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Hormone Receptor-Positive Breast Cancer Outcomes in 628 patients with BRCA1, BRCA2, or PALB2 pathogenic variants:

Real World Data Analysis of Genomics and Targeted Therapy Sequencing

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DECLARATION OF INTERESTS

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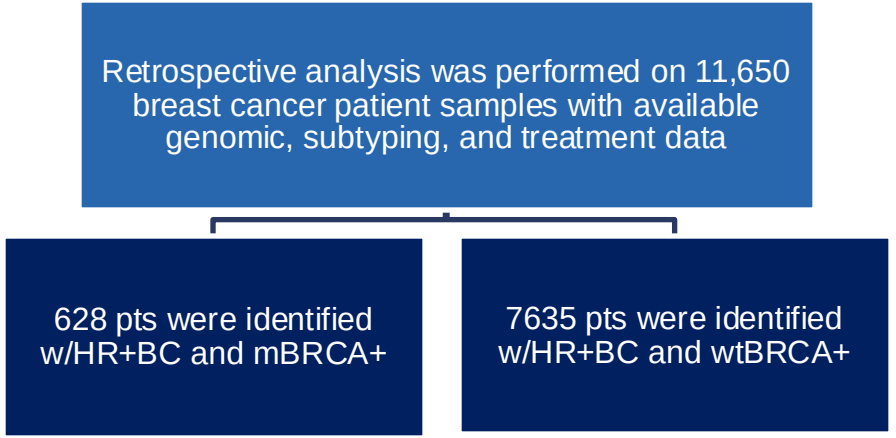
No conflicts of interest

Background and Specific Aims

- Patients with hormone receptor-positive breast cancer (HR+BC)and pathogenic variants in *BRCA1*, *BRCA2* or *PALB2* (BRCA+) have several targeted therapy options including CDK4/6 inhibitors (CDK4/6i), and poly (ADP-ribose) polymerase inhibitors (PARPi).
- Little is known about the sequence of these targeted therapies
- Are there pathogenic variants between BRCA+ and their wildtypes?
- **Specific Aims:**
    1. To compare patients with hormone receptor-positive breast cancer and pathogenic variants in BRCA+ treated with CDK4/6i and/or PARPi
    2. To compare pathogenic variants in BRCA+ with their respective wildtypes in hormone receptor-positive breast cancer patients
    3. Compare low vs high tumor mutation burden for BRCA+ in hormone receptor-positive breast cancer patients

Methods

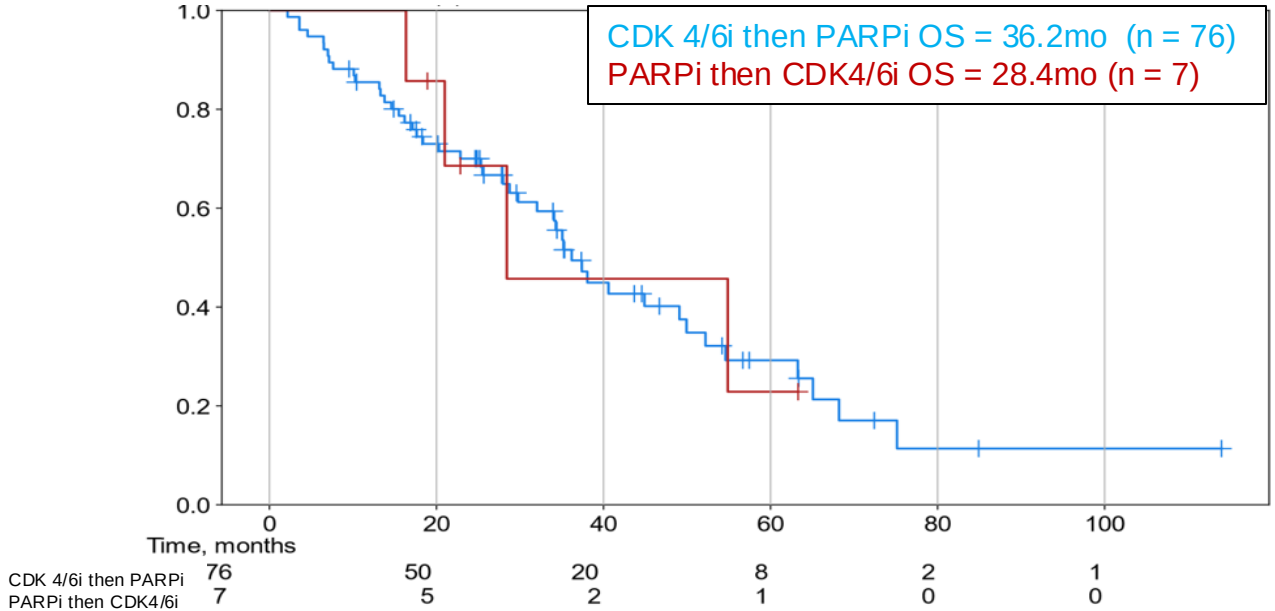
- NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed through Caris Life Sciences (n=11,650).
- Real-world overall survival (OS) information calculated from first treatment time to last contact.



