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# Tepotinib in patients with *MET* exon 14 skipping NSCLC as identified by liquid or tissue biopsy

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# Presenter disclosures

Ineligible company (formerly: commercial interest)	Relationship(s)
Pfizer	Advisory/consultancy, speaker's bureau/expert testimony
Roche	Advisory/consultancy, speaker's bureau/expert testimony
Boehringer Ingelheim	Advisory/consultancy
AstraZeneca	Advisory/consultancy, speaker's bureau/expert testimony
Bristol-Myers Squibb	Advisory/consultancy, speaker's bureau/expert testimony
Guardant Health	Advisory/consultancy
Novartis	Advisory/consultancy, speaker's bureau/expert testimony
Takeda	Advisory/consultancy, speaker's bureau/expert testimony
AbbVie	Advisory/consultancy
Blueprint Medicines	Advisory/consultancy
Lilly	Advisory/consultancy, speaker's bureau/expert testimony
the healthcare business of Merck KGaA, Darmstadt, Germany	Advisory/consultancy
Merck Sharp & Dohme	Advisory/consultancy, speaker's bureau/expert testimony
Janssen	Advisory/consultancy
Samsung	Advisory/consultancy
Medscape	Speaker's bureau/expert testimony
prIME Oncology	Speaker's bureau/expert testimony
Touchtime	Speaker's bureau/expert testimony
Fundación Merck Salud	Research grant/funding (self)
Grant for Oncology Innovation (GOI)	Research grant/funding (self)
Grifols	Officer/Board of Directors (Independent Member)



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# ***MET* exon 14 skipping is an actionable oncogenic driver in NSCLC that can be detected by liquid or tissue biopsy**

- Liquid and tissue biopsy are complementary approaches for the identification of actionable gene alterations in NSCLC<sup>1,2</sup>
- Tissue biopsy has been associated with higher sensitivity and is considered the ‘gold standard’; however, there are limitations to tissue sampling that liquid biopsy may overcome<sup>1</sup>

## **Liquid biopsy**

- Faster turnaround time
- Less invasive
- Ease of re-biopsy for monitoring efficacy
- Overcomes issues of tumor heterogeneity after therapy
- Limited sensitivity with low ctDNA shedding tumors and tumor burden

## **Tissue biopsy**

- Associated with higher sensitivity
- Considered the ‘gold standard’
- Limited by tissue availability/accessibility
- Limited number of tests from the same sample

- *MET* exon 14 skipping is an oncogenic driver that occurs in 3–4% of NSCLC cases, and it can be detected by DNA-based methods (NGS, Sanger sequencing) and/or RNA-based methods (NGS, quantitative PCR assays)<sup>3-5</sup>
- Tepotinib is an oral, once daily, highly selective, potent *MET* inhibitor that has shown clinical activity in *MET*-driven tumors<sup>6</sup>
- The VISION study, conducted to evaluate the efficacy and safety of tepotinib, is one of the first prospective studies to allow enrollment based on *MET* exon 14 skipping detection by liquid and/or tissue biopsy<sup>7</sup>
  - The incorporation of liquid biopsy testing improved the rate of prescreening in VISION<sup>8</sup>

ctDNA, circulating tumor DNA; *MET*, mesenchymal–epithelial transition factor; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

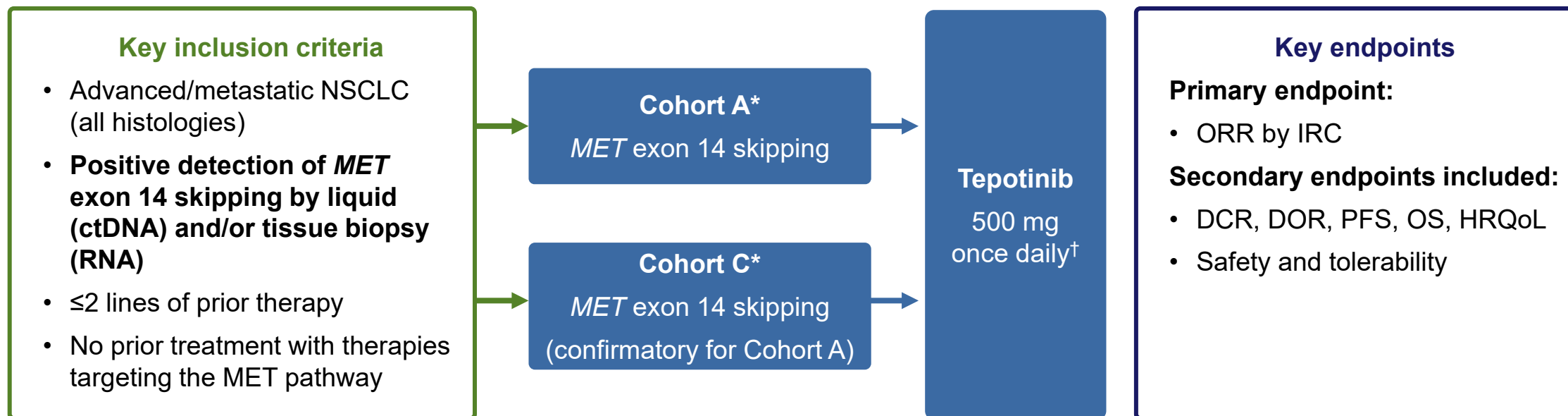
1. Rolfo C, et al. *J Thorac Oncol*. 2021;S1556-0864(21)02284-X; 2. National Comprehensive Cancer Network. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf). Last accessed March 18, 2021;

3. Reungwetwattana T, et al. *Lung Cancer*. 2017;103:27–37; 4. Rosell R, Karachaliou N. *Lancet*. 2016;387(10026):1354–1356; 5. Salgia R, et al. *Cancer Treat Rev*. 2020;87:102022; 6. Falchook GS, et al. *Clin Cancer Res*. 2020;26(6):1237-1246; 7. Paik PK, et al. *N Engl J Med*. 2020;383(10):931–943; 8. Le X, et al. *Cancer Res*. 2020; 80(16 Suppl):3385.



## VISION: Study design

- The VISION study (NCT02864992) is a single-arm, Phase II trial evaluating the efficacy and safety of tepotinib in patients with advanced NSCLC with *MET* alterations<sup>1</sup>
- Enrollment into VISION was completed in May 2021



\*Cohort B enrolled patients with *MET*-amplified NSCLC; data from this Cohort are not presented; <sup>†</sup>500 mg tepotinib hydrochloride hydrate contains 450 mg tepotinib free-base (active moiety); treatment was continued until either progression, withdrawal of consent or unacceptable toxicity.

