

Survival Impact of Histology-Genomic Interactions in Stage III NSCLC Treated with Chemoradiotherapy and Durvalumab

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INTRODUCTION

Clinical context: Definitive chemoradiotherapy (CRT) followed by consolidation durvalumab improves survival in unresectable stage III non-small cell lung cancer (NSCLC) [1–3].

Unmet need: Outcomes remain heterogeneous, with poorer survival reported in squamous cell carcinoma (SCC).

Objective: Assess whether pretreatment DNA damage response (DDR) status refines prognosis by histology.

METHODS

Design: Retrospective single-institution cohort of stage II–III NSCLC treated from 2015 to 2024.

Treatment: Definitive chemoradiotherapy followed by durvalumab.

Eligibility: Baseline next-generation sequencing was required.

Cohort: 114 patients: 30 with SCC and 84 with non-SCC.

DDR definition: At least one pathogenic or likely pathogenic alteration in ATM, ATR, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, MRE11A, PALB2, RAD51B, RAD51C, RAD52, or RAD54L [4–6].

Outcomes: Overall survival and progression-free survival.

Analysis: Kaplan–Meier estimates and Cox models with a histology by DDR interaction term.

Follow-up: Median 45.3 months, range 4.5–85.3.

RESULTS

Characteristic	SCC		Non-SCC		P value
	DDR A N=14	DDR WT N=16	DDR A N=50	DDR WT N=34	
Age (years)					0.02
Median (IQR)	68.6 (62.4, 76.0)	71.5 (67.7, 78.2)	71.9 (66.0, 76.8)	65.7 (60.6, 70.1)	
Gender					0.32
Female	8 (50.0%)	7 (50.0%)	15 (44.1%)	32 (64.0%)	
Male	8 (50.0%)	7 (50.0%)	19 (55.9%)	18 (36.0%)	
Race					0.01
American Indian or Alaska Native	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)	
White	15 (93.8%)	11 (78.6%)	30 (88.2%)	48 (96.0%)	
Asian	0 (0%)	1 (7.1%)	0 (0%)	2 (4.0%)	
Black /African American	0 (0%)	2 (14.3%)	4 (11.8%)	0 (0%)	
Smoking Status					0.06
Current/Former	11 (68.8%)	13 (92.9%)	21 (61.8%)	42 (84.0%)	
Never	2 (12.5%)	0 (0%)	3 (8.8%)	5 (10.0%)	
Unknown	3 (18.8%)	1 (7.1%)	10 (29.4%)	3 (6.0%)	
Stage (AJCC 8th ed)					0.41
Stage II	3 (18.8%)	0 (0%)	3 (8.8%)	6 (12.0%)	
Stage III	13 (81.3%)	14 (100%)	31 (91.2%)	44 (88.0%)	
PD-L1 Expression Level					0.49
≥1%	8 (50.0%)	3 (21.4%)	14 (41.2%)	17 (34.0%)	
<1%	4 (25.0%)	6 (42.9%)	6 (17.6%)	16 (32.0%)	
Unknown	4 (25.0%)	5 (35.7%)	14 (41.2%)	17 (34.0%)	
Chemo Regimen					0.06
Platinum, etoposide	1 (6.3%)	0 (0%)	1 (2.9%)	5 (10.0%)	
Platinum, PACLitaxel	15 (93.8%)	13 (92.9%)	26 (76.5%)	31 (62.0%)	
Platinum, PEMEtrexed	0 (0%)	1 (7.1%)	7 (20.6%)	14 (28.0%)	
Radiation Dose (Gy)					0.72
Median (Range)	60 (60, 70)	60 (60, 70)	60 (60, 70)	60 (60, 70)	
Number of durvalumab infusions					0.40
Median (IQR)	12.0 (5.8, 14.8)	3.0 (2.2, 14.2)	7.0 (3.2, 13.0)	7.0 (4.0, 12.0)	

Table 1. Baseline patient and treatment characteristics according to histology and DDR alteration status. Data are presented as median (IQR) for continuous variables and n (%) for categorical variables unless otherwise indicated. P values were calculated using Wilcoxon rank sum or Kruskal-Wallis tests for continuous variables and chi square or Fisher exact tests for categorical variables, as appropriate. **Abbreviations:** AJCC, American Joint Committee on Cancer; DDR, DNA damage response; IQR, interquartile range; PD-L1, programmed cell death ligand 1; SCC, squamous cell carcinoma; A, altered; WT, wildtype.

