

Homologous Recombination Repair Alterations Does Not Modify the Prognostic Impact of Tumor Mutational Burden in Locally Advanced NSCLC Treated with Chemoradiotherapy and Durvalumab

Frank Weinberg¹, Yumi Taguch², Brooke Rhead⁸, Jacqueline Aredo⁴, Unnati Jariwala³, Jacob Mercer³, Jyoti Patel³, Joel Neal⁴, Katelyn M. Atkins², Karen L. Reckamp², and Kamy Sanka².

¹University of Illinois Chicago, Chicago, IL, ²Cedars-Sinai Health Sciences University, Los Angeles, CA³Tempus AI Inc., Chicago, IL, ⁴Stanford University, Stanford, CA

INTRODUCTION

Chemoradiotherapy followed by durvalumab is standard therapy for unresectable stage III NSCLC, but biomarkers predicting benefit remain limited. While high tumor mutational burden (TMB) has been associated with improved outcomes following immune checkpoint inhibition, the prognostic significance of homologous recombination repair (HRR) alterations and their interaction with TMB is incompletely characterized.

Objective: To evaluate the independent and combined prognostic value of HRR alterations and TMB in patients with stage III NSCLC receiving definitive CRT followed by durvalumab.

METHODS

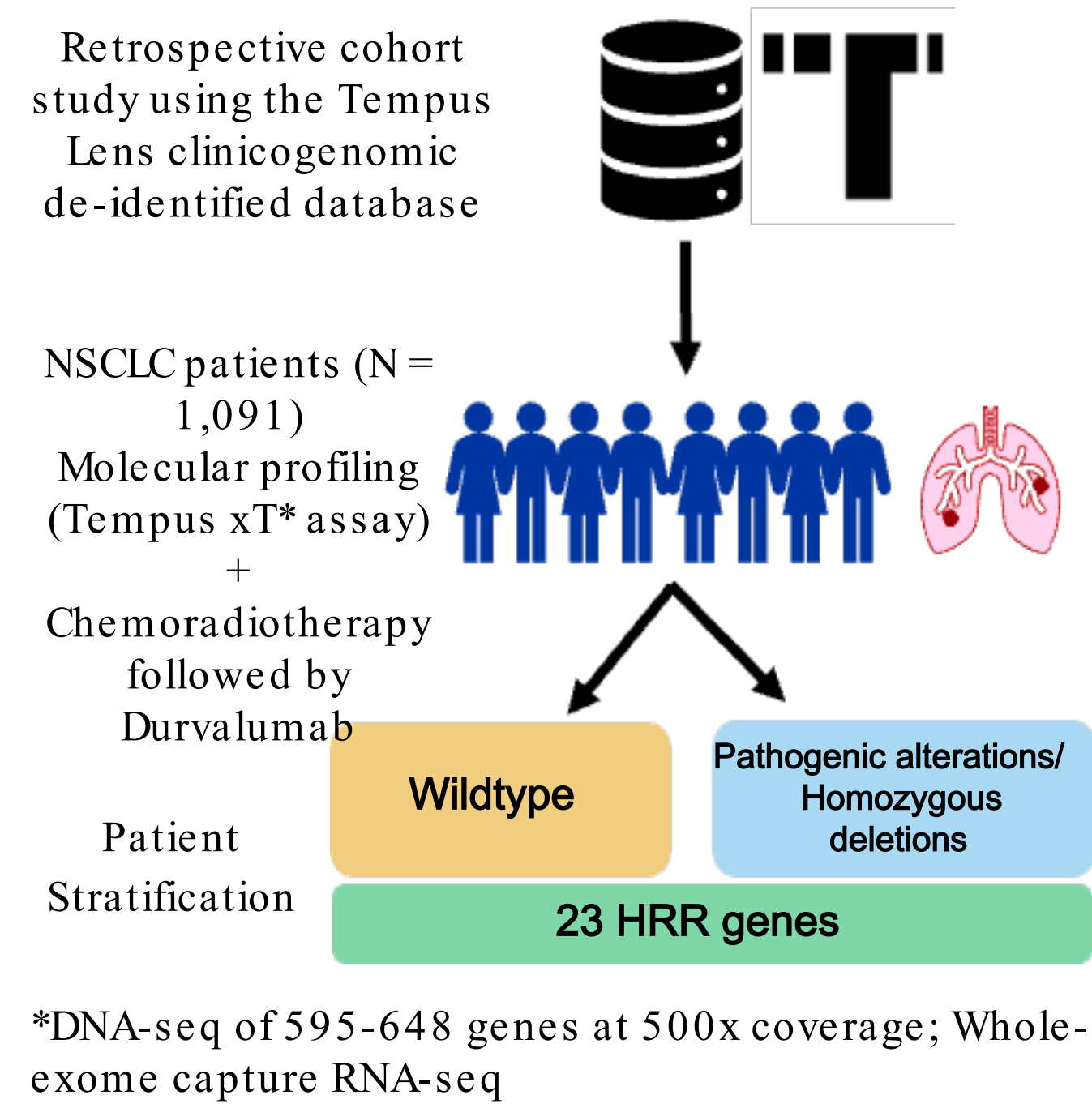


Figure 1. Patients with NSCLC, available Tempus xT (DNA) results, who underwent definitive CRT->durvalumab were included. Patients were stratified based on pathogenic alterations or homozygous deletions in 23 HRR genes. TMB was dichotomized as high (≥10 mut/Mb) or low. The primary endpoint was real-world overall survival (rwOS), defined as time from durvalumab start to death or loss to follow-up.

- Statistical Analysis**
- Kaplan–Meier survival analysis with log-rank tests.
 - Multivariable Cox proportional hazards models adjusted for age, sex, race, smoking status, ECOG performance status, histology, and PD-L1 tumor proportion score.
