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Analysis of MET Amplification (*MET*amp) with FISH and NGS Methods in SACHI Trial

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BACKGROUND

- *MET*amp is widely recognized as one of the key mechanisms of acquired resistance to EGFR-TKI therapy in EGFR-mutated non-small cell lung cancer (NSCLC) patients (pts) [1,2]. Therapeutic strategies targeting MET have therefore emerged as important avenues for overcoming this resistance mechanism.
- Savolitinib is a highly selective oral MET tyrosine kinase inhibitor [3].
- In the Phase 3 SACHI trial (NCT05015608), savolitinib (savo) plus osimertinib (osi) significantly improved mPFS versus standard chemotherapy (pemetrexed plus carboplatin/cisplatin) in pts with *MET*amp NSCLC who had progressed on prior EGFR-TKI treatment. Based on these compelling clinical outcomes, this combination therapy (savo+osi) was approved by NMPA in June 2025.
- Here, using SACHI baseline tumor tissue and ctDNA samples, we evaluated the concordance between Fluorescence in Situ Hybridization (FISH) and Next Generation Sequencing (NGS) in detecting *MET*amp. Furthermore, we analyzed clinical efficacy in NGS-profiled pts enrolled in the SACHI study, with tumor responses evaluated by investigators according to RECIST 1.1 criteria.

METHODS

Study design and tumor/ctDNA collection for *MET*amp analysis

Key eligibility criteria
- Unresectable or metastatic NSCLC
- EGFRm, PD on first-line EGFR-TKI
  - For pts progress on 1st/2nd generation (G) EGFR-TKI, EGFR-T790M negative is required;
- *MET*amp by FISH in central lab
- ECOG PS 0-1

→ **Savolitinib** 600 mg (BW≥50kg) or 400 mg (BW<50 kg) QD, **+ Osimertinib** 80 mg QD, N = 106

→ **Platinum + Pemetrexed** 4~6 cycle, then Pemetrexed maintenance, N = 105

→ Until PD or intolerable toxicity

Primary endpoint:
PFS assessed by investigator review (RECIST v1.1)

- Baseline tumor samples underwent *MET*amp screening via FISH as eligibility assessment.
- A portion of baseline tumor samples underwent NGS testing with subsequent *MET*amp analysis in comparison with FISH.
- 10 mL peripheral blood was collected at baseline for randomized pts.

*MET*amp criteria by FISH

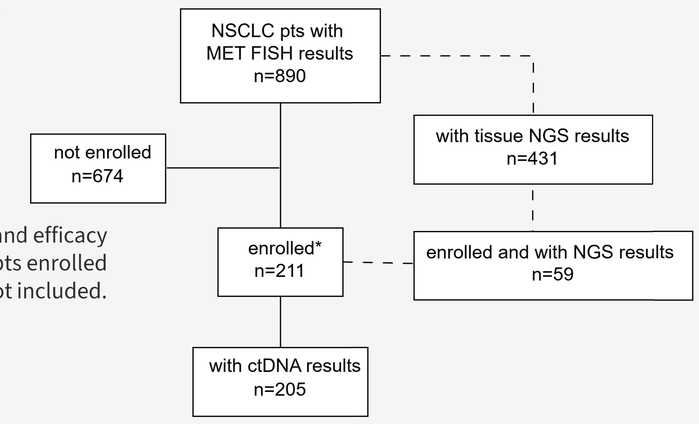
- *MET*amp in tumor tissue by FISH was defined as MET gene copy number (GCN)≥5 or MET/CEP7≥2 for pts treated with prior 1st/2nd generation (G) EGFR-TKIs, and MET GCN≥10 for those with prior 3rd generation EGFR-TKIs, using AmoyDx c-Met Gene Amplification Kit. MET GCN was categorized as <5, 5-10, or ≥10 by FISH for concordance comparison with NGS.

NGS sequencing and analysis

- DNA extraction and sequencing: DNA was isolated from tumor tissue using MagPure FFPE LQ Kit (Magen), and NGS was performed using panel OncoCompass 68-gene panel (Burning Rock).
- ctDNA extraction and sequencing: ctDNA was isolated from the plasma using QIAamp circulating nucleic acid Kit (QIAGEN), and NGS was performed using panel OncoCompass Target ctDNA 168-gene panel (Burning Rock).
- *MET*amp analysis in NGS: The process begins with standardization of sequencing, followed by correction of biases introduced by GC content and probe design. A genomic region is identified as exhibiting copy number variation (CNV) if its coverage data significantly deviates both quantitatively and statistically from a baseline established using a set of CNV-negative samples. The cutoff of gene amplification for CN is set at ≥2.25.

