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DNA damage and repair (DDR) gene mutation profiles in driver gene wild-type advanced non-small cell lung cancer and the predictive role of response to platinum-based chemotherapy.

Wu T, Xu Y, Song Q, et al. Transl Lung Cancer Res. 2025 Apr 30;14(4):1089-1103.

プラチナ製剤ベースの化学療法はドライバー遺伝子変異を持たない進行非小細胞肺癌(NSCLC)患者にとって重要な治療法である。DNA 損傷修復(DDR)遺伝子はプラチナによる DNA 損傷を軽減し、プラチナ製剤に対する耐性を誘導する可能性がある。進行性ドライバー遺伝子野生型 NSCLC において DDR 遺伝子変異が白金製剤ベース化学療法の治療効果および予後予測因子となり得るかを検討した。2016 年から 2021 年までに、治療歴のないドライバー遺伝子野生型 NSCLC 患者 182 名を前向きに研究した。白金併用化学療法を受けた後、腫瘍組織または血清循環腫瘍 DNA(ctDNA)を用いて 7 つの DDR シグナル伝達経路に属する 47 の DDR 変異状態を NGS で評価した。主要評価項目は客観的奏効率(ORR)、副次評価項目は PFS, OS とした。DDR 変異とプラチナ製剤ベース化学療法への反応性および臨床転帰との関連を解析した。

プラチナ製剤化学療法を受けた 136 名、内 101 名の DDR 変異が解析できた。67/101(66.33%)で何らかの DDR 遺伝子変異が認められた。最も高頻度の変異遺伝子は *BARD1*、次に *POLE*、*PRKDC*、*BRCA2*、*ATM* であり、特に相同組換え修復（HR）経路の変異が最も多かった。DDR 変異陽性患者の奏効率は DDR 野生型患者よりも有意に高かった（53．2%　vs. 23.5%, p<0.001)。さらに、より長い PFS(6.3 months vs. 3.3 months, p<0.001), OS(16.8 months vs. 9.4 months, p=0.007)を示した。多変量解析においても、DDR 変異は独立した予後良好因子であった。特に HR 経路変異や、*PRKDC*、*BRCA2*、*ATM*、*POLE* など一部の遺伝子変異は PFS や OS の延長と関連していた。DDR 遺伝子異常は進行 NSCLC における一次治療としての白金製剤化学療法の有効性を予測する有望なバイオマーカーであると結論づけられた。

Take home message:肺癌においても他の癌と同様に DNA 修復遺伝子異常は白金製剤のバイオマーカーとなることが示唆された。本論文は現在行っている研究の論文の書き方の参考になると思い読んでみた。