 - Interaction analyses evaluated whether HRR status modified the association between TMB and rwOS.

SUMMARY

- HRR alterations were not independently associated with real-world overall survival in patients with unresectable stage III NSCLC treated with concurrent chemoradiotherapy followed by durvalumab.
- High tumor mutational burden (≥10 mutations/Mb) was independently associated with improved survival, regardless of HRR status, supporting TMB as a robust prognostic biomarker in this treatment setting.
- HRR alterations did not provide additional prognostic value beyond TMB, suggesting limited clinical utility of HRR status for risk stratification following CRT and consolidation durvalumab.

RESULTS

Table 1. Cohort demographics

Characteristic	Overall N = 1,091 ¹	HRR-WT N = 873 ¹	HRR-Mut N = 218 ¹	p-value ²
Age at Initial Diagnosis	68 (62, 74)	68 (62, 74)	66 (61, 73)	0.2
Unknown	9	6	3	
Age at Sample Collection	69 (63, 74)	69 (63, 75)	68 (62, 74)	0.3
Unknown	9	6	3	
Sex				0.2
Male	622 (57%)	507 (58%)	115 (53%)	
Female	469 (43%)	366 (42%)	103 (47%)	
Race				0.2
White	795 (83%)	628 (83%)	167 (86%)	
Black or African American	106 (11%)	84 (11%)	22 (11%)	
Other Race	36 (3.8%)	33 (4.3%)	3 (1.5%)	
Asian	18 (1.9%)	16 (2.1%)	2 (1.0%)	
Unknown	136	112	24	
Ethnicity				0.2
Not Hispanic or Latino	761 (96%)	602 (97%)	159 (95%)	
Hispanic or Latino	30 (3.8%)	21 (3.4%)	9 (5.4%)	
Unknown	300	250	50	
Smoking Status at Sample Collection				0.2
Ex-smoker	363 (58%)	294 (59%)	69 (54%)	
Current smoker	226 (36%)	172 (35%)	54 (43%)	
Never smoker	34 (5.5%)	30 (6.0%)	4 (3.1%)	
Unknown	468	377	91	
¹ Median (Q1, Q3); n (%)				
² Wilcoxon rank sum test; Pearson’s Chi-squared test; Fisher’s exact test				

