Editorial

METLung: a disappointing result in a challenging patient population

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The landscape of second line therapy and beyond for advanced non-small-cell lung cancer (NSCLC) continues to evolve. In addition to single agent chemotherapy following a platinum doublet, the use of second line tyrosine kinase inhibitors (TKIs) in patients with targetable molecular mutations, as well as the approval of programmed cell death 1 (PD-1) and programmed death ligands 1 (PD-L1) immunotherapies has greatly expanded the available options, making the clinical choice of a subsequent therapy increasingly complicated.

Up until October 2016 when the FDA changed the indication for erlotinib for use in solely epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution advanced NSCLC, it remained an approved second and third line treatment option for patients with EGFR wild type advanced NSCLC. This was based on a 2005 phase III randomized trial, showing a 2-month improvement in overall survival (OS) in patients treated with erlotinib in the second or third setting as compared to placebo (1). Erlotinib has since been used as a control arm in a significant number of studies in unselected patient populations. More significantly, it has been well established as a first line agent in advanced EGFR mutated lung cancer, consistently showing increased response and progression free survival (PFS) when compared to traditional chemotherapy (2,3).

However, resistance mechanisms to erlotinib ultimately develop. The EGFR T790M mutation is well documented (4), but also the amplification/overexpression of the transmembrane tyrosine kinase receptor MET, which is known to be co-expressed with EGFR and upregulate the EGFR ligand leading to EGFR TKI resistance (5,6). Dysregulated MET signaling leads to increased cell proliferation, spread, and invasion. High MET expression is associated with a poor prognosis in both early and late stage lung cancer, thus the vested interest in targeting MET through inhibition (7,8). One such MET targeted agent, onartuzumab, is a humanized monovalent monoclonal antibody that binds the extracellular domain of MET and blocks hepatocyte growth factor (HGF) activation, the MET receptor's only known ligand (9).

In 2013, Spigel *et al*. published the results of the phase II trial of onartuzumab in combination with erlotinib versus erlotinib alone in patients with advanced stage NSCLC. A total of 137 patients with recurrent NSCLC were randomized to either arm, with the results showing no improvement in PFS or OS in the intention to treat population [PFS: hazard ratio (HR) =1.09; P=0.69; OS: HR =0.80; P=0.34]. However, in the subset of 35 MET "positive" patients treated with the combination of onartuzumab plus erlotinib, there was an improvement in both PFS from 1.5 to 2.9 months (HR =0.53; P=0.04) and OS from 3.8 to 12.6 months (HR =0.37; P=0.002) (10). MET "positive" was defined as a 2+ score of MET by immunohistochemistry (IHC). This randomized phase II trial result set the stage for evaluation of the combination

on a greater scale specifically in MET "positive" patients in a phase III randomized trial of onartuzumab plus erlotinib versus erlotinib alone in previously treated stage IIIB or IV NSCLC patients. The METLung study accrued 499 patients from 27 countries with good performance status (PS =0–1) with MET "positive" tumors, again defined as MET IHC score of at least 2+ as centrally confirmed on archived samples. Patients were randomized in a 1:1 ratio to receive onartuzumab (15 mg/kg IV on day 1 of each 21-day cycle) plus erlotinib 150 mg daily or IV placebo plus erlotinib 150 mg daily. Additionally, patients were stratified according to histology, MET score (2+ *vs.* 3+), EGFR status, and treatment line (2^{nd} *vs.* 3^{rd}), with similar demographics noted between the two groups. The primary end point of the study was OS with secondary end points being median PFS, overall response rate (ORR), biomarker analysis, and safety. The study was stopped early after the futility boundary was crossed at an interim analysis.

Despite the selection for patients with tumors with high MET IHC score, the results of the study showed no OS, PFS, or ORR benefit with the addition of onartuzumab. Median OS was 6.8 months in the onartuzumab arm *vs.* 9.1 months in the control arm (HR =1.27; 95% CI, 0.98–1.65). PFS was 2.7 months in the onartuzumab arm *vs.* 2.6 months in the control arm (HR =0.99; 95% CI, 0.81–1.20). In addition, the subgroup analysis of patients with EGFR mutated NSCLC (n=57) did not show added benefit in terms of OS or PFS with the addition of onartuzumab, and surprisingly showed a trend toward shorter OS with onartuzumab (HR =4.68; 95% CI, 0.97–22.63). Multiple exploratory biomarkers were assessed and consistently negative across all biomarker subgroups. The addition of onartuzumab to erlotinib produced a tolerable side effect profile, with only peripheral edema and hypoalbuminemia being significantly noted compared to erlotinib alone. The author's concluded that in conjunction with other negative trials in various solid tumor studies of onartuzumab plus standard of care, MET inhibition in combination with erlotinib may not be an effective therapeutic strategy (11).

In the METLung study, we unfortunately see an example of how a positive randomized phase II trial does not always translate into a positive phase III trial, and the important discretion that should be used in interpreting randomized phase II results (12). False positive rates in randomized phase II trials can range from 20–40%, and thus should not be viewed as conclusive (13). Here, we appropriately see the application of a positive phase II trial as a platform for this phase III design, though we should not lose sight of small sample size in the study population of interest, which was formed from the treatment effect seen in the subset analysis of 35 MET "positive" patients. Despite having a convincing statistically significant overall survival effect with the addition of onartuzumab in this subgroup, it was underpowered to draw broader conclusions representative of the greater population of MET positive patients. This became evident with the phase III results. Interestingly, the phase II study was also a negative overall study in the intention to treat population, with no treatment effect witnessed in either the EGFR wild type or mutated subgroups.

