# *MET* amplification (amp) is a major resistance mechanism to osimertinib

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## BACKGROUND

- Osimertinib is a potent "third-generation" inhibitor of *EGFR* T790M, and is the standard treatment for patients with T790M-positive resistance to first-line EGFR tyrosine kinase inhibitors. In the randomized phase III AURA3 trial, T790M-positive patients treated with osimertinib had an ORR 71% and median PFS 10.1, both significantly improved over platinum-pemetrexed chemotherapy[1].
- To date, reported resistance mechanisms to osimertinib include *EGFR* C797S, *MET* or *ERBB2* amplification, *BRAF* mutations, small cell lung cancer (SCLC) transformation and others. In some cases, T790M "loss" is seen in previously T790M-positive cancers.
- Cancer heterogeneity plays an important role in resistance to third-generation EGFR TKIs[2]
- Larger cohorts of resistance to osimertinib and other T790M-specific EGFR inhibitors are needed.

## METHODS

- We analyzed 23 patients treated at Massachusetts General Hospital with acquired resistance to osimertinib.
- Patients received osimertinib on the phase I AURA trial, on the osimertinib Expanded Access Program or on a commercial basis.
- All patients underwent tissue biopsy and/or plasma circulating tumor DNA (ctDNA) analysis at the time of progression on osimertinib. For pts with both tissue and plasma, plasma results are included if within 90 days of post-osimertinib tissue biopsy.
- Tumor biopsies were analyzed by next-generation sequencing (NGS; SNaPshot, MGH) and Fluorescence *In Situ* Hybridization (FISH) for *MET* and *EGFR* amplification.
- Plasma ctDNA was analyzed by next-generation sequencing (Guardant360, Guardant Health.)
- We retrospectively collected patient characteristics including diagnosis and treatment history.

## RESULTS

### TABLE 1. PATIENT CHARACTERISTICS

| Characteristic | n=23 |
|---|---|
| Gender | 14F/9M |
| Median age at diagnosis | 59 years (43-81) |
| Median time (mos) on osimertinib to first biopsy | 10 mo (2-24) |
| T790M-positive prior to osimertinib start | 23 (100%) |
| - de novo | 2 (9%) |
| - acquired | 21 (91%) |
| *MET* amplified prior to osimertinib | 0/19 tested |

## RESULTS (cont'd)

### TABLE 2. OSIMERTINIB-RESISTANT TISSUE and ctDNA ANALYSIS

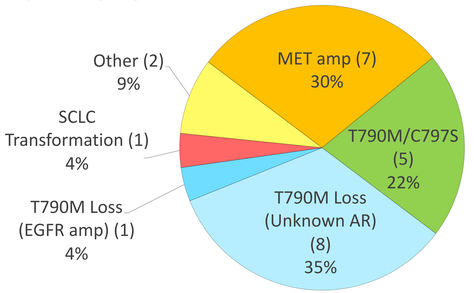
| Pt | EGFR mutation | # Prior Therapies | Prior 3rd gen TKI | TISSUE (NGS, FISH) | PLASMA ctDNA (NGS) |
|---|---|---|---|---|---|
| 1 | L858R | 1 | | *MET* amp, T790 WT | *MET* amp, T790M ND |
| 2 | Del19 | 1 | | - | T790M ND |
| 3 | Del19 | 2 | Y | - | T790M ND |
| 4 | L858R (de novo T790M) | 2 | Y | *MET* amp, *EGFR* amp T790M (germline) | - |
| 5 | L858R | 3 | Y | T790wt, *EGFR* amp | T790M ND |
| 6 | L858R | 4 | Y | T790 WT | T790M ND |
| 7 | Del19 | 3 | Y | - | T790M ND |
| 8* | Del19 | 3 | | T790M/C797S | T790M/C797S |
| 9 | L858R | 4 | Y | T790 WT | - |
| 10 | Del19 | 3 | Y | - | *PIK3CA* E545K, *PIK3CA* amp, T790M ND |
| 11 | Del19 | 2 | Y | *MET* amp, *EGFR* amp, T790 WT | T790M ND |
| 12 | Del19 | 2 | Y | - | T790M/C797S |
| 13 | Del19 | 9 | | T790 WT | - |
| 14 | Del19 | 2 | Y | T790 WT | T790M ND |
| 15 | Del19 | 1 | | T790 WT | *FGFR1* D60N, *FGFR1* amp, T790M ND |
| 16 | L858R | 2 | | *MET* amp, T790 WT | *MET, EGFR* amp, T790M ND |
| 17 | L858R | 3 | Y | T790 WT | T790M ND |
| 18 | Del19 (de novo T790M) | 3 | | SCLC, T790 WT | T790M ND, *EGFR* amp |
| 19 | Del19 | 3 | Y | T790 WT | T790M/C797S, *MET* amp, *EGFR* amp |
| 20 | L858R | 2 | | *MET* amp, *EGFR* amp, T790 WT | - |
| 21 | L858R | 3 | | - | T790M/C797S, *EGFR* amp |
| 22* | L858R | 1 | | MET amp, T790 WT | - |
| 23 | Del19 | 4 | Y | - | T790M/C797S |

