**Background**

Endometrial carcinoma (EC) is typically divided into endometrioid (Type I) and non-endometrioid (Type II) subtypes, despite considerable heterogeneity within each category. Microarray and single-cell analysis have revealed considerable complexity among individual EC cases, with no single treatment strategy applicable to all. Exploitation of the molecular landscape of ECs might identify optimal treatment strategies.

**Methods**

Out of a total of 3133 ECs submitted to Caris Life Sciences between Mar 2011 and Jul 2014, 1364 cases were Type I and 1268 were Type II EC based on reported pathology. Multiparameter molecular analysis included gene sequencing (Sanger or next generation sequencing), immunohistochemistry (IHC) of protein expression, and/or gene amplification (FISH/CISH).

**Results**

- **Type I** was characterized and included 682 cases of uterine cancer (USC). USC showed 44% CTNNB1 mutation rate.
- **Type II** carcinomas were characterized and included 588 cases of clear cell adenocarcinoma, 363 cases of carcinosarcoma (CS), 38 cases of mucinous, and 36 cases of squamous cell carcinoma. Overall, there was a high frequency of ERCC2 homologous recombination expression: USC (90%/32%), CC (75%/15%), CS (75%/6%), and squamous (90%/40%).
- USC expressed high AR compared with other non-endometrioid EC: USC (97%), CC (7%), CS (12%), mucinous (16%), and squamous (0%).
- PI3K/AKT pathway was high in USC (80%/12%), CC (75%/30%) and CS (40%/25%).
- Suggesting potential benefit with PD-1/PD-L1 inhibition, c-met overexpression was notably high in CC (40%) and mucinous (43%) tumors, suggesting promise with anti-cMET therapy.
- TP53 was mutated most frequently in USC (76%) and CS (69%), followed by endometrioid subtypes that could guide future therapy. Correlating molecular profiles with clinical outcomes will assist in developing rational guidelines for therapy in individuals with EC.

**Conclusion**

- 3133 cases of endometrial cancer were submitted to Caris Life Sciences from March 2011 to July 2014.
- Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (FISH or FISH/CISH), and/or RNA fragment analysis.
- The analysis was performed on formalin-fixed paraffin-embedded tumor samples using commercially available detection kits, automated staining techniques (PathVysion, Ventana, and Automated In situ Hybridization kits), and commercially available antibodies.
- Fluorescent in situ hybridization (FISH) was used for evaluation of the HER-2 (CEP 17/HER-2 probe), EGFR (CEP 7/EGFR probe), and ERBB2 (CEP 7/ERBB2 probe) antibody targets. Immunohistochemistry (IHC) and MGMT promoter analysis were also performed for the IHC probe (HER-2/neu probe) and the MGMT probe (Abbott). The same scoring system was applied as for FISH.
- Primary squamous tissue, either formalin fixed paraffin embedded, was used in the Illumina platform. The study included 3133 ECs: USC, CC, CS.
- Mutations in the TP53 gene were among the most frequent mutations, affecting 76% of USC tumors, 69% of CS tumors, and 70% of CC tumors. This was followed by mutations in the PIK3CA gene (40%) and the KRAS gene (10%).
- In the USC cohort, the most frequent mutations were in the TP53 gene (76%), followed by the PIK3CA gene (40%) and the KRAS gene (10%).
- In the CC cohort, the most frequent mutations were in the TP53 gene (70%), followed by the PIK3CA gene (20%) and the KRAS gene (13%).
- In the CS cohort, the most frequent mutations were in the TP53 gene (93%), followed by the PIK3CA gene (63%) and the KRAS gene (4%).

**Discussion**

- Endometrial carcinoma has traditionally been divided into Type I and Type II disease based on unique histopathologic and genetic characteristics.1
- Type I disease typically arises in the setting of unopposed estrogen stimulation and has a well-defined precursor lesion (complex atypical hyperplasia or CAH). Patients usually present with early stage disease and have an overall good prognosis.2
- Type II disease, on the other hand, typically arises in the setting of an atrophic endometrium without a hormonally driven pathologic process associated with CAH, with higher stage, aggressive behavior, and worse prognoses.3
- Characteristic mutational profiles and overexpression profiles were seen more in association with each type with although some overlap exists. Thereby, it may be more helpful from a therapeutic standpoint to understand their mutational alterations.
- Because the non-endometrioid subtypes are uncommon, using a large tumor database with molecular and genetic information helps to identify unique tumor profiles and identify thematic pathways for therapeutic exploration.

**References**

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Distinct molecular landscape between endometrioid and non-endometrioid uterine carcinoma

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