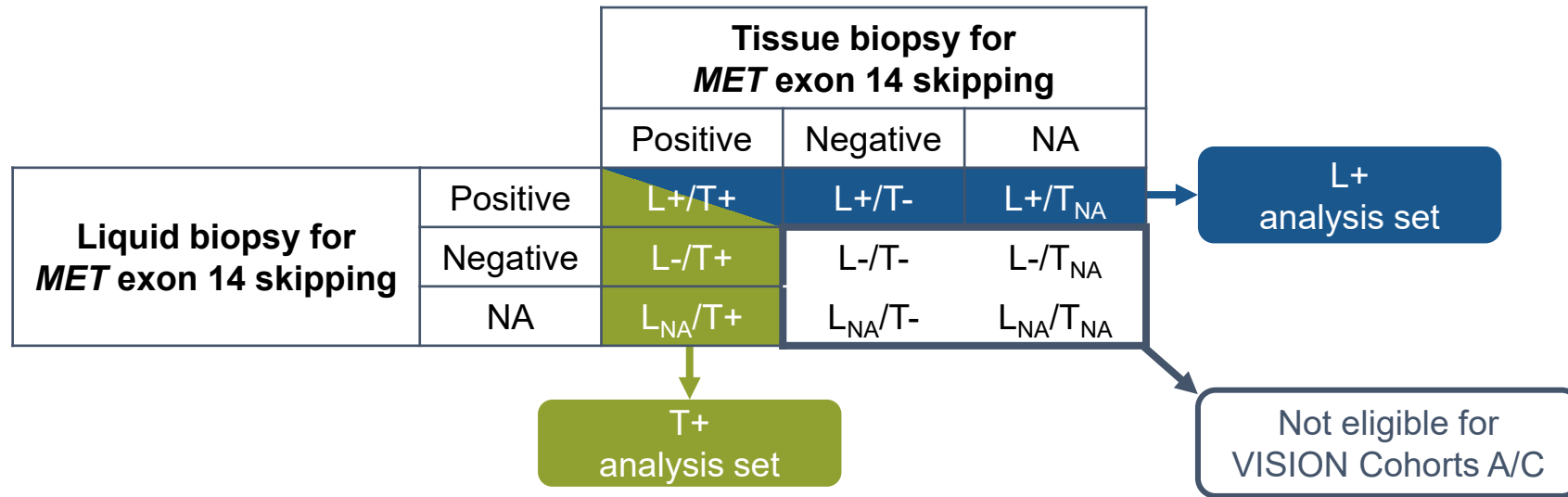
DCR, disease control rate; DOR, duration of response; IRC, independent review committee; HRQoL, health-related quality of life; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Paik PK, et al. *N Engl J Med.* 2020;383(10):931–943.



# VISION: Analysis according to biopsy type

- The study protocol defined analysis sets based on the detection method for *MET* exon 14 skipping
- Patients with *MET* exon 14 skipping detected by both liquid and tissue biopsy are included in both analysis sets



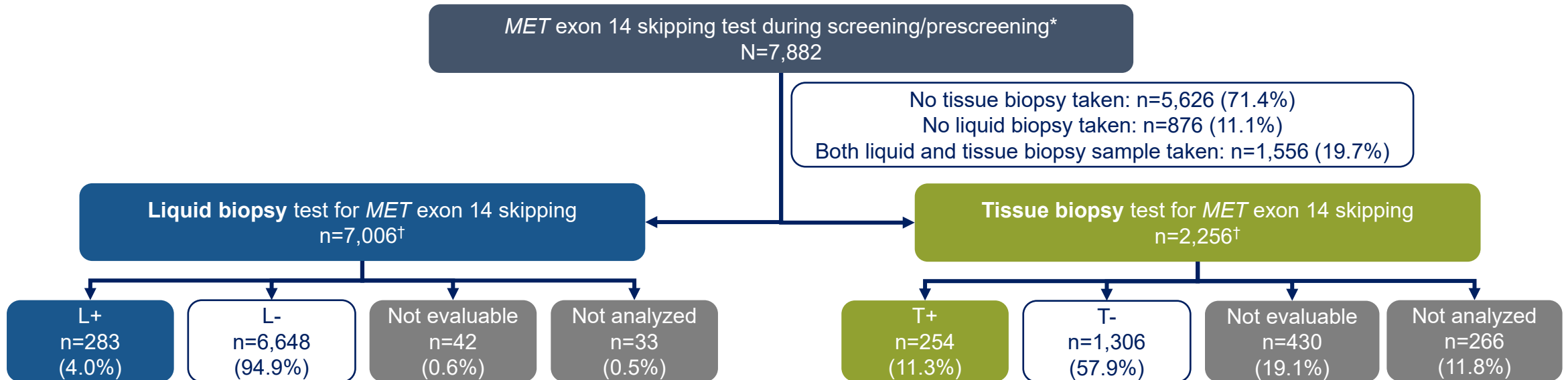
Here, we report patient characteristics, efficacy, and safety outcomes with tepotinib in the L+ and T+ analysis sets

L+/-, positive or negative detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; NA, not available (biopsy sample was not taken or was not evaluable/analyzed); T+/-, positive or negative detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION screening/prescreening: *MET* exon 14 skipping detection

- 7,006 patients received a liquid biopsy test and 2,256 received a tissue biopsy test for *MET* exon 14 skipping
- Overall, 5.7% of patients screened/prescreened tested positive for *MET* exon 14 skipping by liquid and/or tissue biopsy
- 1.1% of liquid biopsy tests and 30.9% of tissue biopsy samples were not evaluable or not analyzed



\*Data cut-off: February 1, 2021; <sup>†</sup>Liquid biopsy samples were analyzed using the DNA-based Guardant360<sup>®</sup> assay (73 genes), or the ArcherDX<sup>®</sup> MET Variant Test on the RevealDX Assay. Tissue biopsies were analyzed using the RNA-based Oncomine Focus Assay (52 genes) or the ArcherDX<sup>®</sup> MET Variant Test on the RevealDX Assay. In Japan, patients were allowed to enroll based on RT-PCR through the LC-SCRUM program. Patients tested for *MET* exon 14 skipping by liquid and/or tissue biopsy are included in both populations and, as such, the number of patients with liquid biopsy testing and patients with tissue biopsy testing is not equal to the total number of patients who received a test for *MET* exon 14 skipping.

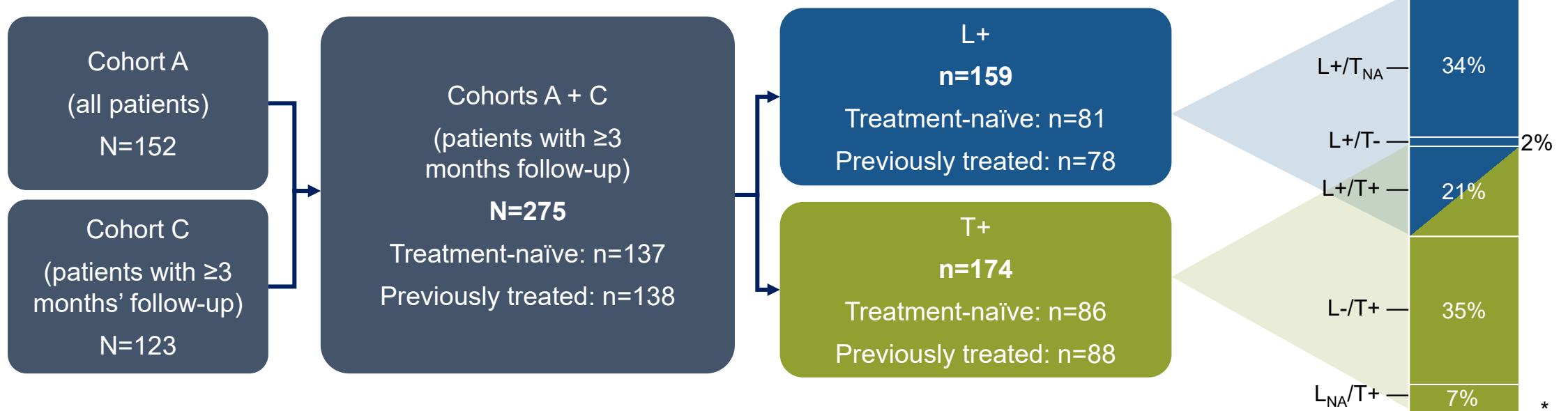
L+/-, positive/negative detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; RT-PCR, reverse transcription polymerase chain reaction; T+/-, positive/negative detection of *MET* exon 14 skipping in tissue biopsy sample.





