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# Liquid biopsies (LBx) and tissue biopsies (TBx) for identifying *MET* exon 14 skipping (*MET*ex14) in advanced NSCLC: Analyses from the Phase II VISION study of tepotinib

Christian Rolfo<sup>1</sup>, Aurora O'Brate<sup>2</sup>, Christoph Menzel<sup>3</sup>, Rolf Bruns<sup>4</sup>, Dilafuz Juraeva<sup>5</sup>, Christopher Stroh<sup>3</sup>, Andreas John<sup>6</sup>, Paul K. Paik<sup>7,8</sup>

<sup>1</sup>Center for Thoracic Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; <sup>2</sup>Global Medical Affairs, Merck Healthcare KGaA, Darmstadt, Germany; <sup>3</sup>Companion Diagnostics & Biomarker Strategy, Merck Healthcare KGaA, Darmstadt, Germany; <sup>4</sup>Department of Biostatistics, Merck Healthcare KGaA, Darmstadt, Germany; <sup>5</sup>Oncology Bioinformatics, Merck Healthcare KGaA, Darmstadt, Germany; <sup>6</sup>Global Clinical Development, Merck Healthcare KGaA, Darmstadt, Germany; <sup>7</sup>Department of Medicine, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; <sup>8</sup>Department of Medicine, Weill Cornell Medical College, New York, NY, USA

## CONCLUSIONS

- Baseline disease burden was higher in patients enrolled based on *MET*ex14 skipping detection in LBx (L+) versus TBx (T+)
- Tepotinib had robust, durable activity in 1L and +2L, with a more favorable treatment outcome when *MET*ex14 skipping was undetectable in blood (L-)
- TBx and LBx are both suitable and complementary for detecting *MET*ex14 skipping,<sup>1</sup> but LBx may select patients with a worse prognosis, potentially due to greater disease burden
- Differences in populations identified by TBx and LBx should be considered when interpreting trial data

## INTRODUCTION

- Tepotinib, a highly selective MET TKI,<sup>2</sup> is approved for treatment of advanced/metastatic *MET*ex14 skipping NSCLC
- The VISION study of tepotinib is one of the first trials in NSCLC to enroll patients based on detection of an oncogenic driver alteration (*MET*ex14 skipping) in TBx and/or LBx<sup>2-4</sup>
  - LBx are complementary to TBx for detecting alterations,<sup>1</sup> can facilitate genetic monitoring during treatment, and enable assessment of ctDNA burden as a potential surrogate for tumor burden<sup>5</sup>
- VISION showed robust, durable efficacy of tepotinib in patients treated in 1L and +2L<sup>2</sup>
  - Efficacy was meaningful in patients with *MET*ex14 skipping detected in TBx (T+) or LBx (L+), with trends for better time-dependent endpoints in the T+ subgroup<sup>2</sup>
  - To understand differences in patients identified by TBx and LBx, we further evaluated patient characteristics and outcomes in VISION according to T+ and/or L+ status, and ctDNA burden (data cut-off: Nov 20, 2022)

## METHODS

- VISION (NCT02864992) is a Phase II trial of once-daily, oral tepotinib 500 mg (450 mg active moiety) in 1L or +2L patients with advanced NSCLC with *MET*ex14 skipping, as detected by NGS in TBx and/or LBx (Figure S1)<sup>2-4</sup>
  - Archival or fresh TBx were analyzed using the Oncomine Focus Assay (Thermo Fisher Scientific, Inc., Waltham, MA, USA) or Archer<sup>®</sup>MET assay (ArcherDX Inc., Boulder, CO, USA)
  - Fresh LBx were analyzed using the Guardant360<sup>®</sup> (Guardant Health, Inc., Palo Alto, CA, USA) or Archer<sup>®</sup>MET assays
- Exploratory analyses evaluated patient characteristics and outcomes according to TBx and/or LBx status (based on *MET*ex14 skipping detection), and ctDNA burden (based on detection of any variants in any gene) (Table 1)

**Table 1. Summary of analyses according to TBx and/or LBx status, and ctDNA burden**

Population	Subgroups	Analyses
Overall (N=313)	T+ (n=208*)	Baseline characteristics (efficacy reported previously <sup>2</sup> )
	L+ (n=178*)	
T+ patients with matched LBx results from either LBx assay (n=180)	T+/L- (n=106)	Efficacy
	T+/L+ (n=74)	
T+ or L+ patients with baseline Guardant360 <sup>®</sup> LBx data (n=165)	Undetectable ctDNA <sup>†</sup> (n=25)	Baseline characteristics, efficacy
	Detectable ctDNA <sup>†</sup> (n=140)	

