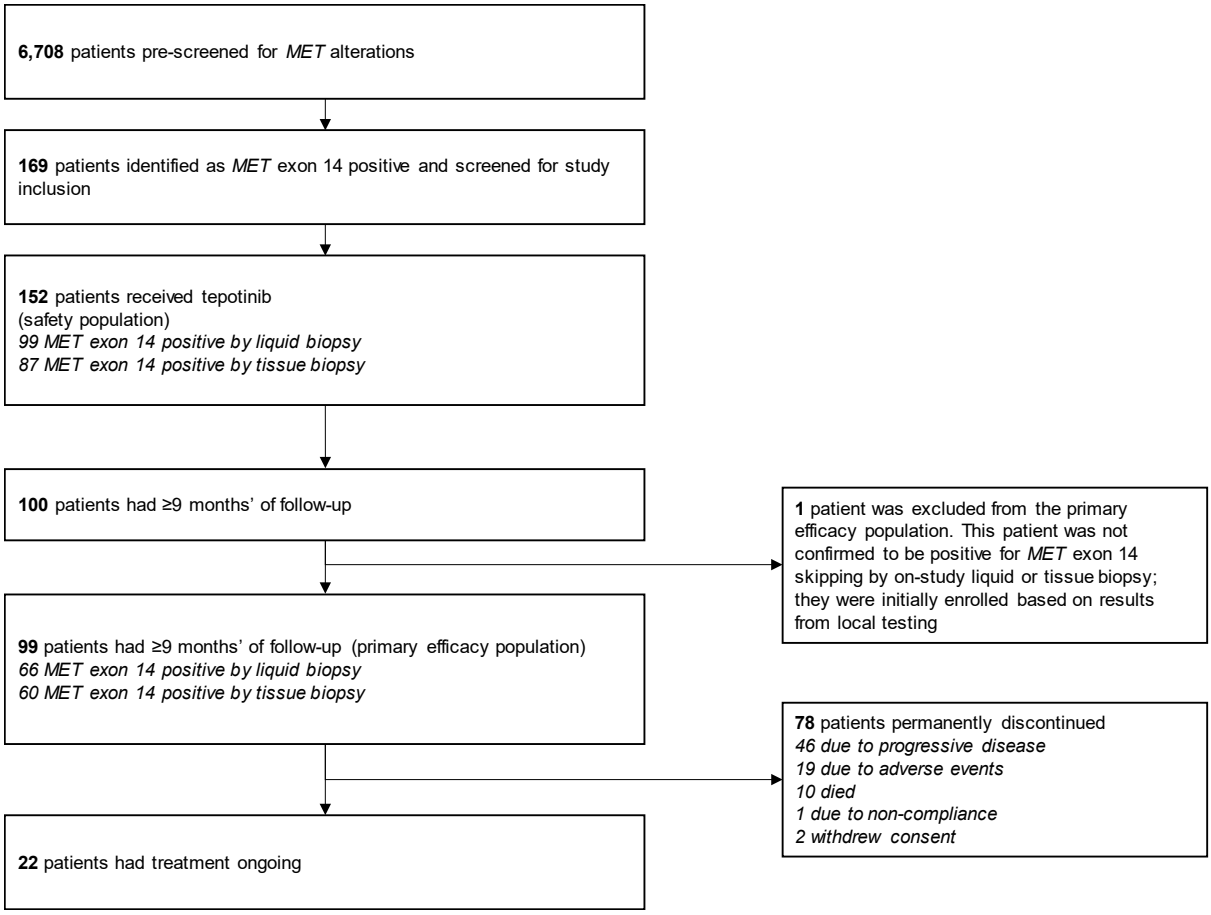
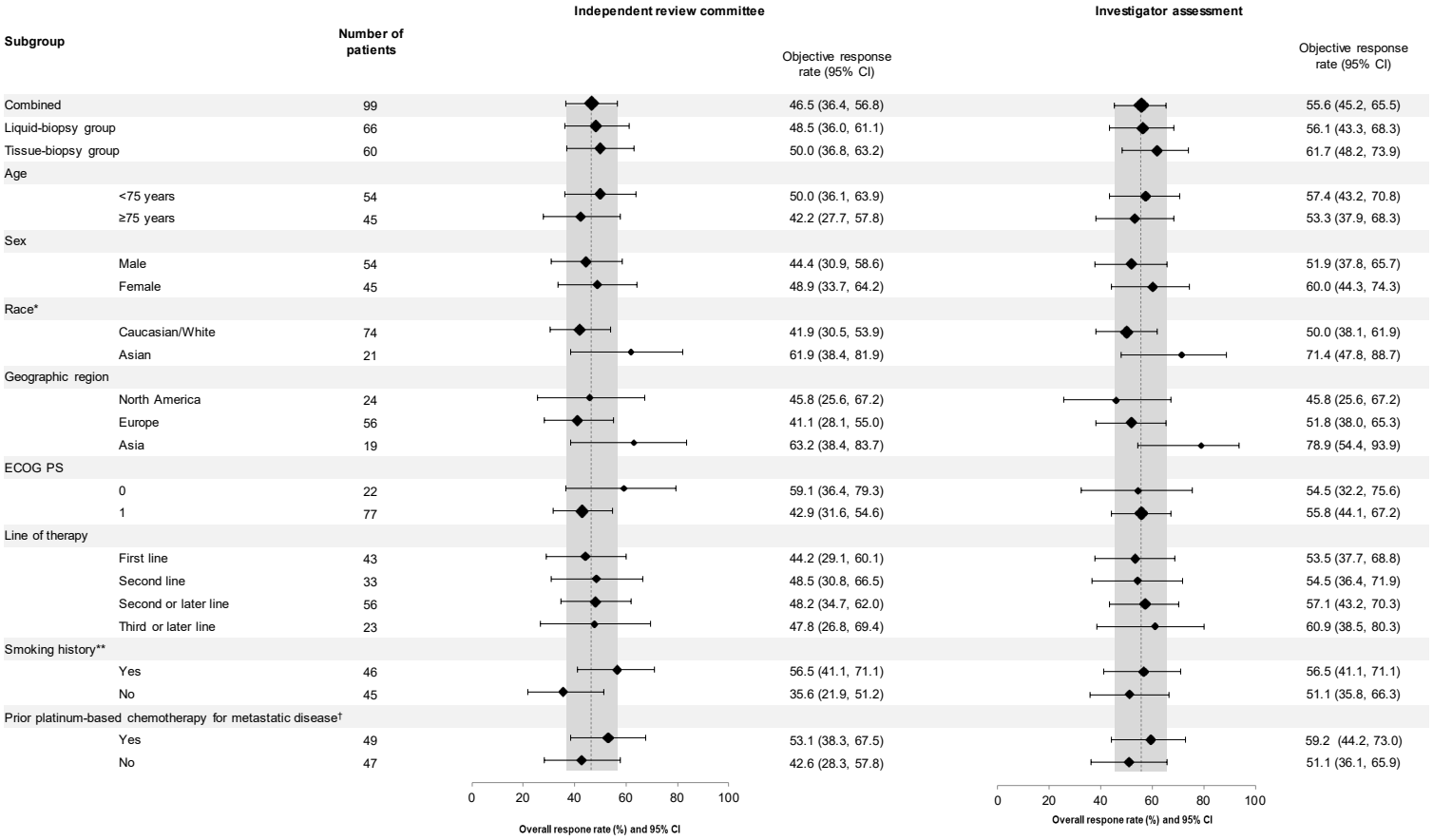


