ESMO 2022 (1046P)

Homologous recombination deficiency (HRD) and genomic associations in non-small cell lung cancer (NSCLC) using a novel HRD signature (HRDsig)

Jonathan W. Riess[1], Russell W. Madison[2], Alexa B. Schrock[2], Geoffrey R. Oxnard[2], Khaled Tolba[2], Ethan S. Sokol [2]

[1]*UC Davis Comprehensive Cancer Center, Sacramento, CA* [2]*Foundation Medicine, Inc., Cambridge, MA*

BACKGROUND

Poly (ADP-ribose) polymerase inhibitors (PARPi) have received approval in BRCA-associated cancers and shown efficacy in ovarian cancers exhibiting genomic scarring or HRD mutational signatures. Despite these successes, PARPi trials in BRCA mutant or high genomic loss of heterozygosity (gLOH) NSCLC have shown little clinical activity. We hypothesize that HRDsig, a recently described, scar-based biomarker of HRD, would improve patient selection for PARPi treatment in NSCLC.

MATERIALS AND METHODS

- Targeted next generation sequencing was performed on 48,344 NSCLC specimens
- A gLOH high cutoff of 21% was based off the S1900A LUNGMAP sub-study[1] and was calculated based on specimen copy number profiles[2]
- Comparisons of proportions were made with chi-squared test. A non-parametric Mann–Whitney U test was used to compare continuous variables.
- This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB)
- Retrospective longitudinal clinical data were derived from electronic health record (EHR) data, and were linked to genomic data derived from FMI comprehensive genomic profiling (CGP)[3]
- The de-identified data originated from ~280 US cancer clinics (~800 sites of care)
- Patients included in outcomes analysis received FMI tissue CGP with specimen collection prior to first line therapy and were treated with cisplatin or carboplatin combined alone or combined with any of the following therapies: paclitaxel, pemetrexed, docetaxel, gemcitabine and bevacizumab
- For outcomes analysis, patients with *EGFR, ALK, RET, ROS1, and NTRK* positive tumors were excluded
- Real-world overall survival (rwOS) accounting for delayed entry and real-world progression free survival (rwPFS) were estimated with Kaplan-Meier analysis
- Hazard ratios (HR) were calculated using univariate Cox proportional hazard models

PREDICTING BRCAness BY HRDsig

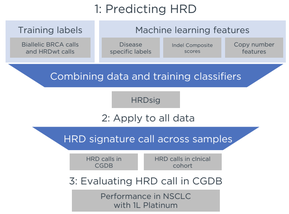


FIGURE 1: A pan-cancer genomic profiling dataset (n = 202,472) was split 70:30 for training and validation using an XGB model. A broad set of copy number[4] and indel features[5] were used to identify signatures of HRD. Biallelic alterations were predicted using a computational zygosity algorithm[6]. The HRR geneset included *BRCA1, BRCA2, PALB2, RAD51C, RAD51D, BARD1, ATM, CHEK1, CHEK2, BRIP1, CDK12, FANCL, RAD51B, RAD54L.*

First Author: jwriess@ucdavis.edu
Corresponding Author: rmadison@foundationmedicine.com

CLINICAL FEATURES OF HRDsig POSITIVE [HRDsig(+)] NSCLC

	HRDsig(+) (n = 2,201)	HRDsig(-) (n = 46,143)	p-value
Histology: Adenocarcinoma, n (%) Squamous, n (%) Large cell neuroendocrine, n (%)	 1,328 (60) 809 (37) 64 (3)	 33,766 (73) 11,349 (25) 1,028 (2)	<1.0E-05
Gender: F, n (%) M, n (%)	 1,015 (46) 1,186 (54)	 23,237 (50) 22906 (50)	1.1E-04
Age, median [IQR]	68 [61-74]	68 [60-75]	0.76
Genomic LOH (%), median [IQR]	19.1 [13.9-25.2]	10.4 [6.0-15.8]	<1.0E-05
Genomic LOH (cut off 21%) High, n (%) Low, n (%)	 903 (41) 1,298 (59)	 4,751 (10) 41,392 (90)	<1.0E-05
TMB (mut/mb), median [IQR]	10.0 [6.1-17.5]	7.5 [3.8-12.5]	0.26
PD-L1 Status Negative, n (%) Low Positive, n (%) High Positive, n (%)	 362 (39) 303 (32) 269 (29)	 8,128 (38) 6,911 (33) 6,204 (29)	0.95

