Characterization of DNA damage repair (DDR) alterations and the tumor immune microenvironment (TIME) in advanced non-small cell lung cancer (NSCLC)

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INTRODUCTION

Exploiting the DDR pathway with synthetic lethality agents such as PARP inhibitors has been clinically validated in several cancers. In NSCLC, novel agents leveraging defects in the DDR pathway are being studied alone and in combination with checkpoint inhibitors. To expand on combination approaches and inform biomarker selected strategies, we analyzed DDR alteration prevalence and impact on the TIME in metastatic NSCLC.

METHODS

We retrospectively analyzed de-identified next-generation sequencing data from patients with metastatic NSCLC in a real-world patient database.

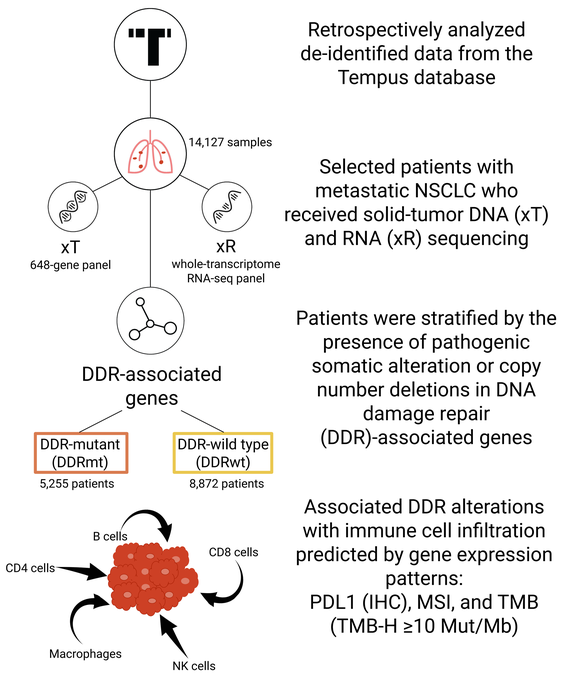

Figure 1. Workflow

SUMMARY

- DDRmt tumors were associated with distinct TIME patterns including TMB-H, MSI-H, and modest changes in immune cell infiltrates
- Additional analysis focused on DDRmt and their association with the immune landscape is warranted
- Further studies may inform biomarker selection for novel combinatorial immunotherapeutic approaches in NSCLC

RESULTS

Table 1. Cohort Characteristics

The patient cohort comprised a diverse population (78% White, 12% African American/Black, 4.5% Asian and 5.5% other). Median age at diagnosis was 67 (IQR, 60, 74). There was a higher percentage of current/former smokers in DDRmt patients compared to DDRwt patients (p-value, <0.001).

	Overall N = 14,127[†]	DDRmt N = 5,255[†]	DDRwt N = 8,872[†]	p-value[2]
Gender				<0.001
Male	7,175 (51%)	2,567 (49%)	4,608 (52%)	
Female	6,952 (49%)	2,688 (51%)	4,264 (48%)	
Age at Diagnosis				0.093
Median (IQR)	67 (60, 74)	67 (60, 74)	67 (60, 75)	
Range	20, 90	24, 90	20, 90	
Race				
White	7,529 (78%)	2,876 (79%)	4,653 (78%)	
Black or African American	1,124 (12%)	448 (12%)	676 (11%)	
Other Race	482 (5.0%)	167 (4.6%)	315 (5.3%)	
Asian	435 (4.5%)	132 (3.6%)	303 (5.1%)	
American Indian or Alaska Native	34 (0.4%)	15 (0.4%)	19 (0.3%)	
Native Hawaiian or Other Pacific Islander	9 (<0.1%)	2 (<0.1%)	7 (0.1%)	
Unknown	4,514	1,615	2,899	
Ethnicity				0.7
Not Hispanic or Latino	5,632 (94%)	2,107 (94%)	3,525 (94%)	
Hispanic or Latino	386 (6.4%)	141 (6.3%)	245 (6.5%)	
Unknown	8,109	3,007	5,102	
Smoking Status				<0.001
Current/former smoker	10,445 (83%)	4,021 (86%)	6,424 (82%)	
Never smoker	2,100 (17%)	673 (14%)	1,427 (18%)	
Unknown	1,582	561	1,021	
Histology within 30 Days of Primary Diagnosis				
Adenocarcinoma	10,315 (73%)	3,796 (72%)	6,519 (73%)	
Squamous cell carcinoma	2,617 (19%)	999 (19%)	1,618 (18%)	
Non-specific or NOS	952 (6.7%)	374 (7%)	578 (6.5%)	
Large cell neuroendocrine carcinoma	212 (1.5%)	78 (1.5%)	134 (1.5%)	
Adenocarcinoma with neuroendocrine differentiation	24 (0.2%)	6 (0.1%)	18 (0.2%)	
Adenosquamous carcinoma	7 (<0.1%)	2 (<0.1%)	5 (<0.1%)	