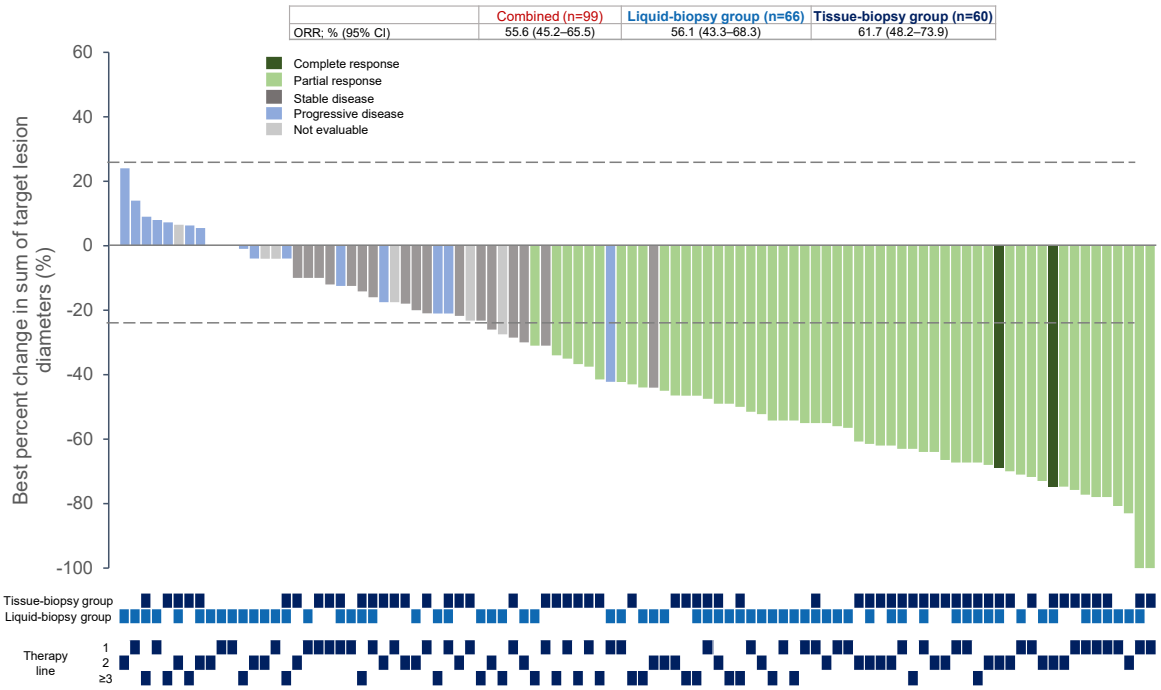
Figure S3. Objective response rate by subgroup



