SUPPLEMENTARY MATERIALS

Supplemental Methods

MET exon 14 skipping identification

Patients had to test positive for *MET*ex14 skipping from either circulating tumor DNA collected from plasma (liquid biopsy) or RNA collected from tumor tissue (tissue biopsy). Liquid biopsy samples were analyzed using the Guardant360 assay (73 genes), or the Archer®MET diagnostic assay. Tissue biopsies were analyzed using the Oncomine Focus Assay (52 genes) or the Archer®MET diagnostic assay. In Japan, patients were allowed to enroll based on RT-PCR through the LC-SCRUM program (1).

Intracranial response per RANO-BM criteria

In our analysis, disease control rate was defined as complete response (CR)/partial response (PR)/stable disease (SD) or non-CR/non-progressive disease (PD). For patients with non-measurable lesions only (enhancing and non-enhancing non-target lesions [NTLs]), non-CR/non-PD was defined as a best objective response (BOR) of disease control, i.e. persistence of at least one non-progressing NTL. Prior to a protocol amendment in January 2020, brain imaging had no mandatory schedule, as such, data for the retrospective Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) analysis are incomplete. Confirmation of response was therefore not required in this analysis.

Intracranial best overall response per RANO-BM is a composite of radiographic responses, corticosteroid use and clinical status, giving a more comprehensive overview of the patient compared to RECIST (2). Measurable lesions are defined as

contrast enhancing lesions ≥1 cm that can be measured accurately in at least one dimension. Up to five measurable lesions can be selected as target lesions, selected on the basis of their size (longest diameter) and those that can be measured reproducibly; lesions not previously treated with local therapies are preferred for selection as target lesions. All other brain lesions are identified as non-target lesions; measurements for non-target lesions are not required. Intracranial BOR of CR (or PR) requires disappearance of all target and non-target lesions (or ≥30% decrease in target lesions from baseline and stable/improved non-target lesions), with no new lesions, no use of corticosteroids (or stable to decreased corticosteroids), and stable/improved clinical status. Requirements for tumor response assessments in target and non-target lesions are shown (2).

	Target lesions	**Non-target lesions**
Complete response	Complete disappearance	Complete disappearance
Partial response	≥30% decrease in sum of longest diameters relative to baseline	Stable or improved
Stable disease	<30% decrease relative to baseline, but <20% increase in sum of longest diameters relative to nadir[a]	Stable or improved
Progressive disease	≥20% increase in sum longest diameters relative to nadir[a]	Unequivocal progressive disease

[a]Nadir is the smallest sum of longest diameters at any time point.

Supplemental Results

Further Investigation of IRC Assessments in Patients Whose Best Objective Response Assessment Changed Between January 2020 and July 2020 Data Cut-Offs

According to the charter for independent review committee (IRC) assessment in VISION, the response assessment for an individual patient could potentially change at every IRC assessment point. Reasons regarding changes in response assessment were further investigated in the five patients, whose objective response assessments had changed between the January 2020 and July 2020 data cut-off (3,4).

For two patients (one treatment-naïve and one previously treated), objective response assessments were updated from progressive disease in the January 2020 data cut-off to partial responses in the July 2020 data cut-off, based on additional contextual information received by the independent reviewers. In our analysis, based on the July 2020 data cut-off, these patients were considered as responders; however, based on the contextual information, they could subjectively be considered non-responders.

In one patient, new imaging time-points and newly received clinical data (two late negative cytology results) led to an updated assessment of partial response, which was read as progressive disease initially. According to investigator assessment, this patient had a best objective response of partial response, and the best change in sum of target lesions was –73.4%. This patient received tepotinib for 20.1 months, and discontinued due to an adverse event.

In the second patient, one reviewer had changed their assessment based on a negative histology biopsy, however, the second reviewer did not. According to investigator assessment, this patient had a best objective response of partial response, and the best change in sum of target lesions was –89.6%. This patient received tepotinib for 10.6 months, and discontinued due to disease progression.

Interstitial lung disease occurred in one patient who received prior immune checkpoint inhibitor therapy

Prior to tepotinib treatment, this patient received pembrolizumab for 8.5 months. The independent panel found moderate bilateral changes consistent with interstitial lung disease (ILD) at baseline, which were deemed to be due to smoking. ILD occurred after 84 days of tepotinib treatment (155 days after pembrolizumab was completed). ILD was managed with treatment interruptions, dose reductions and steroid treatment, and the patient stayed on tepotinib treatment for a further 169 days. This patient died due to disease progression, at which point the ILD had not resolved.

Supplemental Tables

TABLE S1. Tepotinib efficacy according to investigator assessment (efficacy population).

