Overcoming drug resistance with EAI-432, an allosteric EGFR inhibitor for non-small cell lung cancer

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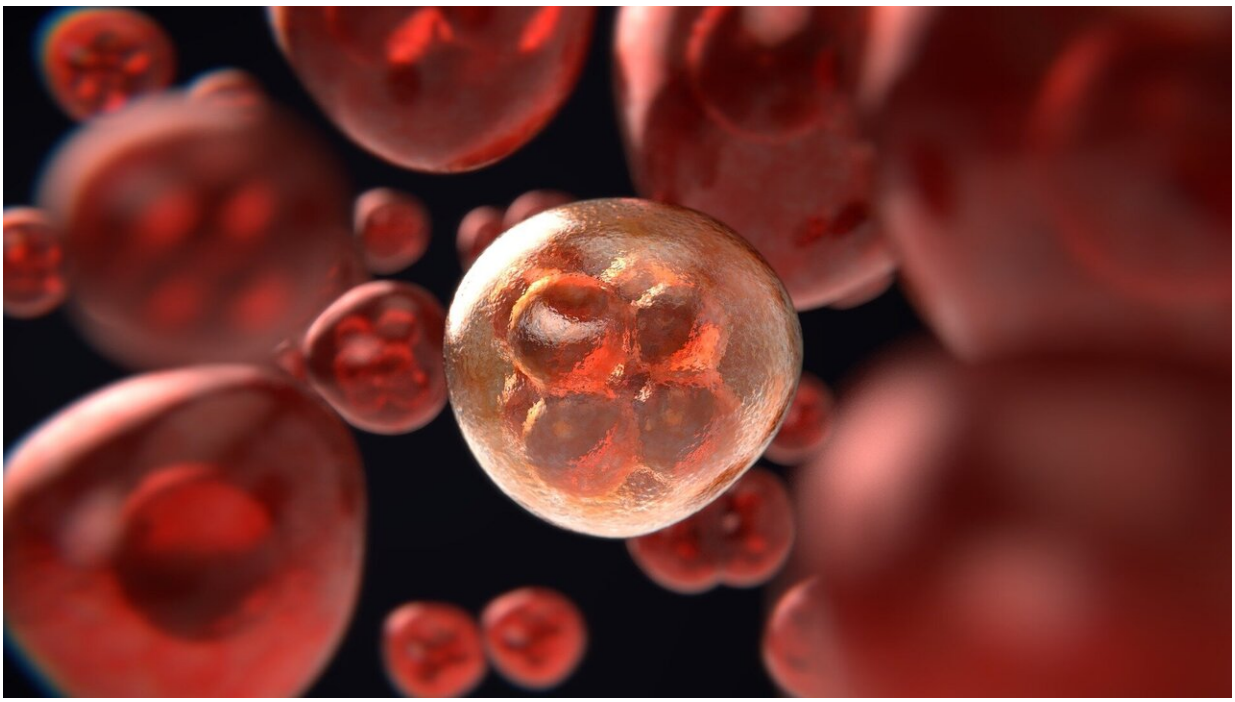

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Researchers at Dana-Farber Cancer Institute have developed a promising new drug candidate, EAI-432, to treat non-small cell lung cancers (NSCLC)driven by mutations in the EGFR gene, particularly the L858R mutation which is present in about one-third of NSCLC patients.

EAI-432, an allosteric inhibitor with high selectivity for the L858R mutation and subsequent clinical resistance mutations, provides a potential new approach for NSCLC patients for whom there are currently no approved targeted therapies. Combination with the current frontline therapy may also lead to enhanced outcomes, delaying the emergence of resistance in that patient population.

Approved EGFR inhibitors bind to the active site of the EGFR target, known as the ATP binding pocket. Unlike other fourth-generation compounds in development, EAI-432, binds to a site separate from the active ATP pocket on EGFR, causing conformational changes and effectively inhibiting it.

Preclinical studies presented at the AACR-NCI-EORTC meeting in October show that EAI-432 can co-bind with other EGFR-targeted inhibitors, representing a potential strategy for improving patient outcomes. In the poster presentation, Dana-Farber scientists shared that EAI-432 co-binds with osimertinib, a third-generation EGFR inhibitor, which is the standard-of-care therapy for patients with EGFR mutations. EAI-432 has good oral pharmacokinetics, is brain-penetrant, and has demonstrated promising efficacy in mouse xenograft models.

"Since EAI-432 binds in a different pocket to other EGFR inhibitors, it should address many of the resistance mechanisms that emerge and represents a potential new therapy for patients who have become resistant to the standard of care," says David Scott, Ph.D., director, Medicinal Chemistry Core at Dana-Farber. The compound may also be helpful in combination with current EGFR inhibitors like osimertinib as initial treatment in patients with the L858R mutation.

"Our approach represents a co-binding strategy—essentially a double-drugging with EAI-432 and osimertinib—that might provide patients with a better chance of delaying the emergence of resistance," adds

Michael Eck, MD, Ph.D., professor of Biological Chemistry and Molecular Pharmacology at Dana-Farber who has pioneered the allosteric EGFR program for the past 15 years.

"We also believe the combination of two agents may provide an improved overall impact on the target, potentially hitting it harder." With the allosteric plus ATP-site approach, both inhibitors can bind simultaneously, and if one dissociates the receptor remains inhibited.

Osimertinib is the leading treatment for patients with EGFR-mutant NSCLC, but resistance mutations, including L858R/C797S and L858R/T790M/C797S, have emerged in the clinic. No targeted therapies are approved for NSCLC patients with these mutations, representing a significant unmet need.

"EAI-432 has potential for NSCLC patients with these mutations who have developed resistance to osimertinib," explains Pasi Jänne, MD, Ph.D., director of the Lowe Center for Thoracic Oncology at Dana-Farber, adding that there are no allosteric EGFR inhibitors in the clinic at this time. "Only the allosteric approach allows for double-drugging of the mutant receptor, a potentially significant advance for the patient population with emerging mutation status."

Provided by Dana-Farber Cancer Institute