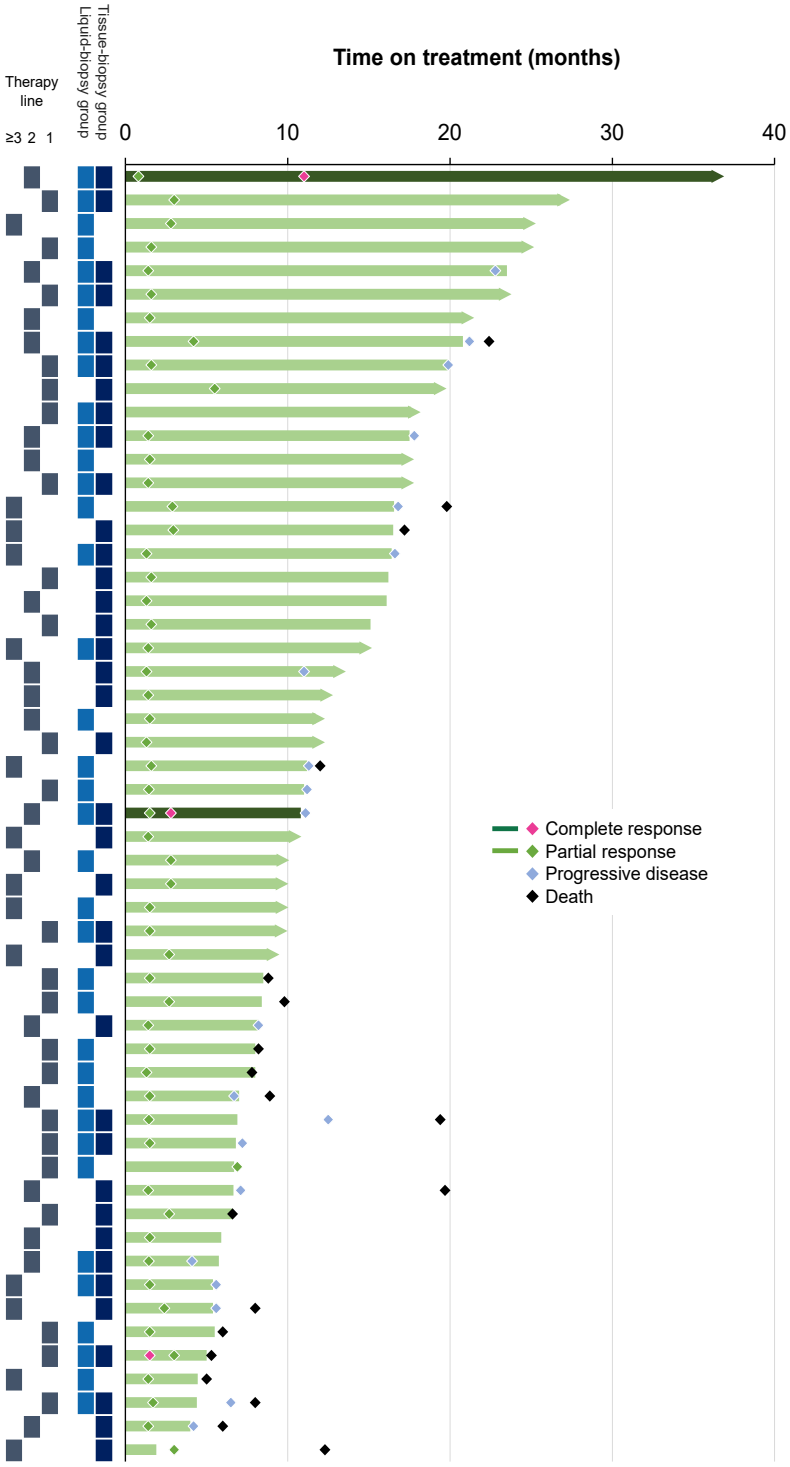
*Four patients had other race categories; **Eight patients were missing information on smoking history; †Excludes three patients with stage IIIB disease at study entry. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

