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Tepotinib + osimertinib in *EGFR*-mutant NSCLC with *MET* amplification following 1L osimertinib: INSIGHT 2 primary analysis

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INSIGHT 2: an Open-label, Two-arm Phase II Study[1]

- *MET*amp is a common driver of secondary resistance in patients with *EGFR*m NSCLC following treatment with 1L osimertinib,[2,3] that may be responsive to MET inhibition
- TBx FISH is the gold standard for *MET*amp detection, with rates of ~50% compared with ~15% by LBx NGS testing[4,5]

Key inclusion criteria

- Locally advanced/metastatic *EGFR*m NSCLC
- Acquired resistance to 1L osimertinib
- ***MET*amp** by:
  - **TBx FISH** (GCN ≥5 and/or *MET*:*CEP7* ≥2) and/or **LBx NGS** (≥2.3 Archer®)
- ECOG PS of 0 or 1

Tepotinib 500 mg QD
+
Osimertinib 80 mg QD

Tepotinib monotherapy 500 mg QD*

Endpoints

Primary endpoint
- **Objective response by IRC** in patients with **TBx FISH** *MET*amp

Selected secondary endpoints
- Objective response in patients with LBx NGS *MET*amp
- DOR
- PFS
- OS
- HRQoL
- Safety
- Biomarkers

Selected tertiary endpoints
- RANO-BM

- The trial aims for an ORR in the range of ~50% with a lower limit of the corresponding exact 2-sided 95% CI (according to Clopper–Pearson) to exceed an ORR of 35%
- Subgroup analysis of Asian patients† was preplanned
- Data cut-off: March 28, 2023
- Efficacy population has ≥9 months follow-up

We now report the primary analysis

*Patients receiving tepotinib monotherapy (n=12, 2:1 randomization) could switch over to the combination at the time of disease progression. †Defined as patients enrolled in Asia.
Abbreviations defined on last slide.

1. Smit EF, et al. *Future Oncol*. 2022;18:1039–1054; 2. Ríos-Hoyo A, et al. *Cancers (Basel)*. 2022;14(8):1931; 3. Wang Y, et al. *Lung Cancer*. 2018;118:105–110;
4. Yu HA, et al. *J Clin Oncol*. 2023;41(Suppl 16):9074–9074; 5. Ramalingam SS, et al. *Ann Oncol*. 2018;29 (Suppl 8):viii740.

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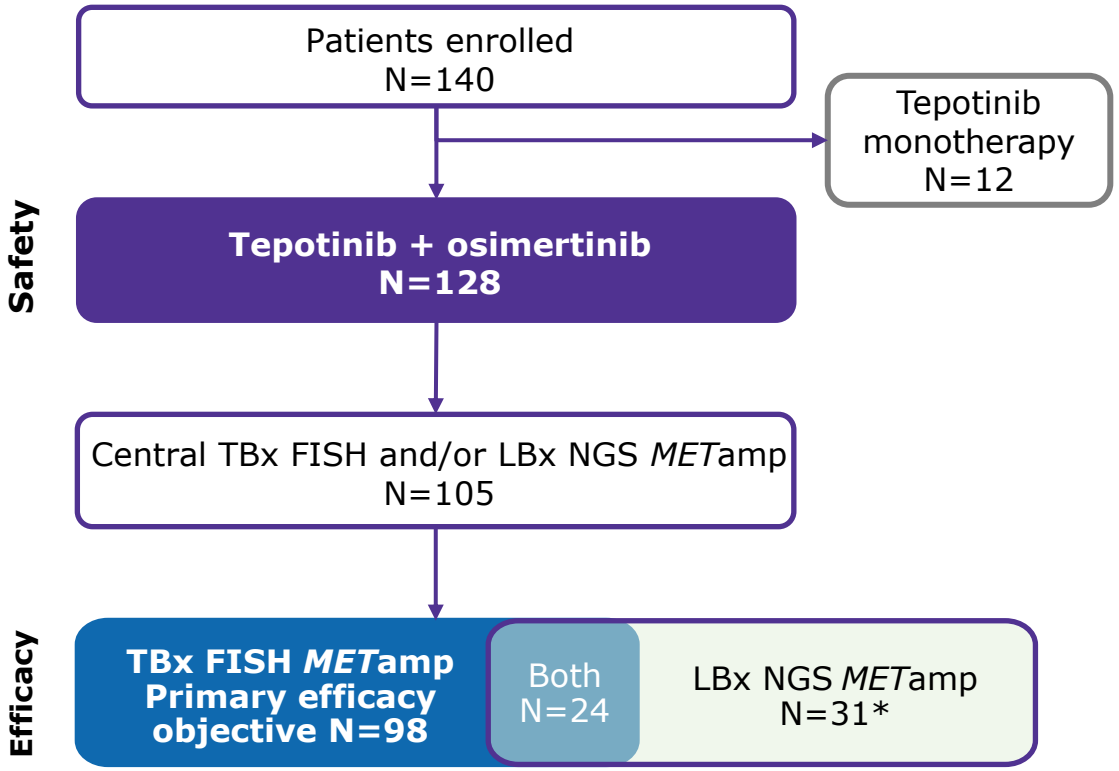
Patient Disposition and Baseline Characteristics

