Endometrial Stromal Sarcoma: An Analysis of 96 Cases
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Objectives: Endometrial stromal sarcoma (ESS) is a rare form of uterine cancer, traditionally categorised as low-grade (HG) or high-grade (LG) ESS. Molecular and genomic changes that underlie the distinct clinical characteristics associated with each subtype are largely uncharacterised. We aim to identify genomic and protein expression differences between high-grade and low-grade tumours in a large cohort of ESS.

Methods: OUT of 3133 uterine cancers submitted for a molecular profiling test from March 2013 to July 2014, 143 ESS were identified based on reported pathology. Testing was ordered per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC and immunohistochemistry), and/or gene amplification (FISH/CISH). Results: OF 144 LG ESS, 52 (36%) were HG ESS, 44 (31%) were LG ESS, and 47 (33%) were unspecified. Compared with HG ESS, LG ESS were more likely to be somatic mutations in SRK/EML4 (HG 20% vs 1%, p<0.0001). LG ESS were ER and PR positive while only 7% of HG ESS were ER and PR positive. LG ESS showed significantly more TP53 mutations (HG 17% vs 1%, p<0.0001), suggesting potential utility of inhibitors of the PI3K pathway. Increased TOP2a expression, associated with higher proliferation and anthracycline efficacy, was more common in HG ESS (87% vs 26%, p<0.0001). A significant higher proportion of HG ESS patients expressed TS and RRM1, known to confer resistance to folate analogue and gemcitabine, respectively (75% vs 26%, p<0.0001 and 52% vs 26% RRM1, p<0.0001, respectively).

Conclusions: Our findings suggest HG ESS and LG ESS have distinct molecular signatures. LG ESS rarely carry mutations and are highly by activity, suggesting potential utility with folate preservation and endocrine therapy. HG ESS are largely hormonally independent with frequent TP53 mutation. Anthracyclines, and drugs targeting the PI3K/PIK3CA pathway may warrant consideration in a subset of patients with HG ESS.

Background
• Uterine sarcomas are a rare form of endometrial cancer arising from the connective tissue (stroma) of the endometrium.
• Uterine sarcoma accounts for approximately 3% of all uterine malignancies [1, 2].
• Endometrial stromal sarcoma (ESS) are the most common types of uterine sarcoma and are traditionally categorised as either high-grade (HG) or low-grade (LG) ESS [3].
• Compared with other uterine sarcomas, ESS affects younger women with mean age from 42-78 years [3].
• LG ESS are typically indolent and have excellent prognosis, while HG ESS behave as high grade sarcomas and carry a poor prognosis [4].

Molecular and genomic changes that underlie the distinct clinical characteristics associated with each subtype are largely uncharacterised.

Broader understanding of the molecular and genomic characteristics could provide alternative treatment options with targeted therapies.

Methods
• 3133 cases of uterine cancers were submitted to Caris Life Sciences from March 2013 to July 2014.
• Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC) and gene amplification (FISH or CISH).
• HG analysis was performed on formalin-fixed paraffin-embedded tumor samples using commercially available detection kits, automated staining techniques (Benchmark XT, Ventana, and Autostainer Link 48, Dako), and commercially available antibodies.

Results
• Fluorescence in situ hybridisation (FISH) was used for evaluation of the HER2 (CISH/CEP 17), GSK3B (CISH/CEP 21), and AMN (CISH/CEP 20) (Abbott Molecular/CN). HER2/CEP 17 and CISH status were also evaluated chromogenically in this hybridisation (INFORM HER 2 Dual 2 DNA CISH Probe Kit) commercially available and CISH and chromosome 17CISH (Genentech). The same staining system was applied for FISH.

• Direct sequence analysis was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the Illumina MiSeq platform. Specific regions of interest were amplified using the TruSeq Amplicon Cancer Health panel.

• Mutation analysis by Sanger sequencing included selected regions of BRAF, KRAS, NRAS, EGFR, and PIK3CA genes and was performed by using NGS-based PCR primers designed to capture targeted regions.

• Retrospective data analysis, Statistical analysis (unpaired t-tests to compare biomarker expression across histologic subtypes) performed using Prism® 4. Biomarker associations were calculated by two-tailed Fisher Exact tests.

Conclusions
• We identified several pathways that warrant further exploration in the histologic subtypes of a relatively large cohort (n=96) of endometrial stromal sarcomas.
• There was a significantly higher frequency of hormone receptor expression in low grade ESS suggesting potential benefit with hormone therapy.
• The proliferation marker TOP2A was significantly higher in high-grade ESS.
• TS and RRMM1 were more often expressed in high-grade ESS.
• TP53 was exclusively and very frequently mutated in high-grade ESS.
• Low-grade ESS carried no mutations except for an E442K mutation, which is a variant of unknown significance.

• Overall, there were significant differences in histologic subtypes within high-grade and low-grade sarcoma that could guide future therapy.

• Correlating molecular profiles with clinical outcomes will assist in developing new guidelines for therapy in patients with ESS.

References