Clinical Trials

Major finding: The ALK inhibitor CH5424802 is well tolerated and active in patients with *ALK*-rearranged NSCLC.

Approach: The safety and activity of CH5424802 were evaluated in a single-arm phase I–II trial.

Impact: CH5424802 may be more effective than crizotinib for patients with *ALK*-rearranged NSCLC.

A SELECTIVE INHIBITOR SHOWS ANTITUMOR ACTIVITY IN *ALK*-REARRANGED NSCLC

Gene fusions involving anaplastic lymphoma kinase (*ALK*) have been implicated as oncogenic drivers and therapeutic targets in non–small cell lung cancer (NSCLC). Treatment with crizotinib, a small-molecule receptor tyrosine kinase inhibitor that targets ALK, MET, and ROS1 and is approved for use in *ALK*-rearranged NSCLC, is associated with improved survival; however, resistance often develops, in part via *ALK* mutations. Seto and colleagues assessed the safety and antitumor activity of CH5424802 (RO5424802), an orally available, highly selective ALK inhibitor that is active against *ALK* fusions and resistant *ALK* mutations *in vitro*, as a potential therapeutic alternative. Patients with advanced *ALK*-rearranged NSCLC who had not previously been treated with ALK inhibitors were enrolled in a single-arm phase I–II study. In the phase I portion, no dose-limiting toxicities or grade 4 adverse events were detected at any dose, and high plasma drug concentrations were achieved. The primary endpoint of the phase II portion was the proportion of patients who experienced an objective response; among 46 patients treated with the highest tested dose from the phase I trial, the objective response rate was 93.5%, including 41 (89.1%) partial responses, 2 (4.3%) complete responses, and prolonged disease control in patients with brain metastases. Rapid reductions in tumor size of greater than 30% were detected within 3 to 6 weeks, and 87% of patients currently remain on treatment. CH5424802 was well tolerated, as treatment-related side effects were generally minor; grade 3 adverse events occurred in 26% of patients but did not necessitate dose reduction. Although additional studies are necessary to investigate the efficacy of this drug in crizotinib-resistant tumors, these findings show that CH5424802 has potent antitumor activity and suggest that this inhibitor may be more effective than crizotinib in *ALK*-rearranged NSCLC. ■

Seto T, Kiura K, Nishio M, Nakagawa K, Maemondo M, Inoue A, et al. CH5424802 (RO5424802) for patients with ALK*-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. Lancet Oncol 2013 Apr 30 [Epub ahead of print].*

Prostate Cancer

Major finding: Interdependent genomic restructuring, or "chromoplexy," drives prostate cancer progression.

Approach: Somatic alterations and clonal tumor progression were characterized by whole-genome sequencing.

Impact: Prostate cancer evolution may be punctuated by successive genomic derangement events.

COMPLEX GENOMIC REARRANGEMENTS CONTRIBUTE TO PROSTATE CANCER EVOLUTION

Exome sequencing of human prostate cancer samples has characterized recurrent oncogenic mutations and chromosomal deletions that are critical for tumor initiation and progression. In addition, structural genomic rearrangements, such as *ETS* gene fusions, commonly occur in prostate adenocarcinomas and contribute to tumor progression, but how these chromosomal rearrangements accumulate during prostate carcinogenesis is unclear. To profile the genome-wide spectrum of somatic alterations in prostate cancer, Baca and colleagues performed whole-genome sequencing and DNA copy number profiling of 57 prostate tumors and matched normal tissues. This analysis identified complex chains of DNA rearrangements accompanied by significant DNA deletions that spanned breakpoints from distinct fusions. Computational modeling of this chromosomal rearrangement signature indicated that these events occurred in an interdependent process, referred to as "chromoplexy," which was detected in the majority of prostate cancers and frequently involved concurrent fusions between several distant chromosomal regions. In particular, chromoplexy was prevalent in highly expressed genomic regions of *ETS* fusion–positive prostate tumors and induced coordinated dysregulation of multiple cancer genes, including deletion of tumor suppressors and generation of oncogenic *ETS* fusions, suggesting that this process imparts a selective growth advantage that promotes prostate carcinogenesis. Analysis of common genomic deletions in relation to germline single-nucleotide polymorphisms classified these alterations as clonal or subclonal events in tumorigenesis and uncovered a consensus path of prostate cancer evolution consisting of sequential disruption of specific genes. Furthermore, a subset of chromoplexy-associated rearrangement chains was uniquely subclonal, suggesting that additional rounds of chromoplexy may drive prostate cancer progression. Although the mechanisms underlying this process are yet to be determined, these results support a continuum model of prostate cancer evolution in which several successive, punctuated chromoplexy events induce the accumulation of widespread structural rearrangements. ■

Baca SC, Prandi D, Lawrence MS, Mosquera JM, Romanel A, Drier Y, et al. Punctuated evolution of prostate cancer genomes. Cell 2013;153:666–77.