# Detection of *MET* amplification (*MET*amp) in patients with *EGFR* mutant (m) NSCLC after first-line (1L) osimertinib

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## CONCLUSIONS

- **In this large comprehensive analysis of INSIGHT 2 prescreening data, FISH$^+$ *MET*amp was detected in ~50% of patients progressing on 1L osimertinib, while LBx NGS$^+$ *MET*amp was detected in only 11.7% of patients**
- **Therefore, *MET*amp, which is a common mechanism of resistance after 1L osimertinib,[1–3] can frequently go undetected using NGS alone**
  - **Given the high specificity but low sensitivity of LBx NGS, a negative NGS *MET*amp result should be confirmed by FISH**
  - **FISH and NGS are complementary assays and should ideally be performed at the time of progression to support treatment decisions**
- **FISH allows optimal identification of *MET*amp after 1L osimertinib, can be delivered in a clinically meaningful timeframe, and may allow more patients to benefit from an oral MET inhibitor**

## INTRODUCTION

- *MET*amp is a common mechanism of resistance to osimertinib[1–3]
- Although NGS (either LBx or TBx) is frequently used to detect *MET*amp, FISH is still considered the current gold-standard[4–7]
  - The reported prevalence of *MET*amp in patients with *EGFR*m NSCLC after treatment with osimertinib is generally lower with NGS of TBx or LBx samples compared with TBx FISH (**Table S1**)[6]
- INSIGHT 2 is an international, open-label, Phase II study of tepotinib + osimertinib in patients with advanced/metastatic *EGFR*m NSCLC with *MET*amp and acquired resistance to 1L osimertinib[6]

Please see INSIGHT 2 Poster Discussion by **Tan et al. (Abstract 9021)** in this same session at ASCO 2023

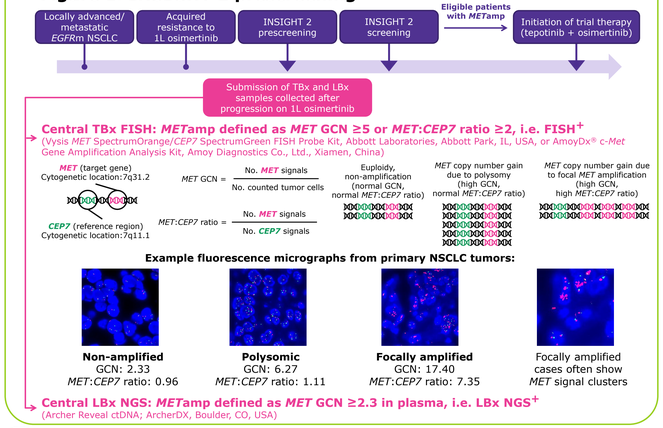
- INSIGHT 2 eligibility was based on detection of *MET*amp by TBx FISH and/or LBx NGS
  - We report **a large comprehensive analysis of *MET*amp detected by TBx FISH and/or LBx NGS after 1L osimertinib** during prescreening for INSIGHT 2 (data cut-off: September 26, 2022)

## METHODS

- To be eligible for INSIGHT 2 (NCT03940703), patients progressing on 1L osimertinib were required to have *MET*amp, as determined by central or local TBx FISH or central LBx NGS (**Figure 1**)
- All patients were required to submit tumor tissue (TBx) and a blood sample (LBx), each obtained after progression on 1L osimertinib, which were used for central *MET*amp testing

## METHODS

**Figure 1. INSIGHT 2 prescreening**

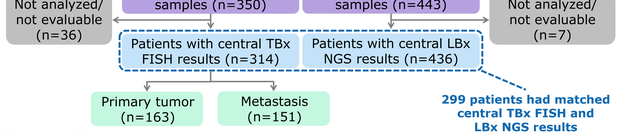



## RESULTS

### Patients and samples

- Of 472 patients prescreened between July 2020 and September 2022, 64% were female, 57% were Asian, and 97% had adenocarcinoma
- *MET*amp results were available for 314 TBx and 436 LBx samples (**Figure 2**)

