EDITORIAL

Treatment of *KRAS*-Mutant Non–Small Cell Lung Cancer
The End of the Beginning for Targeted Therapies

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The development of biomarker-driven targeted therapy has resulted in substantial benefits for patients with non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) mutations, and rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene or the *ROS1* gene. For patients with *EGFR*-mutant NSCLC *EGFR* tyrosine kinase inhibitors (eg, gefitinib, erlotinib, and afatinib) have a superior objective response rate and progression-free survival compared with chemotherapy in the first-line setting.[1-3] For patients who have disease progression on *EGFR* tyrosine kinase inhibitor and with NSCLC with an *EGFR* T790M mutation osimertinib has demonstrated a superior response rate and progression-free survival compared with chemotherapy in the second-line setting.[4] For patients with *ALK* rearrangements *ALK* tyrosine kinase inhibitors (eg, crizotinib, ceritinib) have a superior response rate and progression-free survival compared with chemotherapy in the first-line setting, and for patients who experience disease progression, ceritinib and alectinib have demonstrated clinically relevant response rates and progression-free survival.[5-9] For patients with *ROS1* rearrangements, targeted therapy, is associated with a higher response rate and longer progression-free survival than has been observed with chemotherapy. These molecular alterations are more common in NSCLC with adenocarcinoma histology and in the minority of patients with a light smoking or never smoking history. The success of these targeted therapies in molecularly defined subsets of NSCLC made the development of targeted therapies and identification of predictive biomarkers a focus of thoracic oncology research. Routine molecular testing is now the standard of care for patients with NSCLC with adenocarcinoma histology.[10,11]

Related article page 1844

The most common oncogenic mutation detected in patients with NSCLC is *KRAS*, which is found in 25% to 30% of lung adenocarcinomas, and associated with tobacco use.[12,13] Patients in this molecular subgroup do not have a targeted therapy available to them. A prior phase 2 trial in this population (involving 87 patients) that compared docetaxel alone or with selumetinib, a potent inhibitor of mitogen-activated protein kinase kinase 1 (MEK1) and MEK2, reported promising results.[14] This trial had a compelling preclinical rationale, because MEK signaling is downstream from *KRAS*, and selumetinib demonstrated activity in *KRAS*-mutant NSCLC xenograft models.

However, these promising preclinical and phase 2 results did not translate into an improvement in progression-free survival or overall survival in the SELECT-1 study—the phase 3 multicenter, randomized trial reported in this issue of the *JAMA* by Jänne et al.[15] In this study of 510 patients (mean age, 61.4 years; women, 41%), 251 received selumetinib + docetaxel and 254 received placebo + docetaxel. Median progression-free survival and overall survival were not significantly different in the selumetinib + docetaxel group compared with the placebo + docetaxel group (median progression-free survival: 3.9 months for the selumetinib + docetaxel group vs 2.8 months for the placebo + docetaxel group; hazard ratio [HR], 0.93 [95% CI, 0.77-1.12]; P = .44; median overall survival: 8.7 months for the selumetinib + docetaxel group vs 7.9 months for the placebo + docetaxel group; HR, 1.05 [95% CI, 0.85-1.30]; P = .64). The objective response rate in the selumetinib + docetaxel group was 20.1% vs 13.7% in the placebo + docetaxel group (odds ratio, 1.61 [95% CI, 1.00-2.62]; P = .05) The oncology community will be left seeking an explanation for these nonsignificant trial results and wondering what next investigational path should be pursued in this population.

One possibility is that clinical benefit may only occur in a subset of tumors that exhibits a favorable genetic or signaling environment. In SELECT-1, possible differences in response and outcome were investigated for the various codon-specific *KRAS* mutations, as these may influence downstream pathways and influence the efficacy of targeted therapies.[16,17] A retrospective analysis of the prior phase 2 trial revealed a trend toward superior outcome in these *KRAS* G12C or *KRAS* G12V mutant subtypes.[18] However, in the current study by Jänne et al, although *KRAS* G12C or *KRAS* G12V were associated with a higher response rate to selumetinib + docetaxel compared with docetaxel alone, the progression-free survival was similar. A post hoc subgroup analysis of 28 patients with *KRAS* Q61 found a nonsignificant improvement in progression-free survival among those receiving selumetinib + docetaxel compared with docetaxel alone. In pancreatic adenocarcinoma, *KRAS* Q61 mutations have been associated with improved outcomes and decreased *ERK* phosphorylation compared with other *KRAS* mutations suggesting a biological explanation for this observation worth pursuing further.[19]

