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# ctDNA dynamics, prognostic markers and resistance mechanisms in tepotinib-treated *MET*ex14 skipping NSCLC in the VISION trial

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# Tepotinib in the VISION trial

- *MET*ex14 skipping is an oncogenic driver in 3–4% of NSCLCs[1,2]
- Tepotinib, a highly selective MET TKI, is approved in multiple countries for treatment of advanced/metastatic *MET*ex14 skipping NSCLC based on the outcomes of the VISION study (NCT02864992)[3–5]
- VISION allowed enrolment based on TBx and/or LBx detection of *MET*ex14 skipping[3–5]
- Using LBx samples from VISION, we investigated:
  - Circulating MET-related protein markers (HGF and soluble MET)[6,7]
  - Genomic alterations in ctDNA at baseline
  - Dynamics of *MET*ex14 VAF changes on treatment
  - Potential resistance mechanisms

## Clinical efficacy of tepotinib[5]

| Efficacy outcomes (IRC) | Overall (N=313) | 1L (n=164) | 1L T+ (n=111) |
|---|---|---|---|
| ORR, % (95% CI) | 51.4 (45.8, 57.1) | 57.3 (49.4, 65.0) | 58.6 (48.8, 67.8) |
| mDOR, months (95% CI) | 18.0 (12.4, 46.4) | 46.4 (13.8, ne) | 46.4 (15.2, ne) |
| mPFS, months (95% CI) | 11.2 (9.5, 13.8) | 12.6 (9.7, 17.7) | 15.9 (11.0, 49.7) |
| mOS, months (95% CI) | 19.6 (16.2, 22.9) | 21.3 (14.2, 25.9) | 29.7 (18.8, ne) |

Abbreviations defined on last slide.

1. Le X and Heymach JV. *Oncologist.* 2020;25(10):822–825; 2. Hong L, et al. *Ther Adv Med Oncol.* 2021;13:1758835921992976; 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. Mazieres J, et al. *JAMA Oncol.* 2023:e231962; 6. Ujiie H, et al. *Anticancer Research.* 2012;32(8):3251–3258; 7. Le Fu, et al. *Biomarkers.* 2013;18(2):126–135.

# Biomarker analyses: Methods

| | Baseline | Every 6 weeks during treatment | End of treatment |
|---|---|---|---|
| | **Baseline profiles** | **Paired baseline and on-treatment profiles** | **Progression profiles** |
| **HGF/ soluble MET (ELISA)** | • HGF (**N=233**) and soluble MET (**N=245**) levels | • Relative change from baseline in soluble MET (**N=244**) | |
| **ctDNA (NGS Guardant360®; Guardant Health)** | • *MET*ex14 skipping LBx status (i.e. L+ by GH360 [n=114] or L– by GH360/T+ [n=51]) (**N=165**)<br>• Concomitant mutations, amplifications, and fusions (**N=165**) | • *MET*ex14 VAF dynamics, including on-treatment response:<br>– **Undetectable:** L–/T+ patients who remained L– in two consecutive early on-treatment samples (**N=38**)<br>– **Molecular Response:** *MET*ex14 VAF >75% depletion from baseline in two consecutive on-treatment samples (**N=65**)<br>– **Molecular Progression:** *MET*ex14 VAF increase from baseline in ≥1 of two consecutive on-treatment samples (**N=12**) | • End of treatment samples (**N=73**)<br>• Resistance mechanisms in post-progression samples (**N=55**) |

- Outcomes per IRC assessment were evaluated according to biomarker status (data cut-off: November 20, 2022)
- GH360 73-gene panel includes key oncogenic and tumor suppressor alterations: ***MET*** (exon 14 skipping, amplification, secondary resistance mechanisms), ***EGFR*** (mutation, amplification), ***ERBB2*** (mutation), ***BRAF*** (mutation), ***KRAS/NRAS/HRAS*** (mutation, *KRAS* amplification), ***PIK3CA*** (mutation), ***PTEN*** (mutation), ***NF1*** (mutation), ***RB1*** (mutation), ***TP53*** (all non-silent mutations), ***ALK/ROS1/RET*** (fusions)