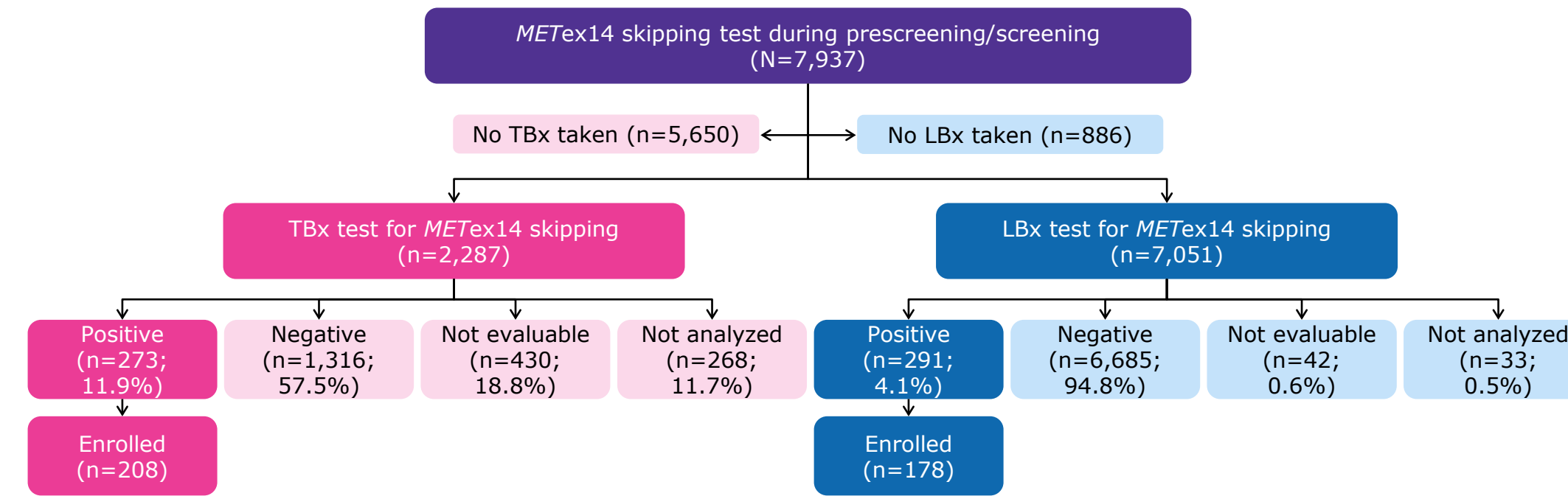
\*Patients could test positive for *MET*ex14 skipping in TBx and/or LBx samples. <sup>†</sup>No variants in any gene detected in ctDNA (excluding variants without COSMIC identifiers). <sup>‡</sup>≥1 variant in any gene(s) detected in ctDNA (excluding variants without COSMIC identifiers).

## RESULTS

### Patient disposition

- During prescreening/screening, *MET*ex14 skipping was assessed in 7,937 patients, including 2,287 with TBx and 7,051 with LBx samples (Figure 1)
- 469 patients (5.9%) had *MET*ex14 skipping detected in TBx and/or LBx
- Of 313 patients enrolled, 208 (66.5%) were T+ and 178 (56.9%) were L+

**Figure 1. VISION trial prescreening/screening**



- A total of 186 patients (59.4%) had matched TBx and LBx results; 106 were T+/L- (33.9%), 74 were T+/L+ (23.6%), and six were T-/L+ (1.9%) (Figure 2)

**Figure 2. Detection of *MET*ex14 skipping in TBx and LBx in the enrolled VISION population**

	T+/L-/N/A	T+/L-	T+/L+	T-/L+	T-/L+/N/A
Overall (n=313)	n=28 (8.9%)	n=106 (33.9%)	n=74 (23.6%)	n=6 (1.9%)	n=98 (31.3%)
1L (n=164)	n=17 (10.4%)	n=52 (31.7%)	n=42 (25.6%)	n=3 (1.8%)	n=50 (30.5%)
+2L (n=149)	n=11 (7.4%)	n=54 (36.2%)	n=32 (21.5%)	n=3 (2.0%)	n=48 (32.2%)

\*One patient (0.3%) was enrolled based on local testing (without central confirmation) in a protocol violation.