	Treatment-naïve (*n* = 69)	**Previously treated (*n* = 83)**	**Overall (*N* = 152)**
BOR, *n* (%) Complete response Partial response Stable disease Progressive disease Not evaluable	 1 (1.4) 34 (49.3) 17 (24.6) 7 (10.1) 10 (14.5)	 2 (2.4) 44 (53.0) 16 (19.3) 16 (19.3) 5 (6.0)	 3 (2.0) 78 (51.3) 33 (21.7) 23 (15.1) 15 (9.9)
ORR, % (95% CI)	**50.7** (38.4, 63.0)	**55.4** (44.1, 66.3)	**53.3** (45.0, 61.4)
DCR, % (95% CI)	**75.4** (63.5, 84.9)	**74.7** (64.0, 83.6)	**75.0** (67.3, 81.7)
Median DOR, Months (95% CI)	**10.9** (7.1, ne)	**12.7** (9.7, 17.1)	**12.5** (9.7, 18.3)
Median PFS, Months (95% CI)	**8.6** (6.8, 12.2)	**8.3** (5.8, 11.0)	**8.5** (6.9, 11.0)

Abbreviations: BOR, best objective response; CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; PFS, progression-free survival.

TABLE S2. Efficacy according to biopsy type used to detect *MET* exon 14 skipping (efficacy population).

Efficacy according to IRC	**Treatment-naïve (*n* = 69)**		**Previously treated (*n* = 83)**	
	Liquid biopsy (*n* = 44)	**Tissue biopsy (*n* = 42)**	**Liquid biopsy (*n* = 55)**	**Tissue biopsy (*n* = 46)**
BOR, *n* (%)				
Complete response	0	0	0	0
Partial response	23 (52.3)	17 (40.5)	24 (43.6)	23 (50.0)
Stable disease	7 (15.9)	14 (33.3)	14 (25.5)	11 (23.9)
Progressive disease	9 (20.5)	6 (14.3)	8 (14.5)	9 (19.6)
Not evaluable	5 (11.4)	5 (11.9)	9 (16.4)	3 (6.5)
ORR, % (95% CI)	**52.3** (36.7, 67.5)	**40.5** (25.6, 56.7)	**43.6** (30.3, 57.7)	**50.0** (34.9, 65.1)
DCR, % (95% CI)	**68.2** (52.4, 81.4)	**73.8** (58.0, 86.1)	**69.1** (55.2, 80.9)	**73.9** (58.9, 85.7)
Median DOR, Months (95% CI)	**7.6** (6.6, ne)	**ne** (5.7, ne)	**11.1** (8.4, 18.5)	**12.4** (9.7, ne)
Median PFS, Months (95% CI)	**8.3** (4.2, 11.3)	**10.8** (6.8, ne)	**8.9** (5.7, 11.0)	**12.4** (8.2, 16.8)

Abbreviations: BOR, best objective response; CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; ne, not estimable; ORR, objective response rate; PFS, progression-free survival.

TABLE S3. Tepotinib efficacy (patients in efficacy population with ≥9 months' follow-up).

	Treatment-naïve (*n* = 65)		**Previously treated (*n* = 81)**		**Overall (*N* = 146)[a]**	
	IRC	Investigator assessment	IRC	Investigator assessment	IRC	Investigator assessment
BOR, *n* (%)						
Complete response	0	1 (1.5)	0	2 (2.5)	0	3 (2.1)
Partial response	29 (44.6)	33 (50.8)	37 (45.7)	43 (53.1)	66 (45.2)	76 (52.1)
Stable disease	15 (23.1)	16 (24.6)	21 (25.9)	16 (19.8)	36 (24.7)	32 (21.9)
Progressive disease	12 (18.5)	6 (9.2)	13 (16.0)	15 (18.5)	25 (17.1)	21 (14.4)
Not evaluable	9 (13.8)	9 (13.8)	10 (12.3)	5 (6.2)	19 (13.0)	14 (9.6)
ORR, % (95% CI)	**44.6** (32.3, 57.5)	**52.3** (39.5, 64.9)	**45.7** (34.6, 57.1)	**55.6** (44.1, 66.6)	**45.2** (37.0, 53.6)	**54.1** (45.7, 62.4)
DCR, % (95% CI)	**67.7** (54.9, 78.8)	**76.9** (64.8, 86.5)	**71.6** (60.5, 81.1)	**75.3** (64.5, 84.2)	**69.9** (61.7, 77.2)	**76.0** (68.3, 82.7)
Median DOR, Months (95% CI)	**10.8** (6.9, ne)	**10.9** (7.1, ne)	**11.1** (9.5, 18.5)	**12.7** (9.7, 17.1)	**11.1** (8.4, 18.5)	**12.7** (9.7, 18.3)
Median PFS, Months (95% CI)	**8.5** (5.5, 11.3)	**9.7** (6.8, 13.5)	**10.9** (8.2, 12.7)	**8.3** (6.7, 11.0)	**8.9** (8.2, 11.0)	**8.6** (6.9, 11.0)

Abbreviations: BOR, best objective response; CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; ne, not estimable; ORR, objective response rate; PFS, progression-free survival.