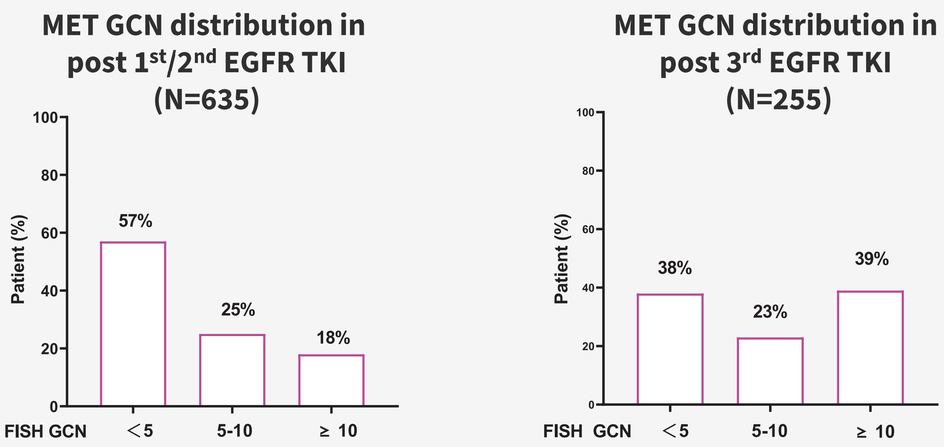
RESULTS

Patients disposition



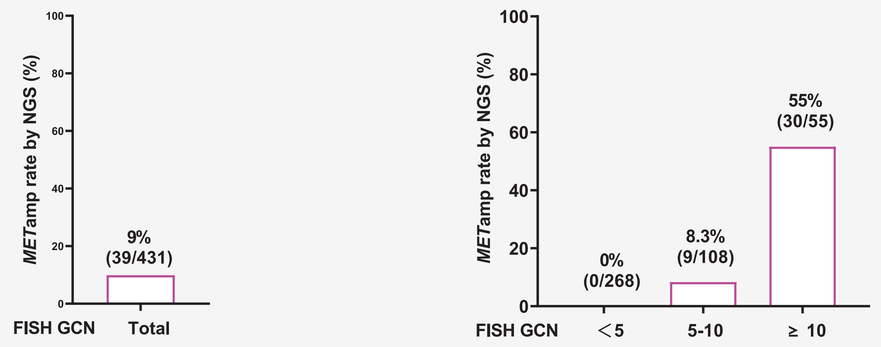
*The cut-off date for enrollment and efficacy analysis was Aug 30, 2024. 5 pts enrolled afterward were not included.

*MET*amp prevalence by FISH in EGFR-TKI resistant NSCLC patients



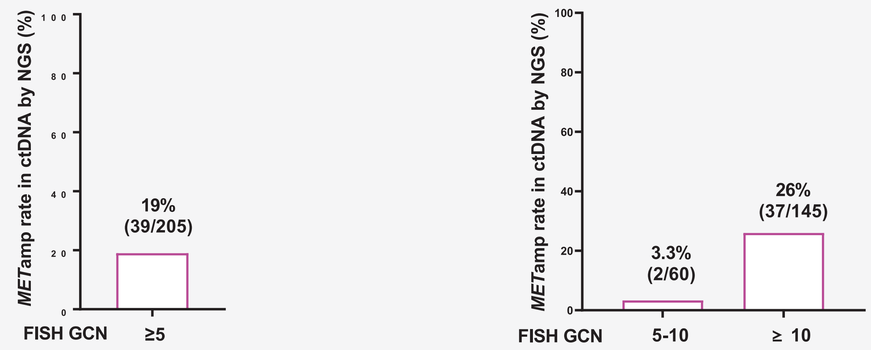
- *MET*amp was detected by FISH in 43% (272/635) of pts with 1st/2nd G EGFR-TKI-resistance and in 39% (99/255) of pts with 3rd G EGFR TKI-resistance.
- High-level *MET*amp (GCN≥10) were enriched in 3rd G EGFR TKI-resistant pts. The proportions of MET GCN≥10 is 39% in 3rd G EGFR TKI-resistant pts while 18% in 1st/2nd G EGFR TKI-resistant pts.