Figure S4. The change in sum of longest diameters between baseline and best post-baseline assessment by investigator assessment (Panel a). Panel b shows the time on treatment in patients with response (n=55), as determined by investigator assessment. Results of a computerized tomography scan for a representative patient at baseline and at Week 6, 12 and 92 of treatment are shown in Panel c

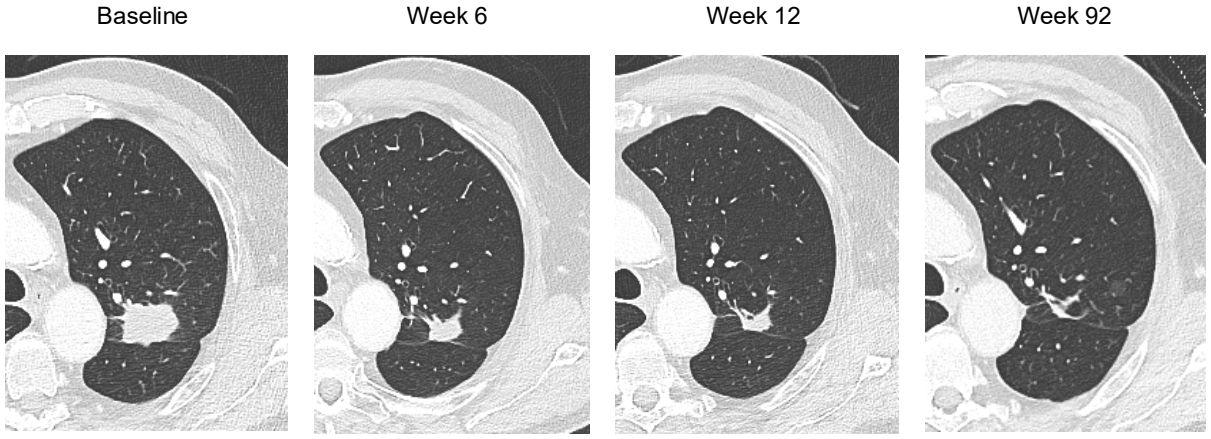
(a)



(b)


Therapy line
≥3 2 1
Tissue-biopsy group
Liquid-biopsy group
Time on treatment (months)
0
10
20
30
40
Complete response
Partial response
Progressive disease
Death

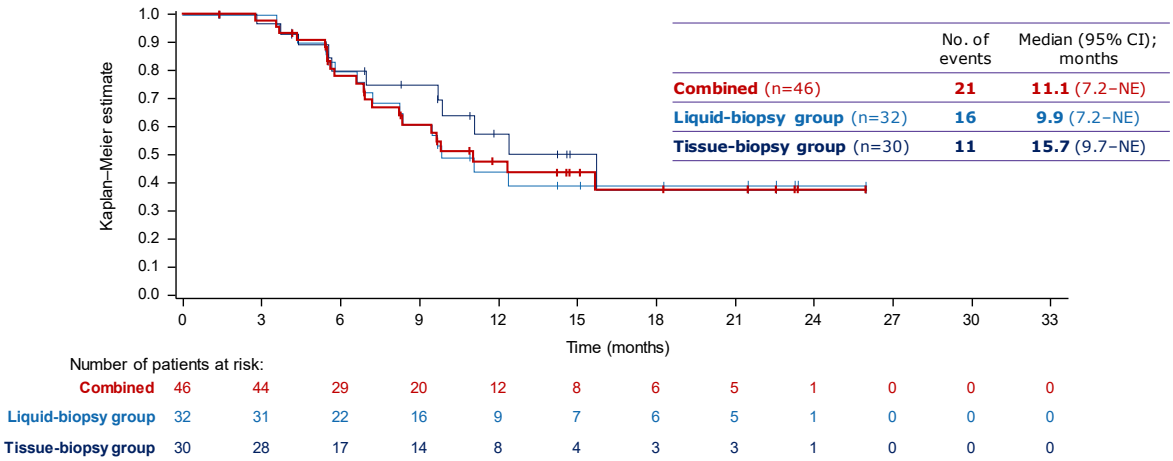
(c)



Three patients are not shown in Panel a: two patients did not have baseline/on-treatment measurements not available and one patient requires further evaluation.