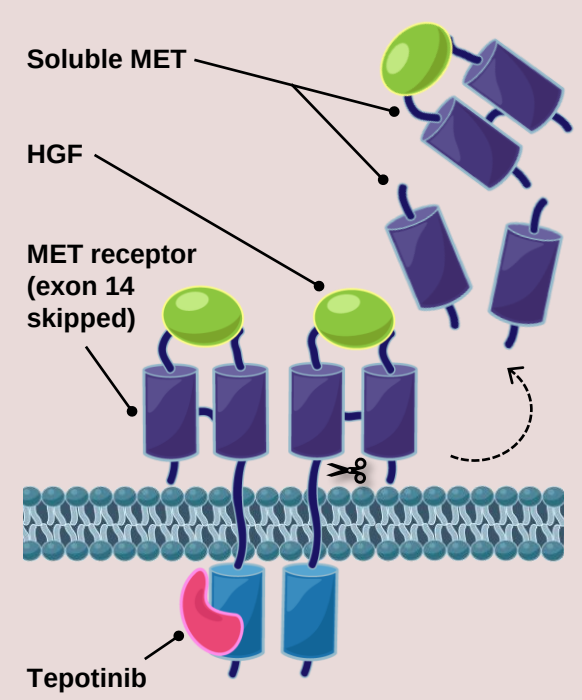
Abbreviations defined on last slide.

# Baseline HGF and soluble MET

Potential biomarkers of response or resistance to MET inhibitors:[2,3]

- **HGF**: the MET ligand
- **Soluble MET:** generated by proteolytic cleavage, associated with MET levels

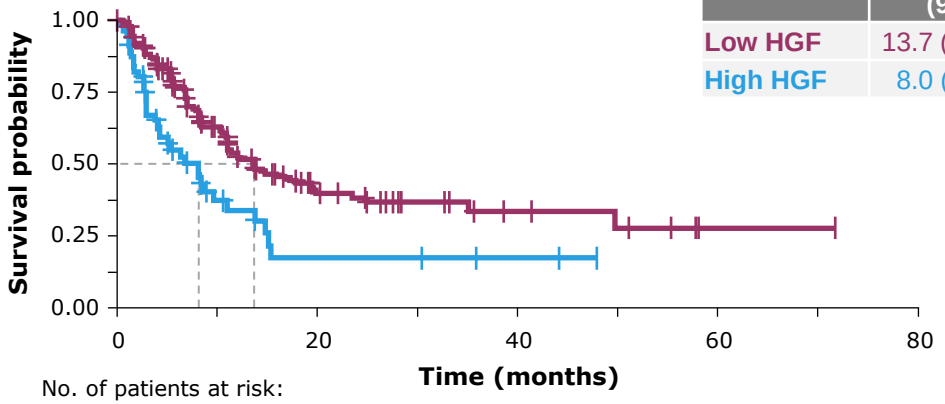
## MET receptor[1]




- Baseline HGF and soluble MET levels did not differ by treatment line, race, or age
- Lower baseline HGF levels were associated with better PFS and OS; no difference in ORR

## PFS by baseline HGF levels

| | mPFS, months (95% CI) |
|---|---|
| Low HGF | 13.7 (11.0, 19.7) |
| High HGF | 8.0 (4.1, 11.0) |




No. of patients at risk:

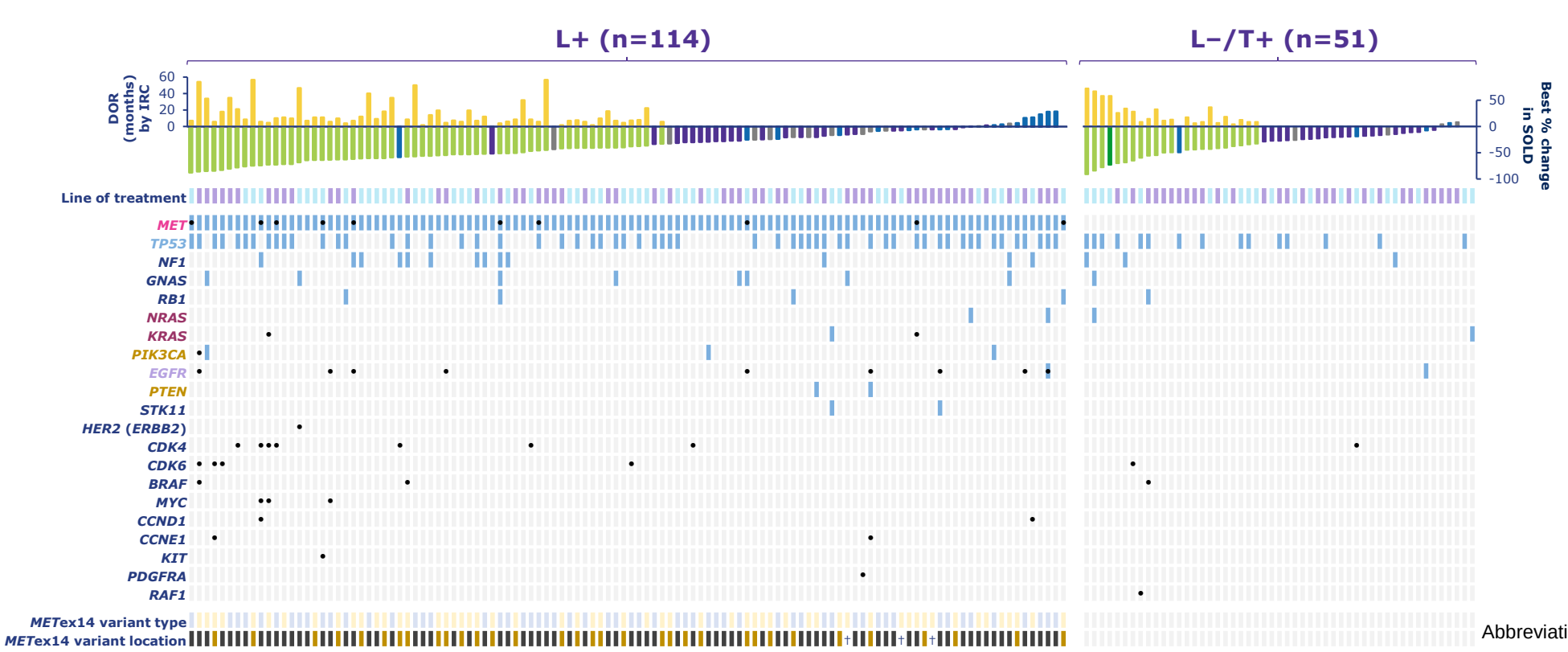
| | | | | | |
|---|---|---|---|---|---|
| Low HGF (≤upper quartile) | 175 | 32 | 7 | 1 | 0 |
| High HGF (>upper quartile) | 58 | 4 | 2 | 0 | 0 |

- Low relative on-treatment change* in soluble MET was associated with better ORR, PFS, and OS

Abbreviations defined on last slide.
*Relative change <1 indicates a decrease from baseline, while >1 indicates an increase from baseline.
1. Adapted from Albers J, et al. *Mol Cancer Ther*. 2023;22(7):833–843 under a Creative Commons CC BY license;
2. Ahn SY, et al. *Anticancer Res*. 2017;37(3):1127–1138; 3. Moosavi F, et al. *Crit Rev Clin Lab Sci*. 2019;56(8):533–566.