Study Demographics

	HR+BC	HR+ BC mBRCA	HR+ BC wtBRCA
Median age, N (range)	64 (22 - >89)	57 (23 - >89)	63 (22 - >89)
Female , N	11448	604	7512
Male, N	202	24	123
White	6773	329	4512
Black Or African American	1489	84	970
Asian Or Pacific Islander	362	29	211
Unknown/Other	1514	85	965
RNA sequencing data, N	9450	495	6193
DNA sequencing data, N	11,508	628	7635
PARP inhibitors, N (olaparib or niraparib or rucaparib or talazoparib)	238	156	33
CDK4/6 inhibitors, N (Palbociclib or ribociclib or abemaciclib)	5548	285	3571

Overall survival when comparing the sequence of CDK4/6 inhibitors and PARP inhibitors in HR+BC mBRCA patients

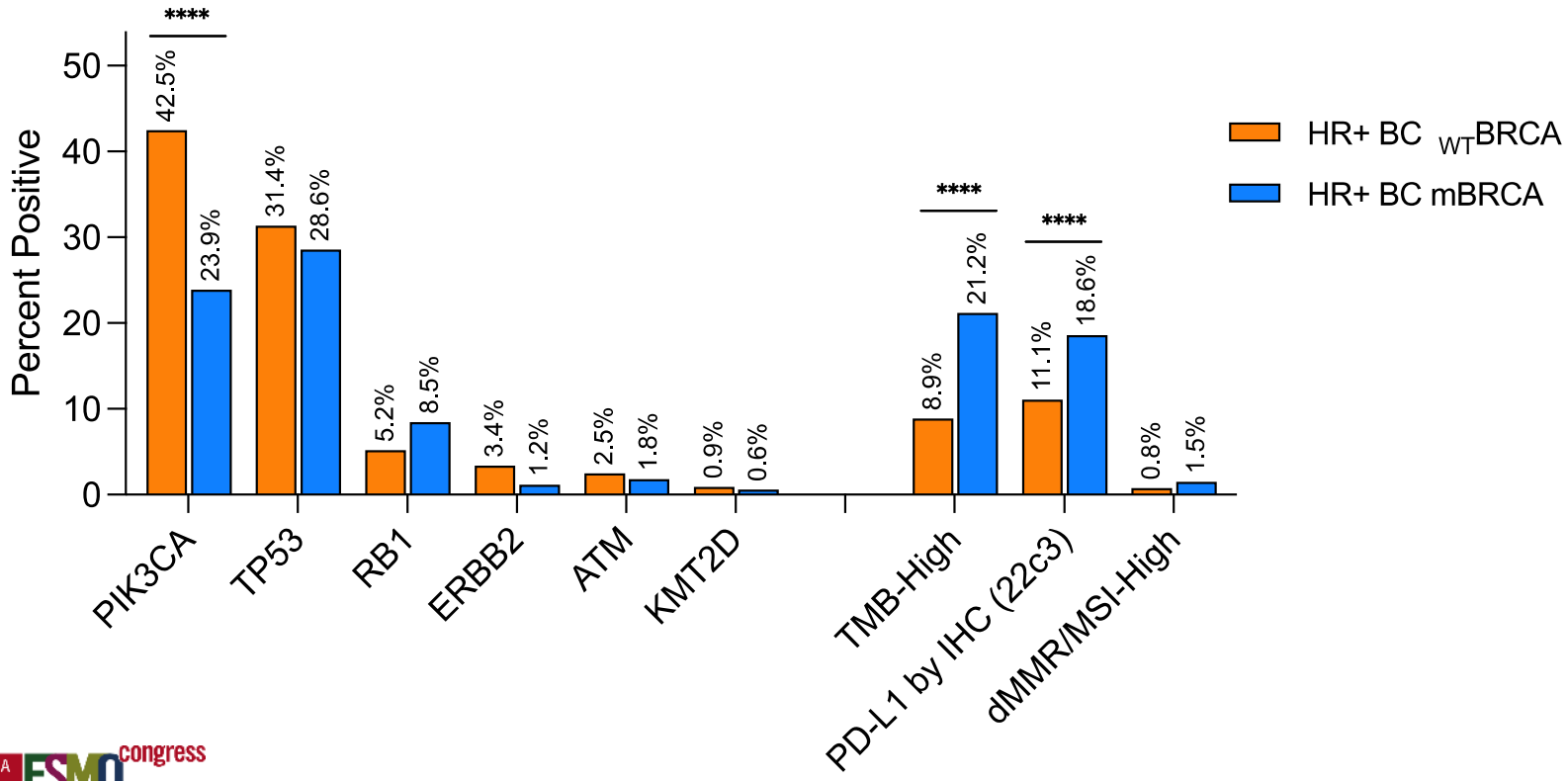


	Median OS	95% CI
CDK4/6i then PARPi	36.19 mo	29.774 mo-49.942 mo
PARPi then CDK4/6i	28.426 mo	16.351 mo-Inf

HR = 1.072 (95% CI: 0.383 - 2.999), p = 0.895

Median OS difference: 7.764m

Genomic alterations associated with HR+BC mBRCA patients compared to HR+BC wtBRCA



Genomic alterations associated with HR+BC mBRCA patients compared to HR+BC wtBRCA