- Of 481 patients prescreened, METamp detected by TBx FISH in 35.1% and by LBx NGS in 10.8%



Baseline characteristics		Tepotinib + osimertinib (N=128)
Age, median (range)	Years	61 (20–84)
Sex, n (%)	Male Female	54 (42.2) 74 (57.8)
Smoking history, n (%)[†]	Yes No	41 (32.1) 86 (67.2)
ECOG PS, n (%)	0 1	35 (27.3) 93 (72.7)
Brain metastases, n (%)[‡]	Yes	45 (35.2)
Time on 1L osimertinib, median (range)[§]	Months	15.4 (4.1–45.5)
***MET*amp by FISH**, median (range)[‖]	GCN *MET/CEP7*	11.2 (2.1–50.6) 2.3 (0.9–11.6)
***EGFR* mutation**, n (%)[#]	Del19 L858R Other (e.g. L861Q)	76 (59.4) 44 (34.4) 8 (6.3)
Region, n (%)	**Asia** Europe North America	**76 (59.4)** 49 (38.3) 3 (2.3)

**METamp* detected by LBx NGS only (n=7): FISH not evaluable (n=5); FISH negative (n=2). [†]Smoking history missing (n=1). [‡]As determined by IRC and/or investigator. [§]Did not receive 1L osimertinib (n=7). [‖]FISH data available from 114 patients. [#]Two patients reported to have both del19 and L858R mutations were counted as del19 mutation cases.
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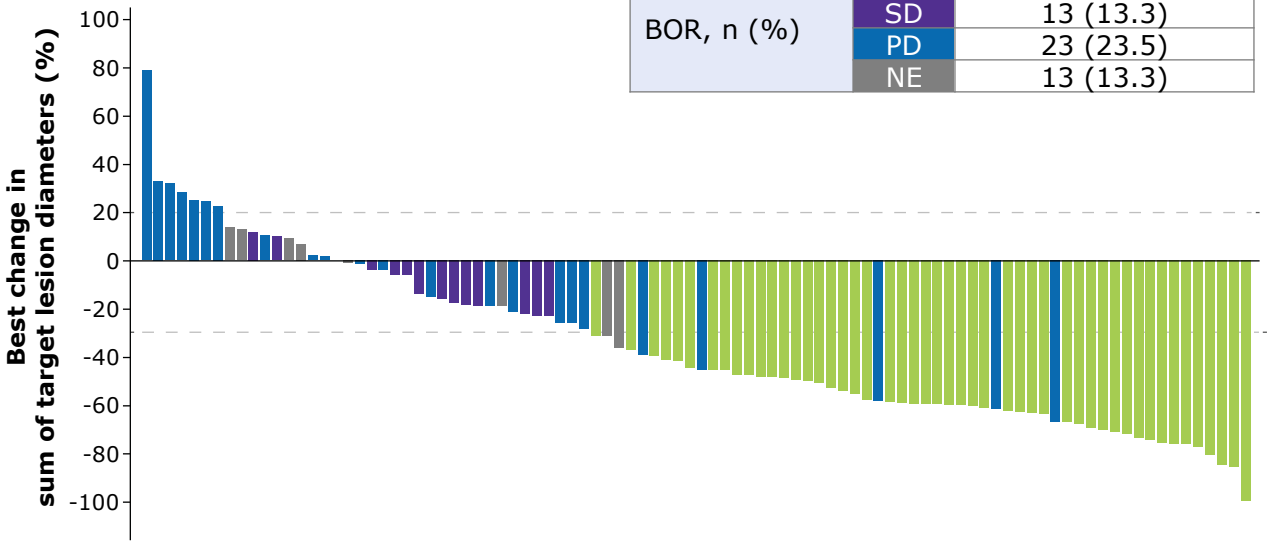
INSIGHT 2 Primary Analysis: Objective Response by IRC