# Baseline ctDNA profiling in the VISION trial

- *MET* amplification in 10/114 L+ patients (8.8%), no *MET* kinase domain mutations detected
- No *ALK*, *ROS1* or *RET* fusions or *BRAF* mutations detected, *TP53* mutations were common 58/114 (50.9%)

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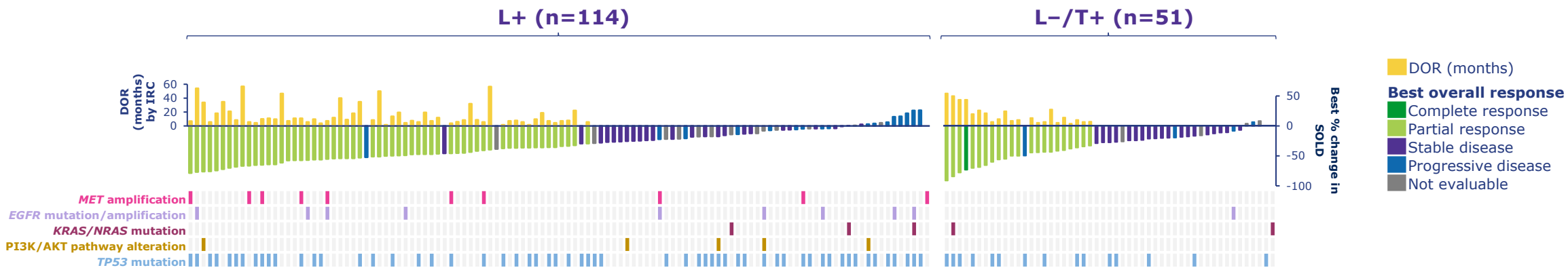
# Baseline co-occurring alterations: Association with outcomes




***MET* amplification (n=10):**
7 responses (70%)

***EGFR* mutation/amplification (n=10):**
4 responses (40%)

***EGFR* mutations:**
L858R (n=1), T790M (n=1)

***EGFR* amplification** (n=9)

***KRAS/NRAS* mutation (n=5):**
1 response (20%)

***KRAS* mutations:**
G12C (n=1), G12R (n=1)

***NRAS* mutations:**
G12D (n=2), G13C (n=1)

**PI3K/AKT pathway alterations (n=5):**
1 response (20%)

***PIK3CA* activating mutations:**
E545K (n=1), P471L (n=1), N1044K (n=1)

***PTEN* inactivating mutations:**
Q171* (n=1), P244fs (n=1)

***TP53* mutation:** comparable ORR but trend for shorter PFS and OS versus wild-type, as seen in other NSCLC subtypes[1,2]

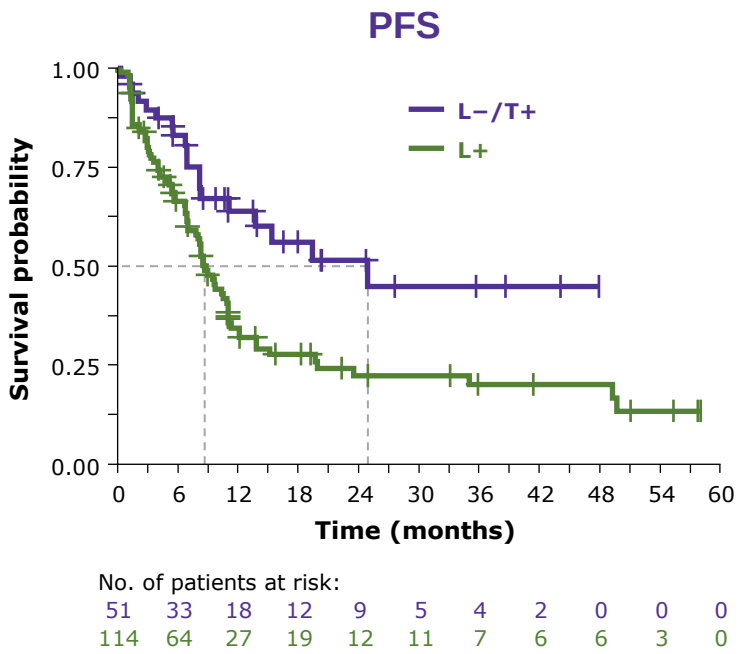
Abbreviations defined on last slide.