How else can we explain the results of this negative study? It is important to note that the basis of erlotinib resistance through amplification of MET has been previously studied in patients with EGFR resistance mutations after treatment with an EGFR TKI (6). This was not the patient population that was focused on in this study, where despite EGFR status, all patients had received prior chemotherapy, but no targeted therapy. Despite MET amplification in the treatment population, the interplay between the development of a MET resistance mechanism after treatment with an EGFR TKI in patients with EGFR mutated NSCLC is not directly assessed as patients were EGFR TKI naïve. Furthermore, only a minority of patients evaluated in this study carried EGFR mutations (11.4%), with 8.6% being EGFR wild type. Thus, a true treatment effect would be challenging to find, but does not explain the potential negative interaction seen in the trial.

In addition, amplification of the MET oncogene is associated with TKI resistance in only 5–20% of cases (5), thus MET positivity and targeting MET with onartuzumab does not prevent more common secondary mutations in EGFR. The most common of these is the T790M mutation, seen in approximately 50% of cases of acquired resistance to first or second generation EGFR TKIs (14,15). Biological mechanisms of resistance other than MET are duly noted, and MET amplification does not seem to be a major factor in the majority of patients with NSCLC, except in those with EGFR mutated disease resistant to EGFR TKIs. MET amplification may play a larger role in resistance to third generation EGFR TKIs, but that question is not addressed in METLung. In this study, the trend of worsening median OS in the EGFR mutated group treated with onartuzumab remains unclear, with low sample size preventing broader interpretation and generalization.

Perhaps of more clinical significance is that erlotinib

in EGFR wild type NSCLC for the use of second line treatment and beyond has slowly fallen out of favor. This is based on a paucity of data supporting its efficacy, with an increase in other therapeutic options such as single agent chemotherapies, but most notably, immunotherapies. Recent trials comparing erlotinib to single agent chemotherapy in patients with EGFR wild type NSCLC have not shown significant benefit with erlotinib. In the Italian TAILOR trial, 222 EGFR wild type patients were randomized to erlotinib or docetaxel in the second line setting, with results showing a median OS of 8.2 months in the docetaxel group *vs.* 5.4 months in the erlotinib group (HR =0.73; 95% CI, 0.53–1, P=0.05) (16). In the Japanese DELTA trial, 301 patients were randomized to erlotinib or docetaxel with no difference in OS in the subgroup of EGFR wild type, but increased PFS in the docetaxel group of 2.9 *vs.* 1.3 months with erlotinib (HR =1.45; 95% CI, 1.09–1.94, P=0.01) (17).

Taken together, these trials support the notion that targeting EGFR in wild type tumors is overall a less viable therapeutic approach and lends credence to the FDA's recent change of erlotinib's indications for use only in EGFR mutated NSCLCs. This change was in itself, fueled by the randomized phase III IUNO trial, which found no difference in overall survival when erlotinib was administered as maintenance therapy or at the time of progression in patients with advanced EGFR wild type NSCLC first treated with four cycles of standard platinum based therapy (18). Going forward, chosen controls when evaluating therapies in EGFR wild type tumors will need to be reassessed.

With regard to MET testing, consistency and reproducibility in technique seemed to be preserved with agreement between central laboratory pathologists of greater than 88% on IHC staining intensity. However, was a cutoff of IHC 2+ possibly too liberal? Though in the subset analysis no difference was seen between IHC 2+ and 3+, 78% of the patients in the study were in the IHC 2+ group, thus raising the question of whether a stricter 3+ cutoff would have had any bearing on the results. It appears unlikely, though is a consideration. As was also seen in the phase II study, there was no correlation between MET fluorescence in situ hybridization (FISH) score and treatment effect, though a greater proportion of patients with IHC 3+ were also FISH positive. As mentioned by the authors, differing techniques for measuring MET status through splice-site mutations such as MET exon 14 mutations, rather than IHC or FISH status, may be a better predictor of response to MET inhibition and has been actively studied *in vitro* (19). The optimal tool for evaluating this biomarker still remains undetermined.

In summary, the METLung study had a solid design with optimistic expectation as evidenced by the previous phase II trial. Unfortunately, a treatment effect was not observed with several factors potentially playing a role. Targeting MET in EGFR wild type NSCLC may not be an effective target, despite positive expression, as amplification does not always translate into a resistance pattern and subsequent treatment effect. Negative overall survival results have also been seen in the phase III MARQUEE and ATTENTION studies, both using tivantinib, a highly selective MET inhibitor in combination with erlotinib in advanced EGFR wild type NSCLC (20,21). In contrast with onartuzumab, tivantinib is a MET kinase inhibitor. Perhaps the MET pathway remains highly relevant, but neither onartuzumab nor tivantinib are sufficiently active agents. Further EGFR and MET combined inhibition trials are ongoing.

The possibility of multiple other signaling pathways and tyrosine kinases may be important in tumor proliferation in this population. The recently published phase II study ECOG-ACRIN 1512 found that the small molecule inhibitor cabozantinib, which not only targets MET, but also VEGFR, RET, ROS1, AXL, KIT, and TIE-2, combined with erlotinib or used as a single agent produced a significant PFS benefit when compared to erlotinib alone (22). Though a small study, this may highlight the importance of hitting multiple targets in advanced EGFR wild type disease refractory to prior therapy, rather than targeting MET alone. All in all though, the METLung study highlights that in EGFR wild type advanced NSCLC with a high MET score by IHC, the addition of MET inhibition with onartuzumab is not the answer, and based on previous mounting studies, neither is erlotinib. Current and future studies using MET inhibitors are underway, however now focused on the EGFR mutated rather than wild type population, with the goal of further understanding acquired resistance to both older and newer generation EGFR TKIs (23).

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Footnote

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