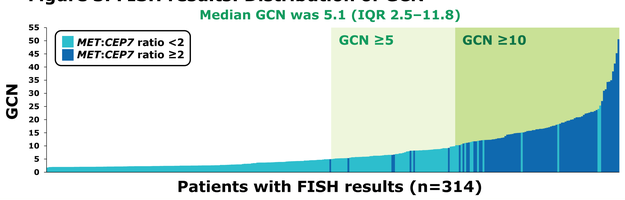
**Figure 2. Patient flow during prescreening**




### FISH *MET*amp results

- FISH$^+$ *MET*amp (GCN ≥5 and/or *MET*:*CEP7* ratio ≥2) was detected in 159/314 patients (50.6%) (**Figure 3**)
- In 159 FISH$^+$ patients:
  - Median GCN was 11.8 (range 5.0–50.6). 158/159 patients (99.4%) had GCN ≥5 and one patient had GCN 4.96
  - Median *MET*:*CEP7* ratio was 2.3 (range 0.8–12.7). 85/159 patients (53.5%) had *MET*:*CEP7* ratio ≥2 and 74/159 (46.5%) had *MET*:*CEP7* <2
- High-level *MET*amp was detected in 90/314 patients (28.7%) based on GCN ≥10 and 53/314 (16.9%) based on *MET*:*CEP7* ratio ≥4

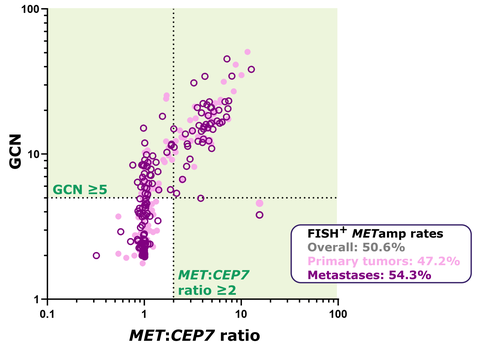
**Figure 3. FISH results: Distribution of GCN**




## RESULTS

- Mean FISH turnaround time from shipment to results was 6.8 business days
- FISH$^+$ rates were similar in samples taken from primary tumors (77/163, 47.2%) or metastases (82/151, 54.3%) (**Figure 4**)
- Metastatic site samples included liver (n=34), pleura (n=21), lung (n=20), lymph nodes (n=19), and bone (n=14)

**Figure 4. FISH result according to source of TBx (primary tumor or metastasis)**




Shaded quadrants indicate FISH$^+$ samples.

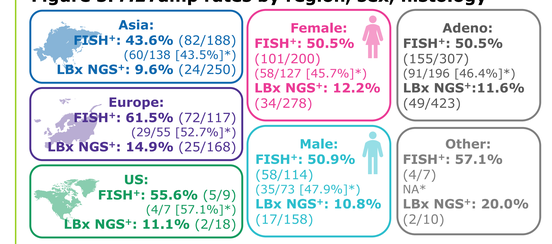
### LBx NGS *MET*amp results

- Overall, LBx NGS$^+$ *MET*amp was detected in 51/436 patients (11.7%)
- Mean LBx NGS turnaround time from sample collection to reporting (including shipment) was 11 business days

### *MET*amp rates by patient characteristics

- Similar *MET*amp rates by region, sex, and histology (**Figure 5**)

**Figure 5. *MET*amp rates by region, sex, histology**




*FISH$^+$ rates for sites without reported local FISH prescreening for *MET*amp.

