Homologous Recombination Deficiency (HRD) in Non-Small Cell Lung Cancer: Genomic Analysis Using an RNA-based HRD Algorithm

Abstract 3123

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INTRODUCTION

Recent evidence has suggested that some patients with non-small cell lung cancer (NSCLC) harbor a HRD signature that represents a distinct genomic subtype that could be targeted by PARP inhibitors (PARPi). However, there is little data on HRD prevalence in NSCLC or its genomic associations. Here, we evaluated the co-occurence of driver mutations and established immune biomarkers with an RNA-based HRD signature in a large, real-world NSCLC cohort.

METHODS

We analyzed 5119 NSCLC patients that underwent sequencing via the Tempus xT test (DNA-seq of 648 genes; RNA-seq with whole exome capture). Clinical and genomic variables were assessed between HRD-RNA+ and HRD-RNA- patients, as predicted by the Tempus HRD-RNA test (Figure 1).

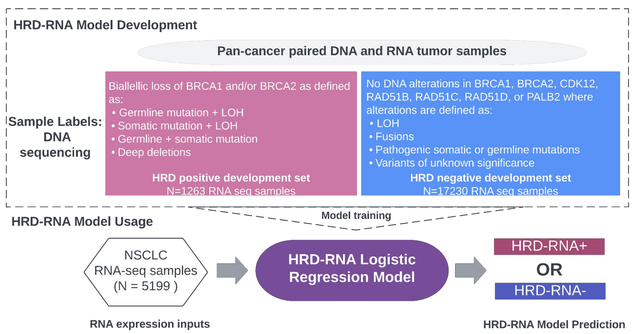

Figure 1. **HRD-RNA Model Development:** The Tempus HRD-RNA test is a pan-cancer logistic regression classifier that uses an RNA gene expression signature optimized to distinguish between BRCA-biallelic loss and homologous recombination repair (HRR)-WT samples (Leibowitz et al, 2022*). **HRD-RNA Model Usage:** NSCLC cohort samples analyzed in this poster (N = 5119) were not included in model training.

*Leibowitz et al. (2022) *Validation of genomic and transcriptomic models of homologous recombination deficiency in a real-world pan-cancer cohort.* BMC Cancer.

SUMMARY

- An RNA-based HRD algorithmic signature classifies 3.53% of NSCLC samples as HRD-RNA+; 78% of HRD-RNA+ patients had no alterations in any HRR genes.
- Compared to HRD-RNA- NSCLC, HRD-RNA+ NSCLC represents a unique, molecularly defined subset that has a decreased prevalence of NCCN-driver mutations and is not enriched for TMB-H or PD-L1 expression.

RESULTS

Characteristic	HRD-RNA+ N = 181[1]	HRD-RNA-, N = 4,938[1]	p-value[2]
Smoking Status			0.032
Current/former	142 (91%)	3,630 (85%)	
Never	14 (9.0%)	651 (15%)	
Unknown	25	657	
Age, median (range)	70 (64, 78)	69 (62, 76)	0.040
Unknown	0	2	
Sex			0.068
Female	77 (43%)	2,442 (49%)	
Male	104 (57%)	2,496 (51%)	
Race			0.7
Asian	3 (1.7%)	132 (2.7%)	
Black or African American	9 (5.0%)	341 (6.9%)	
White	90 (50%)	2,335 (47%)	
Other	79 (44%)	2,130 (43%)	
Stage			0.2
Stage 1	4 (2.8%)	262 (6.9%)	
Stage 2	13 (9.0%)	283 (7.5%)	
Stage 3	27 (19%)	644 (17%)	
Stage 4	101 (70%)	2,596 (69%)	
Unknown	36	1,153	
Histology Status			<0.001
Adenocarcinoma	68 (38%)	2,947 (60%)	
Squamous cell carcinoma	84 (46%)	1,247 (25%)	
Other	29 (16%)	744 (15%)	

1 n (%); Median (IQR)
2 Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Table 1. Overview of NSCLC patient population stratified according to HRD-RNA status.

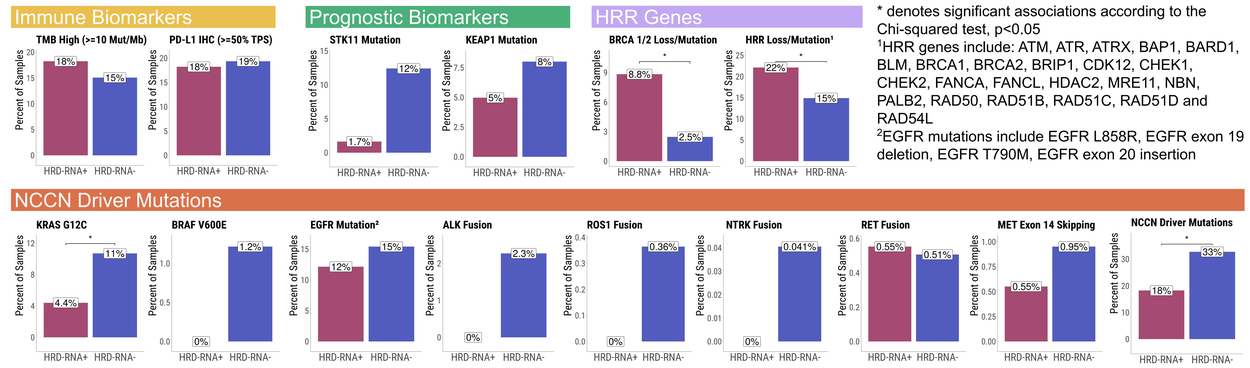

Figure 2. The percentage of patients with important immunological, gene mutation, gene fusion, exon skipping and presence of any NCCN driver mutations stratified by HRD-RNA status.

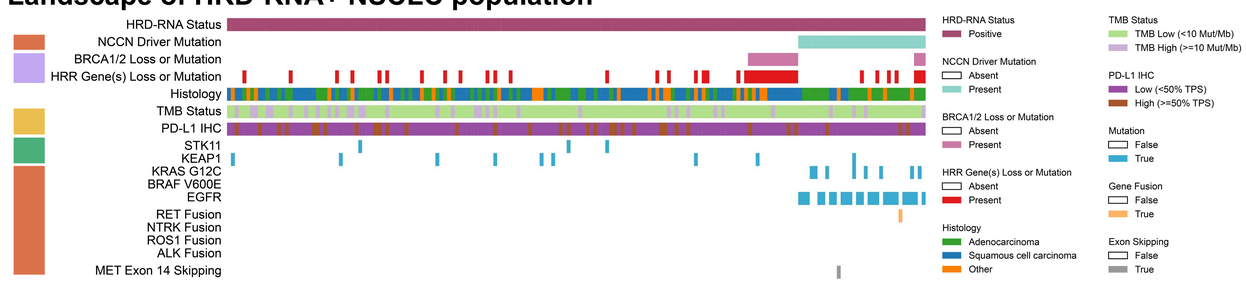

Figure 3. Comutation plot of the HRD-RNA+ patients showing the overlap between various immunological, gene mutation and fusion markers.