Germline and Somatic Variants in DNA DAMAGE Repair (DDR) Genes in Patients with Untreated, Early-Stage Triple Negative Breast Cancers (TNBC)

Litton JK[1], Zhao L[2], Song X[2], White J[1], Ravenberg E[1], Zhang J[2], Arun BK[1], Moulder S[1]

Dept. of Breast Medical Oncology[1], Genomic Medicine[2], The University of Texas MD Anderson Cancer Center, Houston, USA

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Background

Mutations in DDR genes, most notably BRCA1/2 and have been predictive to respond to PARP inhibitors and other DNA-damaging systemic therapies.

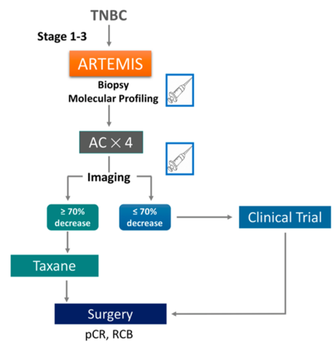
Reports of detected germline and somatic variants in other DDR-related genes in early-stage, untreated breast cancers is limited.

Here we report variants identified in multiple DDR-related genes in patients with untreated TNBC and association with pathologic complete response (pCR).

Materials & Methods

- Pretreatment core biopsies were obtained from 193 patients with early-stage (I-III) TNBC enrolled on the ARTEMIS trial (NCT02276443).
- DNA was extracted from blood for germline as well as from tumor samples for somatic testing and underwent whole exome sequencing and RNAseq.
- Enrichment of gene alterations were compared using a Fisher exact test in patients (pts) with and without pCR.
- Whole exome sequencing was performed and pair-end sequencing reads in FASTQ format were generated and aligned to the hg19 human reference genome.
- Platypus was used to call germline mutations on DDR genes. MuTect was used to identify somatic point mutations, and Pindel was used to identify somatic insertions and deletions. A series of post-calling filtering were applied for somatic mutations.

Parent Trial: ARTEMIS

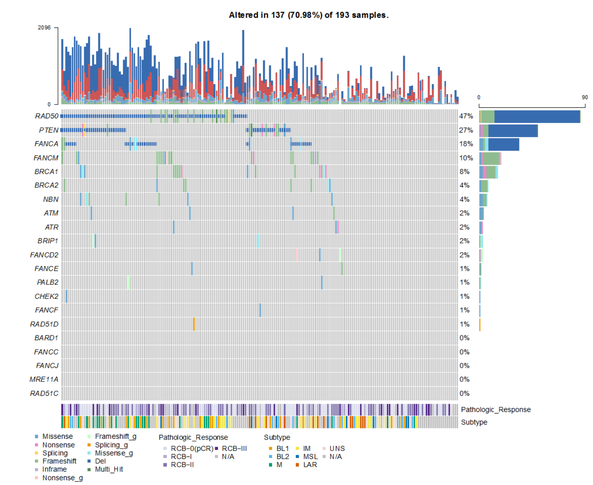


Results

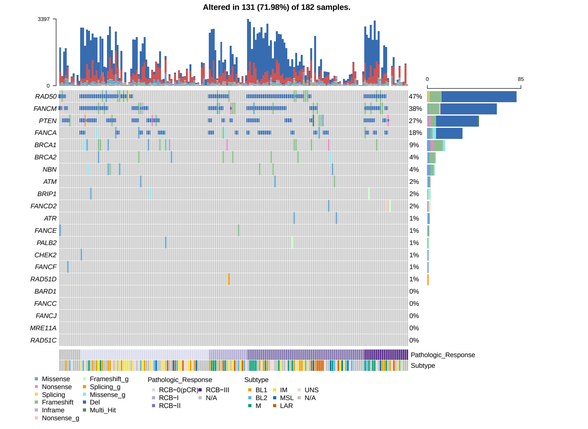
Overall DDR Variants were identified in 42% (82/193) patients and 110 total variants identified

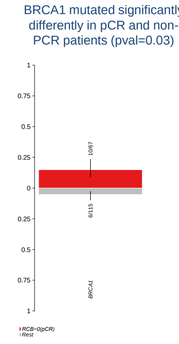
Somatic and Germline mutations in BRCA was associated with an increase in pCR (p=0.03)

Gene	No. of germline variants	No. of somatic variants	No. Frameshift	No. missense	No. other variant type
ATM	0	4	1	3	
ATR	0	3		2	1
BRCA1	2	14	8	5	3
BRCA2	1	7	5	3	
BRIP1	1	2	1	2	
CHEK2	0	1		1	
FANCA	3	5	2	6	
FANCD2	0	3	1	1	1
FANCE	0	2	1	1	
FANCF	0	1		1	
FANCM	0	20	15	2	3
NBN	1	6	3	4	
PALB2	0	2	1	1	
PTEN	0	12	6	1	5
RAD50	0	19	16	2	1
Rad51D	1	0			1



- Mutations include both somatic and germline (_g).
- Copy number variations were also shown (GISTIC2, cutoff log2 ratio=0.3, confidence interval 0.99).
- Out of 21 DDR genes, 16 were mutated in at least one patient.





Conclusion

- Both germline and somatic variants in DDR-related genes were identified in patients with early-stage, untreated TNBC.
- Somatic and germline mutations were associated with pCR
- Although filtering against known databases were completed to exclude polymorphisms as much as possible, some of these findings may still be consistent with variants of uncertain significance.