Existing cancer drug ponatinib could be repurposed to fight certain aggressive cancers

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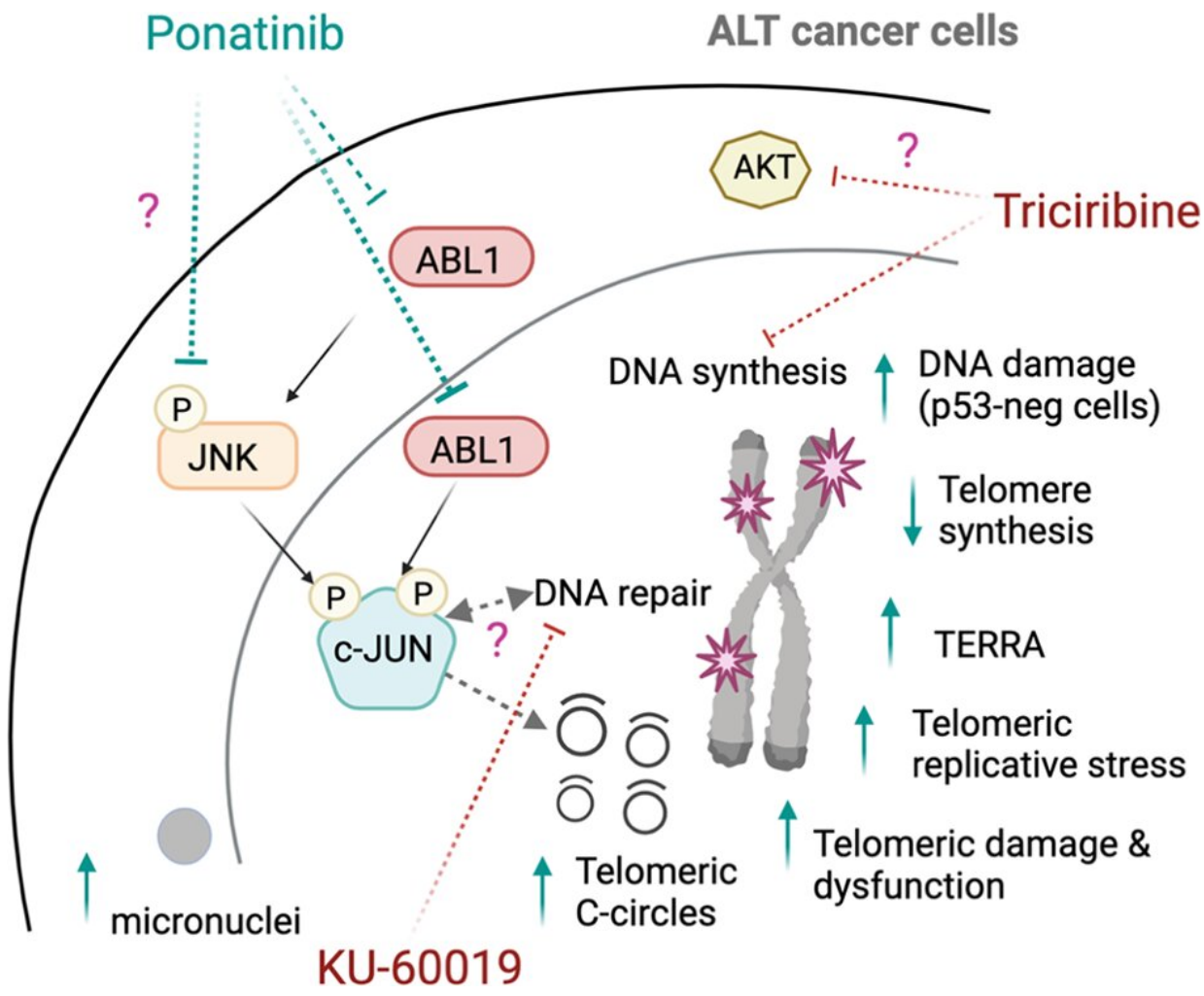

Schematic summary of mechanisms of action of ponatinib in ALT cells. Ponatinib disrupts alternative lengthening of telomeres mechanisms by inducing telomeric C-circles and telomere dysfunction concomitant with an inhibition of

telomere synthesis in ALT cells. The effects of ponatinib on ALT activity are mediated by at least an inhibition of an ABL1-JNK-JUN signaling circuit leading to JUN degradation. Furthermore, synergistic combinations of ponatinib and either triciribine or KU-60019 could be effective on cancer cells relying on ALT. P phosphorylation, neg negative. Created with BioRender.com. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-37633-3

A team of scientists led by Nanyang Technological University, Singapore (NTU Singapore) has found that an existing cancer drug could be repurposed to target a subset of cancers that currently lack targeted treatment options and are often associated with poor outcomes.

