editorial

MET Copy Number as a Secondary Driver of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance in *EGFR*-Mutant Non–Small-Cell Lung Cancer

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In a subset of patients with non–small-cell lung cancer (NSCLC), increases in *MET* copy number have been hypothesized to lead to excessive amounts of MET protein, autoaggregation, ligand-independent MET signaling, and oncogenic addiction to the MET pathway.[1] The same process has also been described as one mechanism of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in *EGFR*-mutant NSCLC.[2-4] Changes in *MET* copy number represent a continuous variable that can be assessed in different ways: either the ratio of *MET* relative to another region of chromosome 7, such as *CEP7* (to show true amplification), or the absolute number of *MET* copies, which can also be increased by polysomy.[1] Consequently, the persistent problem with *MET* copy number studies has been to define a threshold for any given methodology above which a MET-directed therapy will likely be active. Less stringent criteria may include more patients but could dilute the clinical benefit in the treated population. More stringent criteria will identify fewer patients: those who may derive the greatest clinical benefit, but potentially excluding others who will still derive some benefit.

In the article that accompanies this editorial, Lai et al[5] conducted *MET* fluorescence in situ hybridization (FISH) analysis on 200 metastatic *EGFR*-mutant NSCLC samples. Using a mean *MET*/cell value of more than five to define *MET* high and a mean *MET*:*CEP7* ratio of 2.0 or greater to define *MET* amplified, 26% of treatment-naïve patients were able to be defined as *MET* high, but only 3% exhibited amplification. Among 154 patients subsequently treated with EGFR TKI, the baseline *MET*-high group at either greater than 5 or greater than 6.8 copies showed no differences in median time to treatment failure (TTF), the proportion of patients with a TTF of 6 months or fewer, or objective response rate (ORR) compared with the *MET*-low group. In contrast to the *MET*-high group, in whom median TTF was 12.5 months, median TTF among the five EGFR-treated *MET*-amplified patients was only 5 months. The two patient cases with the highest *MET*:*CEP7* ratio—3.7 and 4.5—both had progression as their best response and TTFs of 1.0 and 0.5 months, respectively.

MET copy number gain has been described as the mechanism of acquired resistance in 5% of *EGFR*-mutant cases post–first- and –second-generation EGFR TKIs and approximately 20% of cases post-osimertinib.[2-4] As treated patients in the work by Lai et al[5] had only received first- and second-generation TKIs, a 3% frequency of clinically relevant *MET* amplification seems plausible. Data from their use of FISH in pretreatment specimens also offers the promise of predefining a population that might benefit most from upfront combined MET and EGFR inhibition. Without preselection, demonstrating efficacy from a first-line MET-EGFR combination when only a minority of patients may be sensitive to this approach has been challenging. For example, the combination of emibetuzumab, a monoclonal antibody directed against surface MET expression, and erlotinib showed no difference compared with erlotinib alone in treatment-naïve *EGFR* mutant NSCLC (median PFS, 9.3 months and 9.5 months, respectively; HR, 0.89; 90% CI, 0.64 to 1.23; $P = .534$).[6]

Results presented by Lai et al[5] are also consistent with data that examined *MET* copy number as a primary oncogenic driver in which increases in mean *MET*/cell, at least up to seven copies, were unlikely to reflect a MET-dependent state and estimates of true amplification were a potentially better determinant of MET dependency.[7] Specifically, among previously untreated adenocarcinoma cases screened using *MET* FISH, a coincident, alternative driver oncogene was commonly identified across all categories of mean *MET*/cell assessed.[7] Even in the highest mean *MET*/cell category of seven or more copies, oncogene overlap occurred in 40% of cases. Similarly, oncogene overlap was identifiable in approximately 50% of low (ratio, 1.8 or greater to 2.2 or less) and intermediate (ratio, greater than 2.2 to less than 5.0) *MET*:*CEP7* categories. In contrast, in the highest *MET*:*CEP7* category (ratio, 5 or greater), no oncogene overlap was observed, which is more consistent with

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this level of amplified *MET* acting as a true oncogenic driver. Although only four such cases were available for analysis, this also represents the same *MET*:*CEP7* category with the highest reported ORR (67%; four of six) to crizotinib to date.[8]

In *EGFR*-mutant NSCLC, *MET* amplification as a mechanism of acquired resistance to EGFR TKIs is believed to represent the selection of a subclone, rather than a truncal genetic event. Indeed, overt clinical waxing and waning of *MET* copy number in response to EGFR TKI selection pressure can be observed.[9] For this reason, exact copy number levels that are suggestive of MET dependence may seem to be lower in the established EGFR acquired resistance setting compared with in the primary driver setting as a result of the potential dilutional impact of non–MET-driven cells in any analyzed sample. In the treatment-naïve setting, this dilution should be even more pronounced. Prior studies have shown that *EGFR*-mutant NSCLC cell lines and clinical samples that later manifest *MET* amplification in response to EGFR TKIs do have detectable preexisting *MET* amplification, but only in less than 1% of cells.[10] Consequently, the observation by Lai et al[5] that baseline *MET*:*CEP7* ratios of 2.0 or more detected with routine FISH testing, which averages signals more than 50 to 100 cells, can still be linked to different TKI outcomes is unexpected and deserves additional study.