# VISION: Interim analysis of patients enrolled in Cohorts A and C (data cut-off: February 1, 2021)

- The analyses presented here include all patients enrolled in Cohort A, and patients enrolled in Cohort C with  $\geq 3$  months' follow-up
- 159 patients with positive detection of *MET* exon 14 skipping by liquid biopsy, and 174 by tissue biopsy, were enrolled
  - 59 patients had positive detection of *MET* exon 14 skipping by both liquid and tissue biopsy
  - 6/159 L+ patients had a negative result by tissue biopsy
  - 97/174 T+ patients had a negative result by liquid biopsy

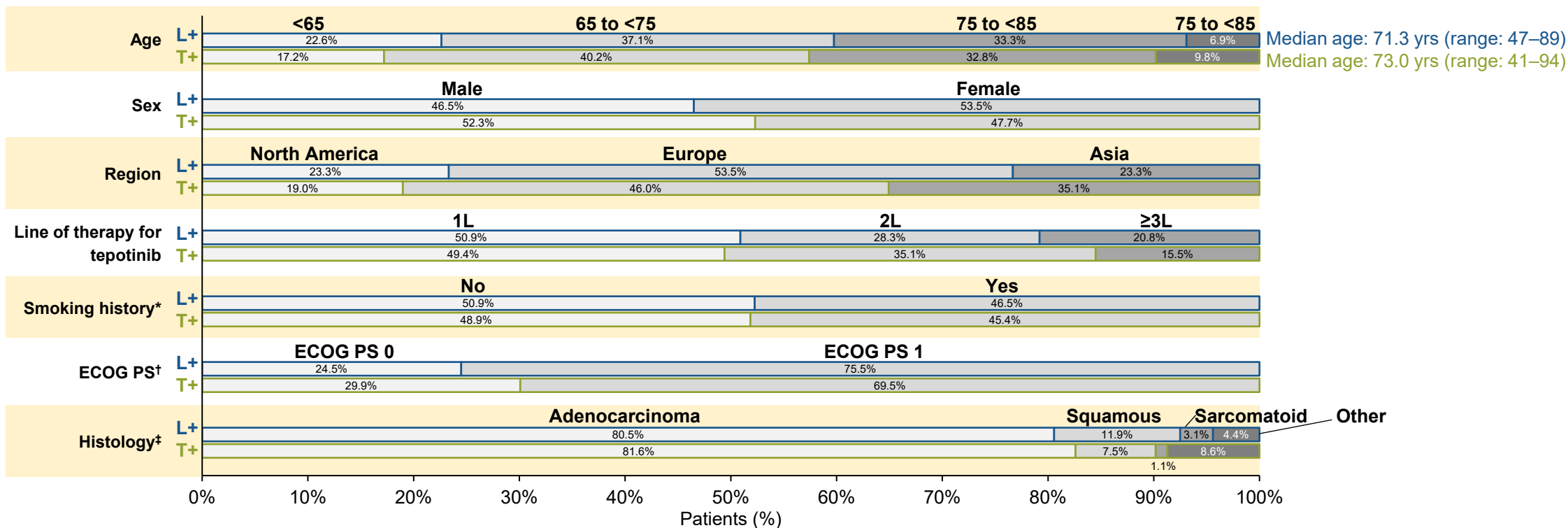


\*One patient (0.4%) enrolled in VISION did not have centrally confirmed *MET* exon 14 skipping by liquid or tissue biopsy and is, therefore, not included in L+ or T+ analysis sets; this patient was initially enrolled based on local testing. L+/-, positive/negative detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal-epithelial transition factor; NA, not available (biopsy sample was not taken or was not evaluable/not analyzed); T+/-, positive/negative detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: Patient characteristics across treatment lines

- Baseline demographics were broadly consistent between patients enrolled based on liquid (n=159) or tissue biopsy (n=174)
  - A higher proportion of T+ patients had ECOG PS 0, and a higher proportion were Asian



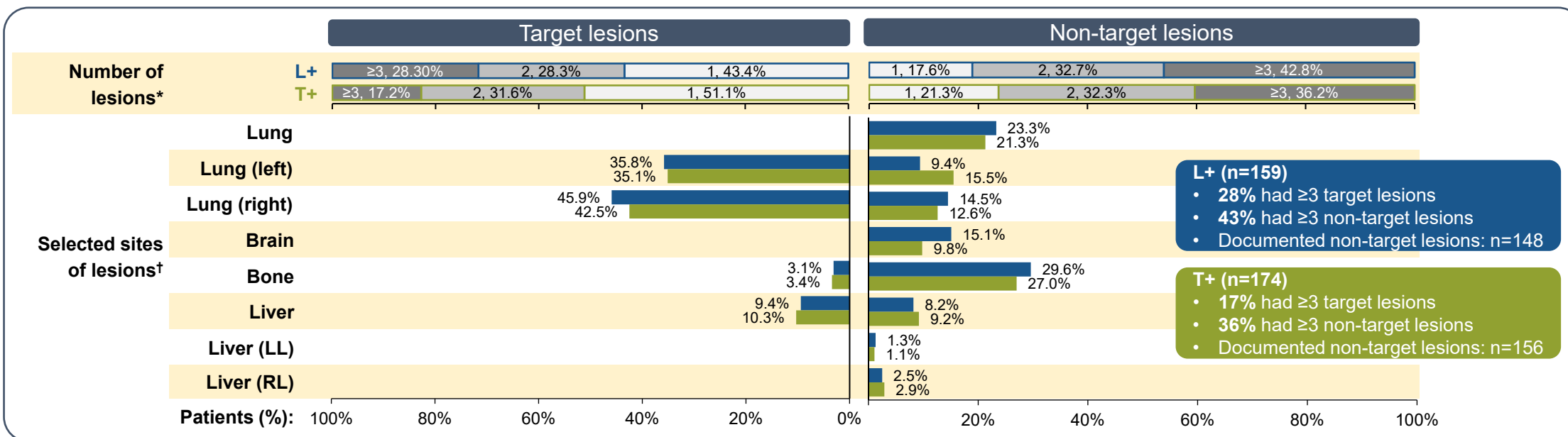
\*Smoking history data were missing for ten patients (3.6%); †One patient (0.4%) had an ECOG PS of 2; ‡Histology data were missing for two patients (0.7%).  
 1L, first-line; 2L, second-line; 3L, third line; ECOG PS, Eastern Cooperative Oncology Group performance status; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: Tumor burden at study entry across treatment lines

- Patients enrolled based on liquid biopsy had characteristics associated with a worse prognosis, such as higher tumor load and more brain metastases

	Median tumor load of target lesions, mm (range)	Median time since diagnosis, ‡ years (range)
L+ (n=159)	68.0 (11.6–227.8)	0.25 (<0.1–4.4)
T+ (n=174)	52.9 (10.2–227.8)	0.39 (<0.1–25.3)



\*Target and non-target lesions as identified by IRC; †There were no patients with target lesions in the brain, liver (left lobe), or liver (right lobe). Data for non-target lesions were missing for 23 patients (8.4%) (L+, n=11; T+, n=18); ‡Median time since initial cancer diagnosis.

ctDNA, circulating tumor DNA; IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; LL, left lobe; MET, mesenchymal–epithelial transition factor; RL, right lobe; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



## VISION: HRQoL at baseline across treatment lines

- HRQoL scores at baseline indicate that patients with *MET* exon 14 skipping detected by liquid biopsy entered the study with lower quality of life scores and worse symptom scores

Patient-reported outcomes, mean (SD)	L+ (n=159)	T+ (n=174)
EORTC QLQ-LC13 symptom scores <i>Lower scores indicate milder symptoms (scale 0–100)</i>		
Cough	35.8 (30.10)	32.7 (27.72)
Dyspnea	30.1 (25.39)	25.5 (21.97)
Chest pain	19.3 (27.16)	20.9 (29.51)
EORTC QLQ-LC30 patient functioning scales <i>Higher scores indicate greater function (scale 0–100)</i>		
Global health score	52.5 (24.78)	58.6 (23.49)
<b>Functional scales:</b>		
Physical	67.7 (26.90)	70.7 (24.18)
Role	62.6 (33.30)	69.6 (31.13)
Cognitive	80.1 (23.26)	80.6 (21.90)
Emotional	71.1 (23.76)	74.3 (22.70)
Social	70.7 (30.71)	75.9 (26.97)
EQ-5D-5L <i>Higher scores indicate greater function (scale 0–100)</i>		
VAS	61 (21.7)	64 (19.8)

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; EQ-5D-5L, EuroQol 5-dimension 5-level scale; HRQoL, health-related quality of life; MET, mesenchymal–epithelial transition factor; SD, standard deviation; VAS, visual analog score.