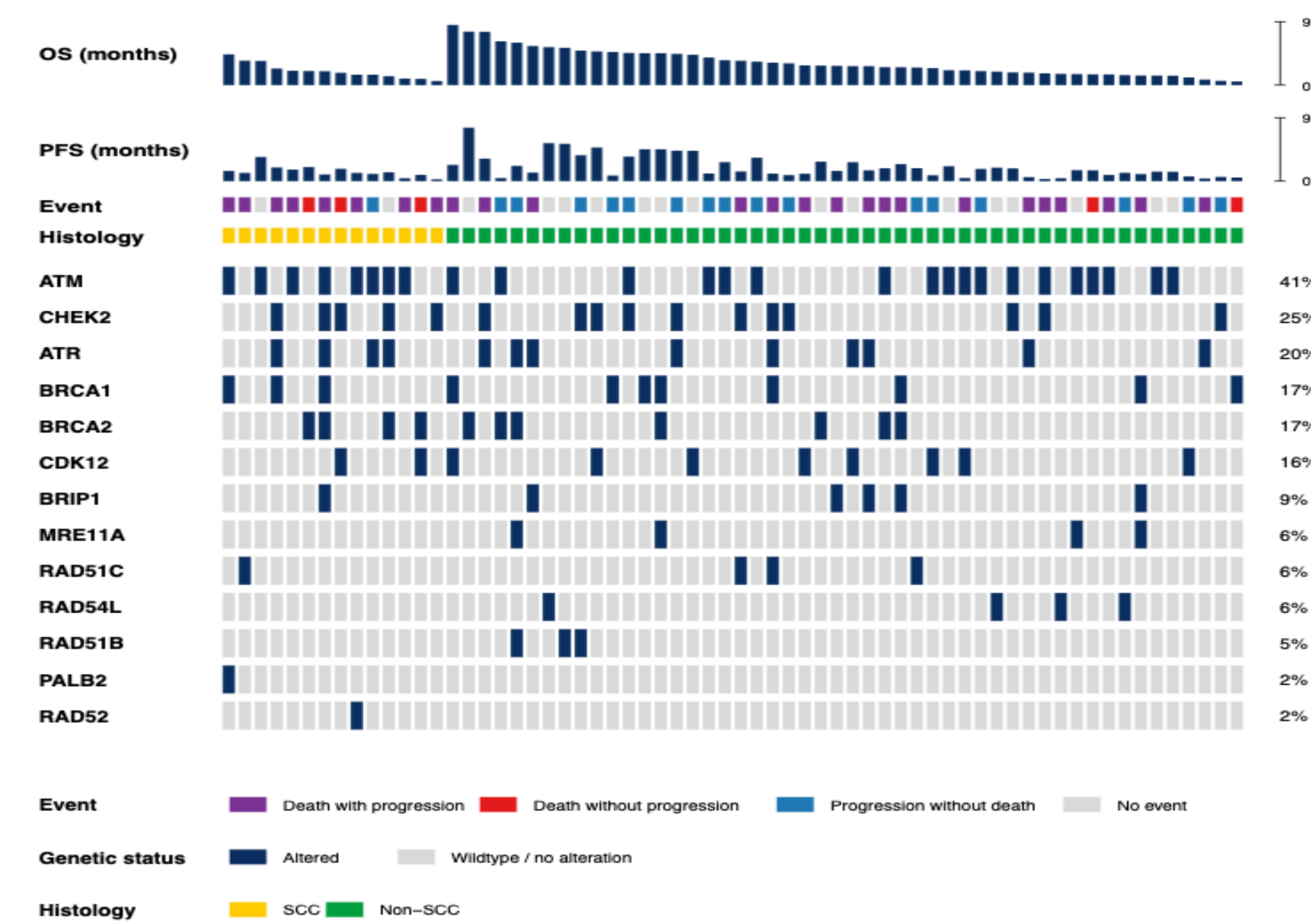


Figure 1. Molecular landscape of 13 predefined DDR genes among DDR-altered patients. OS and PFS bars show observed durations; event categories distinguish death with or without prior progression, progression without death, and no event. **Abbreviations:** DDR, DNA damage response; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

HISTOLOGY × DDR

Median OS by histology: SCC 20.4 months (95% CI, 19.1 to NA) versus non-SCC 53.9 months (95% CI, 34.3 to NA); log-rank $p = 0.022$.

3-year OS: SCC/DDR altered 13.3%; SCC/DDR wildtype 56.2%; non-SCC/DDR altered 59.4%; non-SCC/DDR wildtype 55.9%.