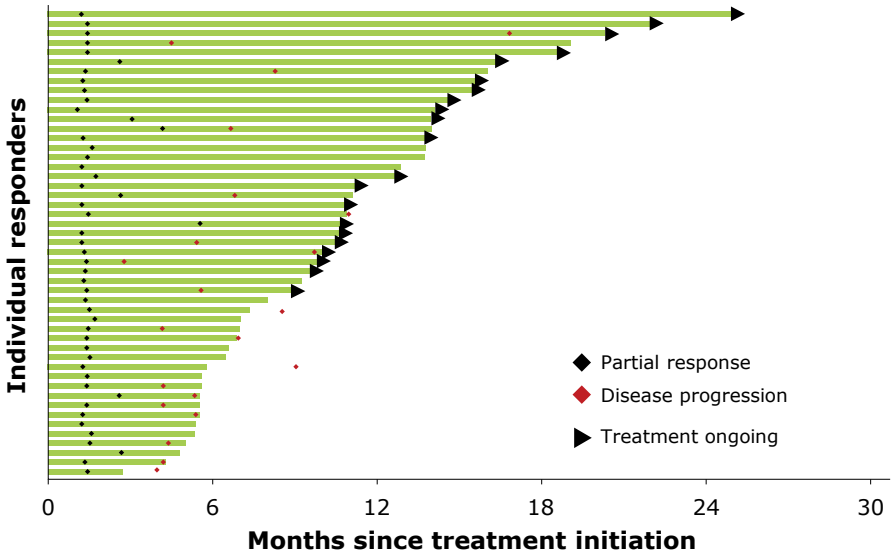
- **The INSIGHT 2 primary analysis showed an ORR of 50% in patients with *EGFR*m NSCLC who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)**

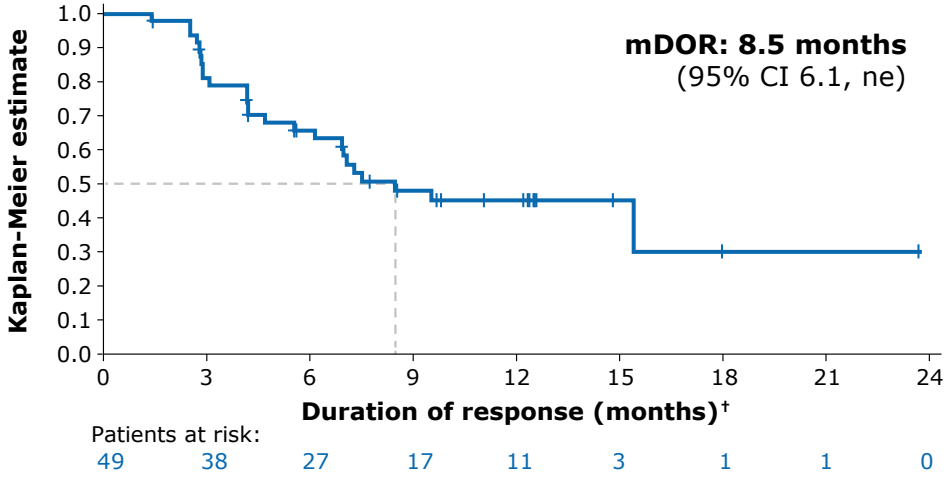
Tumor shrinkage (n=98*)



ORR, % (95% CI)		50.0 (39.7, 60.3)
BOR, n (%)	PR	49 (50.0)
	SD	13 (13.3)
	PD	23 (23.5)
	NE	13 (13.3)

Responses were rapid and long-lasting





- Patients in the monotherapy arm (n=12) showed an ORR of 8.3% (95% CI 0.2, 38.5), which has been reported previously[1]

*Four patients were excluded due to baseline/post-baseline measurement not being available.
†Only patients with a response were included in Kaplan-Meier analyses.
Abbreviations defined on last slide.

1. Mazieres J, et al. *Ann Oncol.* 2022;33:S808–S869.

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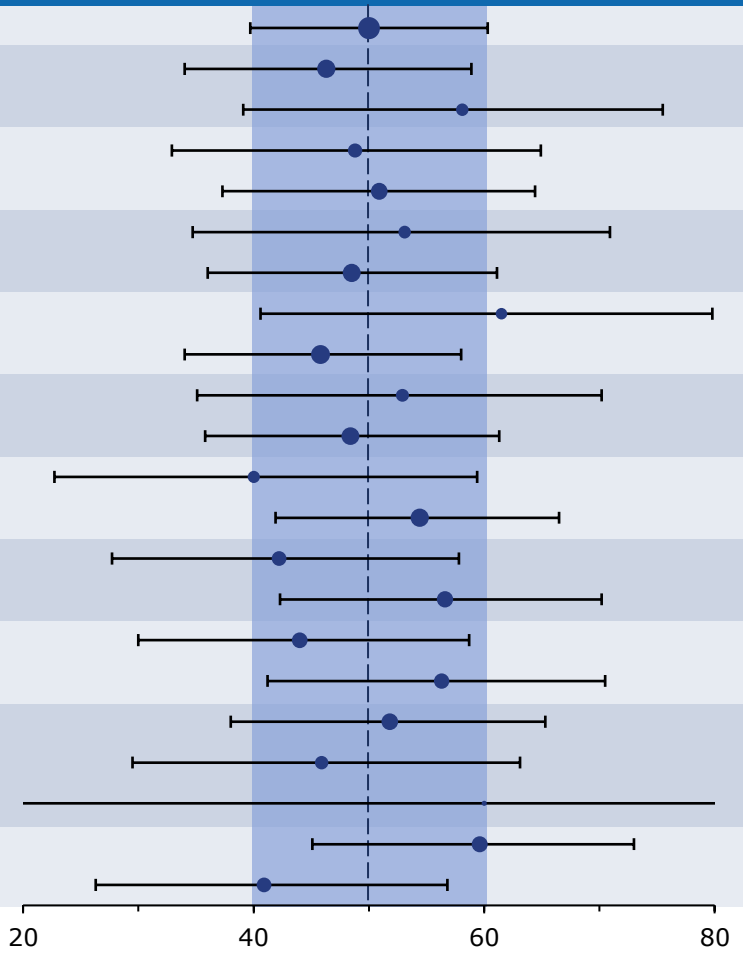
ORR was Consistent Across Patient Subgroups

