Study identifies two promising molecular targets for drug development in recurrent and metastatic cervical cancer

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NRG Oncology GOG-0240 is the phase 3 randomized trial that demonstrated that the incorporation of bevacizumab with chemotherapy

resulted in a statistically significant and clinically meaningful survival benefit for women with recurrent and metastatic cervical carcinoma (NCT00803062). GOG-0240 was a proof of concept in anti-angiogenesis therapy and a proof of principle in supportive care and led directly to an indication for bevacizumab in this disease in more than 60 countries.

Whole genome sequencing and whole exome sequencing of tumor samples obtained in GOG-0240 suggest that ARID1A and PIK3CA could represent potential targets for drug development in the recurrent/metastatic cervical cancer space. These results were presented by lead author Anjali Y. Hari, MD of the University of California, Irvine, during the late-breaking oral session of the Society of Gynecologic Oncology's (SGO) Annual Meeting, March 25–28, 2023.

"Although the adoption of anti-angiogenesis therapy and immunotherapy have fulfilled previously unmet clinical needs in advanced cervical cancer, nearly all patients will ultimately progress, creating new populations in need of novel treatment. This study, by identifying two promising targets, could potentially lead to new treatment options," stated Dr. Hari.

From April 6, 2009, and Jan 3, 2012, the Phase III NRG-GOG-0240 trial enrolled 452 patients, who provided 112 tumor samples with sufficient DNA and RNA for mutational analysis. In this study, DNA/RNA were co-extracted from FFPE samples after central pathology review at the NRG Biospecimen Bank at Nationwide Children's Hospital in Columbus, Ohio. DNA/RNA analytes were shipped to the New York Genomic Center and University of North Carolina for whole genome sequencing, whole exome sequencing, RNA sequencing, and microRNA sequencing. Mutational frequencies were compared with those reported in the TCGA and potential molecular targets for biologic therapy were identified. Pattern recognition,

mutational clusters, and bioinformatics are ongoing.

Greater than 35,917 total mutations were identified, and >90% of mutations identified from DNA were present in RNA sequences when the expression level was sufficient. Similar to early-stage cases from the TCGA, PIK3CA (an integral component of the mTOR pathway that modulates angiogenic factors) was mutated in 25% (28/112) of advanced/recurrent GOG-0240 specimens. Median OS among PIK3CA mutants was 15.4m (HR 1.0; 95% CI 0.61–1.62) and median PFS was 7.5m (HR 0.85; 95% CI 0.54–1.34). A significantly higher frequency of ARID1A mutants (previously reported to increase tumor mutational load and sensitivity to immunotherapy) were observed in GOG-240 samples (17%, or 19 of 112) compared with TCGA (5%, p

Trial results demonstrated that ARID1A and PIK3CA are potential targets and should be considered for drug development through clinical trials in the recurrent/metastatic cervical cancer space. Concerning these results, Dr. Hari commented that, "We hope that the ongoing bioinformatics, mutational clustering, and pattern recognition incorporating RNA sequencing and microRNA analysis will identify additional potentially druggable targets and further increase our understanding of gene expression in advanced cervical cancer."

More information: A.Y. Hari et al, PIK3CA and ARID1A mutations in recurrent/metastatic cervical cancer, The NRG Oncology/Gynecologic Oncology Group-0240 National Institutes of Health Beau Biden Cancer Moonshot. Presented at the annual meeting of the Society of Gynecologic Oncology. Tampa, FL.

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