DDR alteration: SCC adjusted HR 3.04, 95% CI 1.18–7.83; non-SCC adjusted HR 0.67, 95% CI 0.33–1.28. *Adjusted OS interaction $p = 0.013$*

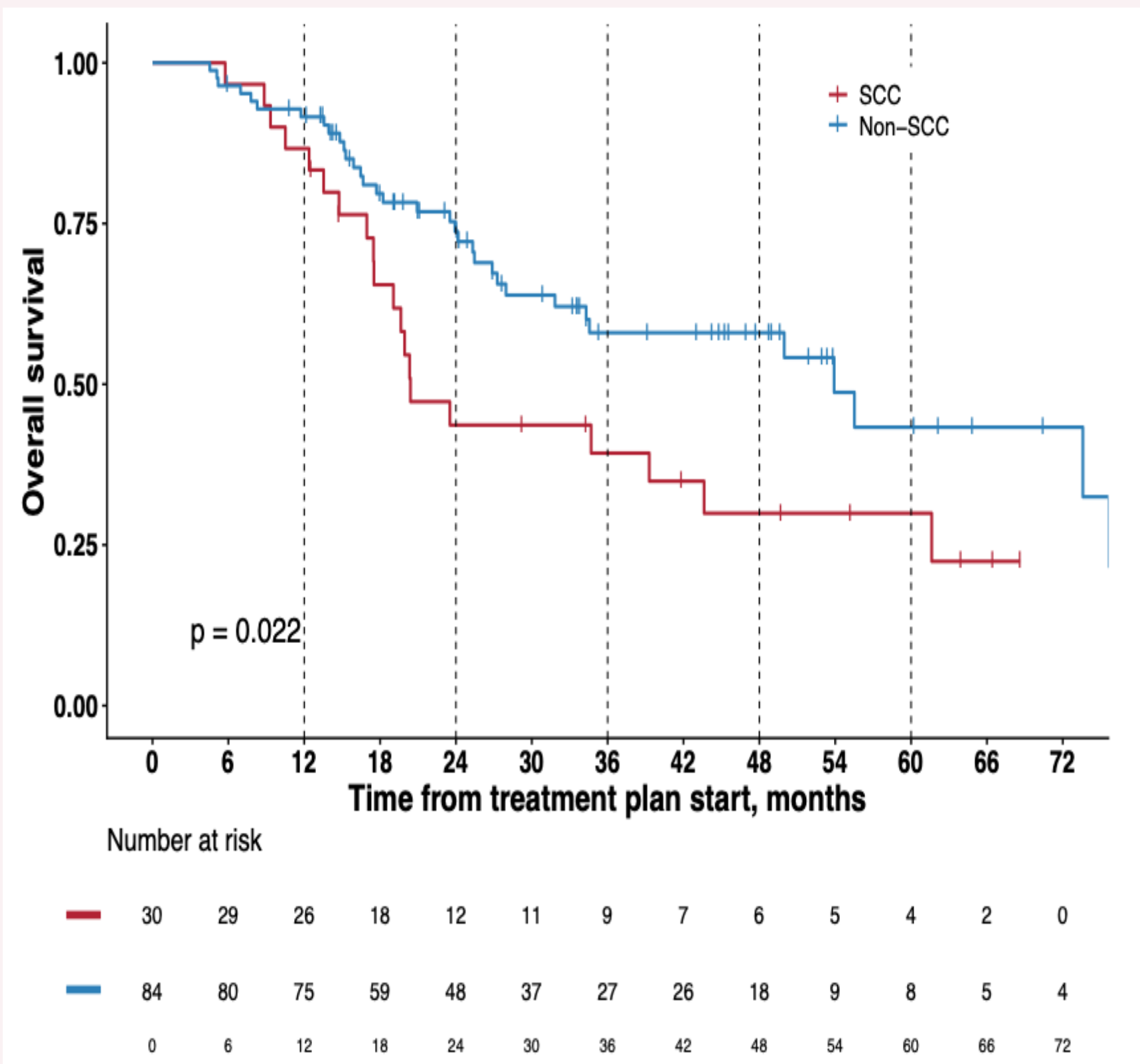


Figure 2A. Overall survival by histology. Median OS was 20.4 months (95% CI, 19.1 to NA) in SCC and 53.9 months (95% CI, 34.3 to NA) in non-SCC; log-rank $p = 0.022$. Censored observations are indicated by tick marks. **Abbreviations:** CI, confidence interval; OS, overall survival; SCC, squamous cell carcinoma.