Subgroups (TBx FISH)		n	ORR, % (95% CI)
Overall		**98**	**50.0 (39.7, 60.3)**
Age	<65 years	67	46.3 (34.0, 58.9)
	≥65 years	31	58.1 (39.1, 75.5)
Sex	Male	41	48.8 (32.9, 64.9)
	Female	57	50.9 (37.3, 64.4)
Smoking history	Yes	32	53.1 (34.7, 70.9)
	No	66	48.5 (36.0, 61.1)
ECOG PS	0	26	61.5 (40.6, 79.8)
	1	72	45.8 (34.0, 58.0)
Brain metastases*	Yes	34	52.9 (35.1, 70.2)
	No	64	48.4 (35.8, 61.3)
Time on 1L osimertinib	<12 months	30	40.0 (22.7, 59.4)
	≥12 months	68	54.4 (41.9, 66.5)
***MET* GCN†**	<10	45	42.2 (27.7, 57.8)
	≥10	53	56.6 (42.3, 70.2)
MET/CEP7	<2	50	44.0 (30.0, 58.7)
	≥2	48	56.3 (41.2, 70.5)
***EGFR* mutation**	Del19	56	51.8 (38.0, 65.3)
	L858R	37	45.9 (29.5, 63.1)
	Others	5	60.0 (14.7, 94.7)
Region‡	Asia	52	59.6 (45.1, 73.0)
	Europe	44	40.9 (26.3, 56.8)



*As determined by IRC and/or investigator. †All patients had *MET* GCN ≥5, with the exception of one patient with a *MET* GCN of 4.96. ‡Two patients enrolled in North America had PD as BOR.
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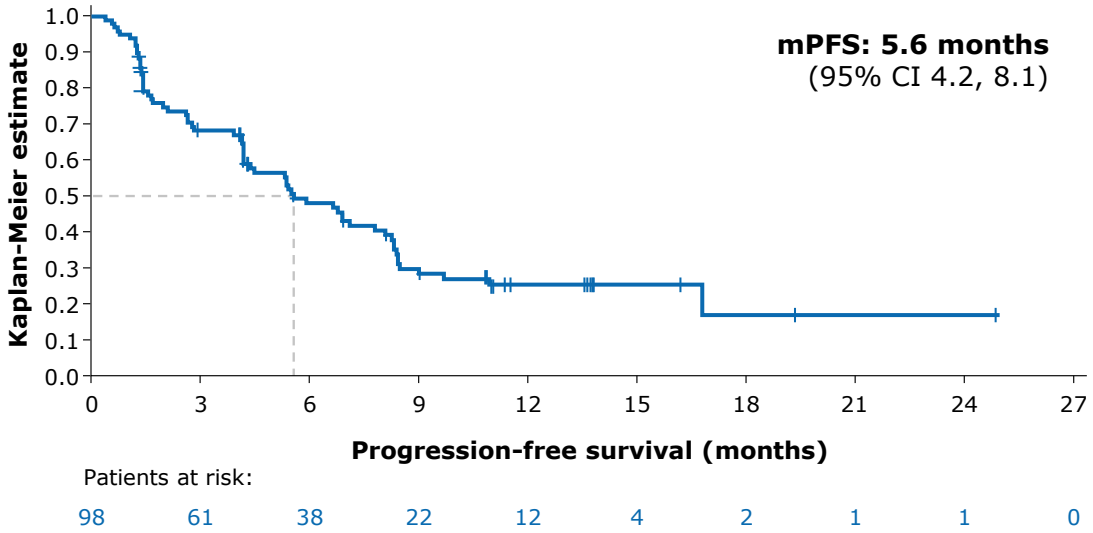
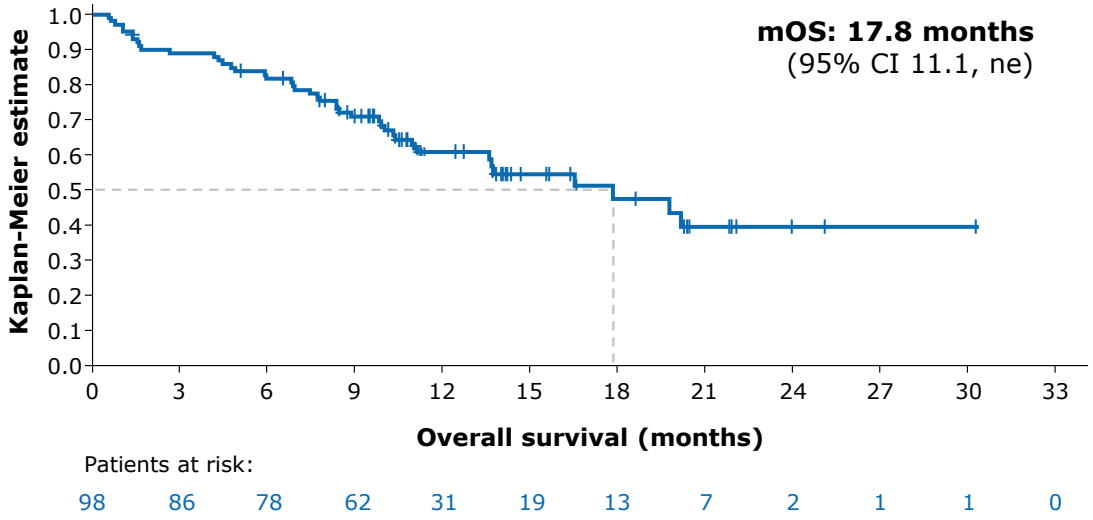
INSIGHT 2 Secondary Objectives: PFS, OS, and LBx NGS Efficacy

