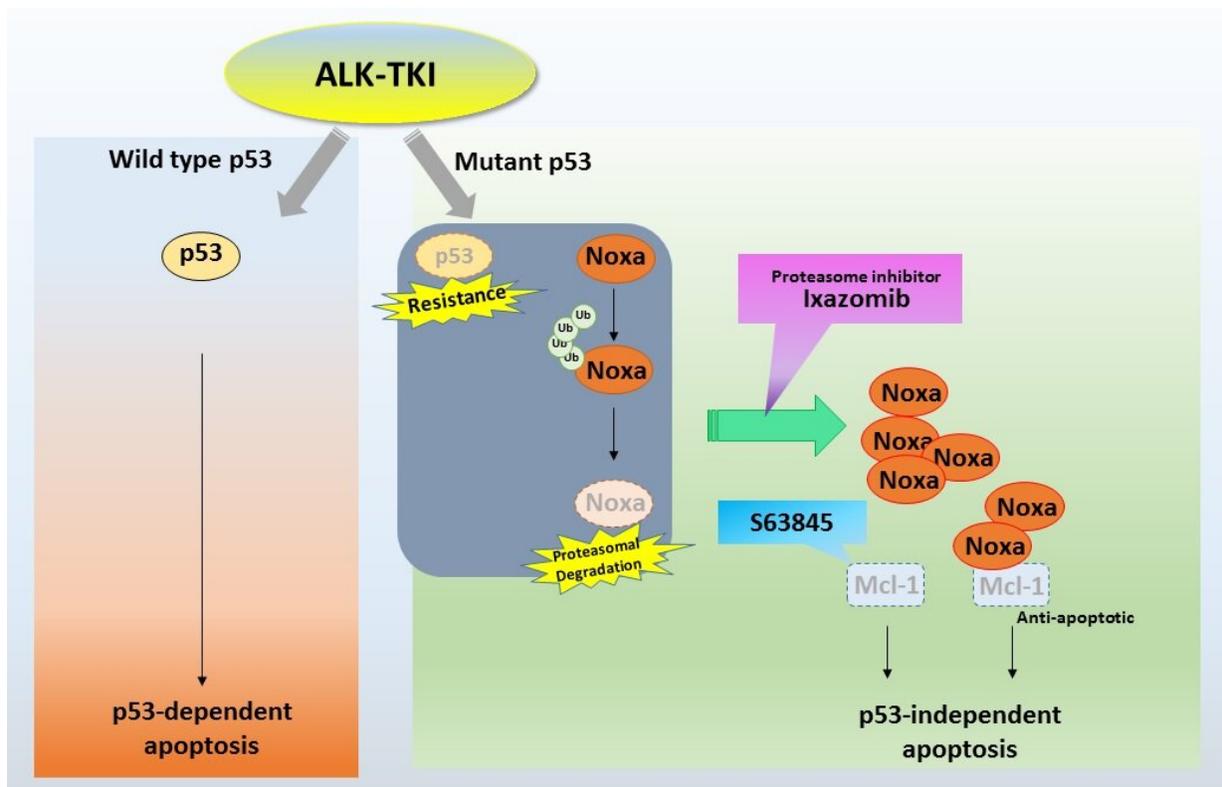


Potential combined drug therapy for lung cancer

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Graphical schema showing the mechanism for overcoming intrinsic resistance to ALK-TKIs owing to TP53 mutations. Credit: Kanazawa University

Most lung cancers are of a type called non-small-cell lung carcinoma (NSCLC). This type of cancer is relatively insensitive to chemotherapy, so NSCLC therapies are usually based on drug treatment. Alectinib is a

drug commonly used for treating patients with NSCLC. It addresses a gene rearrangement known as ALK that occurs in 3 to 5% of NSCLC patients (alectinib belongs to a class of drugs called ALK tyrosine kinase inhibitors). It has been unclear, however, whether there is a correlation between the use of alectinib and the poorer prognosis in ALK-NSCLC patients in which secondary cancer mutations are observed—the latter are known to occur with a frequency of about 25%. Now, Azusa Tanimoto from Kanazawa University and colleagues have investigated this correlation. They found that such secondary mutations reduce the efficacy of alectinib, but they also suggest how to overcome this issue.

The researchers looked at data on 124 NSCLC patients who were treated with ALK [tyrosine kinase inhibitors](#), including alectinib, and who had tested positive for the ALK gene rearrangement. Out of these, for 31 patients, a secondary gene rearrangement known as TP53 mutation was detected. Tanimoto and colleagues looked at whether there is a correlation between alectinib use and TP53 mutations in this group of patients.

The data showed that the cancer's progression-free survival was significantly poorer in patients with TP53 mutations who received alectinib treatment. (The same conclusion was obtained for other treatments with other ALK tyrosine kinase inhibitors.) The resistance to the drugs is linked to the loss of normal p53 function in ALK-rearranged NSCLC; p53 refers to a set of proteins that are known to play a role in preventing cancer formation.

The scientists then investigated how to overcome the adverse effect of alectinib when secondary TP53 mutations occur. Based on their insights into the biochemical mechanisms at play, they proposed to combine alectinib with another drug: ixazomib. The latter is a [drug](#) from the class of proteasome inhibitors, which block the action of proteasomes, which in turn break down proteins. Experiments in mice showed promising

results: general tumor shrinkage, and complete regression of 3 out of 8 tumors.

The findings of Tanimoto and colleagues show that the combined use of a proteasome inhibitor and alectinib restores the latter's unfavorable efficacy in ALK-rearranged NSCLC. The scientists further conclude: "Based on these [clinical and preclinical] data, this combination therapy is needed to be validated in ... [clinical trials](#)."

More information: Azusa Tanimoto et al, Proteasome Inhibition Overcomes ALK-TKI Resistance in ALK-Rearranged/TP53-Mutant NSCLC via Noxa Expression, *Clinical Cancer Research* (2020). [DOI: 10.1158/1078-0432.CCR-20-2853](https://doi.org/10.1158/1078-0432.CCR-20-2853)

Provided by Kanazawa University

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