1. Skoulidis F, et al. *Nat Rev Cancer*. 2019;19(9):495–509; 2. Robles AI and Harris CC. *Cold Spring Harb Perspect Biol*. 2010;2(3):a001016.

# Baseline L−/T+ versus L+ association with outcomes

- Among 165 patients with baseline LBx NGS profiles, 114 were L+* and 51 were L−/T+ for *MET*ex14
- ORR was comparable, but mDOR and mPFS were longer in L−/T+ versus L+ patients
  - Better outcomes in L−/T+ patients may reflect lower ctDNA shedding due to lower tumor burden

| | L−/T+ (n=51) | L+ (n=114) |
|---|---|---|
| **Baseline tumor burden** | | |
| Median SOLD, mm | 52.1 | 64.8 |
| Patients with ≥3 target lesions, % | 11.8 | 27.2 |
| Patients with ≥3 non-target lesions, % | 29.4 | 45.6 |
| **Efficacy** | | |
| ORR, % (95% CI) | 43.1 (29.3, 57.8) | 50.9 (41.3, 60.4) |
| mDOR, months (95% CI) | 20.8 (7.0, ne) | 10.8 (8.4, 33.6) |
| mPFS, months (95% CI) | 24.9 (11.1, ne) | 8.6 (7.0, 11.0) |
| mOS, months (95% CI) | 23.6 (15.6, ne) | 19.1 (13.1, 22.9) |




*TBx *MET*ex14 results in L+ population (n=114): no sample taken (n=39), NE/NA (n=32), T+ (n=38), T– (n=5). Abbreviations defined on last slide.

# ctDNA dynamics: Undetectable *MET*ex14 skipping and molecular response are associated with better clinical outcomes

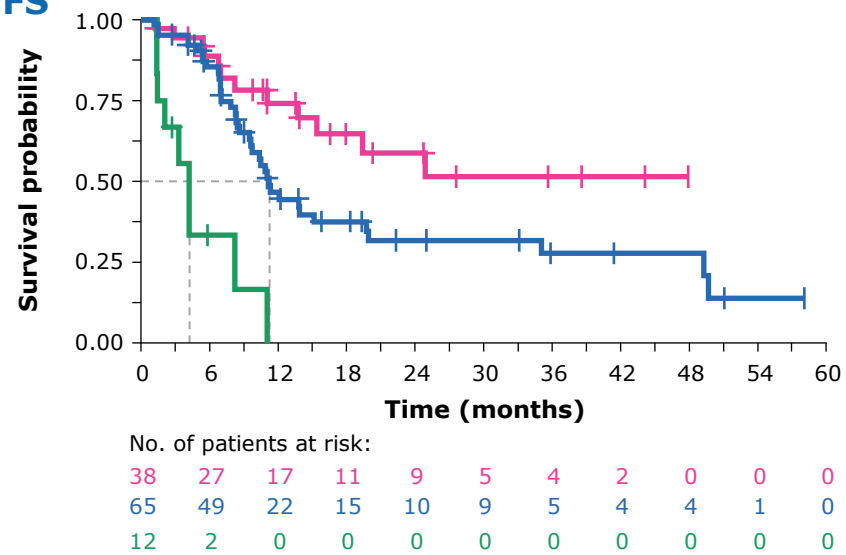
Patients with baseline and two consecutive early on-treatment samples (n=119)

