MOLECULAR PROFILING OF TUMORS FROM A PHASE II, RANDOMIZED, DOUBLE-BLIND, STUDY OF THE USE OF RUCAPARIB VS. PLACEBO MAINTENANCE THERAPY IN METASTATIC AND RECURRENT ENDOMETRIAL CANCER

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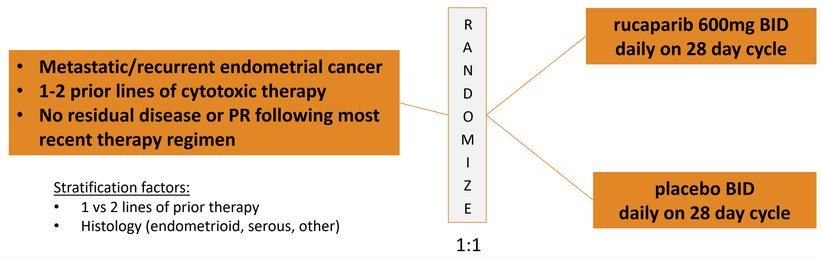
Background

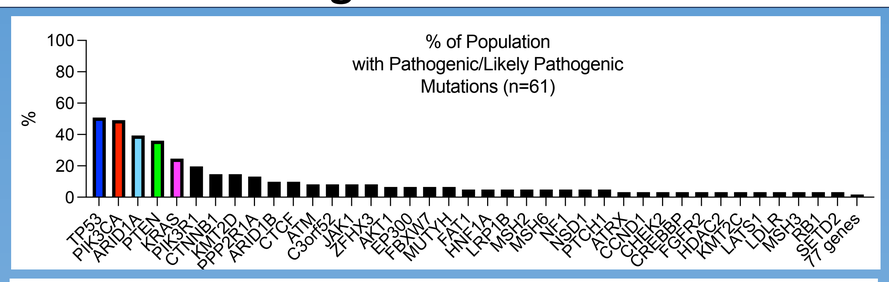
- The placebo-controlled trial of rucaparib maintenance therapy in metastatic and recurrent endometrial cancer (NCT03617679) recently demonstrated an improvement in median progression-free survival (PFS) by 19.4 months (HR 0.45 [95%CI 0.26-0.80]).
- 79 patients were randomized, 39 received rucaparib & 40 received placebo. Median follow-up was 25 (IQR 19.3, 40.3) months.