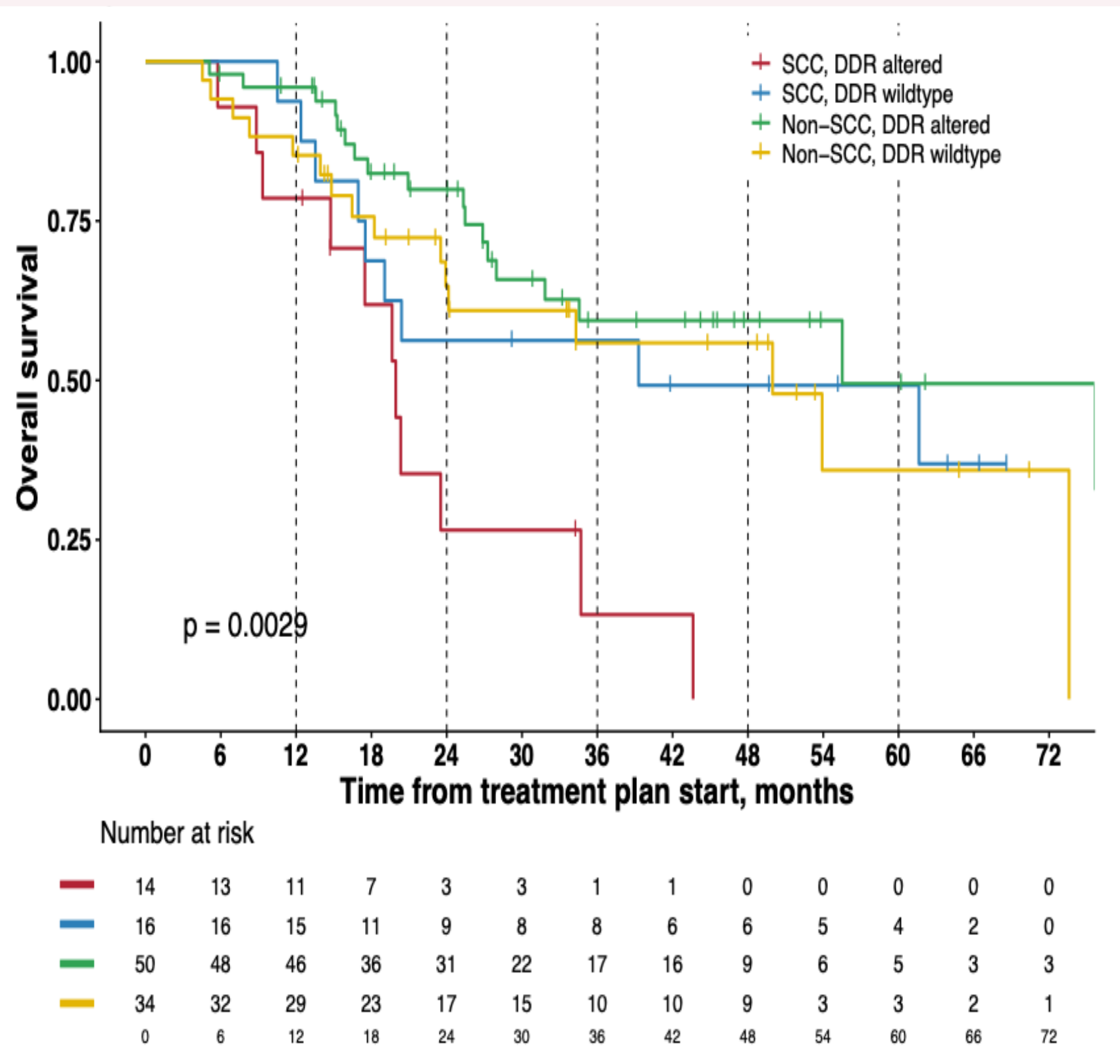


Figure 2B. Overall survival by combined histology and DDR status. Three-year OS was 13.3%, 56.2%, 59.4%, and 55.9% for SCC/DDR altered, SCC/DDR wildtype, non-SCC/DDR altered, and non-SCC/DDR wildtype, respectively; log-rank $p = 0.003$. **Abbreviations:** DDR, DNA damage response; OS, overall survival; SCC, squamous cell carcinoma.

Variable	HR (95% CI)	P value
DDR altered vs wildtype in SCC	3.04 (1.18–7.83)	0.021
DDR altered vs wildtype in non-SCC	0.67 (0.33–1.36)	0.266
Age	0.98 (0.95–1.02)	0.316
Stage: Stage III vs Stage II	1.34 (0.39–4.55)	0.639
Smoking: Current/Former vs Never	0.90 (0.31–2.65)	0.854
Smoking: Unknown vs Never	1.49 (0.43–5.13)	0.531
DDR status x SCC interaction		0.013

Figure 3. Adjusted histology-specific effects of DDR alterations on overall survival. DDR alteration was associated with worse OS in SCC (HR 3.04, 95% CI 1.18–7.83), but not in non-SCC (HR 0.67, 95% CI 0.33–1.28); interaction $p = 0.013$. The model was adjusted for age, clinical stage, and smoking status. **Abbreviations:** CI, confidence interval; DDR, DNA damage response; HR, hazard ratio; OS, overall survival; SCC, squamous cell carcinoma.

CONCLUSION

DDR alterations were associated with worse OS in SCC patients, but not in those with non-SCC, with a significant interaction between DDR status and histology.

Implication: DDR alterations identified a poor-prognosis subgroup within SCC, while SCC/DDR-wildtype outcomes were numerically comparable to non-SCC.

Interpretation: Because all patients received durvalumab, DDR status is prognostic rather than predictive.

Limitations: Retrospective design, baseline sequencing selection, and small SCC subgroups. Prospective validation is required.

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