### Baseline characteristics in T+ and L+ patients (N=313)

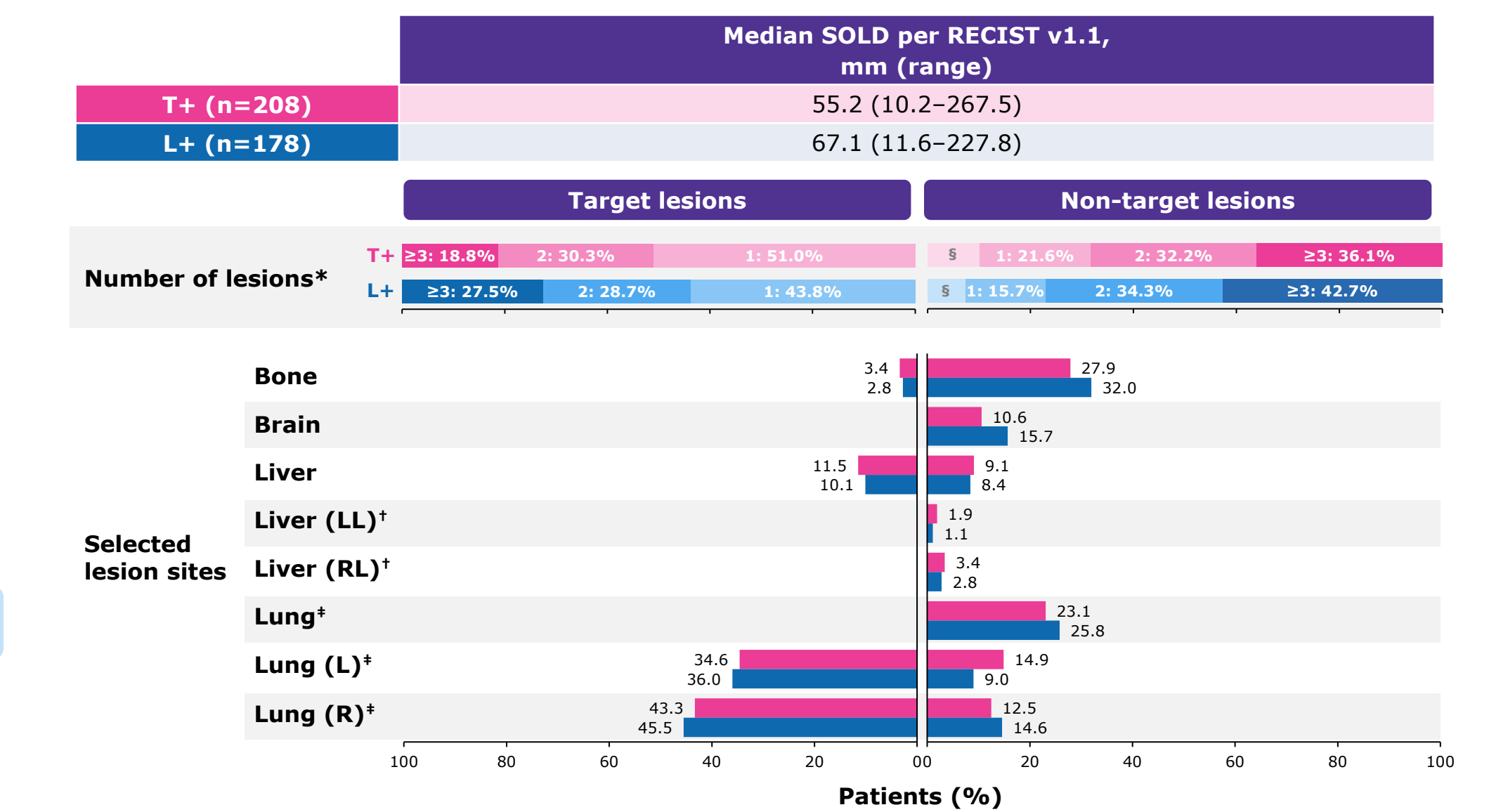
- Baseline demographics were broadly comparable between T+ and L+ patients, overall (Table 2) and in the 1L and +2L subgroups (Table S1)
- However, T+ patients were less likely than L+ patients to be female or White, to be enrolled in North America or Europe, or to have ECOG PS 1
- T+ patients had a lower disease burden than L+ patients with lower median SOLD per RECIST v1.1, and fewer patients with ≥3 target lesions or ≥3 non-target lesions (Figure 3, Figure S2)
- At baseline, T+ patients had better HRQoL than L+ patients with higher EORTC QLQ-C30 GHS and EQ-5D-5L VAS scores, and milder cough and dyspnea symptoms on the EORTC QLQ-LC13 (Table S2)