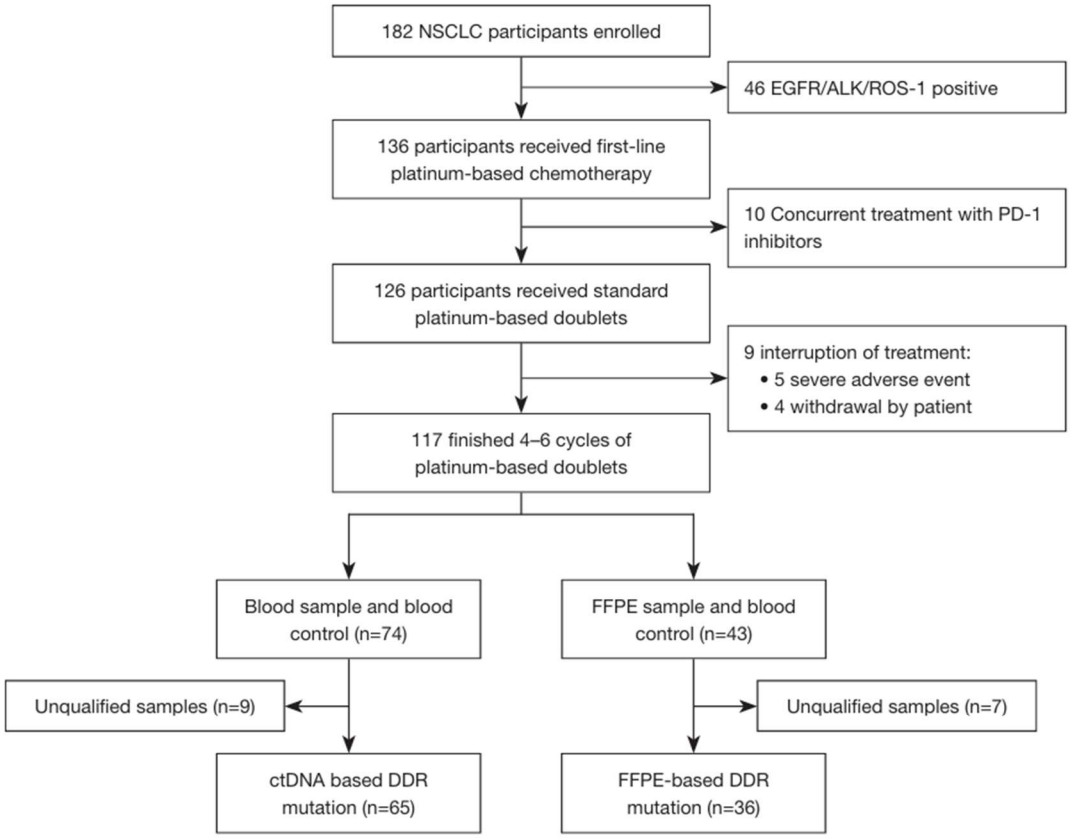

Figure 1 Patients screening and disposition flow diagram. *ALK*, anaplastic lymphoma kinase; ctDNA, circulating tumor DNA; DDR, DNA damage and repair; *EGFR*, epidermal growth factor receptor; FFPE, formalin-fixed paraffin-embedded; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; *ROS-1*, ROS proto-oncogene 1.

Table 1 The baseline characteristics of the cohort

Characteristics	Entire cohort (N=101)	DDRmut (N=67)	DDRwt (N=34)	P value
Age (years)				>0.99
≤60	58 (57.4%)	38 (56.7%)	20 (58.8%)	
>60	43 (42.6%)	29 (43.2%)	14 (41.2%)	
Gender				0.37
Male	87 (86.1%)	56 (83.6%)	31 (91.2%)	
Female	14 (13.9%)	11 (16.4%)	3 (8.8%)	
Smoking history				0.10
No	19 (18.8%)	16 (23.9%)	3 (8.8%)	
Yes	82 (81.2%)	51 (76.1%)	31 (91.2%)	
Pathological type				0.19
Squamous carcinoma	58 (57.4%)	42 (62.7%)	16 (47.1%)	
Adenocarcinoma	42 (41.6%)	24 (35.8%)	18 (52.9%)	
Large cell carcinoma	1 (1.0%)	1 (1.5%)	0	
Stage				>0.99
III	49 (48.5%)	33 (49.3%)	16 (47.1%)	
IV	52 (51.5%)	34 (50.7%)	18 (52.9%)	
Metastasis				0.27
No	4 (4.0%)	1 (1.5%)	3 (8.8%)	
Yes	97 (96.0%)	66 (98.5%)	31 (91.2%)	
ECOG				0.18
0	67 (66.3%)	41 (61.2%)	26 (76.5%)	
1	34 (33.7%)	26 (38.8%)	8 (23.5%)	
Chemotherapy regimen				0.27
Cisplatin + docetaxel	7 (7.0%)	6 (9.0%)	1 (2.9%)	
Cisplatin + gemcitabine	4 (4.0%)	4 (6.0%)	0	
Cisplatin + paclitaxel	52 (51.5%)	35 (52.2%)	17 (50.0%)	
Cisplatin+ pemetrexed	38 (37.6%)	22 (32.8%)	16 (47.1%)	

