Background: Clear cell carcinoma of the endometrium (CCE) is a rare subtype of endometrial cancer (EC) associated with worse prognosis when compared to other high-grade EC subtypes. We aim to evaluate molecular, genomic and protein expression patterns in a large cohort of ECs in order to direct patients to rational therapeutic strategies and clinical trials.

Methods: Out of 3133 EC submitted to Caris Life Sciences from March 2011 to July 2014, 136 CCEs were identified based on reported pathology. Testing was ordered per physician request and included a combination of sequencing (Sanger or next generation sequenced), protein expression (immunohistochemistry), and/or gene amplification (FISH/CISH).

Results: Of the samples evaluated, the most common genetic mutations were P53 (40%) and BRCA2 (35%). Hormone receptor expression was low: ERα (55%), PR (22%) and AR (7%). CDK1 (CDK1A) was mutated in 48%, while PTEN was amplified in 13%. In addition, a biomarker for HER2-directed therapies, HER2, was amplified in 12% and expressed in 5% of patients. Aberrations of the PI3K pathway, including 26% PIK3CA mutation rate, with 69% loss of PTEN expression, highlight potential utility with targeted therapies. Increased TOPO2A expression, known to be associated with anthracycline efficacy, was seen in over 80% of cases. Loss of REML, a DNA synthesis protein key to determine efficacy of gemcitabine, was seen in 70% of cases.

Conclusions: Our findings highlight the genetic heterogeneity of CCE, and identified altered cellular pathways with potential diagnostic and predictive values for therapeutic intervention. Drugs targeting the pathways for DNA repair, PI3K, and receptor tyrosine kinases, as well as gemcitabine and taxanes, may warrant consideration in selected patients with CCE.

Identifying Potential Therapeutics by Molecular Profiling of 136 Cases of Uterine Clear Cell Carcinomas

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Abstract

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Results (cont.)

• 136 out of 3133 (4.3%) of endometrial cancers submitted to Caris Life Sciences from March 2011 to July 2014 were identified as clear cell carcinoma. A combination of sequencing (Sanger, NGS or panneoplastic protein expression, FISH, gene amplification and/or RNA fragment analysis were performed.

• IHC analysis was performed on formalin-fixed paraffin-embedded tumor tissues using commercially available antibodies.

• Fluorescent in situ hybridization (FISH) was used for evaluation of the HER2 (18q11.2) CCND1, EGFR (7p11.2) and ERBB2 (6q12–13) genes.

• Direct sequence analysis was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor tissues using the Illumina MiSeq platform.

• Mutational analysis by Sanger sequencing included selected regions of BRAF, BRAF, NRAS, CDKN2A and PIK3CA genes.

• Prospective studies and additional clinical data are needed to better understand the significance of these findings and offer prognostic and therapeutic guidance.

References