Heterogeneity and Variation in Resistance Mechanisms among 221 EGFR-mutant NSCLC Patients With ≥ 1 Post-resistance Biopsy

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Background

• *EGFR* mutations comprise ~15% of lung adenocarcinomas. *EGFR* TKIs are the standard first-line treatment, but resistance typically develops after 9-13 months.

• Many patients who acquire resistance to *EGFR*-targeted therapy undergo a tumor biopsy at the time of progression. T790M is the most common resistance mechanism seen.

• In practice, patients rarely undergo further biopsies during treatment and are commonly categorized as “positive” or “negative” for a particular resistance mechanism (e.g. T790M) based on a single biopsy and timepoint.

• This binary positive/negative classification may underestimate the heterogeneity of resistant cancers and may prevent patients from accessing potentially effective treatment strategies.
Methods

• Retrospective analysis of 221 patients with advanced EGFR-mutant NSCLC seen at Massachusetts General Hospital (MGH) between 2008 and 2016.

• For each patient, we collected data for all biopsies obtained after resistance, including results of clinical molecular testing, treatment history and biopsy complications.
Resistance mechanisms upon initial resistance to *EGFR* TKI therapy (n=221)

Overall T790M-positive: 61%

- **T790M (1 with PIK3CA)**: 46%
- **No Identified Mechanism**: 21%
- **T790M + EGFR Amp**: 15% (1 with PIK3CA, 2 with HER2 Amp)
- **EGFR Amp**: 3%
- **MET Amp**: 5% (1 with PIK3CA, 2 with EGFR Amp, 1 with EGFR + HER2 Amp)
- **SCLC Transformation**: 3% (3 with PIK3CA)
- **PIK3CA**: 2%
- **BRAF**: 1%
- **Not tested/Insufficient**: 4%
Among 83 patients with two post-resistance biopsies, 41 (49%) had variations in the resistance mechanisms identified between biopsy 1 and 2.

- 20% patients “lost” T790M between biopsy 1 and 2
- 11% “gained” T790M

Of the 17 patients who lost T790M, three had a new resistance mechanism identified on the second biopsy.
Conclusions

• Our data suggest that resistance to \textit{EGFR}-targeted therapy is heterogeneous and that the dominant drivers of resistance can fluctuate over time.

• As much as half of the time, the dominant resistance mechanisms observed on one biopsy may no longer be relevant on a second biopsy, and a second biopsy may uncover a new, potentially targetable, resistance mechanism.

• We hope that these findings will prompt clinicians to consider repeat biopsy when selecting a new therapy.

• While we observed that biopsies were generally safe and feasible, noninvasive testing methods, such as liquid biopsies, may provide another method to more easily characterize resistance over time.