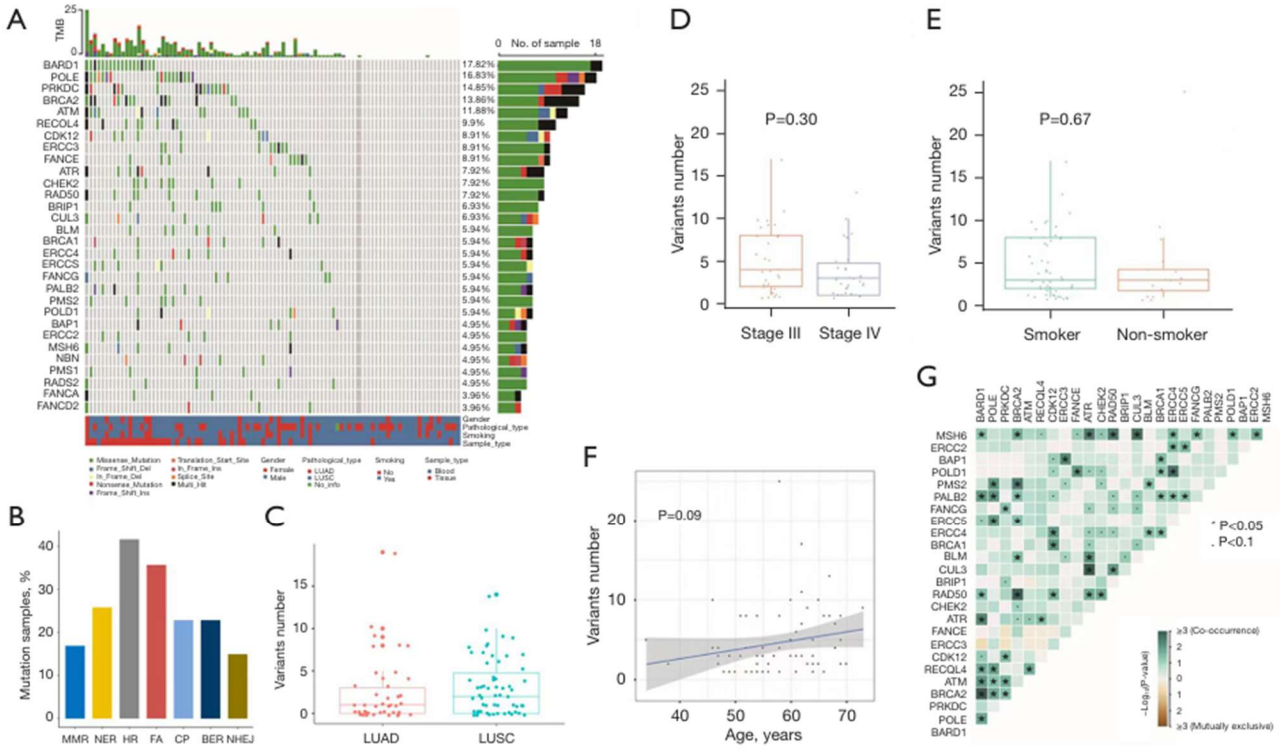

Figure 2 Landscapes of DDR gene mutations in NSCLC. (A) Oncoplot depicting the top 30 most frequently mutated DDR-related genes. The oncoprint (bottom panel) shows details of the types of alterations in DDR genes, as well as clinical characteristics including gender, pathological type, smoking and sample type. (B) The proportion of mutated samples in the 7 DDR-related pathways. (C-F) The correlation of DDR variant number with pathological type (C), TNM staging (D), smoking history (E) and age (F). (G) Co-mutation analysis. The co-mutation included co-occurring (green) and mutual exclusion (brown), "*", P<0.05; "•", P<0.1. BER, base excision repair; CP, cell-cycle checkpoint; DDR, DNA damage and repair; FA, Fanconi anemia pathway; HR, homologous recombination; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; NSCLC, non-small cell lung cancer; TMB, tumor mutation burden; TNM, Tumor, Node, and Metastasis.

Table 2 DDR gene mutation status and response to platinum-based chemotherapy in 101 NSCLC

Response	Entire cohort (N=101)	DDRmut (N=67)	DDRwt (N=34)
CR	1 (1.0%)	1 (1.5%)	0 (0%)
PR	42 (41.6%)	34 (50.7%)	8 (23.5%)
SD	39 (38.6%)	26 (38.8%)	13 (38.2%)
PD	19 (18.8%)	6 (9.0%)	13 (38.2%)
ORR	43 (42.6%)	35 (52.2%)	8 (23.5%)
DCR	82 (81.2%)	61 (91.0%)	21 (61.8%)
mPFS	5 months	6.3 months	3.3 months
mOS	14.9 months	16.8 months	9.4 months
mDDC	3.1 months	4.3 months	1.4 months

CR, complete response; DDR, DNA damage and repair; DDRmut, DDR-mutant; DDRwt, DDR-wild type; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; mDDC, median duration of disease control; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progression disease; PR, partial response; SD, stable disease.

