EORTC-NCI-AACR Symposium Press Information

Researchers find new target for stopping tumours developing their own blood supply: phase I trial shows first drug to inhibit ALK-1 receptor is safe and effective

Researchers have found that a newly developed drug, which is aimed at a particular receptor involved in the development of blood vessels that sustain tumour growth, is active in patients with advanced cancers and, in some cases, has halted the progress of the disease. The drug, ACE-041, targets a different molecular pathway to other anti-angiogenesis drugs and may provide a new option to treat cancer.

Results from a phase I clinical study of ACE-041 were presented at the 22nd EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Berlin today (Friday). The drug targets a receptor known as activin receptor-like kinase-1 (ALK-1), which regulates the formation of new networks of blood vessels needed for tumour growth – a process known as angiogenesis. While existing anti-angiogenic drugs such as bevacizumab, sunitinib and sorafenib target other angiogenesis receptors such as VEGF, ACE-041 is one of the first to target the ALK-1 pathway.

Professor Sunil Sharma, the Jon and Karen Huntsman Presidential Professor of Cancer Research at the Huntsman Cancer Institute, University of Utah, Salt Lake City (USA), told the meeting that the connection of ALK-1 with angiogenesis was made with the discovery that mutations in the ALK-1 gene caused a condition known as hereditary haemorrhagic telangiectasia 2 (HHT2), which is characterised by impaired formation of capillary beds and causes red markings on the skin.

Acceleron Pharma, a biotechnology company in Cambridge, Massachusetts (USA), designed ACE-041 to inhibit ALK-1 signalling and asked Prof Sharma to be one of the investigators to conduct the first-in-man phase I clinical trial of the drug to see if it would inhibit tumour angiogenesis.

“Since ALK-1 is only transiently expressed on proliferating endothelial cells (the cells that line the inner surface of blood vessels), in contrast to the VEGF receptors which are constitutively expressed on endothelial and other cells, it may be a more selective target for the inhibition of angiogenesis,” said Prof Sharma. “ALK-1 expression on tumour vasculature has been noted on tumour biopsy samples from a wide range of tumour types.”

The phase I study enrolled patients with a range of advanced solid tumours that had spread to other parts of the body or that were inoperable, such as multiple myeloma, non-small cell lung cancer (NSCLC), head and neck cancers and carcinoid tumours (carcinoma-like neuroendocrine tumours that typically originate in the small intestine or appendix). Most patients had been treated unsuccessfully with a range of other treatments, including anti-VEGF drugs, before joining the trial. They were treated as out-patients and ACE-041 was given via subcutaneous injection.

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“As of early September, 25 patients have been enrolled in the study, and we have escalated from the starting ACE-041 dose level of 0.1 mg/kg up to 4.8 mg/kg. One patient with head and neck

cancer had a partial response, three patients have had stable disease and several other patients have had strongly positive responses as shown by FDG-PET scans. So far, ACE-041 has been well tolerated, with the most common adverse events being peripheral oedema, fatigue, anaemia, headache and nausea," said Prof Sharma.

"It has been very encouraging to see so many signals of efficacy in this trial, in particular because of the study population. These are end-stage cancer patients, who have already been treated with and become refractory to multiple lines of standard therapy. It has also been encouraging to see signals of ACE-041 activity in a wide range of tumour types, since this aligns with our hypothesis that ACE-041 may have anti-tumour activity in any tumour that has angiogenic activity, regardless of tumour histology. It is also important to note that while we have demonstrated significant activity with ACE-041 monotherapy in this study, we might expect to see even more efficacy in future studies with ACE-041 used in combination with other therapies."

Prof Sharma and his colleagues are planning further investigations of the safety and tolerability of the drug in an additional group of patients and hope to start phase II studies of ACE-041 in 2011.

"The anti-VEGF angiogenesis inhibitors, including bevacizumab, sunitinib and sorafenib, have been an important addition to the armamentarium of anti-cancer therapies," said Prof Sharma. "However, their efficacy is somewhat limited since tumours eventually develop the ability to stimulate angiogenesis with non-VEGF angiogenic factors. They also have serious side-effects that arise from effects on blood vessels in normal tissues. Since ACE-041 inhibits angiogenesis in a completely different way, it may have synergistic efficacy with VEGF-inhibitors, and be effective in patients who have developed resistance to VEGF-inhibitors."

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Abstract no: 465. Poster on Friday 19 November in the Exhibition Hall (ground level) from 07.00/08.00 hrs to 13.00 hrs CET.

Notes:
[1] EORTC [European Organisation for Research and Treatment of Cancer, NCI [National Cancer Institute], AACR [American Association for Cancer Research].
[2] This study was funded by Acceleron Pharma Inc. For further information on ACE-041 and Acceleron Pharma, visit: www.acceleronpharma.com

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