Abstract #11548: Pan-sarcoma analysis of DNA damage response pathway alterations and deficiency

Steven Bialick[1], Kurt Statz-Geary[1], Andrew Elliott[2], Jim Abraham[2], Phillip Walker[2], Andrea P. Espejo-Freire[1], Priscila Barreto Coelho[1], Philippos Apolinario Costa[1], Kirsten Leu[3], Margaret von Mehren[4], Gina Z. D'Amato[1], Emily Jonczak[1], Jonathan C. Trent[1], Andrew Rosenberg[1], Aditi Dhir[1]

[1]University of Miami Miller School of Medicine/Sylvester Comprehensive Cancer Center, Miami, FL; [2]Caris Life Sciences, Phoenix, AZ; [3]Nebraska Cancer Specialists, Omaha, NE; [4]Fox Chase Cancer Center, Philadelphia, PA

SCAN ME

BACKGROUND

- Alterations in **DNA damage response (DDR) pathways contribute to genomic instability** and are of clinical significance in several carcinomas and solid tumors. We identified a gene alteration in *ERCC2* in a patient (pt) with relapsed epithelioid sarcoma, prompting a **wider investigation of DDR pathway alterations in sarcoma**.

METHODS

- Sarcoma pt samples (*n*=5310), representing 38 histologic subtypes, underwent NGS of DNA (592 gene panel or whole exome) and RNA (whole transcriptome sequencing, *n*=3612)
- Homologous recombination deficiency (HRD) scores were calculated as a composite of loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions, using a positive threshold of 42 for HRD-deficiency (*n*=2138).

RESULTS

- A pathogenic **DDR pathway mutation was noted in 842 (15.9%)** of the total samples.
- ***ATRX* was the most commonly altered gene**, with mutations observed across 25 sarcoma subtypes.
- ***CHEK2, ATM,* and *MUTYH*** mutations were observed in 1-2% of sarcoma samples.
- Median HRD scores ranged between 20-58.
- ***ERCC2, ATRX* and *BRCA2*** were associated with increased HRD scores (*p*=0.01).

RESULTS

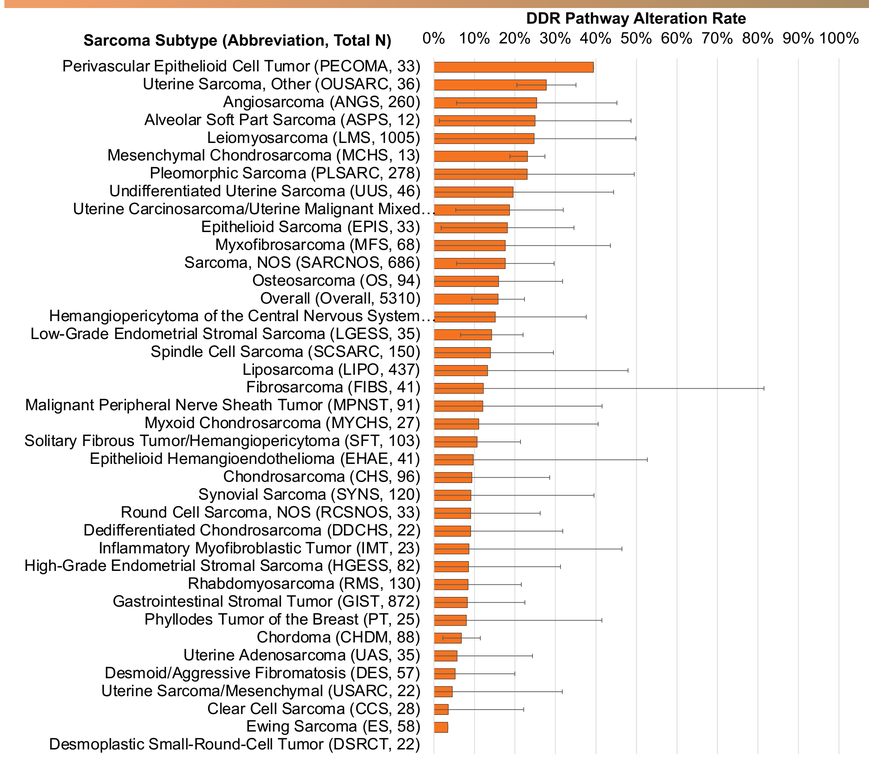

Figure 1. DDR pathway alteration rates across sarcoma subtypes.

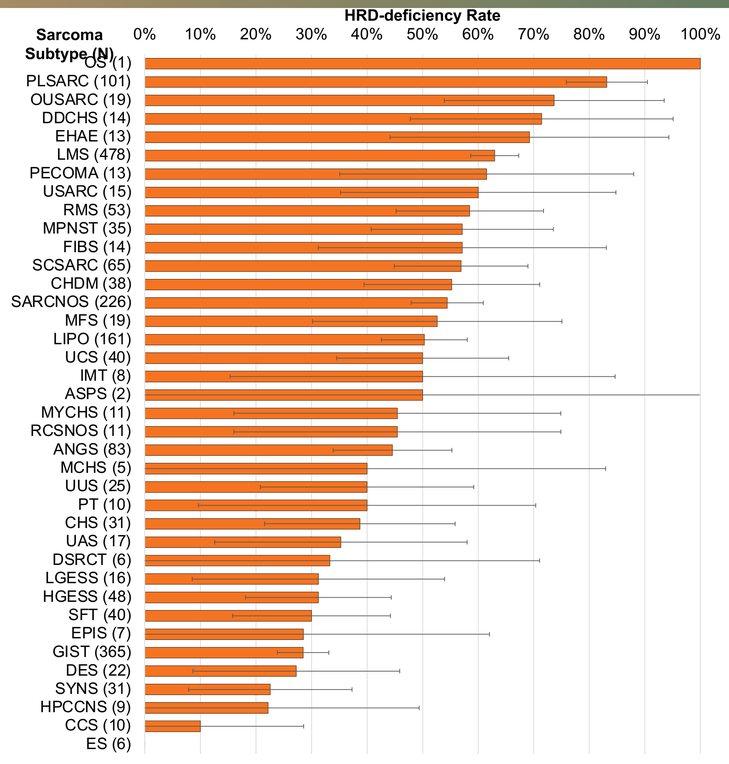

Figure 2. HRD-deficiency rates across sarcoma subtypes.

CONCLUSIONS

DDR pathway alterations are present in numerous histologic subtypes of pediatric and adult sarcoma. Further research will evaluate the clinical implications of these mutations to guide risk stratification and potential therapeutics. **Comprehensive analysis of individual histologic subtypes is in progress.**

UHealth University of Miami Health System | University of Miami Miller School of Medicine

Committee of Interns and Residents SEIU Healthcare | Jackson Health System

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Contact: steven.bialick@med.miami.edu