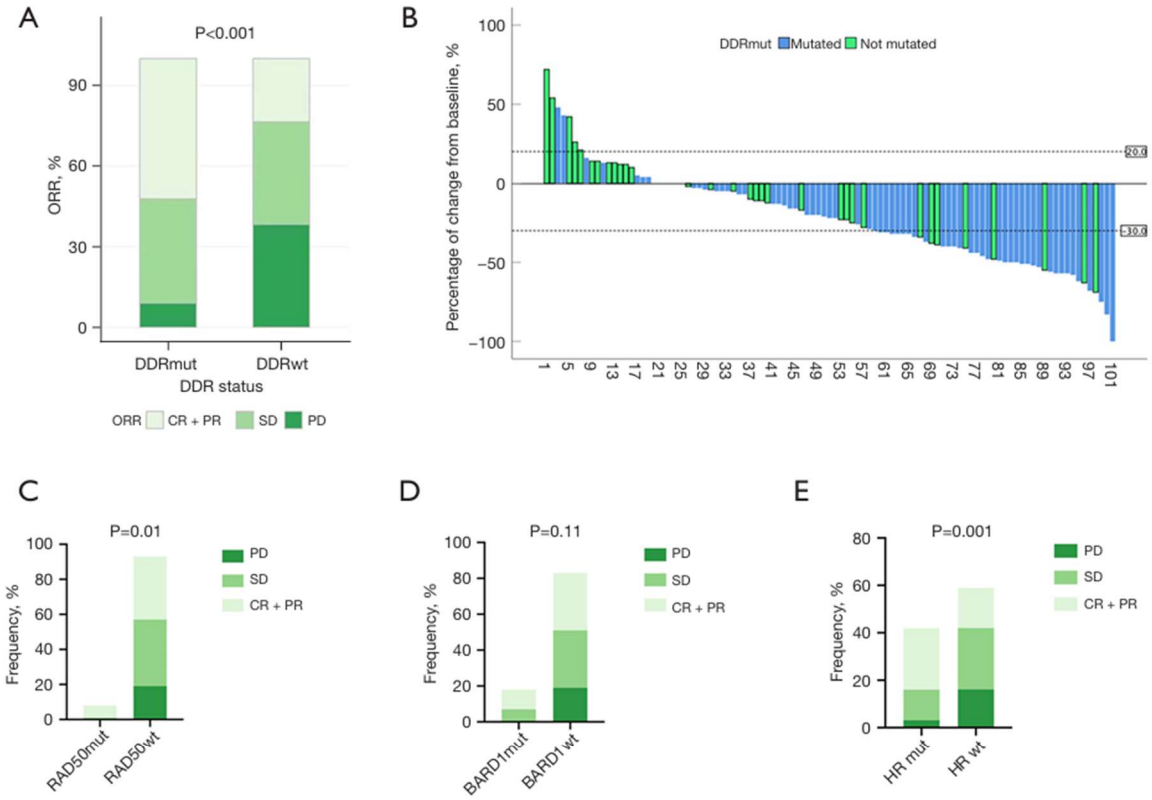

Figure 3 Response to platinum-based chemotherapy in patients with DDRmut and DDRwt disease. (A) Histogram of ORR between DDRmut and DDRwt NSCLC. (B) Waterfall plot showing the best change of target lesion's diameter from baseline for patients with DDRmut and DDRwt disease. (C-E) Histogram of ORR between NSCLC patients with or without *RAD50* (C), *BARD1* (D), or HR pathway (E) alterations. CR, complete response; DDR, DNA damage and repair; DDRmut, DDR-mutant; DDRwt, DDR-wild type; HR, homologous recombination; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

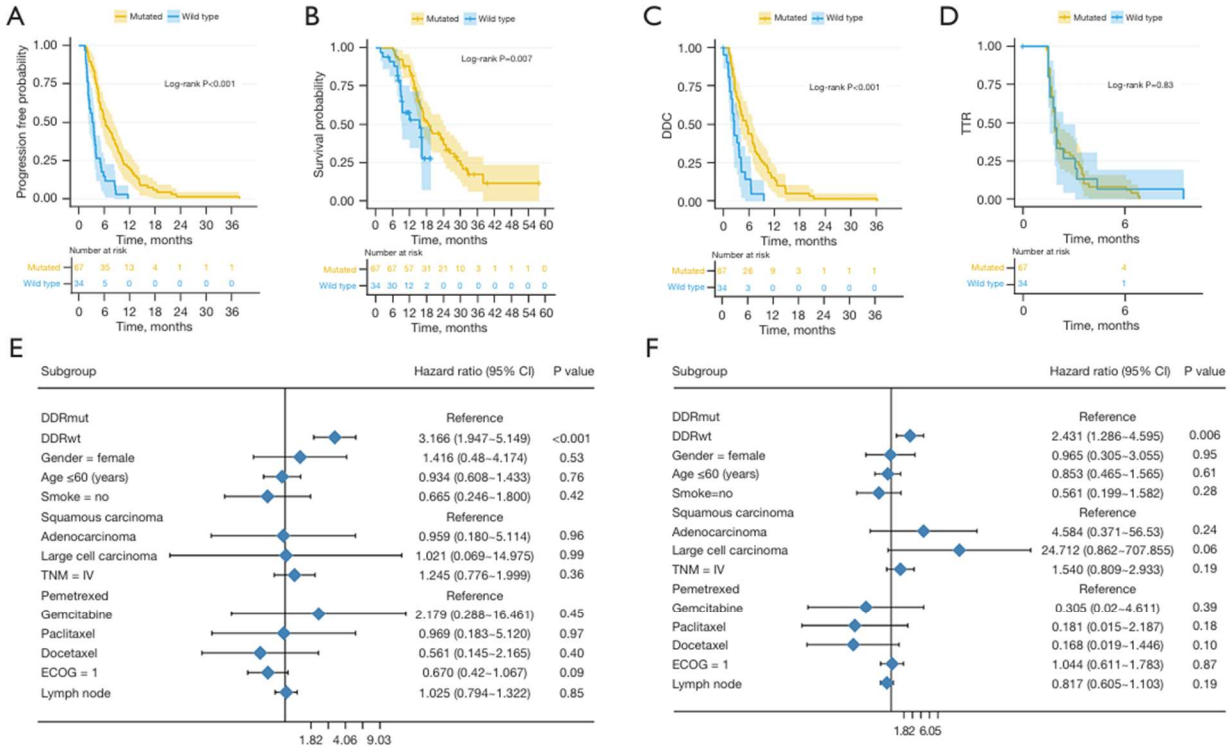

Figure 4 Outcome of NSCLC with DDRmut and DDRwt disease. (A-D) PFS (A), OS (B), DDC (C) and TTR (D) on platinum-based chemotherapy for DDRmut and DDRwt patients. (E,F) Forest plot of NSCLC patients PFS (E) and OS (F) from multivariate Cox regression. CI, confidence interval; DDC, duration of disease control; DDR, DNA damage and repair; DDRmut, DDR-mutant; DDRwt, DDR-wild type; ECOG, eastern cooperative oncology group; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TNM, Tumor, Node, and Metastasis; TTR, time to response.

