

Met in lung cancer

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Receptor tyrosine kinases play important roles in the biology of many tumor cell types. In approximately 10% of non-small cell lung cancer (NSCLC) patients mutational activation of the epidermal growth factor receptor (EGFR) results in tumor cells that are exquisitely addicted to signaling by this receptor.¹ Thus expression of mutant active EGFR but in general not wild-type EGFR predisposes NSCLC cells to inhibitors of EGFR/ErbB2. Use of EGFR inhibitory agents such as gefitinib for this subset of NSCLC patients causes tumor regression and disease stabilization for 12–18 mo, after which tumor cells become resistant to the drug.² Initial studies identified a second mutation within the EGFR, which results in the resistance of the tyrosine kinase to gefitinib, as a major cause of reduced tumor control.³ This has resulted in the development of newer EGFR inhibitors, e.g., afatinib, which inhibited double mutant EGFR.⁴ In a subset of these patients, however, resistance to gefitinib was not associated with EGFR mutations.⁵ Clearly, other mechanisms of gefitinib resistance must be at play.

In approximately 5% of NSCLC patients an activated fusion protein of the anaplastic lymphoma kinase (ALK) is overexpressed and this receptor was defined as the kinase driving this subgroup of NSCLC tumors.⁶ The drug crizotinib was developed as an inhibitor of ALK, and that also inhibits the receptor c-Met.⁷ Overexpression of c-Met and its ligand, hepatocyte growth factor, are found in many tumor types, including NSCLC and NSCLC resistant to EGFR

inhibitors such as gefitinib.⁸ The manuscript by Meng et al. explores the biology of a novel ALK/c-Met inhibitor CM-118 both as a single agent and in combination with EGFR inhibitors.⁹

Initial studies in cells and with isolated proteins demonstrated that CM-118 had a nanomolar potency against ALK and c-Met with good selectivity over other kinases. In a wide variety of tumor cell types studies then demonstrated that CM-118 effectively inhibited the growth of c-Met- or ALK-addicted tumor cells but not those cells that show addiction through EGFR/ErbB2. More interestingly, while CM-118 was not a direct inhibitor of EGFR, it partially suppressed basal levels of EGFR tyrosine phosphorylation in c-Met-addicted cells, arguing that c-Met can trans-phosphorylate EGFR.

In NSCLC and gastric cancer cells CM-118 as well as the approved drug crizotinib caused growth arrest in the nanomolar range that was accompanied with modest increases in tumor cell death. The NSCLC cell line used for these studies, H1993, also expressed EGFR that was phosphorylated. Combined treatment of H1993 cells with CM-118 and afatinib resulted in a profound greater than additive killing effect.¹⁰ This effect was associated with complete dephosphorylation of ERK, AKT, and mTOR, increased expression of the pro-apoptotic protein Bim, and decreased expression of the anti-apoptotic protein Mcl-1. Knockdown of Bim expression or overexpression of Mcl-1 protected cells from the drug combination. Knockdown of mTOR resulted in a profound growth arrest response and interacted with CM-118 to increase killing.

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Finally the authors established in multiple tumor models that CM-118 could inhibit c-Met and ALK phosphorylation in vivo and reduce tumor growth. More importantly they demonstrated that CM-118 and the mTOR inhibitor rapamycin interacted in vivo to abolish NSCLC growth. A key long-term question is whether CM-118 will make the leap from the laboratory to the clinic, and this will be of considerable interest.

At present there are a number of clinical trials combining EGFR inhibitors with the approved c-Met/ALK inhibitor crizotinib.¹¹ These studies are eminently logical based on the parallel protective signaling modules downstream of the EGFR and c-Met/ALK receptors. Whether molecular manipulation of these pathways can also modulate the anti-tumor efficacy of established NSCLC therapies, e.g., cisplatin/pemetrexed; pemetrexed maintenance will be of considerable interest.¹¹

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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