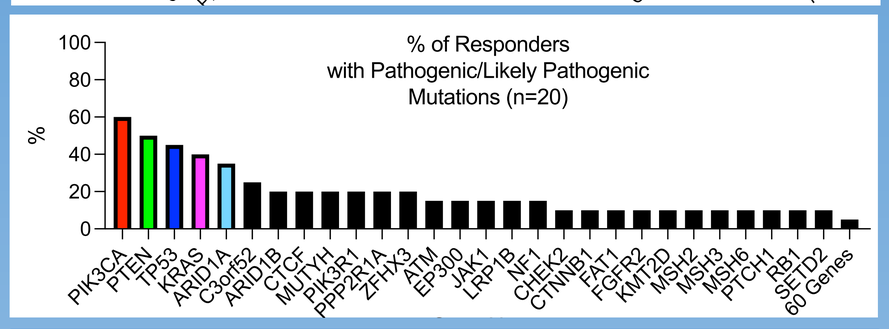


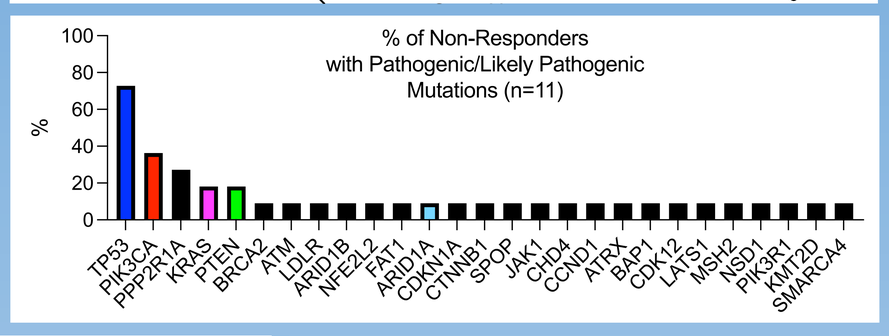
Methods

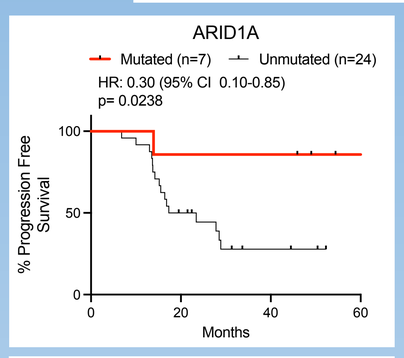
- Molecular testing of somatic and germline mutations or expressions was performed using TEMPUS xT and Homologous Recombination Deficiency (HRD) platforms.
- 61 patients had sufficient tumor material for analysis.
- The xT platform sequences tumor and normal DNA to distinguish between somatic and germline variants. The panel detects single-nucleotide variants, insertions and/or deletions, and copy number variants in 648 genes, as well as chromosomal rearrangements in 22 genes.
- RNA sequencing with whole transcriptome analysis is performed.
- Loss of Heterozygosity (LOH) was performed by TEMPUS research.
- The HRD panel used is an RNA panel logistic regression model that predicts HRD status across all solid tumors and is uniquely ***not*** breast or ovarian cancer specific.

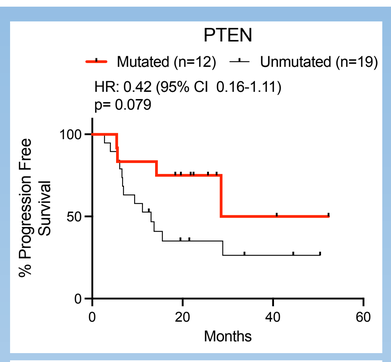
Pathogenic Mutations

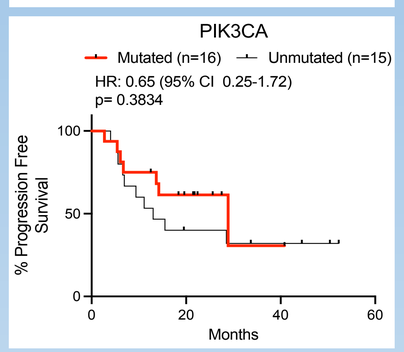


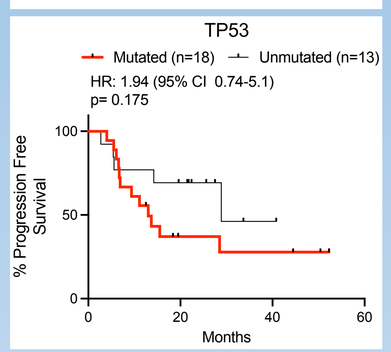












ARID1A pathogenic mutations (7/31, 22%) correlated to improved PFS

HRD Mutational Status

Overall population

- BRCA was identified in 3.0% of patients (2 BRCA2, 0 BRCA1)
- HRD was identified in 17% of evaluable tumors
- HRR pathway mutations were identified in 13.3% of tumors
- LOH was expressed in 13.3% of tumors

Responders vs Non-responders

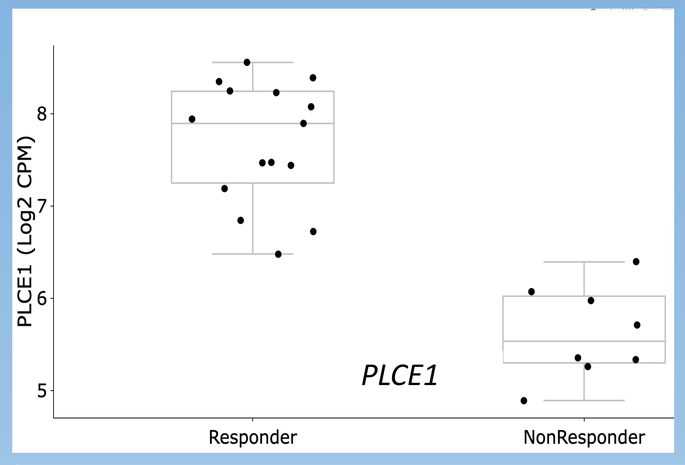
- Response to therapy was defined as PFS ≧ 12 month
- Median HRD score
  - Responders 23.4 (+/- 10.3)
  - Non-responders 27.6 (+/- 9.7)
- No HRD mutational variation
- No LOH variation