**Table 2. Baseline characteristics in T+ and L+ patients**

	T+ (n=208)	L+ (n=178)
Median age, years (range)	72.7 (41-94)	71.2 (47-89)
Female, n (%)	100 (48.1)	95 (53.4)
Race, n (%) <sup>*</sup>		
White	120 (57.7)	123 (69.1)
Asian	83 (39.9)	48 (27.0)
Geographic region, n (%)		
North America	33 (15.9)	37 (20.8)
Europe	88 (42.3)	93 (52.2)
Asia	87 (41.8)	48 (27.0)
Current/former smokers, n (%) <sup>†</sup>	98 (47.1)	84 (47.2)
ECOG PS, n (%) <sup>‡</sup>		
0	57 (27.4)	42 (23.6)
1	150 (72.1)	136 (76.4)
Adenocarcinoma, n (%) <sup>§</sup>	170 (81.7)	143 (80.3)
Median time since diagnosis, years (range) <sup>  </sup>	0.25 (0.01-25.26)	0.24 (-0.02 <sup>¶</sup> -4.44)

<sup>\*</sup>Race was Black or African American in three patients, 'other' in one patient and missing in eight patients. <sup>†</sup>Smoking history was missing in 10 patients. <sup>‡</sup>ECOG PS was 2 in one patient. <sup>§</sup>Histology was missing in two patients. <sup>||</sup>Median time since initial cancer diagnosis. <sup>¶</sup>One patient provided informed consent for prescreening shortly before formal NSCLC diagnosis.

**Figure 3. Disease burden at baseline in T+ and L+ patients**



\*Target and non-target lesions by IRC. <sup>†</sup>Liver (LL) and liver (RL) categories were not included for target lesions. <sup>‡</sup>Lung lesion site was categorized as 'lung', 'lung (L)', or 'lung (R)' for target and non-target lesions, but no target lesions were reported in the overall 'lung' category. <sup>§</sup>No non-target lesions were reported for 10.1% of T+ patients and 7.3% of L+ patients.

### Efficacy in T+ patients with matched LBx samples (n=180)

- Meaningful durable efficacy was seen in T+ patients treated in 1L and +2L, irrespective of LBx status (Table 3)
- ORRs were slightly higher in T+/L+ patients, but T+/L- patients had longer DOR, PFS, and OS (Table 3, Figures S3-5)

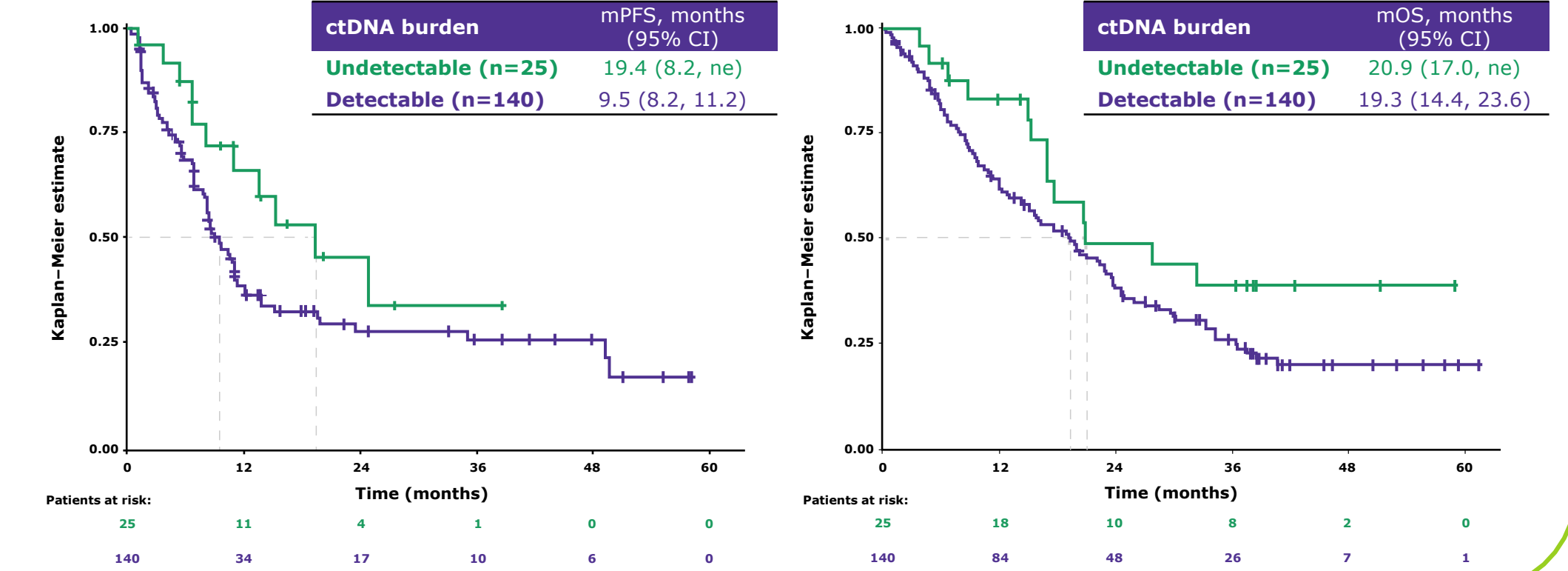
**Table 3. Outcomes in T+ patients with matched LBx samples**