	Median wtBRCA	Percent Positive wtBRCA	Median mBRCA	Percent Positive mBRCA	q-value
NK cells	0.037	99.980	0.033	100.000	0.002
Macrophages M2	0.057	99.648	0.051	99.701	0.005
T cells CD8	0.000	45.925	0.000	50.746	0.029
Neutrophils	0.033	93.395	0.024	86.269	0.000

Conclusions

- No significant differences in overall survival were seen between the sequences among patients with HR+BC mBRCA treated with CDK4/6i or PARPi
- Molecular analysis of HR+ BC mBRCA+ (vs WT) showed
  - Similar amounts of NK cells, macrophage M2
  - more CD8 T cells
  - depletion of neutrophils
- Patients with mBRCA+ had worse OS with TMB-High than TMB-Low
- Limitations of this work included somatic dataset vs working with germline mutations.

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- We thank the patients, their families and clinicians for contributing to this study.

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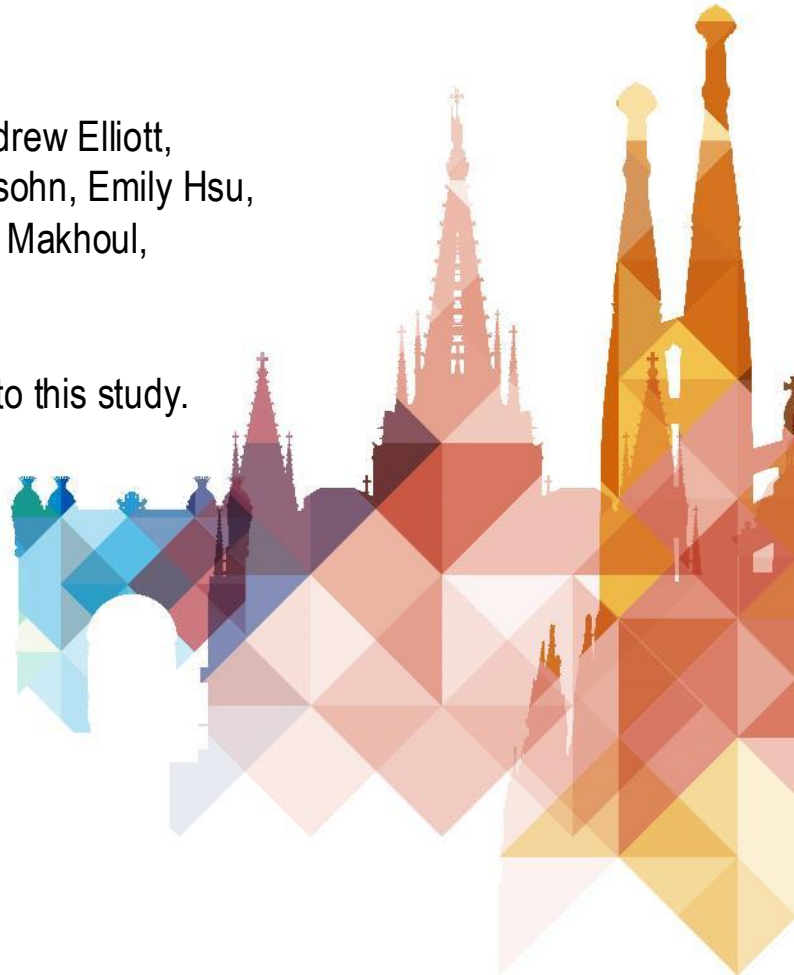

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