## VISION: Tumor responses with tepotinib across treatment lines

- Objective response rate with tepotinib was 49.1% in patients enrolled based on liquid biopsy and 51.1% in patients enrolled based on tissue biopsy

Objective response by IRC	L+ (n=159)	T+ (n=174)
Best objective response, n (%)		
Complete response	0	0
Partial response	78 (49.1)	89 (51.1)
Stable disease	34 (21.4)	50 (28.7)
Progressive disease	22 (13.8)	19 (10.9)
Not evaluable	25 (15.7)	16 (9.2)
Objective response rate, % (95% CI)	<b>49.1</b> (41.1, 57.1)	<b>51.1</b> (43.5, 58.8)
Disease control rate, % (95% CI)	<b>70.4</b> (62.7, 77.4)	<b>79.9</b> (73.2, 85.6)

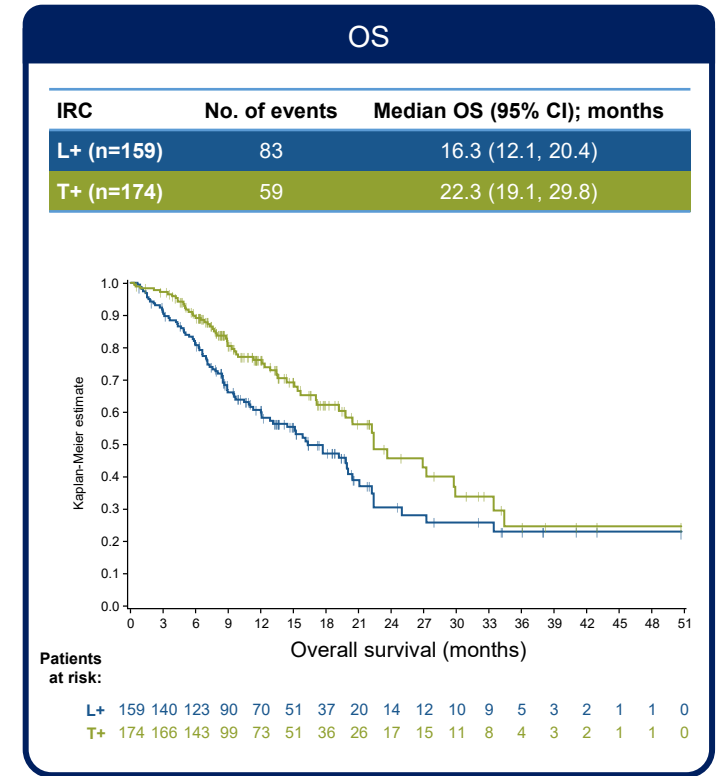
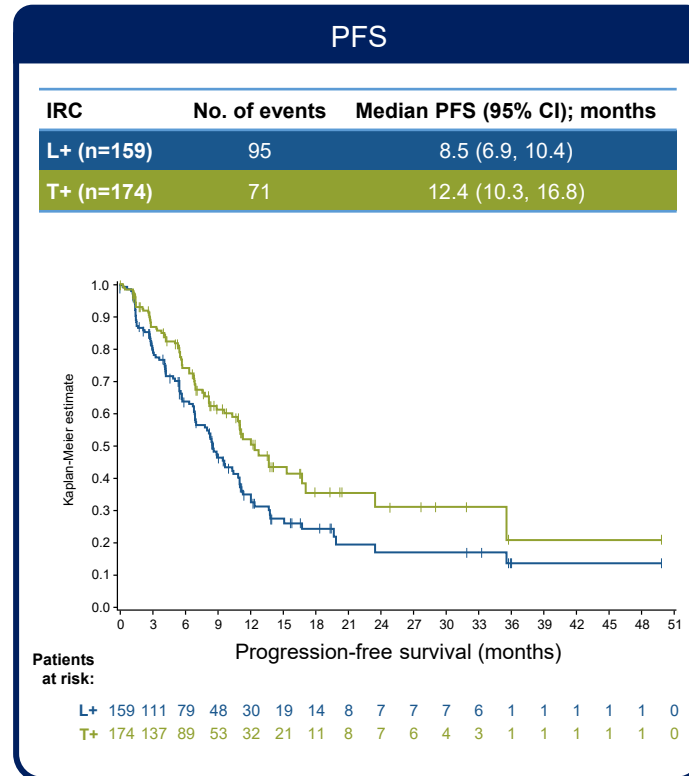
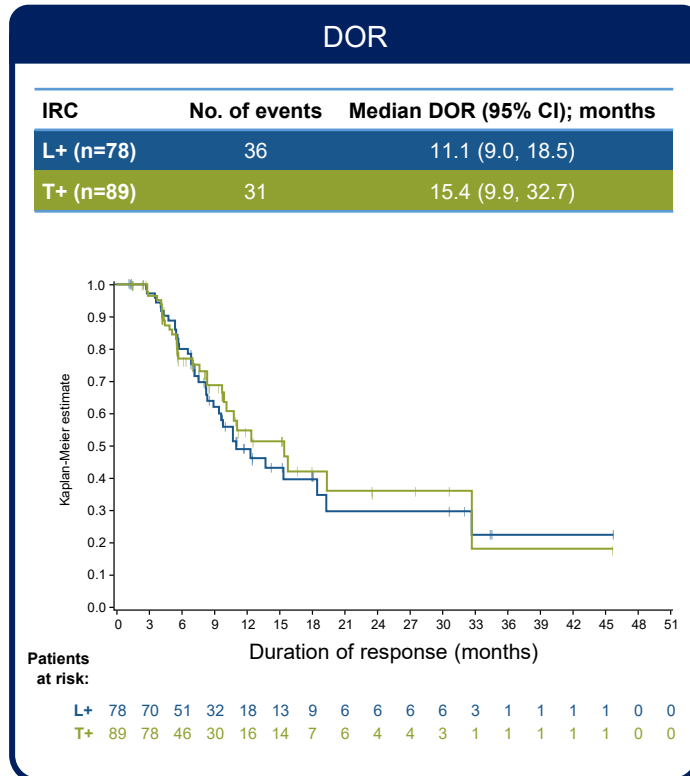
- Patients in the L+ population had a median treatment duration of 6.8 months (range: 0.4–50.6), with 25 (15.7%) patients ongoing at the time of analysis
- Patients in the T+, population had a median treatment duration of 6.6 months (range: <0.1–50.6), with 41 (23.6%) ongoing at the time of analysis

CI, confidence interval; IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: DOR, PFS and OS across treatment lines

- Although ORR was consistent between patients in L+ and T+ populations, time-dependent endpoints showed a trend for improvement in the T+ population