[†] n (%)

[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Table 1. Cohort Characteristics

Figure 2. Breakdown of biopsy sites

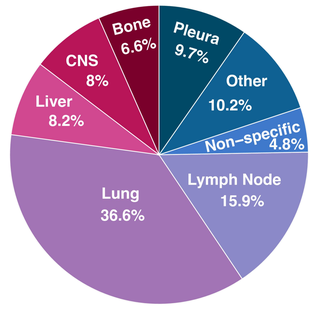

Figure 2. Biopsies were collected from primary and metastatic sites

Figure 3. Prevalence of DDR mutations

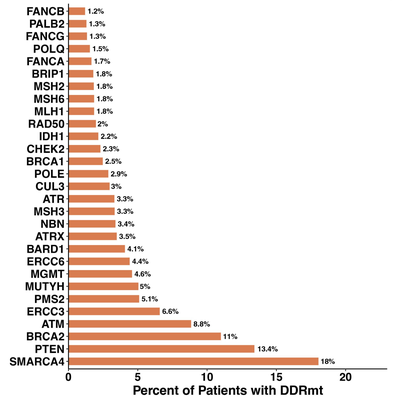

Figure 3. The most prevalent DDRmt was SMARCA4, followed by PTEN, BRCA2, ATM, ERCC3, PMS2, and MUTYH. Percentages were calculated among patients who had DDR alterations (n=5255)

Figure 4. TMB-H frequency

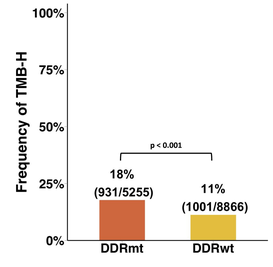

Figure 4. TMB-H was more common (18% [n=931] vs. 11% [n=1001]; p<0.001) and median TMB (5.4 vs. 4.6; p<0.001) was higher in DDRmt patients compared to DDRwt.

Figure 5. PD-L1 positivity prevalence

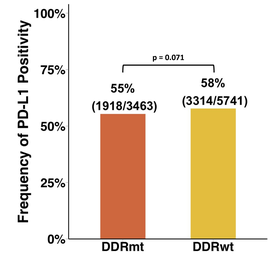

Figure 5. Prevalence of PD-L1 positivity in DDRmt and DDRwt patients.

Figure 6. Distribution of immune cell types

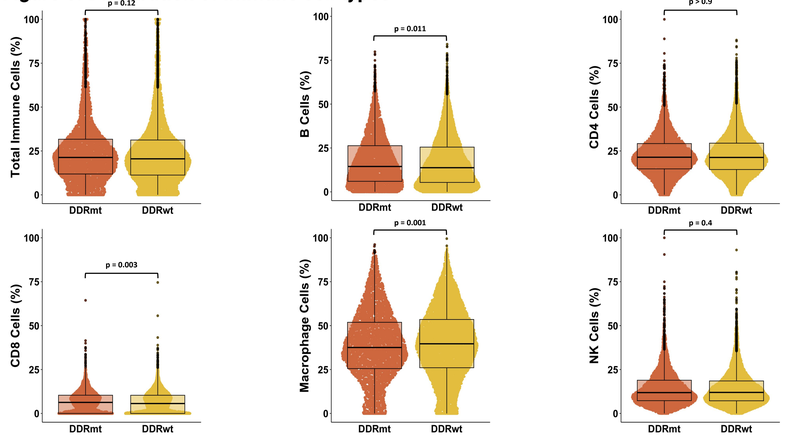

Figure 6. Compared to patients with DDRwt status, patients with DDRmt exhibited modest changes in immune cell infiltration patterns. n=5,255 DDRmt and n=8872 DDRwt.

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