Table 1. Baseline characteristics of patients with NSCLC treated with chemoradiotherapy followed by durvalumab according to homologous recombination repair (HRR) status. Continuous variables are presented as median (interquartile range [IQR]); categorical variables are presented as number (%). Comparisons between HRR-wildtype and HRR-altered groups were performed using Wilcoxon rank-sum tests for continuous variables and Pearson chi-square or Fisher exact tests for categorical variables, as appropriate.

HRR alterations are not associated with improved durvalumab rwOS following cCRT and

Figure 2. Overall survival by homologous recombination repair status among patients treated with durvalumab. Kaplan-Meier estimates demonstrated no significant difference in overall survival between patients with HRR-wildtype and HRR-mutant tumors (median OS 31.4 months vs. 36.0 months; log-rank p=0.181).

High tumor mutational burden is associated with improved survival after cCRT and durvalumab

Figure 3. Overall survival by tumor mutational burden (TMB) status. Kaplan-Meier analysis demonstrated significantly improved overall survival among patients with high versus low TMB (median OS: 41.7 months vs. 27.6 months; log-rank p=0.00098).

HRR status does not provide additional prognostic stratification in high TMB tumors

Figure 4. Impact of HRR status on survival among patients with TMB-high tumors. Among patients with TMB-high tumors treated with cCRT and durvalumab, overall survival was similar between HRR-wildtype and HRR-mutant tumors (median OS 43 months vs. 41.7 months, log-rank p=0.488).

Other factors associated with rwOS

Characteristic	N	Event N	HR	95% CI	p-value
HRR Gene Mutation					
HRR-WT	507	197	—	—	
HRR-Mut	123	42	0.84	0.60, 1.18	0.31
Sex					
Female	287	91	—	—	
Male	343	148	1.36	1.03, 1.78	0.029
Race					
White	490	193	—	—	
Black or African American	63	20	0.78	0.49, 1.26	0.32
Other Race	36	10	0.5	0.26, 0.98	0.044
Unknown	41	16	0.8	0.47, 1.35	0.4
Smoking Status					
Current smoker	162	63	—	—	
Ex-smoker	239	81	0.79	0.56, 1.10	0.17
Never smoker	24	7	0.88	0.39, 1.99	0.76
Unknown	205	88	0.92	0.66, 1.30	0.65
Age (Chemoradiotherapy Start)	630	239	1.03	1.01, 1.05	<0.001
PD-L1 TPS					
<1%	215	105	—	—	
1-49%	257	84	0.69	0.52, 0.93	0.015
50-100%	158	50	0.63	0.44, 0.89	0.009
TMB (mut/Mb) >= 10					
Low	426	180	—	—	
High	204	59	0.58	0.43, 0.79	<0.001
ECOG prior to up to 30 days after CRT start					
0	213	72	—	—	
1	225	86	1.15	0.84, 1.59	0.38
2+	48	25	2.04	1.27, 3.28	0.003
Unknown	144	56	1.33	0.94, 1.90	0.11
Histology					
Adenocarcinoma	257	79	—	—	
Other/Unknown	63	28	1.43	0.92, 2.23	0.11
Squamous cell	310	132	1.84	1.37, 2.47	<0.001
No. of Observations			630		
No. of Events			239		
Abbreviations: CI = Confidence Interval, HR = Hazard Ratio					

Table 2. Multivariable Cox PH model results. Other factors associated with improved rwOS included high PD-L1 expression and younger age; male sex, poor performance status, and squamous histology correlated with poorer rwOS.

ACKNOWLEDGMENTS

We thank Amrita A. Iyer, Ph.D from the Tempus Science Communications team for poster development.