TABLE 1: HRDsig(+) NSCLC had distinct features from the HRDsig(-) population. Tumors were more likely to exhibit squamous histology and come from male patients. Additionally, both TMB and gLOH were elevated in HRDsig(+) NSCLC

HRDsig(+) NSCLC ARE MORE FREQUENTLY DRIVER NEGATIVE

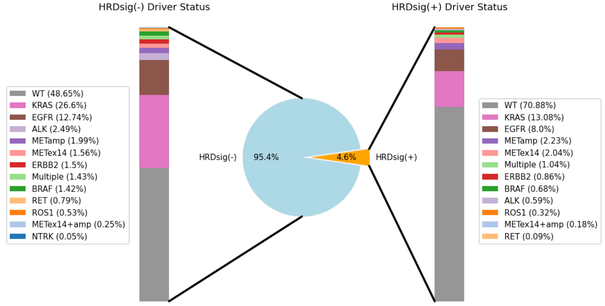


FIGURE 2: Driver alterations were less frequent in HRDsig(+) NSCLC except for MET exon 14 splicing alterations and amplification, both of which were more common in HRDsig(+) NSCLC

HRR ALTERATIONS WERE MORE FREQUENT IN HRDsig(+) NSCLC

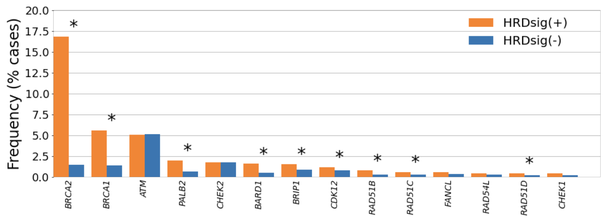


FIGURE 3: HRDsig(+) NSCLC is enriched for HRR alterations, particularly *BRCA2* (17% v 1%), and *BRCA1* (5% v 1%). Other HRR altered genes with statistically significant enrichment in HRDsig(+) NSCLC are marked with *

HRDsig IDENTIFIES BIALLELIC *BRCA1/2* ALTERATIONS

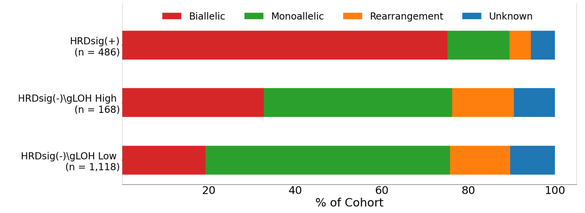


FIGURE 4: *BRCA1/2* alterations were predominantly biallelic in HRDsig(+) NSCLC. Amongst HRDsig(-) NSCLC, *BRCA1/2* alterations were more commonly biallelic in gLOH high tumors (33%) compared to gLOH low tumors (19%)

HRDsig IDENTIFIES BIALLELIC *HRR* ALTERATIONS IN BRCA WT NSCLC

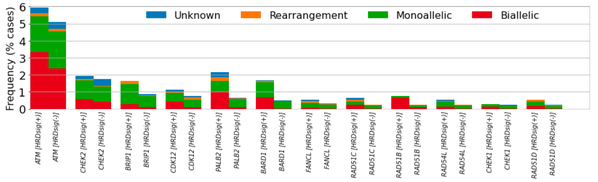
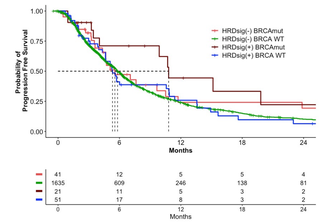


