

## Targeted Therapy

**Major finding:** PF-06463922 is highly efficacious against all known clinically acquired *ALK* mutations.

**Clinical relevance:** PF-06463922 has greater brain penetrance than other clinically available *ALK* inhibitors.

**Impact:** PF-06463922 may be effective in relapsed *ALK*-driven cancers and as first-line therapy for naïve tumors.

### THE *ALK*/*ROS1* INHIBITOR PF-06463922 HAS POTENCY ACROSS RESISTANT *ALK* MUTANTS

Anaplastic lymphoma kinase (*ALK*) is activated in non-small cell lung cancers (NSCLC) by various point mutations or gene fusions and has been clinically targeted by small-molecule inhibitors, including crizotinib and the second-generation *ALK* inhibitors ceritinib and alectinib. However, many patients with NSCLC who initially respond to these *ALK* inhibitors relapse and develop brain metastases, often due to the acquisition of secondary resistant *ALK* mutations and poor brain penetrance of the inhibitors, demonstrating the need to identify more potent *ALK* inhibitors. Zou, Friboulet, Kodack, and colleagues compared the potency and *in vivo* efficacy of PF-06463922, a next-generation ATP-competitive, selective *ALK*/*ROS1* inhibitor, to that of crizotinib, ceritinib, and alectinib. *In vitro*, PF-06463922 was more potent than existing *ALK* inhibitors against wild-type *ALK*, clinically relevant resistant *ALK* mutants, and *EML4-ALK* mutant fusions, resulting in inhibition of *ALK*-dependent cell growth and induction of apoptosis. In subcutaneous *ALK* fusion-driven xenograft models, PF-06463922 induced >95% inhibition of *ALK* phosphorylation and tumor regression at a relatively low dose. Significantly, PF-06463922

induced the regression of crizotinib-resistant tumors, including those harboring the highly resistant *ALK*<sup>G1202R</sup> mutation. Furthermore, in *ALK* fusion-driven intracranial tumor models, PF-06463922 exhibited superior potency against brain metastases compared with crizotinib and alectinib, resulting in dose-dependent regression of intracranial tumors and prolonged survival, suggesting that PF-06463922 has enhanced brain penetrance. Finally, PF-06463922 was well tolerated at all doses and had little toxicity in preclinical studies. In summary, these findings suggest that the potent antitumor activity against known clinically acquired *ALK* mutations, safety profile, and superior central nervous system penetrance of PF-06463922 make it a strong candidate for treating *ALK*-driven lung cancers as a single agent and possibly in combination with other *ALK* inhibitors and/or other agents to overcome or prevent relapse. ■

Zou HY, Friboulet L, Kodack DP, Engstrom LD, Li Q, West M, et al. PF-06463922, an *ALK*/*ROS1* inhibitor, overcomes resistance to first and second generation *ALK* inhibitors in preclinical models. *Cancer Cell* 2015;28:70–81.

## Epigenetics

**Major finding:** Genome-wide H3K4me3 maintains the LSC transcriptional program in *MLL*-rearranged AML.

**Concept:** *KDM5B* suppresses *MLL* leukemia by reducing global H3K4me3 and promoting LSC differentiation.

**Impact:** Inhibition of H3K4me3 may be therapeutically beneficial in *MLL*-associated leukemia.

### THE GLOBAL H3K4 METHYLATION STATE CONTROLS LEUKEMIA STEM CELL FATE

Global changes in the epigenetic landscape have been suggested to contribute to tumorigenesis in various types of cancer, but whether the epigenome specifically regulates the function of cancer stem cells remains unclear. Using chromatin immunoprecipitation sequencing, Wong and colleagues compared the genome-wide epigenetic landscape of c-KIT-positive enriched leukemia stem cells (LSC) and c-KIT-negative differentiated cells in *MLL*-rearranged acute myeloid leukemia (AML). This analysis revealed that, in contrast to c-KIT-negative cells, LSCs were characterized by global hypermethylation of histone 3 lysine 4 (H3K4) and hypomethylation of H3K79. In addition, increased levels of H3K4 dimethylation and trimethylation (H3K4me3) were present on *MLL* target genes that promote AML pathogenesis and LSC maintenance genes in LSCs, whereas reduced H3K4me3 correlated with downregulation of the LSC transcriptional program in c-KIT-negative cells, suggesting that LSC self-renewal and oncogenic potential are negatively regulated by reversion of this epigenetic profile. Consistent with this idea, expression of the H3K4



histone lysine (K)-specific demethylase 5B (*KDM5B*) was increased in c-KIT-negative differentiated cells compared with LSCs. Overexpression of *KDM5B* diminished genome-wide H3K4me3, induced differentiation, and inhibited the growth of *MLL*-transformed and human *MLL*-rearranged leukemia cells, but not leukemia cells transformed by non-*MLL* oncogenes, both *in vitro* and *in vivo*. Conversely, *KDM5B* depletion enhanced H3K4me3 levels, increased the expression of LSC maintenance genes, and augmented bone marrow engraftment and leukemia aggressiveness in xenotransplantation models. These findings provide evidence that the global H3K4 methylation state modulates LSC differentiation and demonstrate that *KDM5B* functions as a tumor suppressor in *MLL*-associated AML by suppressing the oncogenic potential of LSCs. ■

Wong SH, Goode DL, Iwasaki M, Wei MC, Kuo HP, Zhu L, et al. The H3K4-methyl epigenome regulates leukemia stem cell oncogenic potential. *Cancer Cell* 2015;28:198–209.