Heterogeneity due to the presence of other mutations or the relative activity of various signaling pathways may also influence response to MEK inhibition. Concurrent loss of *LKB1* (also known as *STK11*), a tumor suppressor gene, is detected in approximately 30% of *KRAS*-mutant NSCLC and the presence of concurrent mutations may influence

biology and drug response phenotype.[20-22] In human NSCLC-derived cell lines, *LKB1* loss directly induces sensitivity to MEK inhibition in vitro and in xenograft models.[23] However, contrasting results were observed with a genetically engineered mouse model, which showed resistance to selumetinib + docetaxel treatment in NSCLC tumors resulting from mutated *Kras* and *Lkb1*, in comparison with tumors with *Kras* mutations alone or with concurrent *p53* loss.[23] The differences in these results may reflect differences in the models or the method of defining *LKB1* loss.

In some contexts resistance to in vitro MEK inhibition may be due to *AKT*-mediated attenuation of apoptosis through phosphorylation of effectors such as FOXO3 and BIM; thus, there is preclinical rationale to investigate these pathways as determinants of clinical response.[24,25] To identify novel response modifiers, CRISPR-Cas9 methodology has been used to screen the phenotypic effects of hundreds of genes simultaneously, demonstrating that loss of *KEAP1* induced resistance to MEK and other targeted inhibitors.[26] Numerous preclinical studies have characterized biomarkers including gene expression "signatures" correlated with in vitro susceptibility to MEK inhibition as well as *KRAS* dependency.[22,23,27-31] The biological significance of these signatures is not always clear, but some may reflect increased activity of RAS/RAF/MEK signaling, whereas others are associated with *LKB1* loss or an epithelial-mesenchymal transition.[22,27] Correlative analysis of biospecimens from responders and nonresponders in the SELECT-1 trial could help elucidate patient subsets that will benefit from MEK inhibition or to test predictors of clinical response.

Another consideration is that MEK inhibition may be a viable strategy in this tumor subset but other drug candidates may be more effective than selumetinib. Various MEK inhibitors exhibit differences in target binding site and effects on feedback mechanisms. MEK inhibition by selumetinib is thought to result in a RAF-dependent increase in MEK phosphorylation that may partially mitigate its effect. Certain other inhibitors, including trametinib and GDC-0623, disrupt this feedback loop by preventing MEK phosphorylation at serine 212 and may prevent this effect.[32] In preclinical models, these distinct modes of inhibition produce differential effects on *BRAF*- vs *KRAS*-driven cancers, with feedback prevention proving more effective in *KRAS*-mutant tumors.[33] Although selumetinib demonstrated little suggestion of benefit in SELECT-1, it may be premature to conclude that other compounds will be ineffective given differences in their inhibitory mechanism.

Alternatively, combination of MEK inhibition with other targeted therapies may have more synergy than was observed with docetaxel. Rational drug combinations with MEK inhibitors and targeted inhibitors of resistance pathways such as AKT, PIK3CA, and mTOR could be pursued. Combining inhibitors that target different components of the same pathway has been clinically effective in treating *BRAF*-mutant NSCLC and melanoma, with the combination of MEK and *BRAF* inhibitors resulting in superior outcomes to single agent targeted theapy.[34,35] Additionally, inhibitors that bind directly to the mutant cysteine residue on *KRAS* G12C (the most common *KRAS* mutation in NSCLC) and do not bind to wild-type protein have shown promising preclinical activity.[36,37]

The approach of using molecular testing and treating with a corresponding targeted therapy has ushered advances in the treatment of NSCLC as well as other cancers. Molecular testing has helped identify the patients most and least likely to benefit from therapy and accelerated the speed of drug development. However, progress appears to be slowing. This is in part because many of the remaining molecular alterations susceptible to targeted therapies have lower prevalence, which makes identification and performing trials challenging. The research community has encountered the practical limitations related to the ever-expanding breath of tumor testing required, and technical issues related to molecular testing methods. Some of the multitargeted tyrosine kinase inhibitors have been limited due to off-target toxicities. Among the most daunting challenges is the development of acquired resistance to targeted therapy, which has unmasked the issues of intratumor and intertumor heterogeneity.

The current state does not represent the beginning of the end but the end of the beginning for targeted therapies. Molecular testing is rapidly evolving and circulating tumor DNA testing will facilitate tumor testing and may allow for serial monitoring and use of surrogate end points for drug development. The next generation of targeted therapies will likely focus on the primary oncogenic molecular event and the acquired resistance mechanisms, and will be more potent and specific for the oncogenic driver. This will ideally improve efficacy and reduce off-target toxicities.

The development of a targeted therapy is critical to the future management of patients with *KRAS*-mutant NSCLC and may provide a path forward for other solid tumor malignancies that harbor *KRAS* mutations.

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