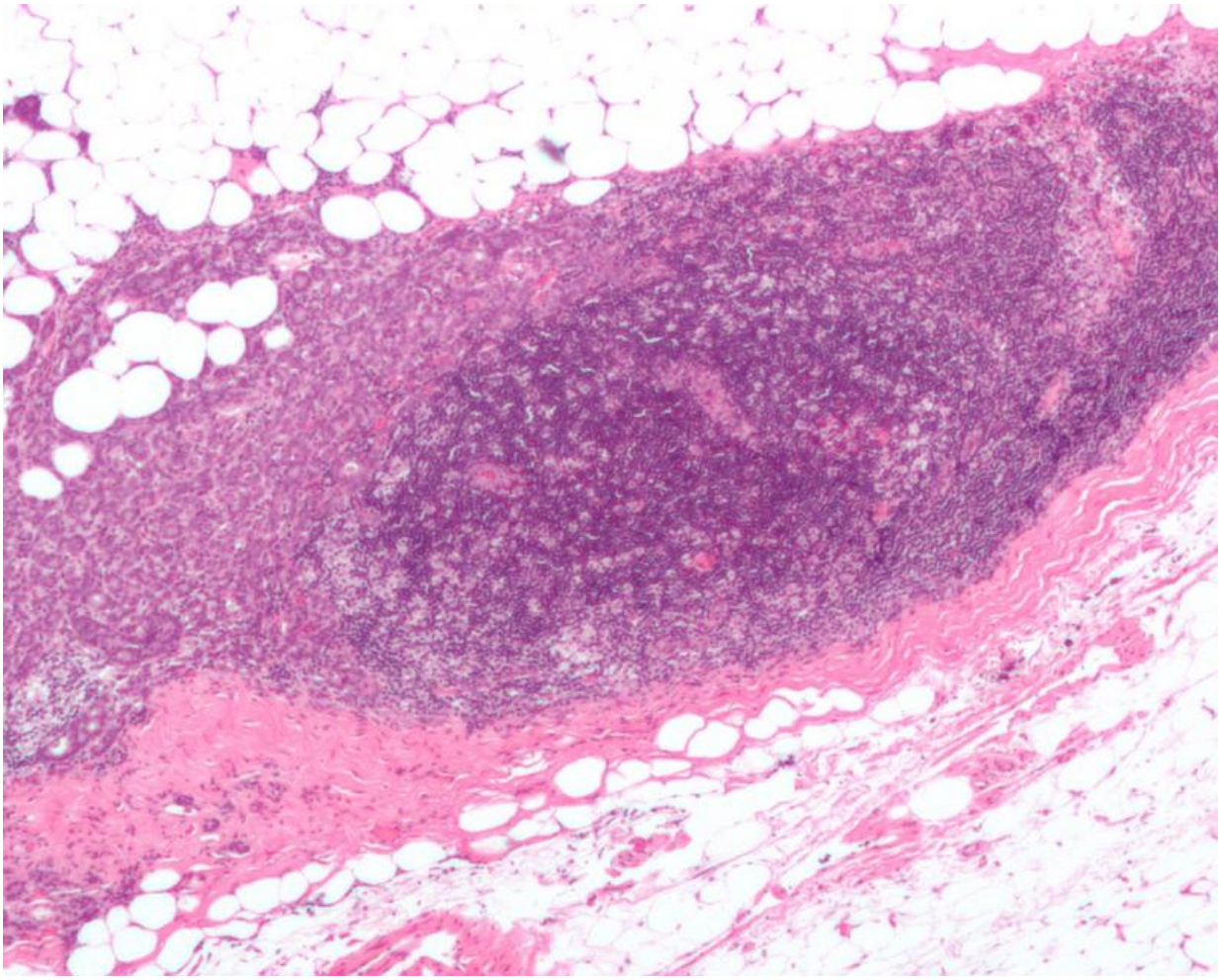
MedicalXpress

Breast cancer resistance to CDK4/6 inhibitors arises in many ways

March 28 2016



Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Breast cancer cells became resistant to therapeutics targeting CDK4/6, such as palbociclib (Ibrance), in multiple ways, and preclinical studies suggested different combinations of therapeutics may prevent and overcome the acquisition of resistance to these anticancer agents, according to research published in *Cancer Research*, a journal of the American Association for Cancer Research.

"The CDK4/6 inhibitor palbociclib is now an important part of treatment for patients with ER-positive breast cancer," said Nicholas C. Turner, FRCP, PhD, a team leader at the The Institute of Cancer Research, London, and consultant at The Royal Marsden in London, United Kingdom. "Unfortunately, most patients eventually have disease progression because their tumors acquire resistance to the anticancer agent.

"We set out to identify how ER-positive breast cancer cells become resistant to CDK4/6 inhibitors, such as palbociclib, in order to identify potential combinations of anticancer agents that could delay the onset of resistance or overcome resistance once it has arisen," continued Turner. "Our preclinical studies identified a triplet therapeutic combination that could significantly delay the onset of resistance to CDK4/6 inhibitors, and this combination is being tested in phase II clinical trials. We also found that resistance arises through multiple mechanisms, suggesting that we will need to develop tests to identify the particular mechanism driving resistance in individual patients in order to determine the best treatment option post acquisition of resistance."

Turner, Violeta Serra, PhD, a principle investigator at the Vall d'Hebron Institute of Oncology in Barcelona, Spain, and colleagues initially screened a library of 3,530 compounds for their ability to work with the CDK4/6 inhibitor palbociclib to block the growth of ER-positive breast cancer cell lines in vitro. Among the compounds that synergized with palbociclib were several that inhibited the PI3K pathway.

In a patient-derived xenograft model, combining a CDK4/6 inhibitor, a hormone therapy (fulvestrant), and a PI3K inhibitor caused greater tumor regression compared with fulvestrant paired with either a CDK4/6 inhibitor or a PI3K inhibitor. These data provide additional biological rationale for recently initiated phase II clinical trials testing these triplets of anticancer agents, and suggest that they have the potential to delay disease resistance, explained Turner.

Further molecular analysis identified several mechanisms by which ER-positive breast cancer cells became resistant to CDK4/6 inhibitors, including amplification of the CCNE1 gene and loss of the RB1 gene. In vitro analysis showed that cells that acquired resistance to CDK4/6 inhibitors through CCNE1 gene amplification were sensitive to targeting of CDK2 whereas those that acquired resistance through RB1 gene loss were not sensitive.

"Our next step is to look at tumor samples from patients with ER-positive breast cancer that has become resistant to CDK4/6 inhibitors to determine whether the mechanisms of resistance that we have identified in our preclinical study reflect what happens in the clinic," said Turner. "If they do, we will need to develop tests to screen for these different resistance mechanisms so that patients can be directed to the most appropriate treatment options."

Provided by American Association for Cancer Research