- PFS and OS were clinically meaningful in patients with *EGFR*m NSCLC who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)





In patients with LBx NGS *MET*amp (n=31)

- ORR: 54.8% (95% CI 36.0, 72.7)
- mDOR: 5.7 months (95% CI 2.9, 15.4)
- mPFS: 5.5 months (95% CI 2.7, 7.2)
- mOS: 13.7 months (95% CI 9.6, ne)

65/98 (66.3%) PFS events. 42/98 (42.9%) OS events.
Abbreviations defined on last slide.

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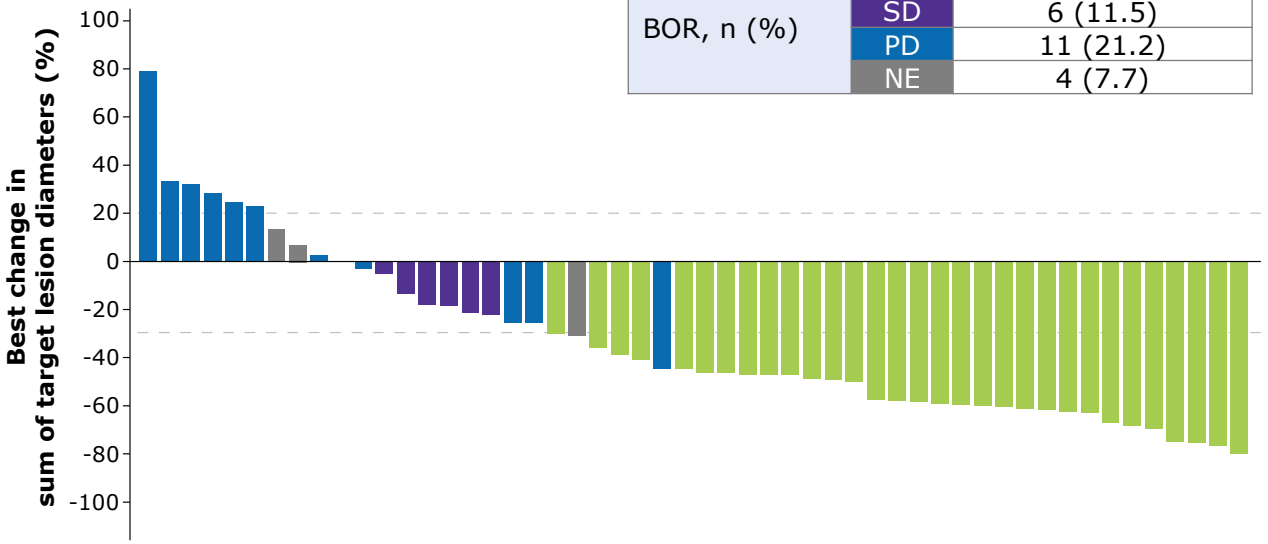
Efficacy in Asian Patients