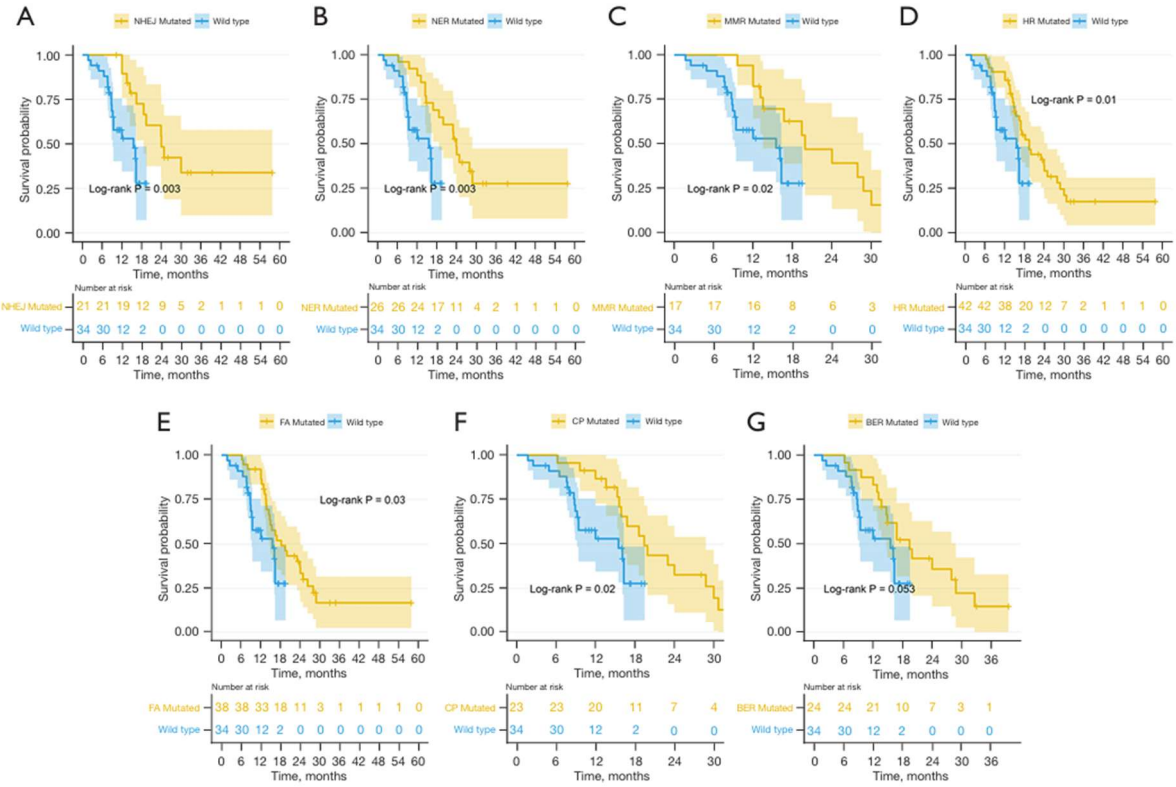

Figure 5 OS of NSCLC patients with alteration in NHEJ pathway (A), NER pathway (B), MMR pathway (C), HR pathway (D), FA pathway (E), CP pathway (F), and BER pathway (G) compared with DDRwt group. BER, base excision repair; CP, cell-cycle checkpoint; DDR, DNA damage and repair; FA, Fanconi anemia pathway; HR, homologous recombination; MMR, mismatch repair; NHEJ, non-homologous end joining; NER, nucleotide excision repair; NSCLC, non-small cell lung cancer; OS, overall survival.