IRC	1L		+2L	
	T+/L- (n=52)	T+/L+ (n=42)	T+/L- (n=54)	T+/L+ (n=32)
ORR, % (95% CI)	57.7 (43.2, 71.3)	64.3 (48.0, 78.4)	44.4 (30.9, 58.6)	53.1 (34.7, 70.9)
mDOR, months (95% CI)	ne (10.4, ne)	19.4 (7.6, ne)	12.6 (5.1, 20.8)	9.9 (4.4, 15.4)
mPFS, months (95% CI)	22.1 (14.8, ne)	12.1 (7.8, 49.7)	13.8 (8.2, 24.9)	8.2 (5.5, 13.7)
mOS, months (95% CI)	32.7 (15.3, ne)	28.5 (14.2, ne)	20.8 (15.6, 32.5)	19.8 (10.0, 26.5)

### Analyses according to baseline ctDNA burden (n=165)

- Among 165 patients with baseline Guardant360<sup>®</sup> LBx data, ctDNA (based on detection of variants in any gene) was undetectable in 25 patients (15.2%) and detectable in 140 patients (84.8%)
- More patients in the detectable than the undetectable ctDNA group had ≥3 target lesions (25.7% vs 4.0%) or ≥3 non-target lesions (45.0% vs 16.0%)
- Patients with detectable ctDNA had shorter PFS and OS than those with undetectable ctDNA (Figure 4)

**Figure 4. PFS and OS according to ctDNA burden**



**Abbreviations:** +2L, second or later line; 1L, first line; CI, confidence interval; COSMIC, Catalogue of Somatic Mutations in Cancer; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, five-level version of the EQ-5D; GHS, Global Health Score; HRQoL, health-related quality of life; IRC, independent review committee; L-, negative for *MET*ex14 skipping in liquid biopsy; L, left; L-, left lobe; L<sub>total</sub>, *MET*ex14 skipping result from liquid biopsy not available; m, median; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14; ne, not estimable; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer-13; R, right; RECIST, Response Evaluation Criteria in Solid Tumors; RL, right lobe; SOLD, sum of lesion diameters; T-, negative for *MET*ex14 skipping in tissue biopsy; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor.

**References:** 1. Rolfo C, et al. *J Thorac Oncol*. 2021;16(10):1647-1662; 2. Mazieres J, et al. *JAMA Oncol*. 2023;9(9):1260-1266; 3. Paik PK, et al. *N Engl J Med*. 2020;383(10):931-943; 4. Le X, et al. *Clin Cancer Res*. 2022;28(6):1117-1126; 5. Dall'Olio FG, et al. *Nat Rev Clin Oncol*. 2022;18(2):75-90.

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Correspondence: christian.rolfo@mssm.edu

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<sup>1</sup>Center for Thoracic Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; <sup>2</sup>Global Medical Affairs, Merck Healthcare KGaA, Darmstadt, Germany; <sup>3</sup>Companion Diagnostics & Biomarker Strategy, Merck Healthcare KGaA, Darmstadt, Germany; <sup>4</sup>Department of Biostatistics, Merck Healthcare KGaA, Darmstadt, Germany; <sup>5</sup>Oncology Bioinformatics, Merck Healthcare KGaA, Darmstadt, Germany; <sup>6</sup>Global Clinical Development, Merck Healthcare KGaA, Darmstadt, Germany; <sup>7</sup>Department of Medicine, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; <sup>8</sup>Department of Medicine, Weill Cornell Medical College, New York, NY, USA