[a]At the time of analysis, 75 patients with ≥9 months' follow-up had died, and the median overall survival was 17.6 months (95% CI: 15.0, 21.0).

TABLE S4. Response to prior treatments (efficacy population).

Efficacy, as evaluated by the physician	**Most recent anticancer therapy (*n* = 83)**	**Prior platinum-based chemotherapy for metastatic disease (*n* = 74)**	**Prior ICI in combination with platinum-based chemotherapy (*n* = 10)**
BOR [a], *n* (%)			
Complete response	1 (1.2)	2 (2.7)	0
Partial response	20 (24.1)	19 (25.7)	3 (30.0)
Stable disease	25 (30.1)	22 (29.7)	1 (10.0)
Progressive disease	24 (28.9)	21 (28.4)	3 (30.0)
Non-complete response/non-progressive disease	1 (1.2)	1 (1.4)	0
Not assessable	4 (4.8)	1 (1.4)	0
Unknown	8 (9.6)	8 (10.8)	3 (30.0)
DOR,			
Patients for whom data are available, *n*	*n* = 16	*n* = 16	*n* = 2
Median longest DOR (range); months	4.5 (1–17)	5.0 (1–17)	6.5 (5–8)
Time to progression,			
Patients for whom data are available, *n*	*n* = 59	*n* = 55	*n* = 5
Median longest PFS (range); months	4.0 (0–36)	3.0 (0–26)	2.0 (0–6)

Abbreviations: BOR, best objective response; DOR, duration of response; ICI, immune checkpoint inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

[a]Criteria used to assess best response included RECIST 1.1, RECIST (unknown), WHO, and others.

TABLE S5. Number of subsequent therapies received according to subgroups (efficacy population).

Category, *n* (%)	**Overall (*n* = 152)**	**Treatment-naïve patients (*n* = 69)**	**Previously treated patients (*n* = 83)**	**<75 years (*n* = 84)**	**≥75 years (*n* = 68)**
Patients who received subsequent anticancer drug therapy	47 (30.9)	18 (26.1)	29 (34.9)	36 (42.9)	11 (16.2)
Number of subsequent lines received					
1	31 (66.0)	12 (66.7)	19 (65.5)	24 (66.7)	7 (63.6)
2	14 (29.8)	5 (27.8)	9 (31.0)	10 (27.8)	4 (36.4)
3	1 (2.1)	0	1 (3.4)	1 (2.8)	0
5	1 (2.1)	1 (5.6)	0	1 (2.8)	0

TABLE S6. Types of subsequent treatments received (efficacy population).

Category, *n* (%)	**Patients who received subsequent therapies (*n* = 47)**
Chemotherapy	
Carboplatin	13 (27.7)
Pemetrexed	12 (25.5)
Docetaxel	9 (19.1)
Paclitaxel	5 (10.6)
Gemcitabine	3 (6.4)
Cisplatin	2 (4.3)
Gimeracil/oteracil potassium/tegafur	2 (4.3)
Immune checkpoint inhibitors	
Pembrolizumab	13 (27.7)
Nivolumab	6 (12.8)
Atezolizumab	5 (10.6)
MET inhibitors	
Crizotinib	12 (25.5)
Capmatinib	3 (6.4)
Cabozantinib	2 (4.3)
Anti-angiogenics	
Ramucirumab	4 (8.5)
Bevacizumab	2 (4.3)
Other	
Venetoclax	1 (2.1)
Vorolanib	1 (2.1)
Zoledronic acid	1 (2.1)

Two patients received treatment listed as ‘investigational agents’.

TABLE S7. Serious adverse events occurring in ≥1% of patients (regardless of causality, safety population).

Category, *n* (%)	Tepotinib (*N* = 255)	
	Any cause	Related
Any serious adverse event	115 (45.1)	31 (12.2)
Pleural effusion	17 (6.7)	9 (3.5)
Disease progression	12 (4.7)	0
Pneumonia	12 (4.7)	0
Dyspnea	10 (3.9)	4 (1.6)
General physical health deterioration	9 (3.5)	0
Peripheral edema	6 (2.4)	6 (2.4)
Generalized edema	5 (2.0)	4 (1.6)
Pulmonary embolism	5 (2.0)	0
Acute kidney injury	4 (1.6)	2 (0.8)
Asthenia	3 (1.2)	2 (0.8)
Pyrexia	3 (1.2)	0
Spinal cord compression	3 (1.2)	0
Cardiac failure	3 (1.2)	0
Back pain	3 (1.2)	0

TABLE S8. Treatment-related adverse events leading to dose reductions and treatment discontinuations in >1% of patients (safety population).