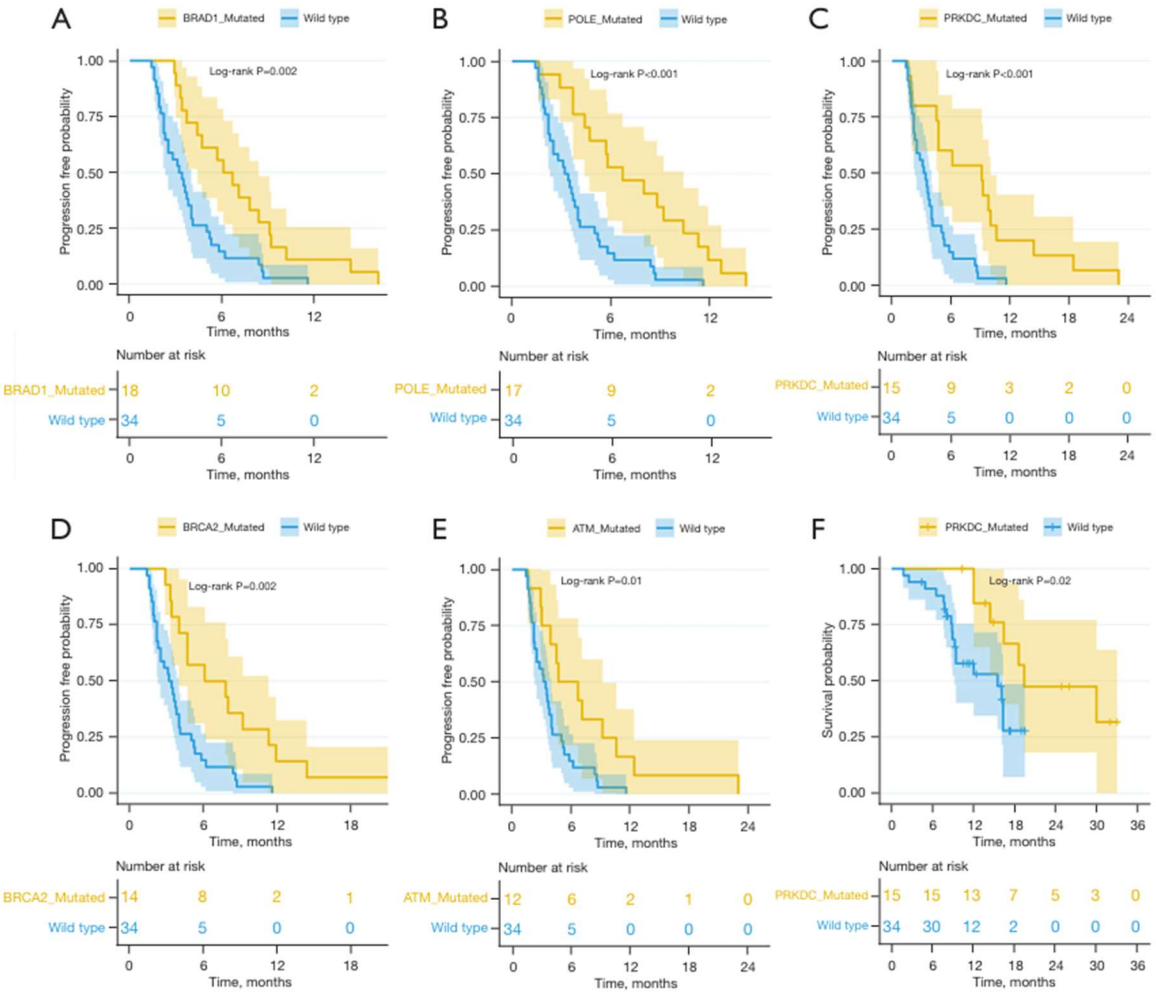

Figure 6 PFS of NSCLC patients with alteration in *BRAD1* (A), *POLE* (B), *PRKDC* (C), *BRCA2* (D), and *ATM* (E) compared with DDRwt group. OS of NSCLC patients with alteration in *PRKDC* (F) compared with DDRwt group. DDR, DNA damage and repair; DDRwt, DDR-wild type; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

Table S1 The univariate Cox regression results for PFS

Characteristics	Hazard ratio (95% CI)	P value
DDR		
DDRwt	Reference	
DDRmut	3.102 (1.981–4.857)	<0.001
Gender =female	0.733 (0.407–1.319)	0.30
Age ≤60 (years)	0.906 (0.608–1.349)	0.63
Smoke =no	0.743 (0.444–1.242)	0.26
Pathological type		
Squamous carcinoma	Reference	
Adenocarcinoma	1.024 (0.684–1.534)	0.91
Large cell carcinoma	0.864 (0.118–6.324)	0.89
TNM =IV	1.009 (0.680–1.499)	0.96
Chemotherapy		
Pemetrexed	Reference	
Gemcitabine	1.175 (0.417–3.307)	0.76
Paclitaxel	1.037 (0.680–1.581)	0.87
Docetaxel	0.468 (0.196–1.117)	0.09
ECOG =1	0.658 (0.428–1.012)	0.056
Lymph node	1.048 (0.836–1.313)	0.68

DDRmut, DDR-mutant; DDRwt, DDR-wild type; PFS, progression-free survival.

Table S2 The univariate Cox regression results for OS

Characteristics	Hazard ratio (95% CI)	P value
DDR		
DDRwt	Reference	
DDRmut	2.217 (1.229–3.997)	0.008
Gender=female	0.516 (0.231–1.149)	0.11
Age ≤60 (years)	0.926 (0.566–1.517)	0.76
Smoke =no	0.555 (0.281–1.099)	0.09
Pathological type		
Squamous carcinoma	Reference	
Adenocarcinoma	0.862 (0.522–1.421)	0.56
Large cell carcinoma	2.849 (0.378–21.438)	0.31
TNM=IV	1.176 (0.717–1.931)	0.52
Chemotherapy		
Pemetrexed	Reference	
Gemcitabine	1.075 (0.372–3.101)	0.89
Paclitaxel	0.802 (0.477–1.348)	0.41
Docetaxel	0.374 (0.113–1.238)	0.11
ECOG =1	0.888 (0.536–1.471)	0.65
Lymph node	0.903 (0.696–1.170)	0.44

DDRmut, DDR-mutant; DDRwt, DDR-wild type; ECOG, eastern cooperative oncology group; OS, overall survival.