## SUPPLEMENTARY RESULTS

**Table S1. Baseline characteristics in T+ and L+ patients, according to line of therapy**

		1L (n=164)		+2L (n=149)	
		T+ (n=111)	L+ (n=95)	T+ (n=97)	L+ (n=83)
Median age, years (range)		75.0 (47-94)	71.6 (47-88)	70.3 (41-89)	70.8 (49-89)
Female, n (%)		52 (46.8)	49 (51.6)	48 (49.5)	46 (55.4)
Race, n (%)*	White	68 (61.3)	73 (76.8)	52 (53.6)	50 (60.2)
	Asian	42 (37.8)	21 (22.1)	41 (42.3)	27 (32.5)
Geographic region, n (%)	North America	16 (14.4)	19 (20.0)	17 (17.5)	18 (21.7)
	Europe	49 (44.1)	54 (56.8)	39 (40.2)	39 (47.0)
	Asia	46 (41.4)	22 (23.2)	41 (42.3)	26 (31.3)
Current/former smokers, n (%) <sup>†</sup>		58 (52.3)	50 (52.6)	40 (41.2)	34 (41.0)
ECOG PS, n (%) <sup>‡</sup>	0	32 (28.8)	23 (24.2)	25 (25.8)	19 (22.9)
	1	78 (70.3)	72 (75.8)	72 (74.2)	64 (77.1)
Adenocarcinoma, n (%) <sup>§</sup>		90 (81.1)	77 (81.1)	80 (82.5)	66 (79.5)
Median time since diagnosis, years (range) <sup>  </sup>		0.10 (0.02-25.26)	0.10 (-0.02 <sup>¶</sup> -4.38)	0.78 (0.01-15.59)	0.76 (0.02-4.44)

\*Race was Black or African American in three patients, 'other' in one patient and missing in eight patients. <sup>†</sup>Smoking history was missing in 10 patients. <sup>‡</sup>ECOG PS was 2 in one patient. <sup>§</sup>Histology was missing in two patients. <sup>||</sup>Median time since initial cancer diagnosis. <sup>¶</sup>One patient provided informed consent for prescreening shortly before formal NSCLC diagnosis.

**Table S2. Baseline HRQoL in T+ and L+ patients**

Mean (SD)	T+ (n=208)	L+ (n=178)
EORTC QLQ-C30 patient functioning scales*		
GHS	60.1 (22.49)	53.9 (24.07)
Physical	72.1 (23.02)	69.0 (25.62)
Role	71.7 (30.02)	65.3 (32.14)
Emotional	75.7 (22.83)	72.3 (23.61)
Cognitive	82.1 (20.59)	81.5 (22.22)
Social	76.9 (25.58)	72.4 (29.49)
EQ-5D-5L*		
VAS	67 (19.0)	63 (20.8)
EORTC QLQ-LC13 symptom scores <sup>†</sup>		
Cough	30.7 (27.27)	34.2 (29.61)
Dyspnea	24.9 (20.09)	29.0 (24.08)
Chest pain	20.1 (28.06)	19.0 (26.43)

\*Higher scores indicate greater function. <sup>†</sup>Lower scores indicate milder symptoms.

Abbreviations: +2L, second or later line; 1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, five-level version of the EQ-5D; GHS, Global Health Score; HRQoL, health-related quality of life; L+, positive for *MET*ex14 skipping in liquid biopsy; LBx, liquid biopsy; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; QLQ-C30, Quality of Life Questionnaire-core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer-13; SD, standard deviation; T+, positive for *MET*ex14 skipping in tissue biopsy; TBx, tissue biopsy; VAS, visual analog scale.

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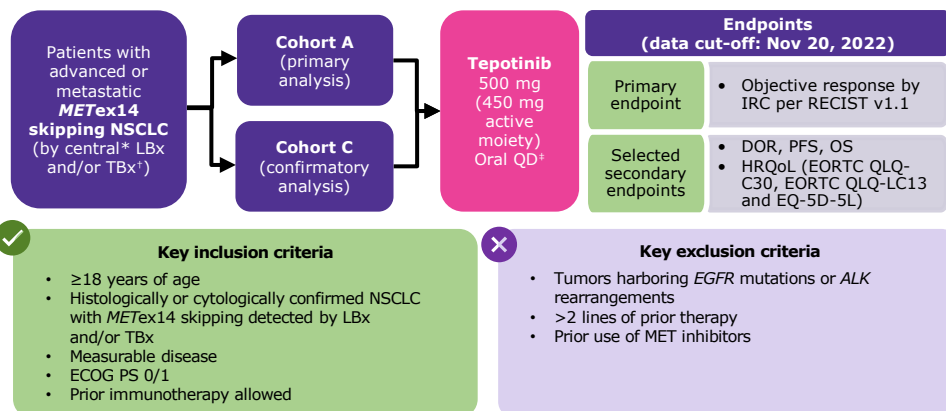
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## SUPPLEMENTARY RESULTS

Figure S1. VISION design, endpoints, and eligibility criteria



\*Patients in Japan could enroll based on local TBx RT-PCR via the LC-SCRUM program. <sup>†</sup>Parallel testing of TBx and LBx samples was recommended but not mandatory. <sup>‡</sup>Treatment continues until disease progression, intolerable toxicity, or withdrawal of consent.