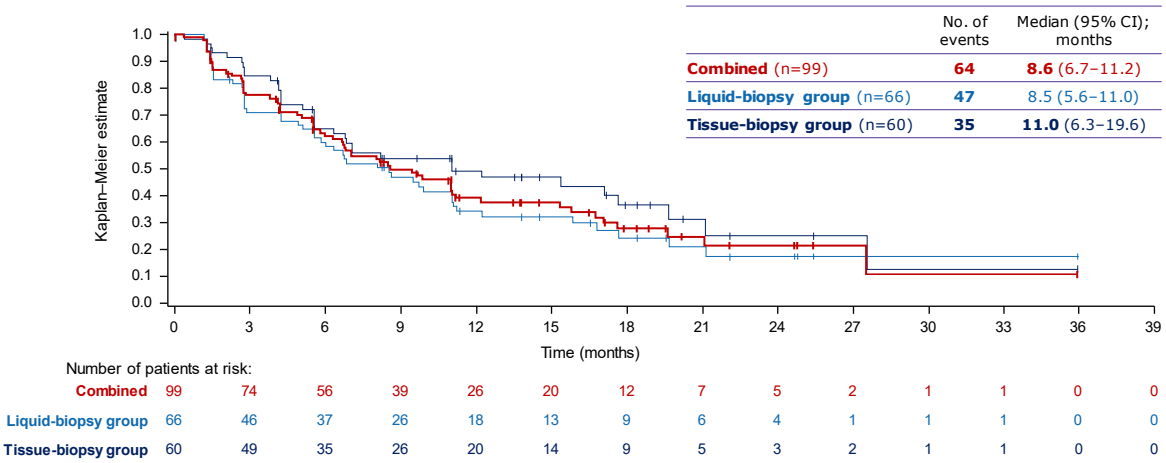
CI, confidence interval; ORR, objective response rate.

Figure S5. Duration of response by independent review for the three primary analysis populations



CI, confidence interval; NE, not estimable.

Figure S6. Progression-free survival by investigator assessment for the three primary analysis populations

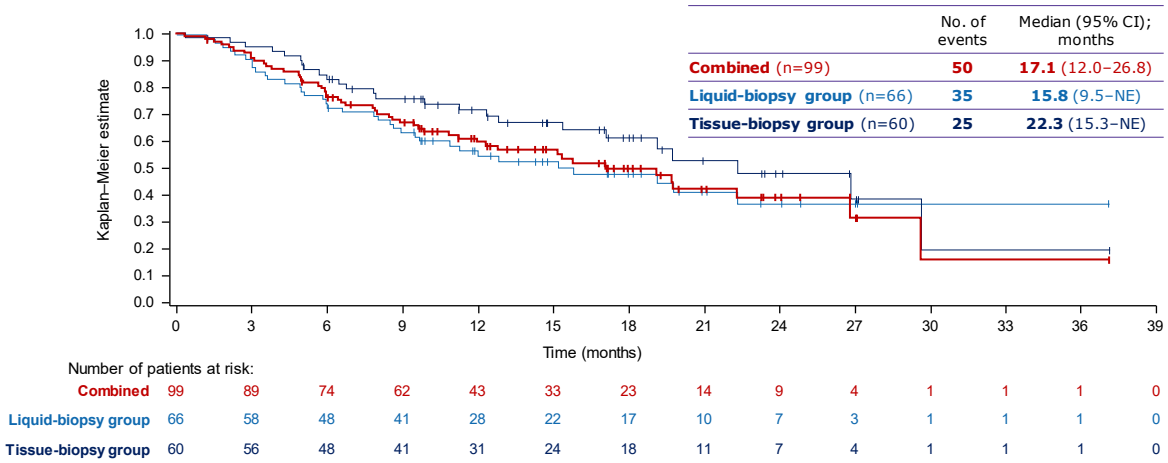


Number of patients at risk:

Combined	99	74	56	39	26	20	12	7	5	2	1	1	0	0
Liquid-biopsy group	66	46	37	26	18	13	9	6	4	1	1	1	0	0
Tissue-biopsy group	60	49	35	26	20	14	9	5	3	2	1	1	0	0

CI, confidence interval.

