Olaparib and Investigational PI3K Inhibitor BKM120 Combination Active Against Ovarian and Breast Cancer Subtypes

PHILADELPHIA — Combination treatment with the poly ADP-ribose polymerase (PARP) inhibitor olaparib and the investigational phosphatidylinositol-3-kinase (PI3K) inhibitor BKM120 was safe and yielded evidence of clinical benefit for women with triple-negative breast cancer and for those with high-grade serous ovarian cancer, according to data from a phase I clinical trial presented at the AACR Annual Meeting 2015, held April 18-22.

“Several years ago, my colleagues on the Stand Up To Cancer [SU2C] Targeting the PI3K Pathway in Women's Cancers Dream Team found that olaparib and BKM120 were more effective in mouse models of BRCA-mutant breast cancer and BRCA-wildtype triple-negative breast cancer than either drug alone,” said Ursula A. Matulonis, MD, director and program leader of Medical Gynecologic Oncology in the Susan F. Smith Center for Women’s Cancers at the Dana-Farber Cancer Institute in Boston. “Using SU2C funding, we then initiated this clinical trial to test whether the preclinical data would hold true in patients.

“We are reassured that it is possible to combine olaparib and BKM120 and that we have seen responses in women with triple-negative breast cancer as well as in women with high-grade serous ovarian cancer,” continued Matulonis who is also an associate professor of medicine at Harvard Medical School.

In the olaparib/BKM120 dose escalation phase of the clinical trial, Matulonis and colleagues have enrolled 46 patients, 12 with breast cancer and 34 with ovarian cancer. Among these patients, 35 were known to have germline BRCA gene mutations. They then enrolled patients with breast cancer and ovarian cancer in the dose expansion phase of the trial after the maximally tolerated dose had been determined.

According to Matulonis, 10 different dose level combinations of olaparib and BKM120 were tested and the maximum tolerated dose was found to be 50 milligrams once per day of BKM120 plus 300 milligrams twice per day of olaparib. The dose-limiting toxicities of a grade three depression in one patient and a grade four liver function test in another patient were concerning, Matulonis explained, and meant the researchers were able to escalate BKM120 doses to only half of the single-agent dose.
“It is important that we saw responses against both BRCA-mutant and BRCA-wildtype cancers,” said Matulonis. “We need to do further analysis to identify biomarkers that we can use to more effectively identify the patient population that will be most positively affected by the olaparib/BKM120 combination.”

Matulonis’ research is funded by the Department of Defense, the Ovarian Cancer Research Fund, and the Breast Cancer Research Foundation. The clinical trial was funded by SU2C, the Kathryn Fox Samway Foundation, and discretionary funds from the participating center. Matulonis has received research funding from AstraZeneca and remuneration for attending a speaker’s bureau; she has no Novartis disclosures.


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Title: Phase I of oral BKM120 or BYL719 and olaparib for high grade serous ovarian cancer or triple negative breast cancer: Final results of the BKM120 plus olaparib cohort

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Abstract Body:

Background: Similarities exist between high grade serous ovarian cancer (HGSC) and triple negative breast cancer (TNBC); both often have gBRCA mutations, are sensitive to platinum agents, and have high copy number alterations per the TCGA. Preclinical data for both BKM120/olaparib and BYL719/olaparib combinations showed synergistic efficacy. These data served as the rationale for this study in pts with either recurrent HGSC or TNBC. The phase I study of BKM120 and olaparib has been completed, and the phase I study of BYL719 and olaparib is currently in dose escalation (NCT01623349).

Methods: This study has a 3 + 3 design, escalating dose levels (DL) if 0/3 or 1/6 pts have a dose limiting toxicity (DLT) during the first cycle (1st 28 days). Objectives were to determine the MTD and RP2D of daily oral olaparib (tablet formulation) and BKM120, assess toxicities, activity of this combination, and PK profiles of both drugs. Planned translational endpts include PI3kinase pathway effects, BRCA1 immunostaining/methylation, IL-8/circulating DNA levels, and somatic mutations in BRCA1/2 using FFPE tissue. Eligibility included: recurrent TNBC or HGSC or any histology of OvCa or BrCa with presence of a gBRCAmut, PS 0-1, and measurable/evaluable cancer. Prior PARP inhibitor use was allowed.

Results: 46 pts to date have received study drugs as part of the ph1 dose escalation of BKM120/olaparib (12 pts w/TNBC and 34 pts w/HGSC). 35 have known gBRCAm. Dosing started at DL1 (BKM120 60 mg and olaparib 100 mg BID); 2 DLTs were observed (1 gr 3 LFTs and 1 gr 3 hyperglycemia). A lower dose (-1) was pursued followed by re-escalation; MTD is BKM120 50 mg and olaparib 300 mg BID. Toxicities that defined DLTs included CNS toxicities (gr 3 depression) and grade 3 LFTs, early in cycle 2 (DL6). At the MTD of BKM120/olaparib, 11 pts with HGSC and 12 pts w TNBC were enrolled into a dose expansion cohort (DEC). Evidence of clinical benefit by RECIST 1.1 was observed on all DL’s and in the DEC’s, in pts with a gBRCApos as well as gBRCAwt, and in TNBC and HGSC; AEs seen were compatible with AE profile of BKM120 and Olaparib.

Conclusions: Combined BKM120 and olaparib is feasible, and evidence of clinical benefit was seen at all DL’s both in gBRCApos and gBRCAwt pts. Toxicities that defined DLTs included CNS toxicities and LFT abnormalities. Clinical trial information: NCT01623349