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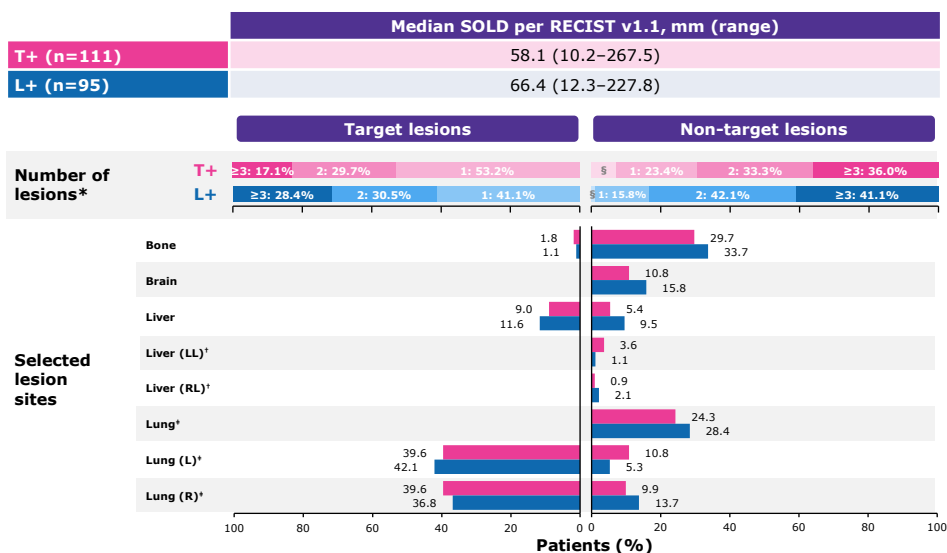
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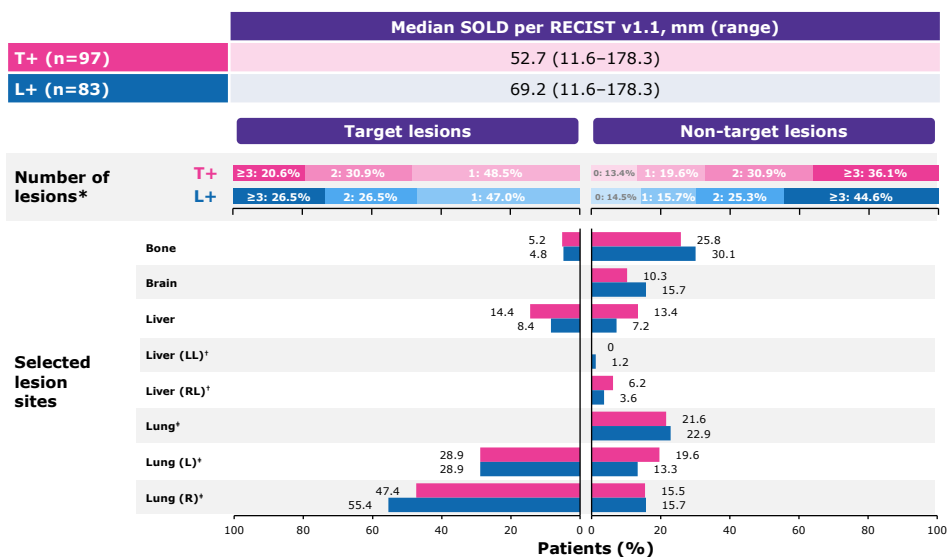
## SUPPLEMENTARY RESULTS

Figure S2. Disease burden at baseline in T+ and L+ patients, according to line of therapy

### A. 1L patients (n=164)



### B. +2L patients (n=149)



\*Target and non-target lesions by IRC. <sup>†</sup>Liver (LL)<sup>†</sup> and 'liver (RL)<sup>†</sup> categories were not included for target lesions. <sup>‡</sup>Lung lesion site was categorized as 'lung', 'lung (L)', or 'lung (R)' for target and non-target lesions, but no target lesions were reported in the overall 'lung' category. <sup>§</sup>No non-target lesions were reported for 7.2% of T+ patients and 1.1% of L+ patients in 1L.