Figure S7. Overall survival for the three primary analysis populations

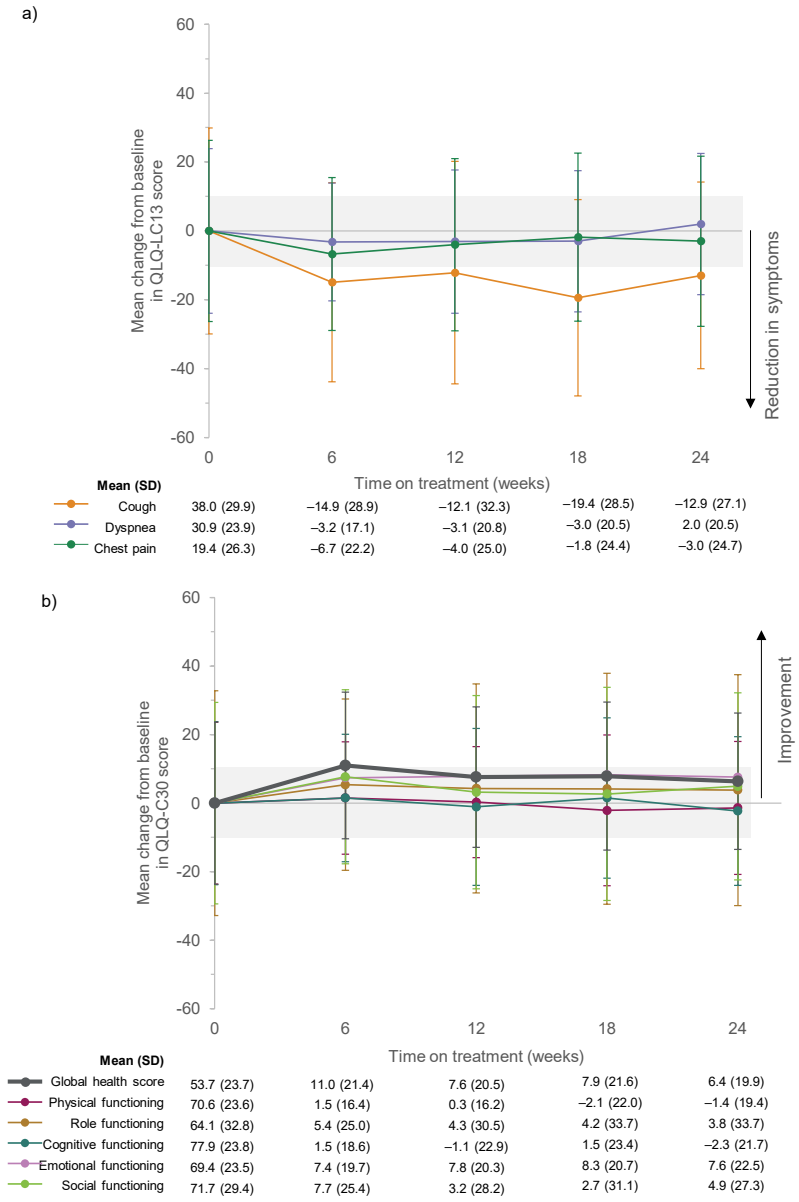


Number of patients at risk:

Combined	99	89	74	62	43	33	23	14	9	4	1	1	1	0
Liquid-biopsy group	66	58	48	41	28	22	17	10	7	3	1	1	1	0
Tissue-biopsy group	60	56	48	41	31	24	18	11	7	4	1	1	1	0

CI, confidence interval; NE, not estimable.

Figure S8. Patient quality of life on-treatment: Mean change from baseline in patient-reported outcomes for (a) EORTC QLQ-LC13 symptom subscales and (b) EORTC QLQ-C30 global health score and subscales



An increase or decrease of >10 points was considered to be clinically meaningful. a) All scores graded out of 100, with lower = better; b) All scores graded out of 100, with higher = better.

SD, standard deviation.

Table S1. Baseline characteristics and clinical characteristics (safety population)

	Liquid-biopsy group (n=99)	**Tissue-biopsy group (n=87)**	**Combined* (n=152)**
Median age, years (range)	72.4 (49–88)	73.2 (41–94)	73.1 (41–94)
Sex, n (%)			
Male	52 (52.5)	48 (55.2)	79 (52.0)
Female	47 (47.5)	39 (44.8)	73 (48.0)
Race, n (%)†			
Asian	21 (21.2)	24 (27.6)	38 (25.0)
White	75 (75.8)	60 (69.0)	108 (71.1)
Smoking history, n (%)‡			
Yes	51 (51.5)	44 (50.6)	79 (52.0)
No	44 (44.4)	35 (40.2)	65 (42.8)
ECOG performance status, n (%)			
0	23 (23.2)	28 (32.2)	41 (27.0)
1	76 (76.8)	59 (67.8)	111 (73.0)

Histological subtype, n (%)[§]			
Adenocarcinoma	84 (84.8)	80 (92.0)	131 (86.2)
Squamous	10 (10.1)	5 (5.7)	14 (9.2)
Sarcomatoid	3 (3.0)	0	3 (2.0)
Lines of prior therapy for advanced/metastatic disease, n (%)			
0	44 (44.4)	42 (48.3)	69 (45.4)
1	31 (31.3)	27 (31.0)	49 (32.2)
2+	24 (24.2)	18 (20.7)	34 (22.4)
Baseline brain metastases[‖] **as identified by independent review, n (%)**	11 (11.1)	6 (6.9)	15 (9.9)

*Combined = liquid-biopsy positive and/or tissue-biopsy positive. [†]Race was unknown or missing in six patients; [‡]Smoking history was unknown or missing in eight patients; [§]Two patients had adenosquamous carcinoma, one patient had carcinoma and one patient had NSCLC not otherwise specified. [‖]Non-target lesions.

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer.