Neither molecular response nor molecular progression
(n=4; 3.4%)
VAF decrease <75%

| | Undetectable (n=38; 31.9%) | Molecular response (n=65; 54.6%) | Molecular progression (n=12; 10.1%) |
|---|---|---|---|
| ORR, % (95% CI) | 47.4 (31.0, 64.2) | 63.1 (50.2, 74.7) | 16.7 (2.1, 48.4) |
| mDOR, months (95% CI) | ne (8.3, ne) | 18.5 (9.0, 46.4) | 6.2 (4.1, ne) |
| mPFS, months (95% CI) | ne (13.7, ne) | 11.2 (9.5, 19.7) | 4.2 (1.4, 8.2) |
| mOS, months (95% CI) | 32.5 (17.1, ne) | 23 (18.8, 28.5) | 18.5 (5.0, 29.7) |

Abbreviations defined on last slide.

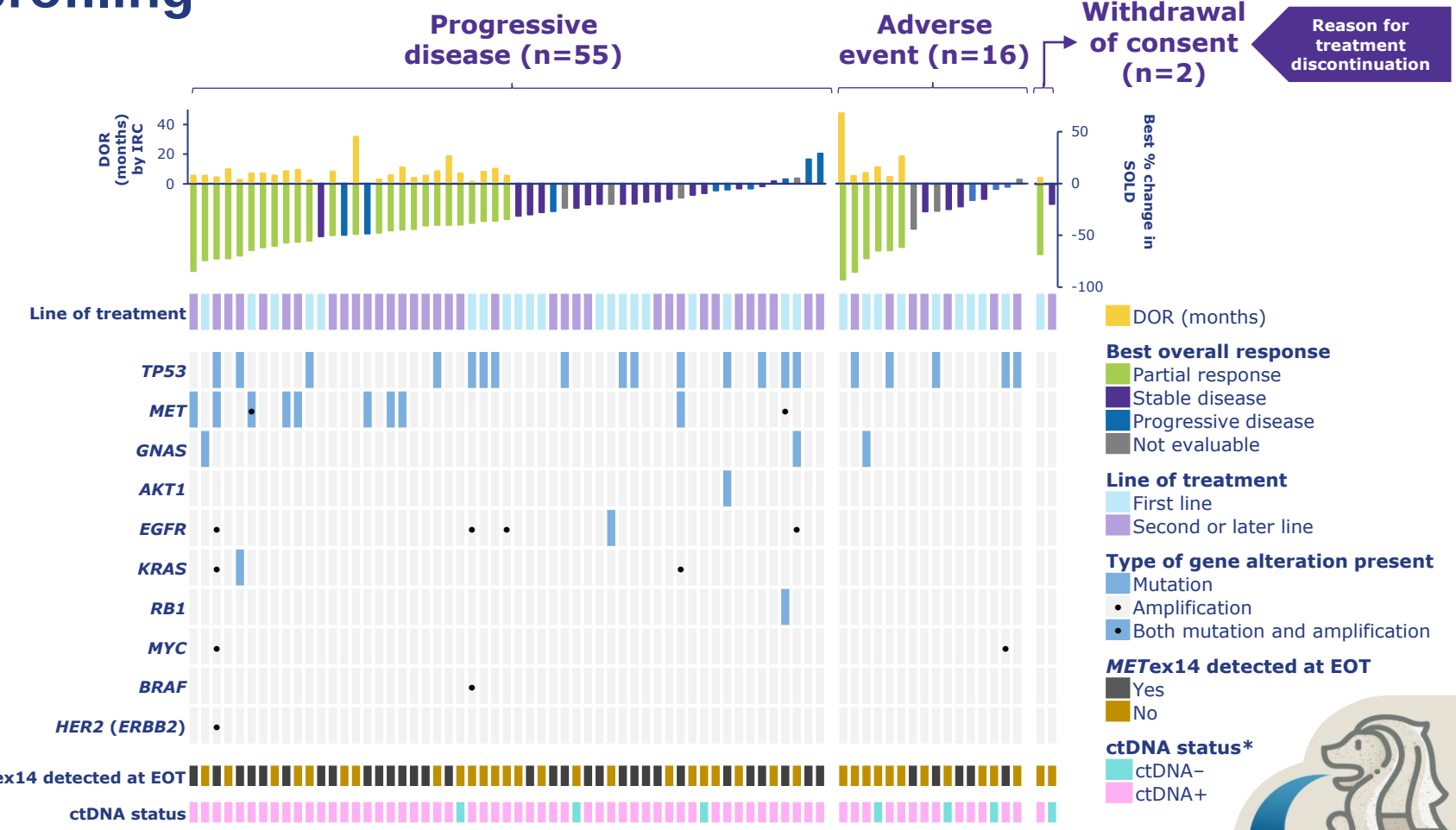
**PFS**




- **Undetectable:** L–/T+ patients who remained L– in two consecutive early on-treatment samples
- **Molecular response:** *MET*ex14 VAF >75% depletion from baseline confirmed in two consecutive on-treatment samples