This subset of cancers makes up 15% of all cancers and is especially prevalent in aggressive tumors such as osteosarcoma (bone tumor) and glioblastoma (brain tumor).

These cancerous cells stay "immortal" using a mechanism called the alternative lengthening of telomeres (ALT), but the team has demonstrated that ponatinib, a cancer drug approved by the US Food and Drug Administration, blocks key steps in the ALT mechanism that leads it to fail.

Reporting their findings based on laboratory experiments and preclinical animal studies, the scientists found that ponatinib helped to shrink bone tumors (a type of ALT cancer) without causing weight loss, a common side effect associated with cancer drugs. In mice with tumors treated with ponatinib, they found a reduction in a biomarker for ALT cancer as compared to untreated mice. The findings are published in the journal *Nature Communications*.

The researchers say that the findings move them a step closer to

developing a targeted therapeutic option for ALT cancers, which lack clinically approved targeted treatments to date.

Dr. Maya Jeitany and a team of researchers from the NTU School of Biological Sciences, together with collaborators from the Cancer Science Institute of Singapore and the Yong Loo Lin School of Medicine, both at the National University of Singapore (NUS), and the Genome Institute of Singapore at the Agency for Science, Technology and Research (A*STAR), are seeking to address this unmet need.

"A prominent feature of cancer is its ability to evade cell death and acquire indefinite replication—to stay immortal, in other words—which it can do through the alternative lengthening of telomeres (ALT) mechanism. While a sizeable portion of cancer cells depend on this mechanism, there is no clinically approved targeted therapy available.

"Through our study, we identified a novel signaling pathway in the ALT mechanism and showed that the FDA-approved drug ponatinib inhibits this pathway and holds exceptional promise in stopping the growth of ALT cancer cells. Our findings may provide a new direction for the treatment of ALT cancers by repurposing an FDA-approved drug for these types of tumors," said Jeitany, study lead and senior research fellow at NTU's School of Biological Sciences

Commenting as an independent expert, Assistant Professor Valerie Yang, medical oncologist with the Department of Lymphoma and Sarcoma at the National Cancer Center in Singapore, said, "Sarcomas and glioblastomas are both highly complex cancers that are more prevalent in young people and currently have limited treatment options. The identification of a drug that is FDA-approved which can be repurposed to target ALT, an Achilles heel in these cancers, is very exciting."

The study aligns with NTU 2025, the University's five-year strategic plan, which aims to address humanity's grand challenges by responding to the needs and challenges of healthy living.

How cancer cells replicate and grow

Telomeres are protective "caps" at the tips of every chromosome, which carries our DNA. With each cell division, a bit of the telomeres is naturally snipped off, until they become too short, leading to cell death.

Most cancer cells bypass this process by activating an enzyme called telomerase, which lengthens the telomeres so that the cells can replicate indefinitely. However, about 15% of cancers lengthen their telomeres through alternative pathways, rather than activating telomerase. This mechanism is known as the alternative lengthening of telomeres (ALT).

To date, there is no clinically approved targeted treatment for ALT cancers. Furthermore, many ALT cancers, such as osteosarcoma and glioblastoma, show resistance to chemotherapy, highlighting the need for a more targeted form of treatment.

Drug affects telomeres in ALT cancer cells

Through high-throughput drug screening—a process of screening large numbers of relevant biological or pharmacological compounds—and subsequent testing of shortlisted compounds, the scientists discovered that ponatinib, a drug approved by the US Food and Drug Administration for a type of bone marrow cancer, can kill ALT cancer cells effectively.

When osteosarcoma and liposarcoma (a tumor that grows in fatty tissues) cells were treated with ponatinib, the scientists found that the

drug led to DNA damage, dysfunctional telomeres, and triggered senescence, a process in which the cell stops dividing. Importantly, the synthesis of telomeres in the cells also dropped after 18 to 20 hours of treatment with the drug.

Pre-clinical studies conducted on mice that had received transplants of human bone cancer cells further validated the potential of ponatinib. The drug reduced the tumor sizes without affecting the mice's body weight, a common side effect associated with cancer treatments.

In mice with tumors treated with ponatinib, there was also a reduction in a biomarker for ALT cancer as compared to untreated mice—an indicator that the drug was effective in inhibiting ALT cancer growth.

The scientists ran further tests to identify ponatinib's mode of action on telomeres in ALT cancer cells and identified a signaling pathway (a series of chemical reactions in which a group of molecules in a cell work together to control a cell function) that could be responsible for the drug's effect on ALT.

The researchers are now studying further how ponatinib affects telomeres to understand in more detail the signaling pathway they have identified. They are also assessing potential ponatinib-based combinatorial drug treatments for ALT cancers.

More information: Frances Karla Kusuma et al, Signalling inhibition by ponatinib disrupts productive alternative lengthening of telomeres (ALT), *Nature Communications* (2023). DOI: 10.1038/s41467-023-37633-3

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