*(-) testing not performed; EGFR – Epidermal Growth Factor Receptor; TKI- Tyrosine Kinase Inhibitor; amp- amplification; WT- wild type; ND- not detected*

- Not all patients had both tissue and plasma biopsies at osimertinib resistance. All genotyped samples are shown.
- Patients 18 and 20 had intervening therapy between progression on osimertinib and biopsy.
- All pts retained the founder *EGFR* mutation on post-osimertinib testing
- 5/7 patients with *MET* amplification had pre-osimertinib *MET* FISH without amplification (2/7 did not have pre-osimertinib *MET* testing.)
- Two patients (*) had two separate biopsies at osimertinib resistance showing distinct resistance mechanisms:
  1. Pt 8: Plasma and lung nodule had T790M/C797S, mediastinal lymph node was T790 and C797 wild-type (Fig 1)
  2. Pt 22: Pleural fluid was *MET* amplified, but lung biopsy did not show *MET* amplification.

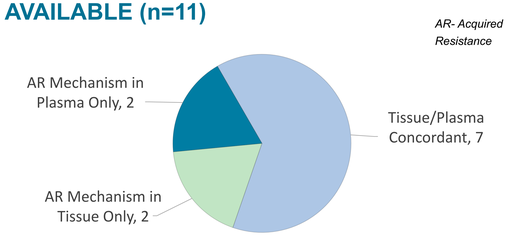
### FIGURE 1. HETEROGENEITY OF RESISTANCE MECHANISMS (PT 8)


### FIGURE 2. DISTRIBUTION OF RESISTANCE MECHANISMS



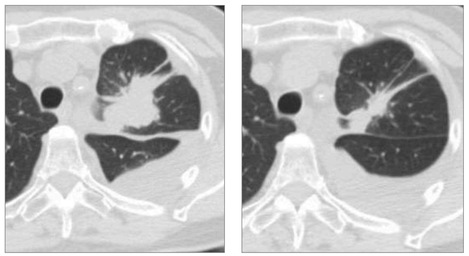

- The pie chart depicts the overall distribution of resistance mechanisms observed in this osimertinib-resistant cohort.
- *MET* amplification, identified by tissue or plasma, was the most common resistance mechanism, identified in 30% of cases.
- T790M "loss" was also commonly seen (35%), typically with no identified resistance mechanism

### FIGURE 3. TISSUE/PLASMA CONCORDANCE AMONG PTS WITH BOTH AVAILABLE (n=11)




- Median interval between tissue and plasma testing: 14 days
- Among 11 patients with both tissue and plasma analyzed at progression, **results were concordant in 7/11** (64%; light blue).
- In 2/11 cases (green), tissue identified a resistance mechanism not identified in plasma (*MET* amp, SCLC transformation)
- In 2/11 cases (dark blue), plasma identified resistance mechanisms not seen on biopsy (*FGFR1* mutation/amp, C797S/*MET* amp).

### FIGURE 4. RESPONSE TO OSIMERTINIB/SAVOLITINIB IN MET-AMPLIFIED PATIENT (PT 22)



LUL Mass Pre-Treatment  6 weeks on treatment

- 3 patients with *MET* amplification following osimertinib were treated with an EGFR TKI and a MET TKI; 3/3 achieved a RECIST partial response to the combination.

## SUMMARY & CONCLUSIONS

- In this cohort of 23 patients with osimertinib-resistant tissue and plasma biopsies, *MET* amplification was the most common resistance mechanism, seen in 30% of cases. *EGFR* T790M/C797S emerged in 22% of patients.
- Our cohort highlights the limitations of relying on a single tumor biopsy to characterize resistance, and underscores the complementary role of tissue and plasma testing.
- Heterogeneity of resistance mechanisms was seen in two patients with >1 osimertinib-resistance biopsies.
- Patients with *MET* amplification can respond to subsequent therapies incorporating MET inhibitors. Clinical trials incorporating MET and EGFR inhibitors are ongoing (NCT02143466) and should be considered for these patients.
- Drivers of resistance are not identified in a substantial minority of patients. Further efforts to elucidate resistance mechanisms to osimertinib are needed.

## REFERENCES

1. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2016.
2. Piotrowska Z, Niederst MJ, Karlovich CA, et al. Heterogeneity Underlies the Emergence of EGFRT790 Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor. Cancer Discov. 2015;5(7):713-722