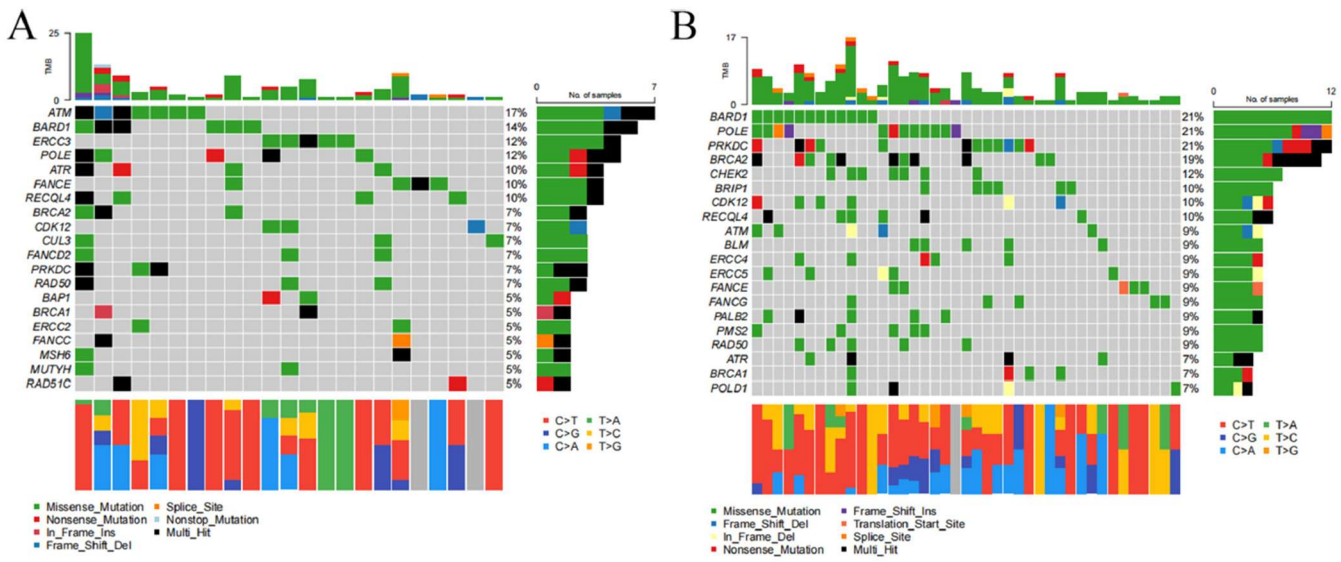

Figure S1 Mutation profile of 47 DNA damage and repair (DDR) genes in lung adenocarcinoma (A) and squamous lung cancer (B).