Category, *n* (%)	Tepotinib (*N* = 255)		
	Dose reduction	**Temporary interruptions**	**Permanent discontinuation**
Any treatment-related adverse event	71 (27.8)	90 (35.3)	27 (10.6)
Peripheral edema	36 (14.1)	41 (16.1)	9 (3.5)
Blood creatinine increased	7 (2.7)	16 (6.3)	2 (0.8)
Generalized edema	6 (2.4)	8 (3.1)	0
Edema	5 (2.0)	6 (2.4)	1 (0.4)
Pleural effusion	5 (2.0)	9 (3.5)	3 (1.2)
Alanine aminotransferase increased	2 (0.8)	7 (2.7)	0
Asthenia	2 (0.8)	3 (1.2)	0
Localized edema	1 (0.4)	3 (1.2)	1 (0.4)
Aspartate aminotransferase increased	1 (0.4)	3 (1.2)	0
Diarrhea	0	5 (2.0)	1 (0.4)
Nausea	2 (0.8)	4 (1.6)	1 (0.4)
Renal impairment	0	3 (1.2)	0
Decreased appetite	2 (0.8)	4 (1.6)	0
Dyspnea	0	1 (0.4)	3 (1.2)
Pneumonitis	0	2 (0.8)	3 (1.2)

TABLE S9. Safety profile and TRAEs occurring in ≥5% of patients who are treatment-naive, previously treated, aged <75 years, or aged ≥75 years (safety population).

Category, *n* (%)	**Treatment-naïve (*n* = 125)**	**Previously treated (*n* = 130)**	**Age <75 years (*n* = 146)**	**Age ≥75 years (*n* = 109)**
Any TRAE	109 (87.2)	111 (85.4)	128 (87.7)	92 (84.4)
Grade ≥3 TRAE	39 (31.2)	25 (19.2)	27 (18.5)	37 (33.9)
TRAEs leading to dose reduction	39 (31.2)	32 (24.6)	34 (23.3)	37 (33.9)
TRAEs leading to temporary interruption	50 (40.0)	40 (30.8)	42 (28.8)	48 (44.0)
TRAEs leading to permanent discontinuation	19 (15.2)	8 (6.2)	11 (7.5)	16 (14.7)
TRAEs occurring in ≥5% of patients in any subgroup				
Peripheral edema	73 (58.4)	65 (50.0)	82 (56.2)	56 (51.4)
Nausea	30 (24.0)	21 (16.2)	29 (19.9)	22 (20.2)
Diarrhea	26 (20.8)	24 (18.5)	28 (19.2)	22 (20.2)
Blood creatinine increased	23 (18.4)	22 (16.9)	29 (19.9)	16 (14.7)
Hypoalbuminemia	21 (16.8)	16 (12.3)	18 (12.3)	19 (17.4)
Alopecia	13 (10.4)	5 (3.8)	6 (4.1)	12 (11.0)
Alanine aminotransferase increased	12 (9.6)	10 (7.7)	14 (9.6)	8 (7.3)
Pleural effusion	11 (8.8)	5 (3.8)	6 (4.1)	10 (9.2)
Vomiting	10 (8.0)	4 (3.1)	10 (6.8)	4 (3.7)
Decreased appetite	10 (8.0)	11 (8.5)	9 (6.2)	12 (11.0)
Constipation	9 (7.2)	6 (4.6)	5 (3.4)	10 (9.2)
Amylase increased	8 (6.4)	11 (8.5)	11 (7.5)	8 (7.3)
Fatigue	8 (6.4)	10 (7.7)	8 (5.5)	10 (9.2)
Lipase increased	8 (6.4)	9 (6.9)	11 (7.5)	6 (5.5)
Aspartate aminotransferase increased	8 (6.4)	7 (5.4)	10 (6.8)	5 (4.6)
Edema	7 (5.6)	9 (6.9)	3 (2.1)	13 (11.9)
Dyspnea	7 (5.6)	3 (2.3)	4 (2.7)	6 (5.5)
Upper abdominal pain	6 (4.8)	8 (6.2)	10 (6.8)	4 (3.7)
Generalized edema	6 (4.8)	5 (3.8)	5 (3.4)	6 (5.5)
Blood alkaline phosphatase increased	6 (4.8)	4 (3.1)	8 (5.5)	2 (1.8)
Pruritus	5 (4.0)	5 (3.8)	8 (5.5)	2 (1.8)
Rash	4 (3.2)	8 (6.2)	8 (5.5)	4 (3.7)

Asthenia	4 (3.2)	10 (7.7)	7 (4.8)	7 (6.4)
Dry skin	3 (2.4)	6 (4.6)	8 (5.5)	1 (0.9)

Abbreviations: TRAE, treatment-related adverse event.

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