- **Molecular progression:** *MET*ex14 VAF increase from baseline in ≥1 of two consecutive on-treatment samples

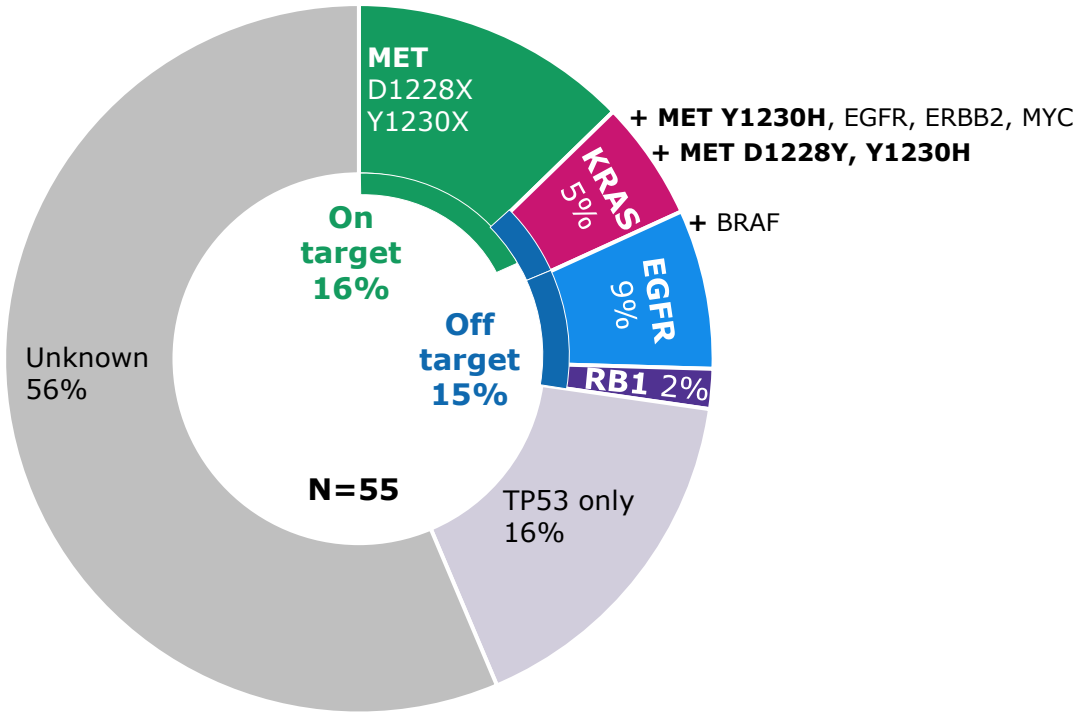
# End of treatment ctDNA profiling

- Among 73 patients with end of treatment samples, 55 had post-progression samples
- Among 55 patients with post-progression ctDNA data, 52 had any positive ctDNA detection, 31 had *MET*ex14 skipping detection
- Largest post-progression ctDNA cohort for evaluating MET TKI resistance in *MET*ex14 skipping NSCLC to date




Abbreviations defined on last slide.
*Samples with no detected variant were defined as ctDNA– and samples with ≥1 detected variant were defined as ctDNA+. Variants flagged as germline by the vendor and variants without COSMIC identifiers were excluded, except for *MET*ex14 variants, which were included irrespective of COSMIC identifiers.