Table S2. Best response to prior treatment (primary analysis population)

	Prior treatment		
	Last anticancer therapy (n=57)	**Prior platinum-based chemotherapy (n=50)**	**Prior immunotherapy (n=26)**
Best response, n (%)			
Complete response	1 (1.8)	2 (4.0)	0
Partial response	10 (17.5)	12 (24.0)	5 (19.2)
Stable disease	15 (26.3)	11 (22.0)	7 (26.9)
Progressive disease	20 (35.1)	17 (34.0)	9 (34.6)
Non-complete response/ non-progressive disease	1 (1.8)	1 (2.0)	0
Not assessable/unknown	10 (17.5)	7 (14.0)	5 (19.2)
Longest duration of response, median (range) months	3.0 (1.0–9.0)	4.5 (1.0–13.0)	7.0 (3.0–9.0)
Longest progression-free survival, median (range) months	3.0 (0–16.0)	3.0 (0–17.0)	3.5 (0–10.0)

The data in this table include information from the one patient was not included in the primary efficacy population as she was not confirmed to have NSCLC positive for *MET* exon 14 skipping (this patient received prior treatment with the abraxane-carboplatin combination, had a partial response as best response with a duration of response/progression-free survival of 3 months).

Table S3. Response (primary efficacy population)

	Liquid-biopsy group (n=66)		**Tissue-biopsy group (n=60)**		**Combined* (n=99)**	
	IRC	**INV**	**IRC**	**INV**	**IRC**	**INV**
Best overall response; n (%)						
Complete response	0	2 (3.0)	0	2 (3.3)	0	2 (2.0)
Partial response	32 (48.5)	35 (53.0)	30 (50.0)	35 (58.3)	46 (46.5)	53 (53.5)
Stable disease	11 (16.7)	9 (13.6)	11 (18.3)	10 (16.7)	19 (19.2)	17 (17.2)
Progressive disease	12 (18.2)	15 (22.7)	12 (20.0)	8 (13.3)	19 (19.2)	18 (18.2)
Not evaluable	11 (16.7)	5 (7.6)	7 (11.7)	5 (8.3)	15 (15.2)	9 (9.1)
Objective response rate, % (95% CI)	48.5 (36.0–61.1)	56.1 (43.3–68.3)	50.0 (36.8–63.2)	61.7 (48.2–73.9)	46.5 (36.4–56.8)	55.6 (45.2–65.5)
Duration of response, months (95% CI)	9.9 (7.2–NE)	14.0 (7.3–NE)	15.7 (9.7–NE)	16.4 (9.7–NE)	11.1 (7.2–NE)	14.0 (9.7– 18.3)

Disease control rate, % (95% CI)	65.2 (52.4–76.5)	69.7% (57.1–80.4)	68.3 (55.0–79.7)	78.3% (65.8–87.9)	65.7 (55.4–74.9)	72.7% (62.9–81.2)

*Combined = liquid-biopsy positive and/or tissue-biopsy positive.

CI, confidence interval; INV, investigator assessment; IRC, independent review committee; NE, not estimable.

Table S4. Objective response rate in the overall efficacy population

	Liquid-biopsy group (n=95)		**Tissue-biopsy group (n=84)**		**Combined (n=146)**	
	IRC	**INV**	**IRC**	**INV**	**IRC**	**INV**
Objective response rate, % (95% CI)	47.4 (37.0–57.9)	54.7 (44.2–65.0)	45.2 (34.3–56.5)	58.3 (47.1–69.0)	44.5 (36.3–53.0)	54.8 (46.4–63.0)
Median duration of response, months (95% CI)	9.9 (7.2–NE)	14.0 (7.2–NE)	12.4 (9.7–NE)	16.4 (9.7–NE)	9.9 (7.2–NE)	14.0 (9.7–18.3)

Patients evaluable for objective response include those who had at least two post-baseline assessments or discontinued for any reason.

CI, confidence interval; INV, investigator assessment; IRC, independent review committee; NE, not estimable.

Table S5. Subsequent treatment

N (%)	**Liquid-biopsy group (n=66)**	**Tissue-biopsy group (n=60)**	**Combined* (n=99)**
Treatment ongoing	14	15	22
Treatment discontinued	52	45	77
Number of patients who received subsequent anticancer drug therapy lines	19	16	27
Number of subsequent anticancer drug therapy lines			
1	13 (19.7)	7 (11.7)	17 (17.2)
2	4 (6.1)	8 (13.3)	8 (8.1)
3	2 (3.0)	1 (1.7)	2 (2.0)
Agents received			
Pembrolizumab	5 (7.6)	6 (10.0)	8 (8.1)
Crizotinib	5 (7.6)	4 (6.7)	7 (7.1)
Docetaxel	2 (3.0)	5 (8.3)	6 (6.1)
Carboplatin	6 (9.1)	5 (8.3)	6 (6.1)
Nivolumab	3 (4.5)	3 (5.0)	5 (5.1)
Ramucirumab	2 (3.0)	3 (5.0)	4 (4.0)
Paclitaxel	3 (4.5)	3 (5.0)	3 (3.0)

Gemcitabine	2 (3.0)	1 (1.7)	2 (2.0)
Atezolizumab	2 (3.0)	1 (1.7)	2 (2.0)
Zoledronic acid	0	1 (1.7)	1 (1.0)
Gimeracil/oteracil potassium/tegafur	0	1 (1.7)	1 (1.0)

No patients had complete response to subsequent therapy; two patients had a partial response.