Lai et al[5] performed detailed single-cell FISH analysis in 10 separate tumor areas that revealed significant spatial heterogeneity in both *MET*/cell and *MET*:*CEP7* positivity. Nevertheless, although the exact degree of heterogeneity was not quantified, from the Data Supplement in Lai et al,[5] spatial consistency did seem to be greater for *MET* amplified than *MET* polysomy-defined positive cells. Whereas these data continue to support the *MET*:*CEP7* ratio as the more robust measure of the cancer's biologic predisposition, concern still exists about the reliability of standard techniques for identifying *MET* amplification in treatment-naïve *EGFR*-mutant cases.

When considering *MET* copy number alterations that may represent only a subpopulation of tumor cells in *EGFR*-mutant NSCLC, the reliability of noncellular level assessments of *MET* is of even greater concern. Next-generation sequencing (NGS) techniques analyze DNA pooled across multiple areas of a tumor together with nontumor DNA. Between two *MET*-amplified and 16 *MET*-polysomy cases, only eight were deemed to have *MET* copy number gain (range, six to 22) by NGS (Oncomine; Thermo Fisher Scientific, Waltham, MA). Of the two patients with *MET*-amplified disease, the case with the lower ratio (*MET*:*CEP7* = 2.0) was not identified by NGS, whereas a *MET* copy number of 13.32 was reported for the higher ratio case (*MET*:*CEP7* = 3.4). These concerns should be even greater when NGS is applied to circulating DNA.

Compared with the treatment-naïve setting, MET–EGFR inhibitor combinations are more commonly being explored in variably preselected populations of *EGFR*-mutant NSCLC after acquired resistance to EGFR TKIs. ORR with savolitinib and osimertinib was 28% (seven of 25 patients) among those with *EGFR*-mutant NSCLC who experienced progression on a prior third-generation EGFR TKI with centrally FISH confirmed *MET* amplification (defined as five or more copies of *MET*/cell or a *MET/CEP7* ratio of 2 or greater).[11] Unfortunately, no details on the exact cytogenetic values recorded in responders versus nonresponders have been shown to date. ORR with capmatinib and erlotinib was 47% (17 of 36 patients) among those with *EGFR*-mutant NSCLC who experienced progression on an EGFR TKI with a FISH-defined mean *MET*/cell of 6 or greater.[12] To some extent, this seems to be at odds with the prior data that favored *MET*:*CEP7* over comparable mean *MET*/cell levels to identify a MET-driven state.[5,7,8] However, again, the exact cytogenetic values—mean *MET*/cell and *MET*:*CEP7*—observed in responders and nonresponders have not been shown to date.

Perhaps, at some high levels or in some settings in which the pretest probability is increased—as in established EGFR TKI acquired resistance—absolute copy number may be as valid a predictor of MET dependency/codependency as the *MET*:*CEP7* ratio. Alternatively, some other relevant heterogeneity within the *MET* copy number–altered NSCLC population could be confounding the efficacy signals in these small data sets. Even in *MET* exon 14–mutated NSCLC, which, in theory, leads to primary oncogenic MET signaling in a manner that is comparable to *MET* copy number gain—increasing MET protein levels, but by altered ubiquitination, rather than by increased gene dosage—ORR to MET TKIs is consistently only approximately 30% to 40%.[13,14] Similarly, in the expanded crizotinib data set looking at NSCLC with primary *MET*:*CEP7* ratios of 4 or greater, ORR was also 40% (eight of 20 cases).[15] These ORRs seem to be significantly lower than with other actionable driver oncogenes. The next steps may therefore involve validating the assumptions that these genetic events actually lead to increased MET protein expression and pathway activation. Whereas MET protein expression alone is not a reliable indicator of a MET-driven state post–EGFR TKI, MET protein levels in the presence of increased *MET* copy number or other estimates of downstream MET activation—for example, using a MET:GRB2 proximity ligation assay—have the potential to increase the predictive value of any *MET* genetic alteration.[16,17] It is only by delving deeply into the exact techniques and values used to call *MET* copy number–driven states (or even *MET* exon 14–driven states) within individual patients and trials that we will be able to better define the optimal patient population for MET-directed therapy in NSCLC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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