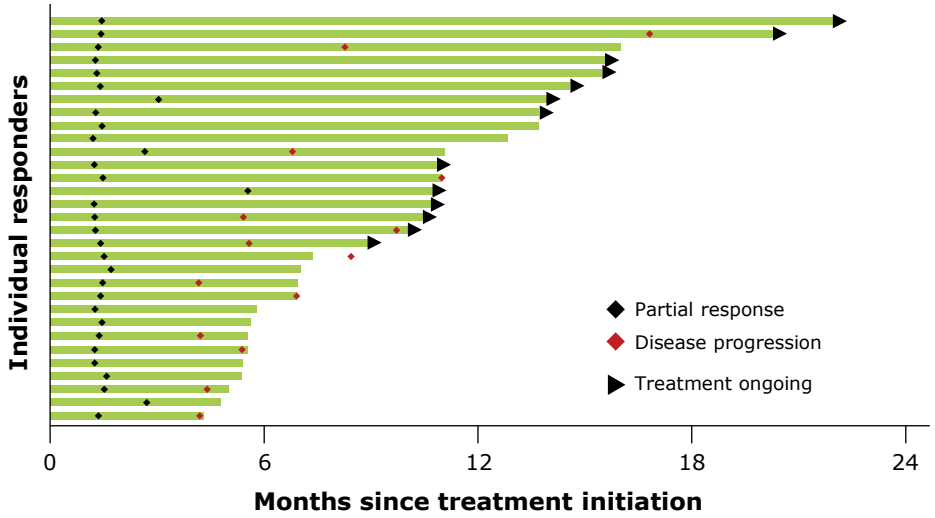
- ORR by IRC of 59.6% in Asian patients who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)

Tumor shrinkage (n=52)



ORR, % (95% CI)		59.6 (45.1, 73.0)
BOR, n (%)	PR	31 (59.6)
	SD	6 (11.5)
	PD	11 (21.2)
	NE	4 (7.7)

Responses were rapid and long-lasting



	TBx FISH (n=52)	LBx NGS (n=14)
ORR, % (95% CI)	59.6 (45.1, 73.0)	71.4 (41.9, 91.6)
mDOR, months (95% CI)	7.3 (4.7, ne)	5.6 (2.9, ne)
mPFS, months (95% CI)	6.9 (5.4, 8.4)	5.5 (4.2, 8.4)
mOS, months (95% CI)	19.8 (13.6, ne)	12.0 (5.9, ne)

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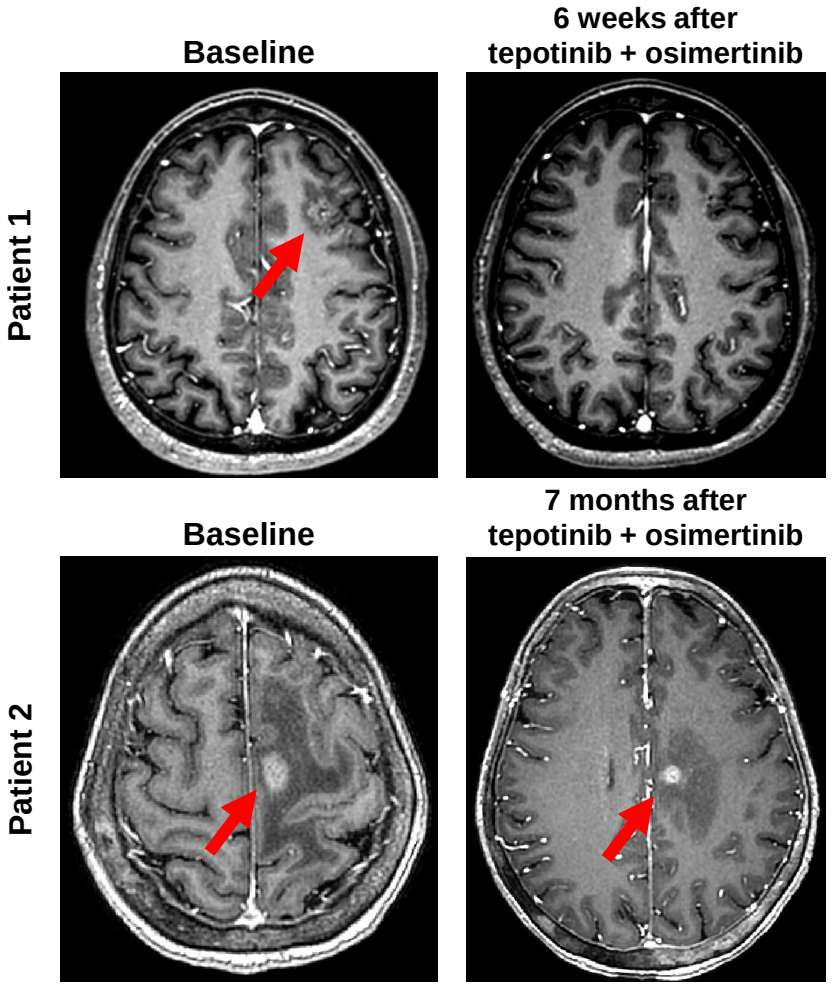
Intracranial Response in Patients with Brain Lesions Evaluable by RANO-BM