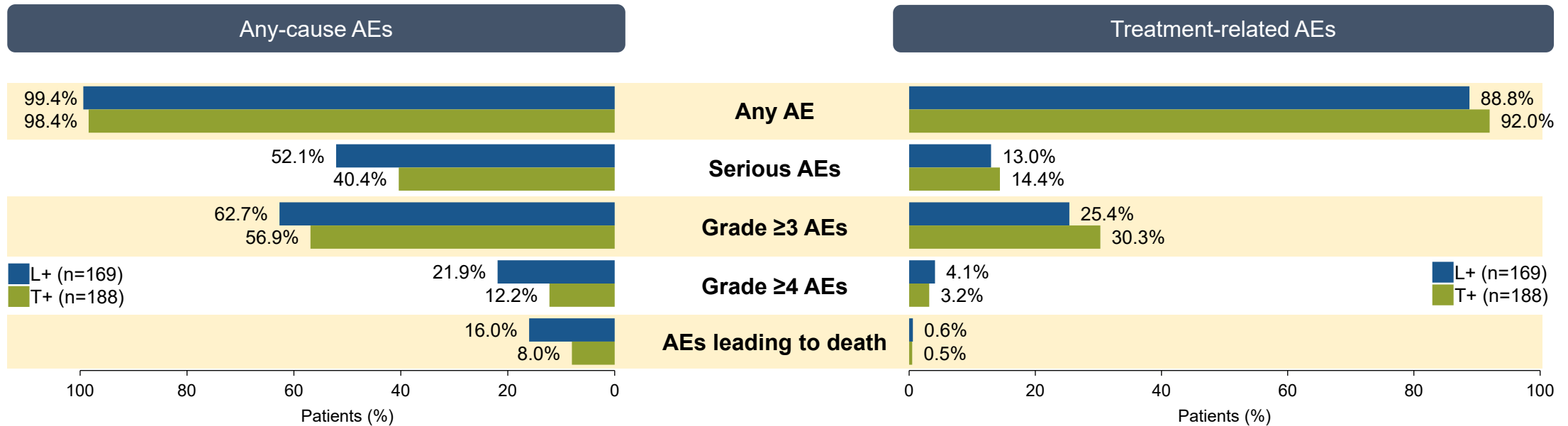


CI, confidence interval; DOR, duration of response; IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal-epithelial transition factor; OS, overall survival; PFS, progression-free survival; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: Tepotinib safety profile across treatment lines

- Across Cohorts A and C, 291 patients received at least one dose of tepotinib and were analyzed for safety\*
- Incidences of serious and Grade  $\geq 3$  treatment-related AEs were similar across the L+ and T+ populations, but any-cause AEs were reported in a larger proportion of L+ patients, suggesting a population with a higher disease burden

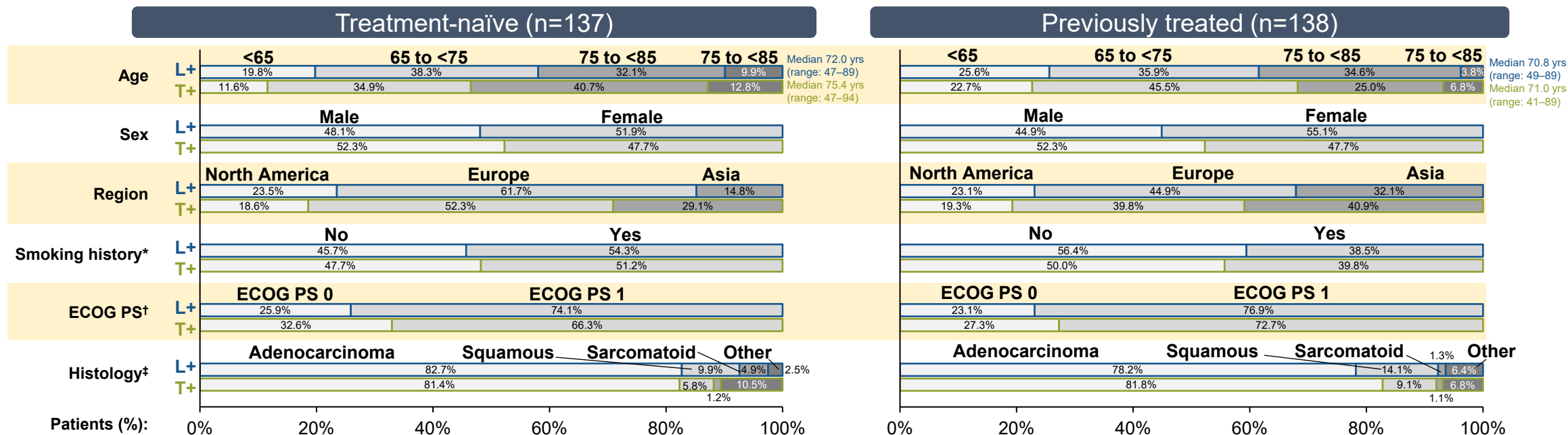


\*Patients analyzed for safety include and additional 16 patients with <3 months' follow-up in Cohort C that were excluded from efficacy analyses. AEs were defined as events that start within the day of first dose of trial treatment until 30 days after last dose of treatment, or started prior to first dose but worsened during the treatment period, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. AE, adverse event; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal-epithelial transition factor; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: Patient characteristics according to therapy line

- Baseline demographics were broadly consistent between patients enrolled based on liquid biopsy (n=81 treatment-naïve; n=78 previously treated) or tissue biopsy (n=86 treatment-naïve; n=88 previously treated)
- A higher proportion of T+ patients had ECOG PS 0 and a higher proportion were Asian, and these differences were more pronounced in treatment-naïve patients