### Local prescreening activity

- When limited to sites without reported local prescreening by FISH, the FISH$^+$ *MET*amp rate was 46.5% (93/200) overall; rates by patient characteristics are shown in **Figure 5**
- Concordance of *MET*amp classification between central and local FISH was high (91.8%; 45/49 samples; **Table S2**)
- Analyses of local detection of *MET*amp by methods other than FISH are ongoing

### *MET*amp in patients with both FISH and LBx NGS

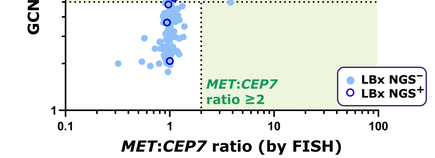
- 299 patients had matched central FISH and LBx NGS results, of whom 152 (50.8%) were FISH$^+$ and 38 (12.7%) were LBx NGS$^+$
- LBx NGS identified *MET*amp with high specificity (negative percentage agreement 98.0%) but low sensitivity (positive percentage agreement 23.0%) compared with FISH (**Table 1**)
  - 3/38 (7.9%) LBx NGS$^+$ samples were FISH$^-$
  - 117/152 (77.0%) FISH$^+$ samples were LBx NGS$^-$

**Table 1. Concordance of central FISH and LBx NGS results (n=299)**

| | FISH$^+$ | FISH$^-$ |
|---|---|---|
| LBx NGS$^+$ | 35 | 3 |
| LBx NGS$^-$ | 117 | 144 |

- LBx NGS$^+$ identified mostly (30/38 [78.9%]) *MET*amp that had focal amplification (*MET*:*CEP7* ratio ≥2) and higher GCN (≥10) by FISH (**Figure 6**)

**Figure 6. *MET*amp LBx NGS result according to FISH GCN and *MET*:*CEP7* ratio (matched samples)**




Shaded quadrants indicate FISH$^+$ samples.

### ORR to tepotinib + osimertinib

- ORR with tepotinib + osimertinib was 43.9% (95% CI: 33.9, 54.3) in 98 patients with FISH$^+$ and 51.6% (95% CI: 33.1, 69.8) in 31 patients with LBx NGS$^+$ *MET*amp

Please see INSIGHT 2 Poster Discussion by **Tan et al. (Abstract 9021)** in this same session at ASCO 2023

### *EGFR* mutation in patients with *MET*amp

- Among prescreened patients with FISH$^+$ and/or LBx NGS$^+$ *MET*amp, sensitizing *EGFR* mutations were detected in 99/141 patients (70.2%) with available results from Archer RUO NGS

### LBx NGS *MET*amp results from Protocol v1.0

- Before an amendment (April 2020), INSIGHT 2 prescreened patients using only LBx NGS (without FISH)[6]
- Of 599 patients prescreened with Protocol v1.0, 594 provided LBx samples, of which 589 were analyzed
- The rate of LBx NGS$^+$ *MET*amp was 4.9% (29/589) overall, 3.8% (18/472) in Asia, 7.7% (7/91) in Europe, and 15.4% (4/26) in the US

**Abbreviations:** 1L, first line; *CEP7*, centromere of chromosome 7; CI, confidence interval; *EGFR*m, *EGFR* mutant; FISH$^-$, negative for *MET* amplification by fluorescence *in situ* hybridization; FISH, fluorescence *in situ* hybridization; FISH$^+$, positive for *MET* amplification by fluorescence *in situ* hybridization; GCN, gene copy number; IQR, interquartile range; LBx, liquid biopsy; *MET*amp, *MET* amplification; NA, not applicable; NGS$^-$, negative for *MET* amplification by next-generation sequencing; NGS, next-generation sequencing; NGS$^+$, positive for *MET* amplification by next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; RUO, research use only; TBx, tissue biopsy.

**References:** 1. Leonetti A, et al. *Br J Cancer*. 2019;121(9):725–737; 2. Wang Y, et al. *Lung Cancer*. 2018;118:105–110; 3. Hartmaier RJ, et al. *Cancer Res*. 2019;79(Suppl. 13):Abstract 4897; 4. Heydt C, et al. *Comput Struct Biotechnol J* 2019;17:1339–1347; 5. Peng L, et al. *J Thorac Oncol*. 2021;16(3):S669; 6. Smit EF et al. *Future Oncol*. 2022;18(9):1039–1054; 7. Savic S, et al. *Arch Pathol Lab Med* 2016;140(12):1323–1330.

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**Supplementary materials**