RANO-BM (IRC)		TBx FISH (N=24)
Intracranial ORR	% (95% CI)	29.2 (12.6, 51.1)
Intracranial BOR, n (%)	CR	6 (25.0)
	PR	1 (4.2)
	SD	12 (50.0)
	PD	2 (8.3)
	NE	3 (12.5)
Intracranial DCR	% (95% CI)	79.2 (57.8, 92.9)
Intracranial mDOR	Months (95% CI)	ne (3.6, ne)
Intracranial mPFS	Months (95% CI)	7.8 (3.9, ne)

Systemic outcome for patients (n=19, TBx FISH) with brain metastases at baseline by RECIST v1.1 (IRC)

- ORR: 57.9% (95% CI 33.5, 79.7)
- mDOR: 6.1 months (95% CI 2.7, ne)
- mPFS: 5.6 months (95% CI 3.9, 9.7)



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Tepotinib + Osimertinib Demonstrated a Manageable Safety Profile

- TRAEs led to a dose reduction in 26 patients (20.3%)
  - Tepotinib was reduced to 250 mg QD in 24 patients (18.8%)
  - Osimertinib was reduced to 40 mg QD in four patients (3.1%)
- Thirteen patients (10.2%) discontinued treatment due to TRAEs, most often due to pneumonitis (six patients [4.7%])
- Four patients (3.1%) had TRAEs leading to death that were considered potentially related to either trial drug
  - Pneumonitis: n=2
  - Respiratory failure after COVID-19 infection: n=1
  - Decreased platelet count: n=1 (disease progression)
- Similar safety profile among Asian patients
- HRQoL was maintained with improvements in cough and pain

TRAEs of any grade in >10% of all patients	Tepotinib + osimertinib (N=128)	
	Any grade n (%)	Grade ≥3 n (%)
Any	**113 (88.3)**	**44 (34.4)**
Diarrhea	63 (49.2)	1 (0.8)
Peripheral edema	52 (40.6)	6 (4.7)
Paronychia	29 (22.7)	1 (0.8)
Nausea	27 (21.1)	3 (2.3)
Decreased appetite	26 (20.3)	5 (3.9)
Hypoalbuminemia	23 (18.0)	1 (0.8)
AST increased	16 (12.5)	0
Anemia	15 (11.7)	2 (1.6)
Vomiting	15 (11.7)	1 (0.8)
Blood creatinine increased	15 (11.7)	0
Lipase increased	14 (10.9)	3 (2.3)
ALT increased	14 (10.9)	2 (1.6)
Rash	14 (10.9)	0 (0.0)

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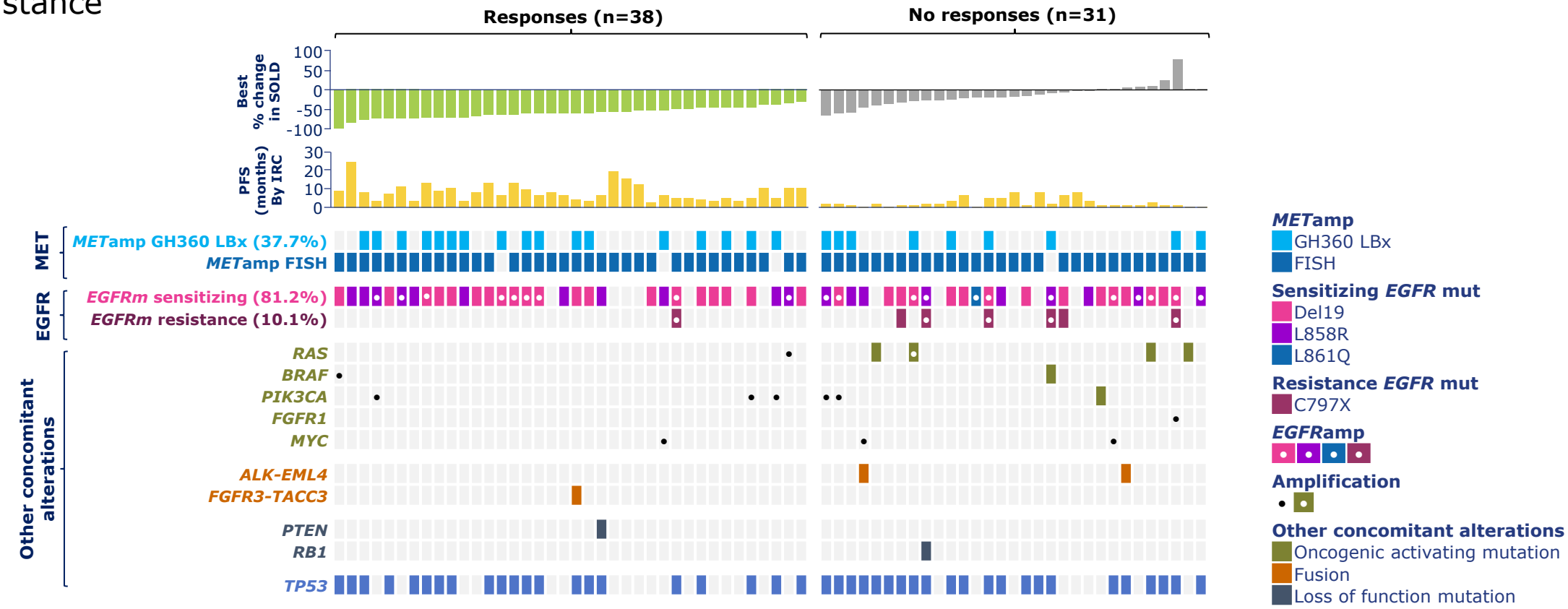
Baseline Biomarker Profiles

