Editorial

Targeting the tyrosine kinase inhibitor-resistant mutant EGFR pathway in lung cancer without targeting EGFR?

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Targeting of mutant EGFR in lung cancer has significantly improved the outcome of patients with advanced lung cancer. Ultimately, all of these patients fail and progress due to the emergence of preexisting or acquired resistant subclones. Chemotherapy is currently the only effective option to treat these patients, immunotherapy being of little value in EGFR-driven lung cancer.

In lung cancer, multitudes of molecular mechanisms are identified that can drive resistance to mutant EGFR inhibition with tyrosine kinase inhibitors (TKI's). Moreover, there is a possibility of mutations that co-drive the malignant phenotype in addition to mutant EGFR, which also needs targeting to obtain a higher treatment efficacy (1).

A major cause of treatment failure is the outgrowth of subclones with secondary EGFR resistance mutations. Osimertinib can overcome the frequently occurring T790M resistance mutation and has become the first-line treatment in advanced EGFR mutant lung cancer (2,3). However, this drug is equally the subject of therapeutic resistance and treatment failure (4).

Mutant EGFR activates the phosphoinositide 3-kinase Pi3K/AKT/mTOR and RAS/RAF/MEK pathways. Various mechanisms that cause downstream activation within these pathways or activate intersecting pathways cause resistance to EGFR TKI's. Some are robust genomic mechanisms, such as amplification of MET and IGF1R or mutations in BRAF and PiK3CA, but many reported mechanisms are regulatory changes such as reduced BIM expression, activation of the NF-kB signaling pathway activation, phenotypic switches, autophagy induction (5,6). Often, the exact mechanism remains unknown. Some of the genomic changes such as MET amplification can be specifically targeted (7) and are under clinical exploration.

A significant practical obstacle is that each of these individual mechanisms occurs only in a fraction of patients. Individually addressing the various modes of resistance would require a sophisticated personalized diagnostic setting to stratify these patients, which is currently not feasible. Moreover, several resistance contributors may act in cooperation in individual patients due to heterogeneous subclonal evolution. Therefore, it is worthwhile to investigate more generic strategies that can accommodate multiple mechanisms of resistance in one. Ito *et al*. (8) have opted to co-target two relatively downstream signal transduction elements that could fulfill this aspiration and thus be applicable in more patients with resistant disease. Both chosen targets are also bona fide genomically activated oncogenes in a subset of lung cancers, either at baseline or in the progression of the disease.

The atypical protein kinase C_{iota} (PKC_{ι}) that belongs to the PKC family regulators of cell differentiation is primarily an effector of KRAS signaling in KRAS mutant lung adenocarcinoma but also belongs to the Pi3K/AKT effector pathway, Wnt (9), NFkB signaling and Hedgehog signaling pathway, which is paracrine-driven in lung adenocarcinoma (10). The gene encoding PKCι is itself

frequently amplified in squamous lung cancer in which it promotes cell proliferation and survival (11). Gene amplification activates this pathway but also localizes the transcriptional regulator YAP1 (HIPPO pathway) to the cell nucleus leading to cell proliferation and survival. Inhibition of PKCι leads to decreased YAP1 in the nucleus (12). YAP1 activation is a common drug escape mechanism for multiple treatment forms in multiple cancers. Ito *et al.* (8) have employed auranofin, an available repurposed drug coming from rheumatology, in which newer treatments have largely replaced it. Auranofin has mostly digestive toxicities that have discouraged further clinical use. Auranofin is nevertheless further explored in a couple of clinical studies in cancer, but newer aPKC inhibitors are in development (13).

The second target, PAK1 (p21-activated kinase), is on the Pi3K/Akt and Wnt-signaling pathway. PAK1 expression is a mechanism of resistance to mutant EGFR inhibition, including phenotypic escape (14,15). PAK1 also is genomically amplified in some squamous lung cancers. Both protein targets are thus on intersecting pathways and it is noteworthy that PKCι also regulates PAK1 signaling. The development of specific PAK1 inhibitors has required a substantial drug screening effort. IPA-3 functions by selectively stabilizing the PAK1 auto-inhibitory conformation. There are other, more stable or more specific PAK1 inhibitors in early development but also inhibitors of other PAK family members that also have anticancer activity (15).

Ito *et al.* (8) show in EGFR-mutant lung cancer cells with different mechanisms of resistance to EGFR TKI's, including osimertinib, that the compounds individually are not effective at clinically relevant doses but have synergistic antitumor activity in vitro. They also show that the combination downregulates several targets downstream, but also upstream targets such as EGFR, although this needs confirmation at lower doses that are achievable *in vivo*.

Thus, they provide proof of principle that EGFR resistance could potentially be addressed without an EGFR inhibitor which represents a new paradigm as in other work, mostly combinations with EGFR inhibition are investigated to overcome resistance.

The same strategy could also be explored in RAS-mutant lung cancer as well as other driver mutations. The strategy might apply to other cancers in which these pathways play a role in resistance including hormone-resistant breast cancer and chemotherapy resistance (16). However, there should be some caution, as aPKC's and the PAR complex, to which they belong, might also be suppressors of some aspects of the malignant phenotype (17).

Advancing this strategy beyond the current proof of principle requires preclinical *in vivo* experiments and examination of the *in vivo* tolerability, the effect on the anti-tumor immune micro-environment (as these pathways also play a role in immune cells) and clinical tolerability. Further clinical development probably needs better drugs. The correlation of therapeutic efficacy with the genomic activation or not of the target genes should be an integral part of the further research.

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Footnote

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