*MET*amp prevalence by tissue NGS in EGFR-TKI resistant NSCLC (N=431)



- In 431 pts with NGS results, the **overall *MET*amp rate by NGS was 9%** (39/431). *(Left Figure)*
- NGS detection rates of *MET*amp demonstrated a tiered correlation with FISH-quantified GCN: **0% (GCN≤5)**, **8.3% (5<GCN<10)**, and **55% (GCN≥10)**. *(Right Figure)*

*MET*amp prevalence in ctDNA among enrolled patients (N=205)

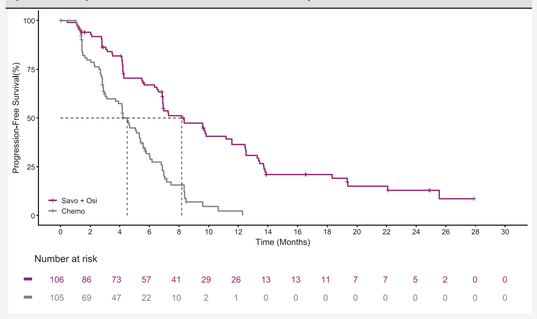


- In enrolled 205 pts with ctDNA NGS data, the **overall *MET*amp rate in ctDNA by NGS was 19%**. *(Left Figure)*
- *MET*amp detection rate in ctDNA elevated with FISH quantified GCN: **3.3% (5≤ GCN<10)** and **26% (GCN≥10)**. *(Right Figure)*

Therapeutic outcomes by NGS (ITT vs *MET*amp)

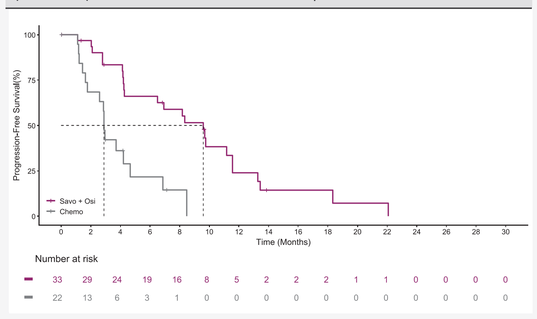
ITT population (N=211)

	Savo + Osi (N=106)	Chemo (N=105)
mPFS (95% CI), months	**8.18 (6.90 – 11.17)**	4.50 (3.02 – 5.39)
Stratified HR (95% CI)	**0.34** (0.23-0.49) $p < 0.0001$	



NGS *MET*amp population (N=55)

	Savo + Osi (N=33)	Chemo (N=22)
mPFS (95% CI), months	**9.59 (4.24 – 11.56)**	2.89 (1.64 – 4.67)
Stratified HR (95% CI)	**0.26** (0.12-0.54) $p < 0.001$	



- In SACHI ITT population, savo+osi combination demonstrated a clinically significant **3.68-month of ΔmPFS versus chemotherapy** (hazard ratio [HR]=0.34, p<0.0001). *(Left Figure)*
- In the enrolled pts with NGS data available, 55 pts were *MET*amp positive in either tumor tissue or ctDNA samples.
- Among the 55 pts with *MET*amp in NGS and FISH, pts treated with savo+osi demonstrated **6.70-month of ΔmPFS versus chemotherapy**. *(Right Figure)*

CONCLUSIONS

- **FISH-based *MET*amp detection demonstrated superior sensitivity compared to NGS in EGFR TKI-resistant NSCLC patients.**
- **Both tissue and plasma (ctDNA) based NGS demonstrated detectable *MET*amp rates exclusively in high-copy populations (GCN≥10), with positivity rates reaching 55% in tumor biopsies versus 26% in plasma.**
- **Savolitinib combined with osimertinib achieved superior median PFS compared to chemotherapy in patients with *MET*amp confirmed by both FISH and NGS.**

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CONFLICT OF INTEREST
Longhua Sun has nothing to declare.

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REFERENCES
1. Clin Cancer Res 19:2240-7 (2013)
2. Br J Cancer 121, 725–37 (2019)
3. J Med Chem 57: 7577–89 (2014)
4. JCO 43, LBA8505 (2025)