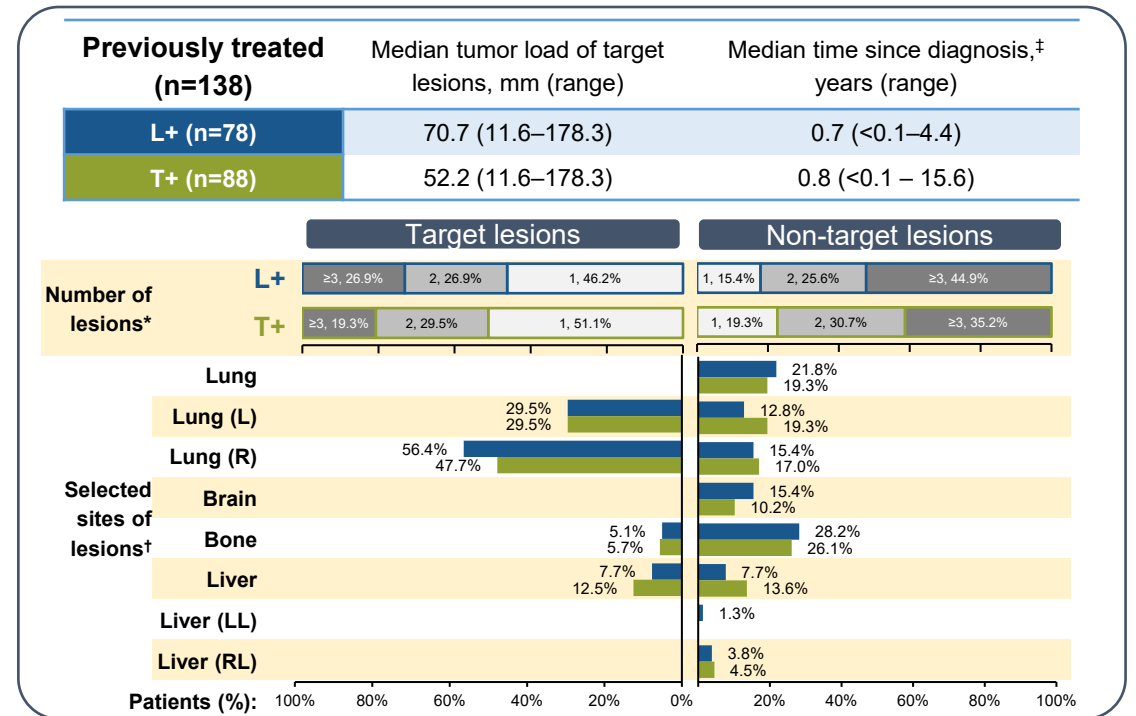
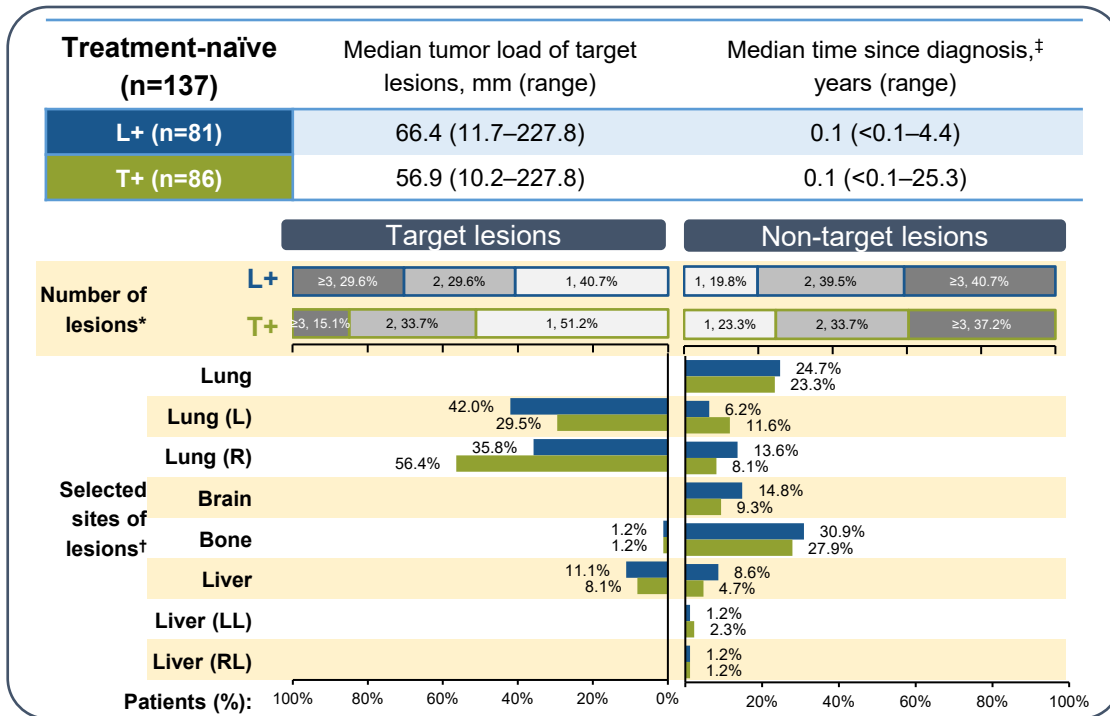
\*Smoking history data were missing for ten patients (3.6%); †One patient (0.4%) had an ECOG PS of 2; ‡Histology data were missing for two patients (0.7%).  
 1L, first-line; 2L, second-line; 3L, third line; ECOG PS, Eastern Cooperative Oncology Group performance status; L+, positive detection of MET exon 14 skipping in liquid biopsy sample; MET, mesenchymal-epithelial transition factor; T+, positive detection of MET exon 14 skipping in tissue biopsy sample.





# VISION: Tumor burden at study entry according to therapy line

- Patients enrolled based on liquid biopsy had characteristics associated with a worse prognosis, such as a higher tumor load and more brain metastases
- This trend occurred both in treatment-naïve and previously treated patients



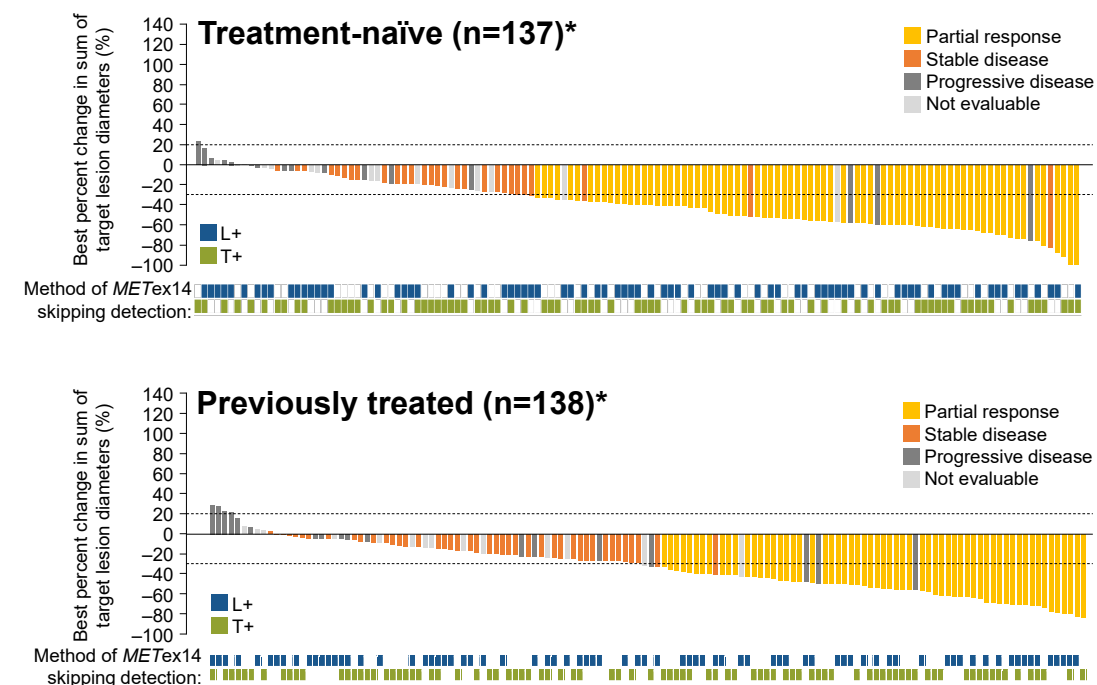
\*Target and non-target lesions as identified by IRC; <sup>†</sup>There were no patients with target lesions in the brain, liver (left lobe), or liver (right lobe). Data for non-target lesions were missing for 23 patients (8.4%) (L+, n=11; T+, n= 18); <sup>‡</sup>Median time since initial cancer diagnosis.  
 IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: Tumor responses with tepotinib according to therapy line

- In the L+ population, objective response rate was 54.3% in treatment-naïve patients and 43.6% in previously treated patients
- In the T+ population, objective response rate was 54.7% in treatment-naïve patients and 47.7% in previously treated patients

Objective response by IRC	Treatment-naïve (n=137)		Previously treated (n=138)	
	L+ (n=81)	T+ (n=86)	L+ (n=78)	T+ (n=88)
Best objective response, n (%)				
Complete response	0	0	0	0
Partial response	44 (54.3)	47 (54.7)	34 (43.6)	42 (47.7)
Stable disease	14 (17.3)	22 (25.6)	20 (25.6)	28 (31.8)
Progressive disease	11 (13.6)	7 (8.1)	11 (14.1)	12 (13.6)
Not evaluable	12 (14.8)	10 (11.6)	13 (16.7)	6 (6.8)
Objective response rate, % (95% CI)	<b>54.3</b> (42.9, 65.4)	<b>54.7</b> (43.5, 65.4)	<b>43.6</b> (32.4, 55.3)	<b>47.7</b> (37.0, 58.6)
Disease control rate, % (95% CI)	<b>71.6</b> (60.5, 81.1)	<b>80.2</b> (70.2, 88.0)	<b>69.2</b> (57.8, 79.2)	<b>79.5</b> (69.6, 87.4)



