EORTC-NCI-AACR Symposium Press Information

NB: due to unforeseen circumstances, Dr Robert Wenham is unable to attend the Symposium. His co-author Dr Shahneen Sandhu will attend the poster session in his place.

PARP inhibitor, MK-4827, shows anti-tumour activity in first trial in humans

A new drug that targets proteins responsible for helping cancer cells to repair damage to their DNA has shown promising anti-tumour activity in its first trial in humans. Some patients with a range of solid tumours, many of whom had been treated unsuccessfully for their cancer with other therapies, have seen their tumours shrink or stabilise for periods of between 46 days to more than a year. The research will be presented at the 22nd EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Berlin today (Thursday).

Laboratory studies of the drug, MK-4827, have shown that it inhibits proteins called PARP1 and PARP2 (poly(ADP)-ribose polymerase). PARP is involved in a number of cellular processes and one of its important functions is to assist in the repair of single-strand breaks in DNA. If one single-strand broken DNA is replicated (replication occurs before cell division) then it results in a double-strand break. By inhibiting the action of PARP, double-strand breaks occur, leading to cell death. Tumours that are caused by a mutation in the BRCA1 or BRCA2 genes are susceptible to cell death through PARP inhibition because correctly functioning BRCA genes assist in repairing double-strand DNA breaks via a process called homologous-recombination-dependent DNA repair, whereas mutated versions are unable to perform this role. Normal cells don't replicate as often as cancer cells and they still have homologous repair operating; this enables them to survive the inhibition of PARP and makes PARP a good target for anti-cancer therapy.

In a Phase I trial conducted at the H Lee Moffitt Cancer Center (Tampa Florida, USA), University of Wisconsin-Madison (Madison, USA) and the Royal Marsden Hospital (London, UK), MK-4827 was given to 59 patients (46 women, 13 men) with a range of solid tumours such as non-small cell lung cancer (NSCLC), prostate cancer, sarcoma, melanoma and breast and ovarian cancers. Some patients had cancers caused by mutations in the BRCA1/2 genes, such as breast and ovarian cancer, but others had cancers that had arisen sporadically.

The drug was given in pill form once a day, and the researchers found that the maximum tolerated dose was 300 mg a day. Dr Robert Wenham, Clinical Director for Gynecologic Oncology in the Department of Women's Oncology at the Moffitt Cancer Center, who is presenting data on behalf of the participating investigators, said: "MK-4827 is generally well tolerated, with the main dose-limiting toxicity being thrombocytopenia – an abnormal decrease in the number of platelets in the circulatory blood. The most common side effects are mild nausea, vomiting, anorexia and fatigue."

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The researchers saw anti-tumour responses in both sporadic and BRCA1/2 mutation-associated cancers. Ten patients with breast and ovarian cancers had partial responses, with progression-

free survival between 51-445 days, and seven of these patients are still responding to treatment. Four patients (two with ovarian cancer and two with NSCLC) had stable disease for between 130-353 days.

Dr Wenham said: “Most patients in the trial had exhausted standard therapies and those who responded to this drug have benefited. Several patients have been receiving treatment for more than a year. The responses mean that MK-4827 is working as hoped and justify additional studies. Just how well MK-4827 works compared to other treatments is the goal of the next set of studies.”

He gave a possible explanation as to why patients with cancers that were not caused by BRCA1/2 mutations also responded to the PARP inhibition. “BRCA is a tumour suppressor gene that assists in repairing double stranded DNA breaks. In BRCA-mutation related cancers, loss of both copies of the gene results in a non-functional protein and thus BRCA deficiency. Because BRCA works with other proteins, BRCA-pathway related deficiency can be seen in the absence of two mutated copies of the BRCA genes. This may explain why responses have been reported for this class of drugs in non-BRCA mutant cancers.”

Dr Wenham and his colleagues are recruiting more patients for additional studies and an expansion of the existing trial. “We want to understand what types of cancers will respond best to treatment with MK-4827,” he said. “Cohorts are currently open for patients with ovarian cancer patients without germ-line BRCA mutations, and prostate cancer patients. Cohorts will open soon for patients with T-cell prolymphocytic leukaemia, endometrial cancer, breast cancer and colorectal cancer. MK-4827 is also being studied in combination with conventional chemotherapy drugs.”

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Abstract no: 362. Poster on Thursday 18 November in the Exhibition Hall (ground level) from 08.00/09.00 hrs to 18.00 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 Merck & Co. Inc. MK-4827 is owned by Merck & Co. Inc.

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