



Commentary

ILK and SHP2 expression identify a poor prognostic cohort of EGFR-mutant lung cancer


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Lung cancer remains the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) predominates, accounting for approximately 85% of all lung cancer diagnoses, most of which can be histologically subdivided into two primary NSCLC subgroups: adenocarcinoma and squamous cell carcinoma. Recent scientific advances have identified several targetable, molecular drivers of NSCLC, the most common of which are mutations in the gene encoding Epidermal Growth Factor Receptor (EGFR). These mutations vary in frequency from approximately 15% of tumors in European populations to more than 50% in East Asian populations and identify a unique subtype of NSCLC with specific therapeutic implications [1]. EGFR-mutant patients are currently treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) with the past 15 years having seen the development and approval of three generations of these agents with progressively higher potency and broader indications [1,2]. Nevertheless, about 20% of EGFR-mutant patients are primary resistant to EGFR-TKIs, yet no predictive biomarkers exist to identify and/or alter the treatment approach for these patients.

Experimental data have demonstrated that multiple mechanisms may mediate resistance to EGFR-TKIs [2]. Resistance can derive from the expansion of resistant sub-clones, already present in a treatment naïve tumor, or from the molecular evolution of previously sensitive sub-clones under the selective pressure of EGFR inhibition. Common mechanisms of EGFR resistance include: the activation of other transmembrane receptors, both tyrosine kinase receptors (RTK), like ERBB2 [2], MET [2,3], or AXL [4,5] and non-RTK, like SMO [3]; constitutive activity of cytoplasmic signaling cascades, like the mitogen-activated protein kinase (MAPK) [2] and signal transducer and activator of transcription 3 (STAT3) [6]; and complex biological processes, such as epithelial to mesenchymal transition (EMT) [2,3].

Rosell et al. have previously shown that, among the EGFR downstream signals, STAT3 and Src are not inhibited by treatment with EGFR-TKIs, even in EGFR sensitive models, since they are regulated also by other proteins [6]. In particular, they described that the

cytoplasmic tyrosine phosphatase Src Homology 2 domain containing Phosphatase 2 (SHP2) is a participant in the intracellular signaling cascades of various RTK, including EGFR, and interleukin-6 (IL-6), all inducing STAT3. Moreover, it is demonstrated that EGFR inhibitors also directly activate Src and integrins [7]. Interestingly, both SHP2 and integrins (through Integrin-Linked Kinase, ILK) are involved in IL-6 signaling cascade, which ultimately promotes EMT and proliferative transcriptional programs, independently from EGFR.

In this work led by Karachaliou and Rosell [8], the authors analyzed gene expression of ILK, gp130 (one subunit of the IL-6 receptor) and SHP2 on tumor cells, and of IL-6 and HGF in the stroma and correlate them with clinical outcomes of a multi-institutional cohort of EGFR mutant patients treated with sequential first generation reversible EGFR-TKIs and second generation irreversible EGFR-TKIs. First, they showed that ILK expression is correlated positively with gp130 ($p = .0183$) and stromal HGF ($p = .0468$). HGF is the physiological ligand of MET and is also involved in activating crosstalk of MET with other receptors in EGFR-TKI resistant models [5], thus they confirm the biological hypothesis that IL-6 signaling activation co-exists with other signals, all converging on STAT3, Src and MAPK. Then, stratifying patients in high- and low-expression groups for each variable, they discovered that high ILK expression correlates with a significantly lower progression free survival (PFS) after treatment with EGFR-TKI (9.4 versus 15.8 months, $p = .0021$), with a Hazard Ratio (HR) of 2.49 ($p = .0029$), that was also maintained in multivariate analysis. Regarding SHP2, they extended their previous report that high SHP2 expression correlates with higher risk of disease progression with EGFR-TKI [5], by displaying that SHP2-high patients have shorter PFS (11.4 versus 24.1 months, $p = .0094$, with HR = 2.40, $p = .0115$). Moreover, they demonstrated that overall survival (OS) is also decreased significantly, both in their patients cohort (18.5 versus 36.7 months, $p = .0182$) and in The Cancer Genome Atlas (TCGA) EGFR mutant NSCLC cohort ($p = .0043$). These results are very straightforward: they identify that ILK and SHP2 expression levels in pre-treatment EGFR mutant NSCLC samples may predict negative outcome from first/s generation EGFR-TKIs therapy.

These conclusions are strengthened by the inclusion of both a multi-institutional clinical cohort, and an independent validation set in the TCGA. These data imply that there is a subset of EGFR-mutant patients that may still derive some benefit from EGFR-TKIs but may require alternative frontline therapy, such as a combination strategy including ILK

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or SHP2 inhibitors, that warrants future investigation. Notably, SHP2 inhibitors have already demonstrated activity in some models of lung cancer and melanoma and ILK inhibitors showed promising results in leukemia studies [5].

Furthermore, it will be interesting to evaluate how these observations hold up in patients treated with third generation EGFR-TKIs (osimertinib) that are now the standard of care for *EGFR*-mutant patients worldwide [1]. Interestingly, one of the main mechanisms demonstrated for osimertinib resistance is MAPK activation and there are various experimental data that the addition of inhibitors of MEK can revert this resistance [9,10], thus emphasizing the importance of studying the role of MAPK, as well as SHP2 and ILK, in prospective studies of EGFR-TKI resistance. These new results presented by Karachaliou et al. confirm that, even in an oncogene addicted cancer type, like *EGFR*-mutant NSCLC, molecularly targeted therapy is not a one-size-fits-all approach and should prompt further studies to identify, and potentially target, novel biomarkers of resistance to design a truly personalized therapy.

Conflicts of interest

CMDC and CMG have no conflicts of interest to disclose.

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FM has participated to advisory Boards for MSD and Lilly and has institutional research grants from AstraZeneca.

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