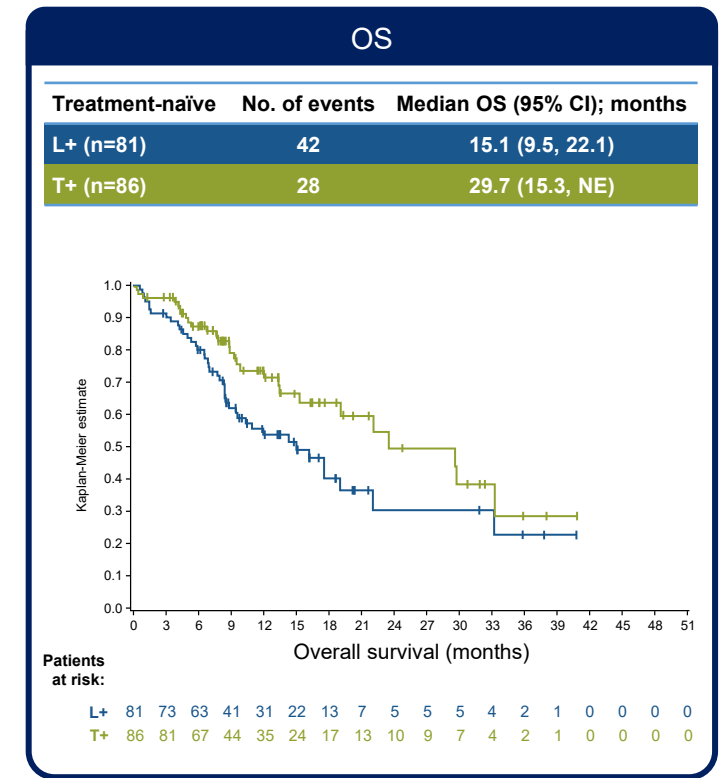
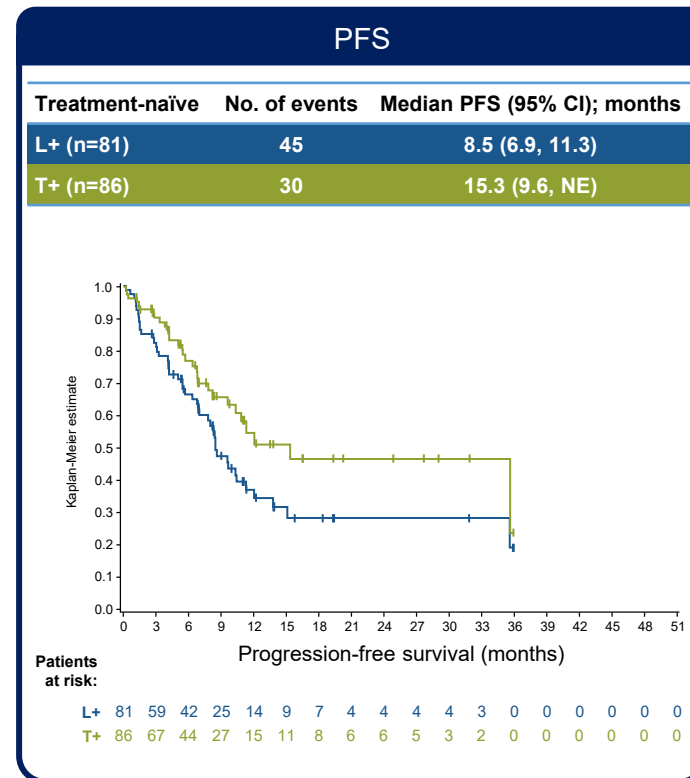
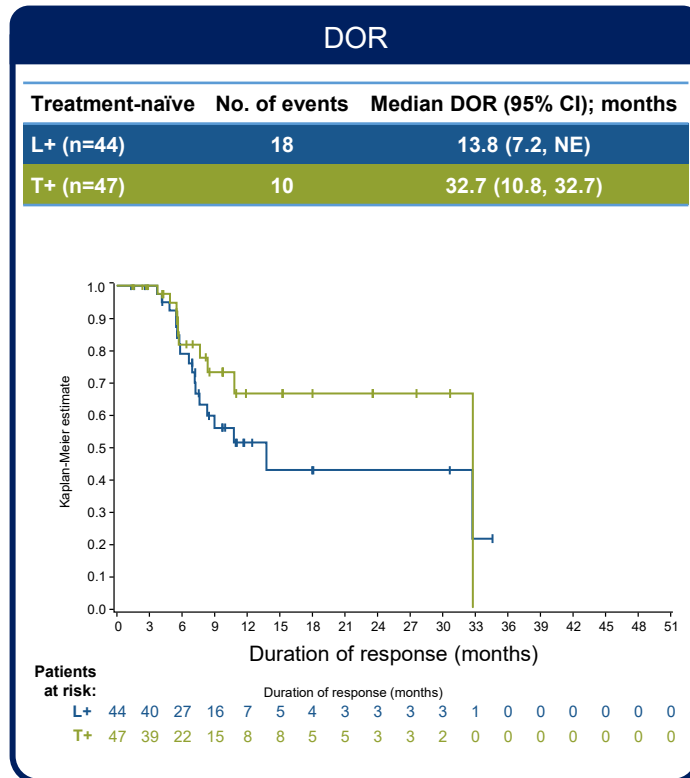
\*Four treatment-naïve patients, and two previously treated patients, are not shown due to baseline/on-treatment measurement not being available.

CI, confidence interval; IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal-epithelial transition factor; T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: DOR, PFS, and OS in treatment-naïve patients

- In treatment-naïve patients, time-dependent endpoints showed a trend for improvement in the tissue biopsy population, despite having comparable objective response rates