- Baseline biomarker profiles by NGS Guardant360® LBx were available for 69 patients
- Better outcomes were reported in patients without other concomitant biomarkers for osimertinib resistance



Patients without *MET*amp detected by FISH (n=4): FISH not evaluable (n=2); FISH negative (n=2).
No *RET* or *ROS* fusions were detected.
Next-generation sequencing Guardant360® panel assay, (Guardant Health, Inc. in Redwood City, CA, USA), covering 74 genes.
Abbreviations defined on last slide.

INSIGHT 2 Primary Analysis: Conclusions

- In the primary analysis (TBx FISH), **ORR was 50.0%** (95% CI 39.7, 60.3), **mDOR was 8.5 months** (95% CI 6.1, ne), **mPFS was 5.6 months** (95% CI 4.2, 8.1), and **mOS was 17.8 months** (95% CI 11.1, ne)
- In Asian patients, ORR was 59.6% (95% CI 45.1, 73.0), mDOR was 7.3 months (95% CI 4.7, ne), mPFS was 6.9 months (95% CI 5.4, 8.4) and mOS was 19.8 months (95% CI 13.6, ne)
- Efficacy outcomes were meaningful in patients with LBx NGS METamp (ORR 54.8%; 95% CI 36.0, 72.7)
- Better outcomes were observed when there were no co-occurring mechanisms of osimertinib resistance
- Tepotinib + osimertinib demonstrated a **manageable safety profile**, while maintaining HRQoL

Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted treatment option for patients with *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib, who have a high unmet need

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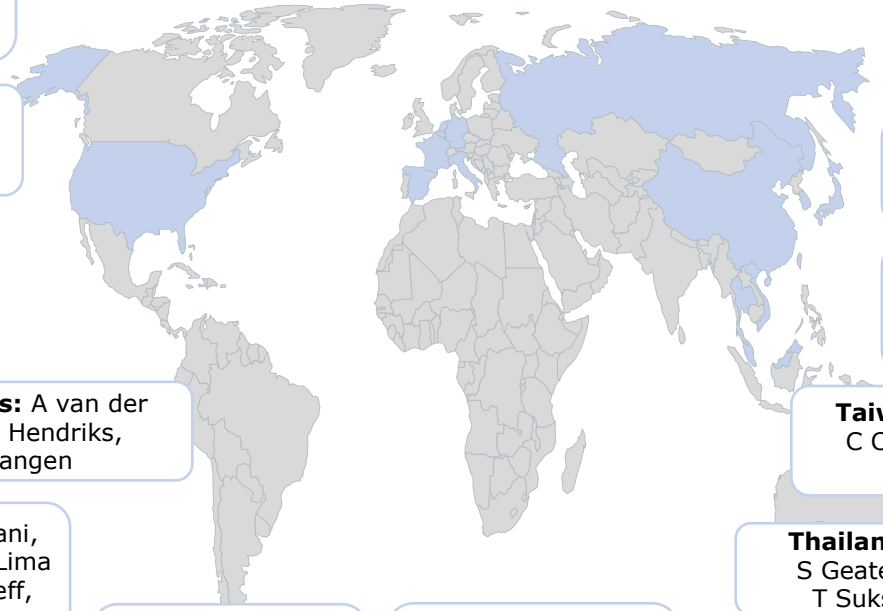

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Abbreviations

1L	first line
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BOR	best overall response
CEP7	centromere of chromosome 7
CR	complete response
CI	confidence interval
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal derived growth factor
*EGFR*m	*EGFR* mutant
FISH	fluorescence *in situ* hybridization
GCN	gene copy number
HRQoL	health-related quality of life
IRC	independent review committee
LBx	liquid biopsy
m	median
MET	mesenchymal–epithelial transition factor
*MET*amp	*MET* amplification
ne	not estimable
NGS	Next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
QD	once daily
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SOLD	Sum of longest diameters
TBx	tissue biopsy
TRAE	treatment-related adverse event

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