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Investigational PARP inhibitor promising in BRCA-related cancers

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An investigational new PARP inhibitor, BMN 673, is showing early responses in patients with heavily pretreated, advanced, BRCA-related cancers of the breast and ovary, according to phase I clinical trial results presented here at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19-23.

When there is damage to DNA in human cells, two proteins, PARP 1 and 2, recruit proteins that can repair the damage associated with loss of BRCA proteins. Mutations in BRCA genes often result in inefficient repair of damaged DNA, which increases the risk for developing certain cancers, including cancers of the breast and ovary. Inhibiting PARP, therefore, prevents the repair of damaged DNA, leading to cell death. While some PARP inhibitors have been tested in various settings, none are approved to date.

"BMN 673 is the most potent PARP inhibitor in clinical development and has optimized pharmaceutical properties: it is well absorbed orally, has substantial single-agent antitumor activity, and has a long half-life allowing once-daily dosing," said Zev A. Wainberg, M.D., assistant professor of medicine at the Jonsson Comprehensive Cancer Center of the University of California Los Angeles School of Medicine. "The clinical data to date are promising and compare favorably with results from clinical trials with other PARP inhibitors. We observed high objective and clinical benefit response rates in BRCA-related breast and ovarian cancers at low, oral, once-daily doses.

"Based on this phase I study, we feel there's a good chance that patients with BRCA-related cancers who meet the study eligibility criteria will have disease control for a meaningful period of time with relatively few side effects. However, randomized trials are necessary to demonstrate whether this will translate into improvements in progression-free and overall survival relative to currently available therapies," said Wainberg.

He and colleagues conducted a phase I trial to evaluate the safety and efficacy of BMN 673 in a two-stage dose escalation/expansion study. So far, they have recruited 39 and 41 patients to the escalation phase and expansion phase, respectively. Patients were 18-82 years old, and they had undergone one to 13 prior therapies.

Fifty participants—18 with breast cancer, 28 with ovarian cancer, three with pancreatic cancer, and one with prostate cancer—had BRCA mutations in their tumors. Wainberg reported that to date, among the patients with BRCA mutations in their tumors, 44 percent of those with ovarian cancer and 44 percent with breast cancer had an objective response. Overall, 82 percent of the ovarian cancer patients and 72 percent of the breast cancer patients had clinical benefit (measured by imaging data and/or CA 125 levels for ovarian cancers and by imaging data for breast cancers).

In patients being treated at the 1 mg dose recommended for future trials, 50 percent of the breast cancer patients with BRCA mutations had an objective response and 86 percent had clinical benefit. Of the three patients with pancreatic cancer, two have had stable disease.

Fewer than 20 percent of the patients had grade 3 adverse events including fatigue, anemia, neutropenia, and thrombocytopenia, and one patient had a grade 4 toxicity.

Given the high objective and clinical benefit response rates in breast

cancer patients, the investigators have recently initiated a phase 3 trial in metastatic breast cancer with BRCA mutations, according to Wainberg.

Among those with BRCA-unrelated cancers recruited to the phase 1 trial, one of the seven currently evaluable patients with small-cell lung cancer (SCLC) has responded, according to Wainberg. This patient, whose tumor metastasized extensively, has an ongoing partial response, he explained. "A solid partial response in a patient with SCLC provides some optimism about finding indications other than BRCA-related tumors that will benefit from treatment with BMN 673," he said.

More information: Abstract Number: C295
Presenter: Zev A. Wainberg, M.D.

Title: Update on first-in-man trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors

Background: BMN 673 is the most potent and specific inhibitor of PARP1/2 in clinical development (IC50