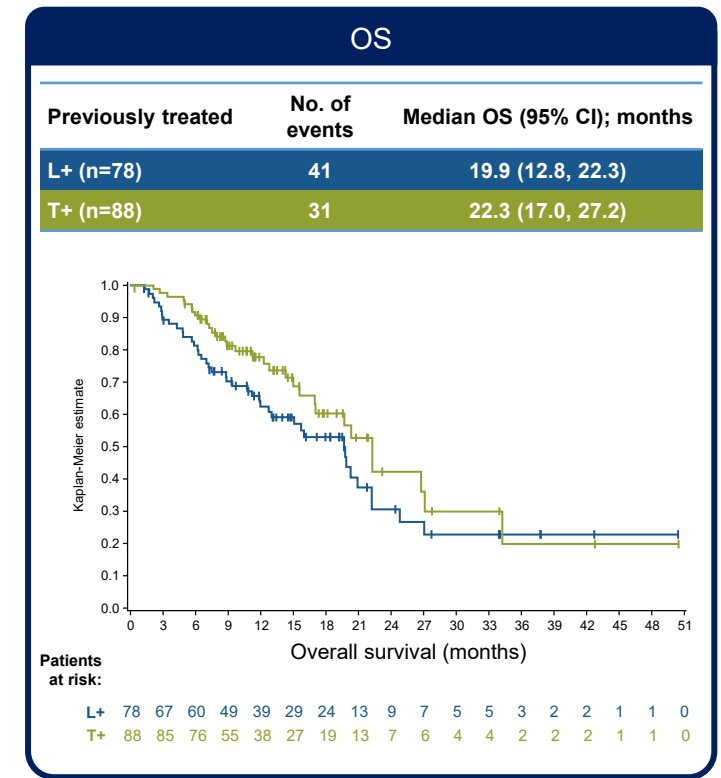
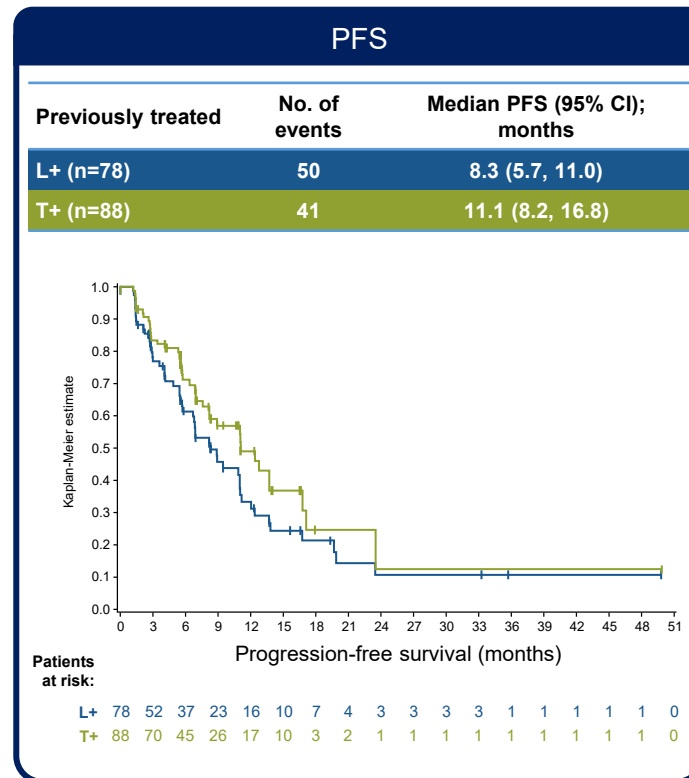
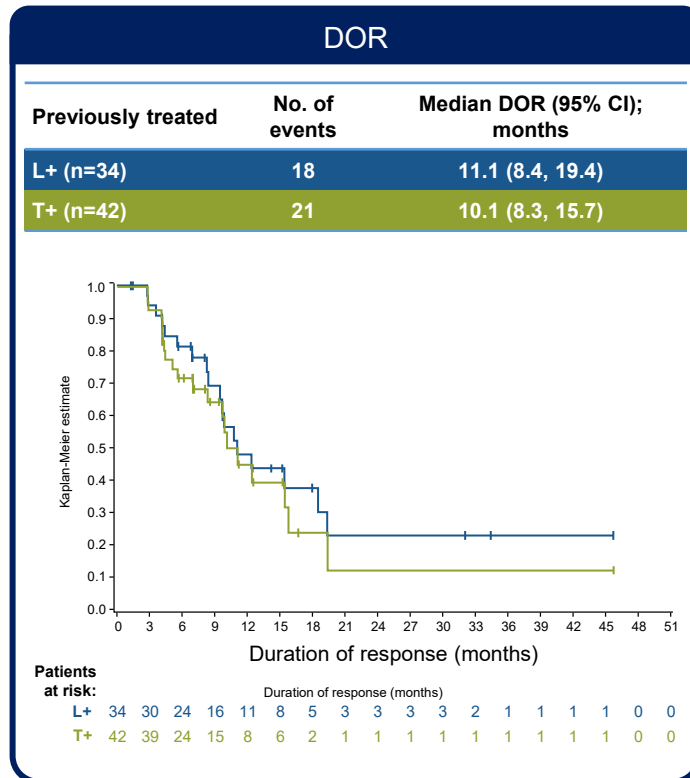


CI, confidence interval; DOR, duration of response; IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; NE, not estimable; OS, overall survival, PFS, progression-free survival, T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



# VISION: DOR, PFS, and OS in previously treated patients

- Time-dependent endpoints showed a trend for improvement in the tissue biopsy population, despite having comparable objective response rates



CI, confidence interval; DOR, duration of response; IRC, independent review committee; L+, positive detection of *MET* exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; OS, overall survival, PFS, progression-free survival, T+, positive detection of *MET* exon 14 skipping in tissue biopsy sample.



## Summary of tepotinib efficacy data

- Tepotinib demonstrated robust and durable clinical activity in patients with *MET* exon 14 skipping NSCLC, enrolled based on liquid or tissue biopsy; the shorter follow-up duration for patients enrolled in Cohort C should be considered
  - Patients enrolled based on liquid biopsy (n=159) had an ORR of 49.1% (95% CI: 41.1, 57.1), with an mDOR of 11.1 months (95% CI: 9.0, 18.5), mPFS of 8.5 months (95% CI: 6.9, 10.4), and mOS of 16.3 months (95% CI: 12.1, 20.4)
    - Treatment-naïve patients (n=81) had an ORR of 54.3% (42.9, 65.4), an mDOR of 13.8 months (7.2, NE), mPFS of 8.5 months (6.9, 11.3), and mOS of 15.1 months (9.5, 22.1)
    - Previously treated patients (n=78) had an ORR of 43.6% (32.4, 55.3), an mDOR of 11.1 months (8.4, 19.4), mPFS of 8.3 months (5.7, 11.0), and mOS of 19.9 months (12.8, 22.3)
  - Patients enrolled based on tissue biopsy (n=174) had an ORR of 51.1% (95% CI: 43.5, 58.8), with an mDOR of 15.4 months (95% CI: 9.9, 32.7), mPFS of 12.4 months (95% CI: 10.3, 16.8), and mOS of 22.3 months (95% CI: 19.1, 29.8)
    - Treatment-naïve patients (n=86) had an ORR of 54.7% (43.5, 65.4), an mDOR of 32.7 months (10.8, 32.7), mPFS of 15.3 months (9.6, NE), and mOS of 29.7 months (15.3, ne)
    - Previously treated patients (n=88) had an ORR of 47.7% (37.0, 58.6), an mDOR of 10.1 months (8.3, 15.7), mPFS of 11.1 months (8.2, 16.8), and mOS of 22.3 months (17.0, 27.2)

CI, confidence interval; mDOR, median duration of response; MET, mesenchymal–epithelial transition factor; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate.



## Discussion & conclusions

- VISION is one of the first clinical trials of a MET inhibitor to prospectively enroll based on liquid and/or tissue biopsy, with predefined analysis sets according to detection method
- Using liquid and tissue biopsy is reflective of the testing options available in clinical practice, and their use in VISION highlights the complementarity of the two methods

	Liquid biopsy	Tissue biopsy
Assays	<ul style="list-style-type: none"> <li>• Enabled more patients to be screened for VISION</li> <li>• Had a lower proportion of samples that were not evaluable</li> </ul>	<ul style="list-style-type: none"> <li>• Had a higher positivity rate for <i>MET</i> exon 14 skipping</li> </ul>
Enrollment	<ul style="list-style-type: none"> <li>• A large proportion of patients enrolled (34%) did not have a tissue biopsy results, reflecting a higher reach of liquid biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• A large proportion of patients enrolled (35%) were positive for <i>MET</i> exon 14 skipping by tissue biopsy and negative by liquid biopsy, indicating higher sensitivity</li> </ul>
Complementary use	<ul style="list-style-type: none"> <li>• May have limited sensitivity with low ctDNA shedding tumors; mutant allele frequency in ctDNA has been associated with tumor volumes<sup>1,2</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Negative liquid biopsy results do not preclude the identification of actionable biomarkers, and should be followed up with tissue biopsy testing<sup>3</sup></li> </ul>
Patients	<ul style="list-style-type: none"> <li>• Patients had characteristics associated with a worse prognosis, such as higher tumor load (which may be required to detect <i>MET</i> exon 14 skipping in ctDNA)</li> <li>• These patients had worse HRQoL scores at baseline, and a higher incidence of AEs considered unrelated to tepotinib, which is in line with a worse overall prognosis</li> </ul>	<ul style="list-style-type: none"> <li>• A higher proportion of patients had ECOG PS 0, and a higher proportion were Asian; these differences were more pronounced in treatment-naïve patients</li> </ul>
Outcomes	Patients with <i>MET</i> exon 14 skipping NSCLC detected by liquid or tissue biopsy had similar tumor responses; however, time-dependent endpoints showed a trend for improvement in the tissue biopsy population, particularly in the treatment-naïve setting, and likely reflect that patients enrolled based on liquid biopsy had a worse prognosis	

AE, adverse event; CI, confidence interval; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; MET, mesenchymal–epithelial transition factor; NSCLC, non-small cell lung cancer.

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