Interrelation of Functional Homologous Recombination Deficiency and Homologous Recombination Repair Pathway Alterations in Prostate Cancer

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TEMPUS

BACKGROUND

- PARP inhibitors (PARPi) may trigger synthetic lethality of tumor cells in the context of deficient homologous recombination repair (HRR)[1].
- 10-20% of patients with prostate cancer harbor mutations in the HRR pathway, but HRR-associated mutations do not consistently predict the response to PARPi[2].
- Considering alternative methods to define Homologous Recombination Deficiency (HRD)—the inability to repair double strand breaks—may aid in identifying additional tumors that are sensitive to PARPi.

METHODS

- Retrospective analysis of 1,022 de-identified patients with prostate cancer that underwent next generation sequencing (NGS) with the Tempus xT assay (DNA-seq of 648 genes at 500x coverage, whole-exome capture RNA-seq).
- Comparison groups were defined based on HRR alterations—either mono- or bi-allelic alterations of *BRCA1* or *BRCA2* (*BRCA1/2*), *ATM*, or other HRR pathway genes.
- Bi-allelic alterations included deep deletions, somatic and germline mutations or either type of mutation combined with overlapping loss of loss-of-heterozygosity (LOH).
- Mono-allelic alterations included any germline or somatic mutation (VUS or pathogenic).
- HRD status was determined via the Tempus RNA-based HRD algorithm, which uses gene expression data from 16,470 RNA-seq samples to predict HRD status

REFERENCES

1. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434(7035):917-921.
2. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. New England Journal of Medicine 2020;382(22):2091-2102. DOI: 10.1056/NEJMoa1911440.

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CONCLUSIONS

An **RNA-based HRD algorithm** found **13% of patients with prostate cancer are HRD+,** which includes a substantial population patients who are **currently undetectable** by methods based solely on sequencing HRR genes.

Further research is needed to assess the clinical response to PARPi in this HRD positive population, as well as the response to PARPi in the population that harbors HRR gene alterations but are nevertheless HRD negative.

RESULTS

HRD assessment by HRR mutational categories

	Overall N = 1,022	*BRCA* -/- N = 20	*BRCA* -/+ N = 89	*ATM* -/- N = 20	*ATM* -/+ N = 69	Other HRR -/- N = 34	Other HRR -/+ N = 177	No HRR alterations N = 613
HRD Results								
negative	892 (87%)	6 (30%)	80 (90%)	19 (95%)	60 (87%)	27 (79%)	160 (90%)	540 (88%)
positive	130 (13%)	14 (70%)	9 (10%)	1 (5.0%)	9 (13%)	7 (21%)	17 (9.6%)	73 (12%)

Table 1. Out of the 1,022 patients included in this cohort, 130 (13%) were deemed HRD positive by an RNA-based HRD algorithm. Of these 130 patients, 14 (11%) had bi-allelic BRCA loss and **73 (56%) had no HRR alterations identified**.

HRD positivity according to specific mono- and bi-allelic HRR gene alterations

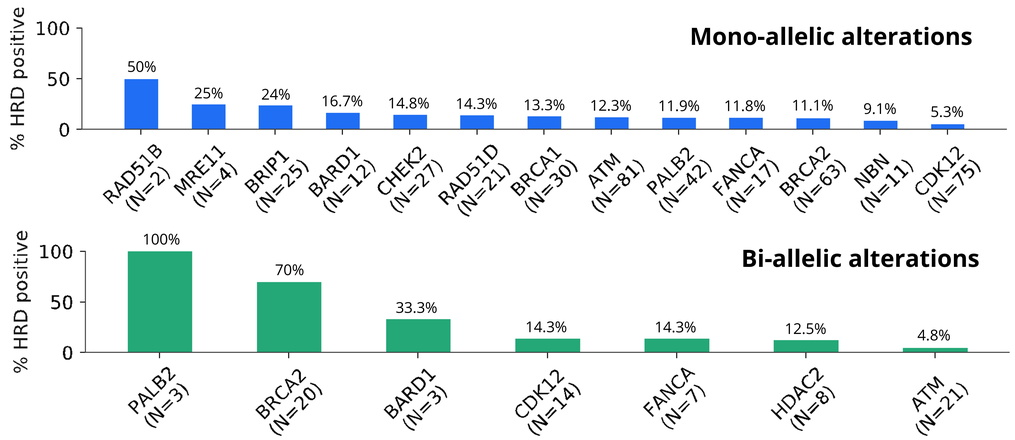

Figure 1. We assessed mono-allelic (top panel) and bi-allelic (bottom panel) alterations in 18 separate genes in the HRR pathway. Shown in each figure are all genes with non-zero HRD positivity in the indicated condition. For each gene, "N=" refers to the total number of records with the indicated alteration pattern that were considered and % HRD positive illustrates the percentage of these were determined to be HRD positive according to the RNA-based HRD algorithm. The HRR genes considered for this analysis were: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCA*, *FANCL*, *HDAC2*, *MRE11*, *NBN*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.