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Novel Drug Combination Showed Antitumor Activity in Patients With Incurable BRCA-deficient Cancers

- Patients received sapacitabine and seliciclib as sequential treatments.
- Several patients with BRCA mutations achieved disease response or experienced prolonged stable disease.
- BRCA mutation carrier status may be a potential biomarker for response.

WASHINGTON, D.C. — When given sequentially, two orally available experimental drugs — sapacitabine and seliciclib — worked together to elicit antitumor effects in patients with incurable BRCA-deficient cancers, according to phase I data presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10. There are no drugs yet approved specifically for this patient population.

"Since we began to enroll predominantly patients who carried a BRCA mutation in the study, we have seen several responses among those patients, as well as instances of prolonged stable disease lasting more than a year," said Geoffrey Shapiro, M.D., Ph.D., associate professor of medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, Mass.

Shapiro and colleagues initially designed the phase I study to exploit preclinical results that suggested that sapacitabine and seliciclib worked together synergistically. Sapacitabine is an oral nucleoside analogue that induces single-strand damage to DNA. If the damaged DNA is not repaired, it ultimately results in cell death. Repair of sapacitabine-induced DNA damage requires BRCA proteins, suggesting that BRCA-deficient cancers may be particularly sensitive.

Seliciclib inhibits cyclin-dependent kinases (CDKs); CDK inhibition has been shown to augment cancer cell death induced by drugs like sapacitabine by multiple mechanisms, in part by suppressing DNA repair pathways.

Researchers enrolled 38 patients with incurable solid tumors and adequate organ function. They assigned patients to treatment with sapacitabine twice daily for seven days followed by seliciclib twice daily for three days.

Four patients with BRCA-deficient pancreatic, breast or ovarian cancers had confirmed ongoing partial responses to the drug combination. Three patients are experiencing partial responses, with the longest lasting more than 78 weeks.

Furthermore, researchers observed stable disease of 12 weeks or more in eight additional patients, including two patients with ovarian and breast cancers who carried the BRCA mutation and whose stable disease lasted 64 weeks and 21 weeks, respectively.

The maximum tolerated doses were 50 mg sapacitabine twice daily and 1,200 mg seliciclib twice daily. Dose-limiting toxicities included reversible transaminase elevations and neutropenia. Adverse events were mild to moderate in intensity.

Results of skin biopsies after treatment showed a 2.3-fold increase in DNA damage induced by sapacitabine, as measured by gamma-H2AX immunohistochemistry. Additional DNA damage occurred after treatment with seliciclib with a 0.58-fold further increase in gamma-H2AX staining.

"Initially in the dose-escalation phase of the trial, this combination produced stable disease of modest duration in some patients, which has been the experience with sapacitabine and CDK inhibitors in solid tumors," Shapiro said. "However, other published research during the course of the study indicated the role of the homologous recombination pathway, dependent on BRCA proteins, for repair of sapacitabine-induced DNA damage. Additionally, the CDK proteins were implicated in DNA repair pathways. These findings prompted us to enroll patients with advanced cancer who had the BRCA mutation and led to the first partial responses and instances of durable stable disease."

Based on these emerging results, Shapiro and colleagues continue to enroll appropriate patients in the trial, where the combination has been most efficacious. Additional schedules of the combination therapy are under evaluation. According to Shapiro, if further work continues to confirm BRCA mutation status as a potential biomarker for response, these drugs, both individually and in combination, should ultimately be evaluated in larger groups of patients who carry BRCA mutation. If successful, these drugs may provide an important treatment alternative for patients with BRCA-deficient cancers.

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Abstract Number: LB-202

Presenter: Geoffrey Shapiro, M.D., Ph.D.

Title: Responses to sequential sapacitabine and seliciclib in patients with BRCA-deficient solid tumors

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Background: Sapacitabine is an orally administered nucleoside analogue; the active metabolite, CNDAC (2'-C-cyano-2'-deoxy-1-β-D-arabino-pentofuranosylcytosine), generates single-strand DNA breaks that are converted to double-strand DNA breaks (DSBs) during subsequent replication, resulting in cell death if unrepaired. Repair of CNDAC-induced DSBs is dependent on the homologous recombination (HR) repair pathway. Depletion or inhibition of components of the HR pathway (including ATM, BRCA1/2, Rad 51 and XRCC3) greatly sensitizes tumor cell lines to CNDAC-induced cell death in vitro. Seliciclib is an orally bioavailable inhibitor of cyclin-dependent kinases (CDKs) 2, 7 and 9. CDK2 has been shown to participate in DNA repair and to be a therapeutic target in BRCA-deficient cancers. Seliciclib inhibits DSB repair, and also reduces BRCA1 and BRCA2 mRNA levels in cancer cell lines, sensitizing tumor cells to CNDAC. This phase I study evaluates sequential sapacitabine and seliciclib.

Methods: Dose escalation was conducted in patients with incurable solid tumors and adequate organ function with sapacitabine b.i.d. x 7 consecutive days (d1-7), seliciclib b.i.d. x 3 consecutive days (d8-10) followed by 11 days of rest. At least 3 patients were evaluated per dose level. MTD was the highest dose level at which less than one-third of at least 6 patients experienced cycle 1 DLT. Skin biopsies were obtained to assess DNA damage following sapacitabine (d8 vs pre-treatment) and further augmentation of DNA damage after seliciclib (d11 vs d8).

Results: 38 patients were treated. The MTD is sapacitabine 50 mg b.i.d./seliciclib 1200 mg b.i.d. DLTs were reversible transaminase elevations and neutropenia. The most frequent adverse events (all cycles, regardless of causality) included, fatigue, abdominal pain, diarrhea, constipation, decreased appetite, nausea, vomiting, anemia, neutropenia, pyrexia, AST elevation, alkaline phosphatase elevation, creatinine elevation, hyperglycemia, hypophosphatemia, cough and alopecia, the majority mild to moderate in intensity. Skin biopsies showed a 2.3-fold increase in γ-H2AX staining post-sapacitabine (n=16; p=0.007) and a further 0.58-fold increase post-seliciclib (n=12; p=0.069). Four confirmed PRs occurred in patients with pancreatic, breast (2 pts) and ovarian cancer, all BRCA mutation carriers, lasting 21, 78+, 36+ and 42+ weeks, respectively. SD as best response >/= 12 weeks was observed in 8 additional patients, including two BRCA mutation carriers with ovarian and breast cancer, lasting 64 and 21 weeks, respectively.

Conclusion: Sequential sapacitabine and seliciclib is safe with preliminary antitumor activity. BRCA mutation carrier status may be a potential biomarker for response across multiple tumor types. An alternative schedule with concomitant administration of sapacitabine and seliciclib is currently under evaluation.