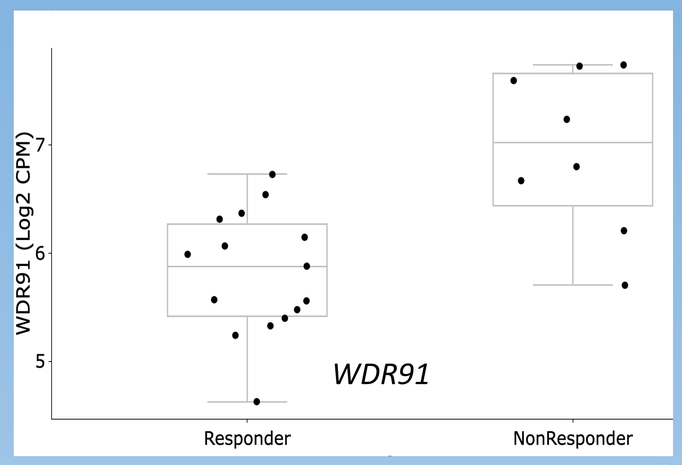
GENE	% Mutated Tumors (N=61)
BRCA1	0%
BRCA2	2%
BRIP1	0%
RAD51B	0%
RAD51C	0%
RAD51D	0%
ATM	8%
ATR	2%
ATRX	3%
PALB2	0%
MAP1A	0%
POLQ	0%
BARD1	0%
BLM	0%
CDK12	2%
CHEK1	0%
CHEK2	3%
FANCA	2%
FANCL	0%
HDAC2	7%
MRE11	0%
NBN	0%
RAD50	2%
RAD54L	0%
RAD51	0%

GENE	% Mutated Responders (N=20)	% Mutated Non-responders (N=11)
BRCA1	0%	0%
BRCA2	0%	9%
BRIP1	0%	0%
RAD51B	0%	0%
RAD51C	0%	0%
RAD51D	0%	0%
ATM	15%	9%
ATR	5%	0%
ATRX	5%	9%
PALB2	0%	0%
MAP1A	0%	0%
POLQ	0%	0%
BARD1	0%	0%
BLM	0%	0%
CDK12	0%	9%
CHEK1	0%	0%
CHEK2	10%	0%
FANCA	0%	0%
FANCL	0%	0%
HDAC2	10%	0%
MRE11	0%	0%
NBN	0%	0%
RAD50	0%	0%
RAD54L	0%	0%
RAD51	0%	0%

Gene Expression

- No Individual HR pathway gene predicted response
- Responders demonstrate a 2.05 log fold change in the expression of Phospholipase C Epsilon 1 (*PLCE1)* ($p=2.13x10^{-8}$). *PLCE1* is a guanine nucleotide exchange that regulates cellular differentiation and growth.
- Responders demonstrate a -1.2 log fold change in the expression of WD Repeat-Containing Protein 91 (WDR91) (p=0.0002). WDR91 is a negative regulator of PI3K signaling





Conclusions

- ATM, CHK2, ATRX, HDAC2 are the predominant HR pathway genes mutated in Endometrial cancers from this clinical trial
- HRD mutational status did not predicted response to therapy
- No single HR pathway gene expression predicted response to therapy

Future Directions

- Negative regulation of PI3K as illustrated by elevation in PLCE1 and reduction in WDR1 is more present in tumors that responded to PARP inhibition compared to those that did not
- ARID1A mutation predicts response to PARP inhibition

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