# Resistance mechanisms to tepotinib in *MET*ex14 skipping NSCLC in VISION




- Secondary *MET* mutations (9/55, 16.4%)
- Acquired bypass pathway activation (8/55, 14.5%) was observed (*KRAS*, *EGFR*, *MYC*, *BRAF*, *RB1*, and *ERBB2* alterations)
- Some tumors had both *MET* kinase domain mutation and bypass activation => resistance heterogeneity

| *MET* resistance mutations | BOR | PFS, months |
|---|---|---|
| D1228N | PR | 13.9 |
| D1228N | PR | 11.2 |
| D1228G | PR | 10.6 |
| D1228H | PR | 8.3 |
| Y1230C | PR | 6.9 |
| Y1230C | PR | 6.9 |
| Y1230H | PR | 5.7 |
| D1228H/Y, Y1230C/H | PD | 2.7 |
| D1228Y, Y1230H | NE | 2.7 |

Abbreviations defined on last slide.

# Conclusions

- These VISION analyses provide the largest on-treatment LBx biomarker dataset for a MET inhibitor in *MET*ex14 NSCLC
- Low baseline HGF and low relative on-treatment change in soluble MET were associated with better outcomes
- In the *MET*ex14 skipping population, L+ was associated with similar ORR but potentially shorter PFS than L–/T+ status
- Patients whose ctDNA remained undetectable for *MET*ex14 during treatment and those who attained confirmed molecular response had improved outcomes, supporting LBx for monitoring response and resistance
- Secondary *MET* mutations and bypass pathway activation were potential mechanisms of tepotinib resistance

**In patients with *MET*ex14 skipping NSCLC receiving tepotinib, undetectable *MET*ex14 skipping in LBx at baseline may define a more favorable treatment outcome.**

**LBx may also enable monitoring of response and resistance, with a view towards refining the therapeutic approach to improve patient outcomes**

Abbreviations defined on last slide.

# Acknowledgements

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# Abbreviations

| | |
|---|---|
| ALK | anaplastic lymphoma kinase |
| BOR | best overall response |
| BRAF | B-rapidly accelerated fibrosarcoma |
| ctDNA | circulating cell-free tumor DNA |
| CI | confidence interval |
| DOR | duration of response |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EOT | end of treatment |
| HGF | hepatocyte growth factor |
| IRC | independent review committee |
| KRAS | Kirsten rat sarcoma viral oncogene homolog |
| L+/− | positive/negative liquid biopsy for *MET*ex14 skipping |
| LBx | liquid biopsy |
| m | median |
| MET | mesenchymal–epithelial transition factor |
| *MET*ex14 | *MET* exon 14 |
| NA | not available |
| NE | not evaluable |
| ne | not estimable |
| NGS | next-generation sequencing |
| NRAS | neuroblastoma RAS viral oncogene homolog |
| NSCLC | non-small cell lung cancer |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PI3K | phosphoinositide 3-kinase |
| PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha |
| PFS | progression-free survival |
| PR | partial response |
| PTEN | phosphatase and tensin homolog |
| RET | rearranged during transfection |
| ROS1 | c-ros oncogene 1 |
| SOLD | sum of longest diameters |
| T+/− | positive/negative tissue biopsy for *MET*ex14 skipping |
| TBx | tissue biopsy |
| TKI | tyrosine kinase inhibitor |
| TP53 | tumor protein p53 |
| VAF | variant allele frequency |