*Combined = liquid-biopsy positive and/or tissue-biopsy positive; one patient was not included in the primary efficacy population as she was not confirmed to have NSCLC positive for *MET* exon 14 skipping (this patient has discontinued treatment and received one subsequent line of treatment with crizotinib).

Table S6. Adverse events regardless of causality occurring in ≥10% of patients (safety population)

Category, n (%)	**Tepotinib (n=152)**	
	All Grades	**Grade ≥3**
Any adverse event	149 (98.0)	83 (54.6)
Peripheral edema	106 (69.7)	12 (7.9)
Nausea	52 (34.2)	2 (1.3)
Diarrhea	47 (30.9)	1 (0.7)
Blood creatine increased	43 (28.3)	1 (0.7)
Hypoalbuminemia	38 (25.0)	8 (5.3)
Dyspnea	36 (23.7)	4 (2.6)
Constipation	26 (17.1)	0 (0.0)
Decreased appetite	26 (17.1)	2 (1.3)
Fatigue	26 (17.1)	1 (0.7)
Asthenia	23 (15.1)	3 (2.0)
Pleural effusion	23 (15.1)	9 (5.9)
Vomiting	23 (15.1)	2 (1.3)
Cough	21 (13.8)	1 (0.7)
Amylase increased	18 (11.8)	6 (3.9)
Back pain	18 (11.8)	2 (1.3)
Alopecia	17 (11.2)	0 (0.0)
Alanine aminotransferase increased	16 (10.5)	6 (3.9)

Table S7. Serious adverse events occurring in ≥2% of patients (regardless of causality) and all related serious adverse events (safety population)

Category, n (%)	**Tepotinib (n=152)**	
	All causality	**Related**
Any serious adverse event	73 (48.0)	23 (15.1)
Pleural effusion	12 (7.9)	4 (2.6)
Pneumonia	8 (5.3)	0
Disease progression	7 (4.6)	0
General physical health deterioration	7 (4.6)	0
Dyspnea	6 (3.9)	2 (1.3)
Generalized edema	5 (3.3)	4 (2.6)
Acute kidney injury	4 (2.6)	2 (1.3)
Pulmonary embolism	4 (2.6)	0
Asthenia	3 (2.0)	2 (1.3)
Back pain	3 (2.0)	0
Edema peripheral	3 (2.0)	3 (2.0)
Spinal cord compression	3 (2.0)	0
Alanine aminotransferase increased	2 (1.3)	2 (1.3)
Aspartate aminotransferase increased	2 (1.3)	2 (1.3)
Pneumonitis	2 (1.3)	1 (0.7)
Acute respiratory failure	1 (0.7)	1 (0.7)
Blood creatinine increased	1 (0.7)	1 (0.7)
Cholecystitis infective	1 (0.7)	1 (0.7)
Dizziness	1 (0.7)	1 (0.7)
Hypersensitivity	1 (0.7)	1 (0.7)
Interstitial lung disease	1 (0.7)	1 (0.7)
Mucosal inflammation	1 (0.7)	1 (0.7)
Nausea	1 (0.7)	1 (0.7)
Rash maculo-papular	1 (0.7)	1 (0.7)

Table S8.

Treatment-related adverse events leading to dose reductions and treatment discontinuations in >1% of patients (safety population)

	Tepotinib (n=152)	
Category	**Patients who had a dose reduction; n (%)**	**Patients who permanently discontinued treatment; n (%)**
Any treatment-related adverse event	50 (32.9)	17 (11.2)
Peripheral edema	25 (16.4)	7 (4.6)
Blood creatinine increased	6 (3.9)	0
General edema	5 (3.3)	0
Pleural effusion	4 (2.6)	0
Abdominal pain upper	2 (1.3)	0
Acute kidney injury	2 (1.3)	0
Alanine aminotransferase increased	2 (1.3)	0
Edema	2 (1.3)	0
Hypoalbuminemia	2 (1.3)	0
Genital edema	1 (0.7)	2 (1.3)
Dyspnea	0	2 (1.3)
Pneumonitis	0	2 (1.3)

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