FIGURE 5: In *BRCA1/2* wildtype NSCLC, biallelic alterations in other HRR genes was observed at higher frequency in HRDsig(+) vs HRDsig(-). *PALB2* (p < 1.0E-05), *BARD1* (p < 1.0E-05), and *RAD51B* (p = 7.2E-03) were most enriched for biallelic inactivation as compared to HRDsig(-) NSCLC

HRDsig(+) *BRCA*mut NSCLC HAVE PROLONGED BENEFIT ON PLATINUM CHEMO

	HRDsig(+) (n = 72)	HRDsig(-) (n = 1,679)
Histology: Non-Squamous, n (%), Squamous, n (%) NOS, n (%)	 35 (49) 32 (44) 5 (7)	 1140 (68) 462 (28) 77 (5)
Female, n (%)	27 (38)	798 (48)
Race: White Non-White Unknown	 49 (68) 17 (24) 6 (8)	 1178 (70) 365 (22) 136 (8)
Age, median [IQR]	68 [61-74]	68 [60-75]
Former/Current Smoker, n (%)	66 (92)	1157 (92)
PD-L1 Status Negative, n (%) Low Positive, n (%) High Positive, n (%) Unknown	 11 (15) 6 (6) 6 (8) 51 (71)	 243 (15) 208 (12) 166 (10) 1062 (64)
ECOG 0-1 2+ Unknown	 53 (74) 12 (17) 7 (10)	 1212 (72) 302 (18) 165 (10)
CNS Mets, n (%)	10 (14)	308 (18)
Liver Mets, n (%)	5 (7)	167 (10)
KRAS Status G12C, n (%) Other, n (%) WT, n (%)	 5 (7) 5 (7) 62 (86)	 219 (13) 330 (20) 1130 (67)
BRCA altered, n (%)	21 (29)	41 (2)



	BRCA WT		BRCA Altered	
	HRDsig(-) [ref]	HRDsig(+)	HRDsig(-) [ref]	HRDsig(+)
Number of Events, n (%)	1190/1638 (73%)	38/51 (75%)	24/41 (59%)	11/21 (52%)
Median rwPFS months [95% CI]	5.8 [5.6-6.3]	5.3 [4.6-10.9]	5.6 [4.7-11.7]	10.8 [9.9-NR]
Hazard ratio [95% CI]	1.04 [0.75-1.44]		0.69 [0.34-1.41]	

FIGURE 6: Patient characteristics from the clinicogenomic subset were like what was observed in the larger genomic database, including increased prevalence of squamous histology and fewer *KRAS* mutants amongst HRDsig(+) NSCLC. In patients with BRCA altered tumors HRDsig(+) was associated with a nominally longer median rwPFS

CONCLUSIONS

- HRDsig(+) is enriched in driver-negative NSCLC however some patients have co-occurring targetable driver alterations
- Biallelic *BRCA1, BRCA2,* and other HRR gene alterations are more frequent in HRDsig(+)
- Although limited by small sample size, HRDsig(+) was associated with longer rwPFS in HRDsig(+)/BRCA altered NSCLC patients treated with first line platinum
- Further investigation is needed to understand if HRDsig can help optimize selection for PARPi in NSCLC, such as in LUNGMAP S1900A

CITATIONS

1. Riess et al. ASCO Annual Meeting, 2021.
2. Coleman et al The Lancet Oncology, 2017. pmid: 28438473
3. Singal et al JAMA, 2019. pmid: 30964529
4. Macintyre et al Nature Genetics, 2018. pmid: 30104763
5. Alexandrov et al Nature, 2020. pmid: 32025018
6. Sun et al PLOS Computational Biology, 2018. pmid: 29415044