

Patients with aberrations in two genes respond better to drugs blocking a well-known cancer pathway

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Cancer patients with mutations or variations in two genes -- PIK3CA and PTEN -- who have failed to respond to several, standard treatments, respond significantly better to anti-cancer drugs that inhibit these genes' pathways of action, according to research presented at the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today.

Dr Filip Janku (MD, PhD), assistant professor in Investigational [Cancer Therapeutics](#) at MD Anderson Cancer Center (Houston, USA), told the meeting that [mutations](#) in PIK3CA and aberrations (loss of function or mutation) in PTEN were present in a wide range of tumours and were thought to be involved in the development of cancer. These genes act via a pathway known as the PI3K/AKT/mTOR pathway, and so inhibiting the pathway could improve the patients' response to treatment.

The researchers tested 1656 patients with a variety of cancers and found that 146 (9%) had PIK3CA mutations, 150 (13%) had PTEN aberrations and 14 (1%) had both.

They treated 134 of the patients who had PIK3CA mutations, PTEN aberrations or both in early-phase clinical trials that included drugs that block the PI3K/AKT/mTOR pathway. The patients had failed an average of three, previous treatments. Of these patients, 107 were also tested for mutations in another, known cancer-causing gene, KRAS.

Dr Janku said: "We found that heavily pre-treated patients with PIK3CA mutations, PTEN aberrations, or both had a significantly higher response rate on protocols incorporating PI3K/AKT/mTOR inhibitors compared to patients without known PIK3CA/PTEN aberrations treated on the same protocols. In addition, we noticed that patients who had these and also simultaneous mutation in codons 12 or 13 of KRAS (which is a likely mechanism of [drug resistance](#)) did not respond to protocols with PI3K/AKT/mTOR inhibitors.

"Furthermore, it looks as if treatment with a single agent may not be sufficient, as patients with PIK3CA mutations and/or PTEN aberrations treated with drug combinations that included PI3K/AKT/mTOR inhibitors had higher response rate than patients treated with PI3K/AKT/mTOR inhibitors alone."

Of the patients who were treated with PI3K/AKT/mTOR inhibitors, 23 out of 134 (17%) had a partial response to the therapy (where the tumour shrinks by at least 30%) and 9 out of 134 (7%) had stable disease for six months or more, while only 26 out of 458 patients (6%) without a PIK3CA mutation or PTEN aberration had a partial response when treated with the same therapies. Of the 26 patients who also had a KRAS mutation in codons 12 or 13, only one (4%) had a partial response, compared to 18 out of 81 (22%) of patients without the KRAS mutation. Among the patients treated with a single agent, PI3K/AKT/mTOR inhibitor, only one out of 40 (2.5%) had a partial response to the treatment compared to 22 out of 94 (23%) of the patients treated with a combination of agents, including a PI3K/AKT/mTOR inhibitor.

Dr Janku said: "These results suggest that heavily pre-treated patients with mutations or aberrations in PIK3CA, PTEN or both are more likely to have tumours that respond and shrink when they are treated with a combination of drugs that include PI3K/AKT/mTOR inhibitors, compared with patients treated the same way but whose PIK3CA and

[PTEN](#) status is unknown. Therefore, screening for these mutations and [aberrations](#), as well as KRAS mutations, can make treatments with PI3K/AKT/mTOR inhibitors more effective for patients."

He said that further investigation was required as the study had several limitations that included the fact that the patients had a variety of cancers, received diverse treatments, were treated on different dose levels and the study was not randomised. "Our findings warrant further prospective investigation especially since many PI3K/AKT/mTOR inhibitors are entering the clinical arena."

There are a number of PI3K/AKT/mTOR inhibitors currently being developed; however, none of the ones that inhibit the PI3K or AKT have been approved yet for use in the clinic. Examples of mTOR [inhibitors](#) that have been approved for treatment of cancers include temsirolimus and everolimus.

Professor Stefan Sleijfer, the scientific chair of the EORTC-NCI-AACR Symposium, from Erasmus University Medical Centre (The Netherlands), commented: "This study is interesting because it provides important hints as to how we can select [cancer patients](#) who are likely to benefit from [PI3K/AKT/mTOR](#) inhibitor-containing regimens. If confirmed, this may be the way to come to a more personalised treatment approach with these compounds."

More information: Abstract no: 246. Proffered papers, plenary session 6, 15.00 hrs, Thursday 8 November.

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