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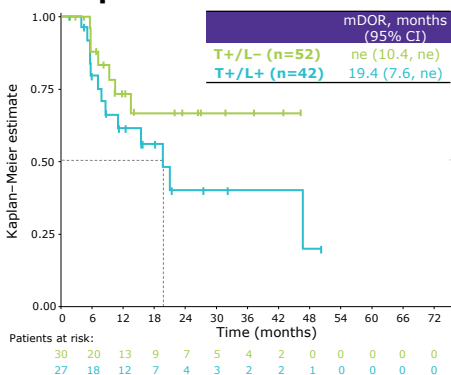
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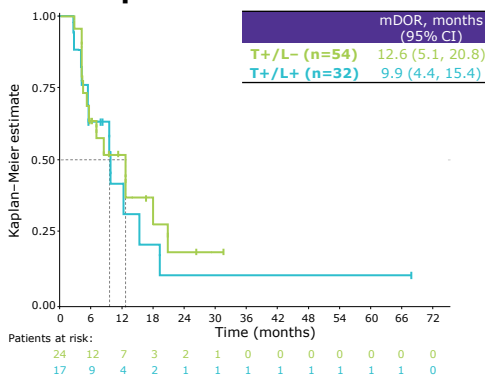
## SUPPLEMENTARY RESULTS

**Figure S3. DOR\* in T+ patients with matched LBx samples**

**A. 1L patients**

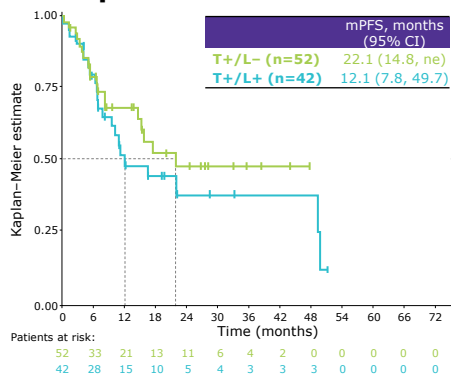


**B. +2L patients**

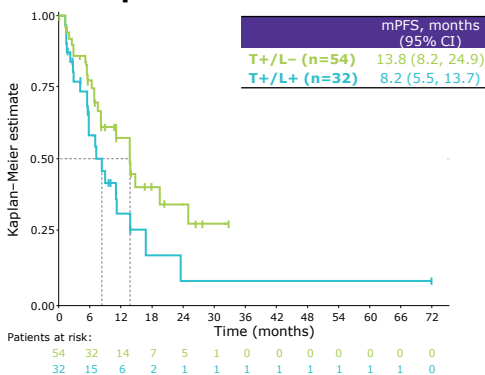


**Figure S4. PFS in T+ patients with matched LBx samples**

**A. 1L patients**

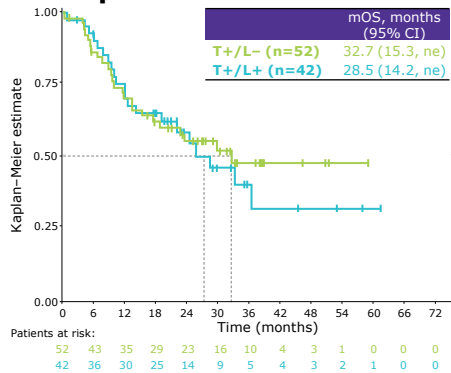


**B. +2L patients**

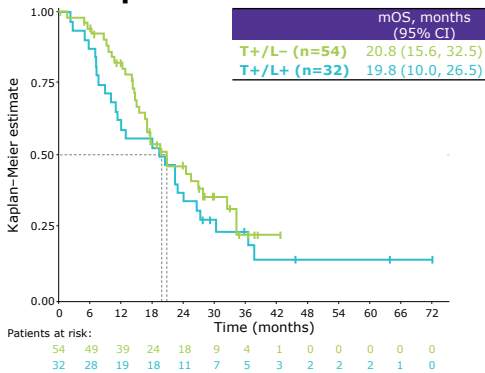


**Figure S5. OS in T+ patients with matched LBx samples**

**A. 1L patients**



**B. +2L patients**



\*Only patients with a response were included in Kaplan-Meier analyses of DOR.

Abbreviations: +2L, second or later line; 1L, first line; CI, confidence interval; DOR, duration of response; L-, negative for *MET*ex14 skipping in liquid biopsy; L+, positive for *MET*ex14 skipping in liquid biopsy; LBx, liquid biopsy; m, median; *MET*ex14, *MET* exon 14; ne, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; T+, positive for *MET*ex14 skipping in tissue biopsy; TBx, tissue biopsy.