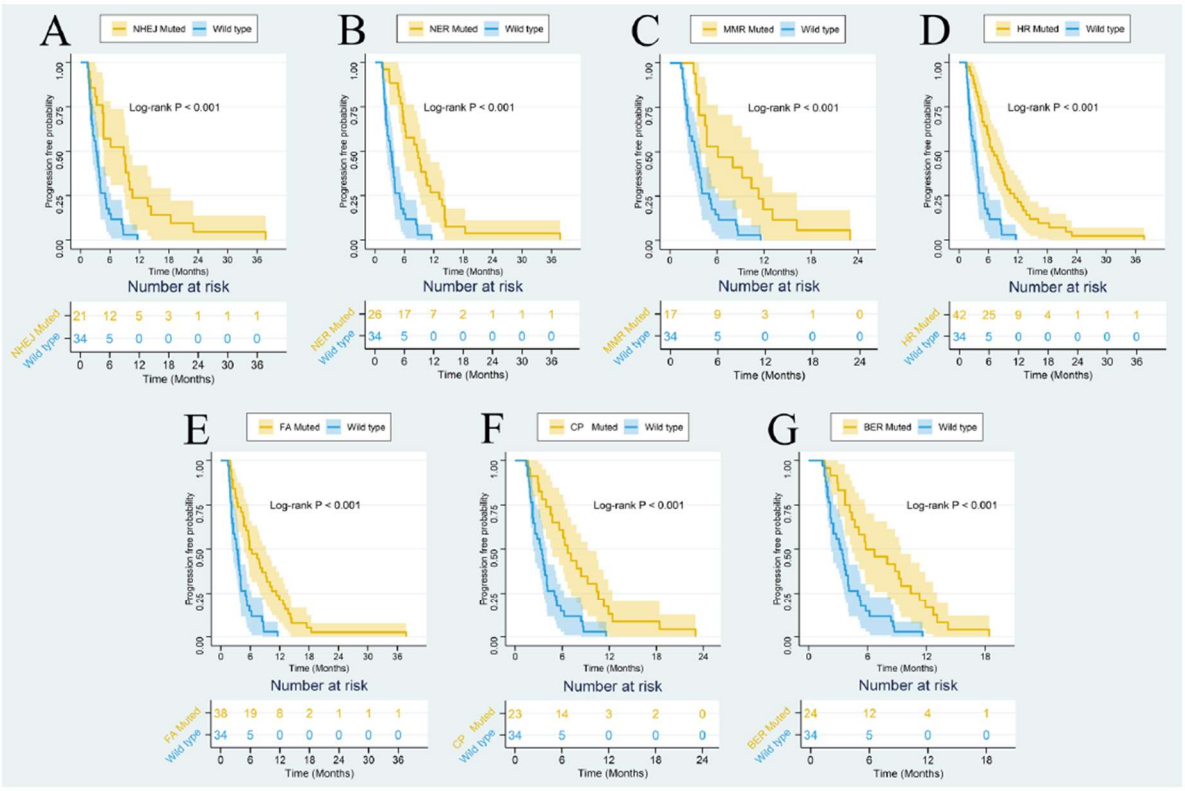

Figure S2 PFS of NSCLC patients with alteration in NHEJ (A), NER (B), MMR (C), HR (D), FA (E), CP (F), and BER (G) compared with DDRwt group. NHEJ, non-homologous end joining; NER, nucleotide excision repair; MMR, mismatch repair; HR, homologous recombination; FA, Fanconi anemia pathway; CP, cell-cycle checkpoint; BER, base excision repair.

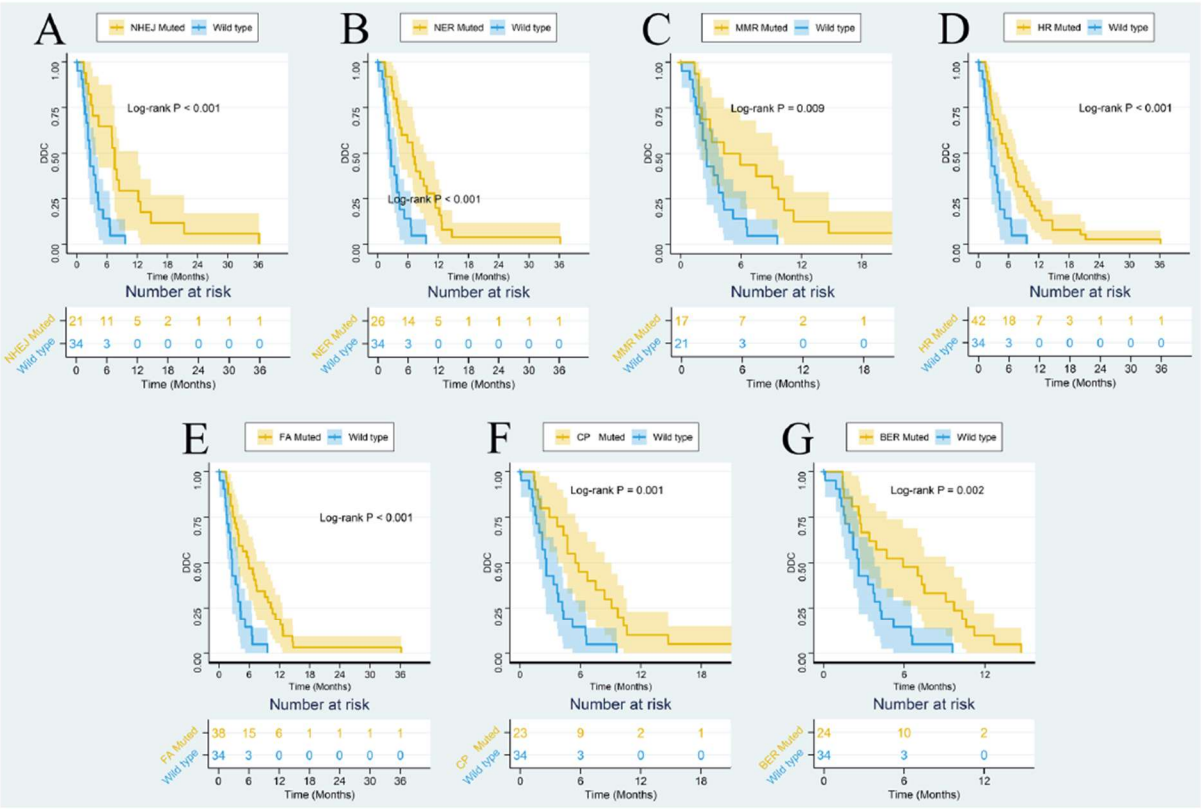

Figure S3 DDC of NSCLC patients with alteration in NHEJ (A), NER (B), MMR (C), HR (D), FA (E), CP (F), and BER (G) compared with DDRwt group. DDC, duration of disease control; NHEJ, non-homologous end joining; NER, nucleotide excision repair; MMR, mismatch repair; HR, homologous recombination; FA, Fanconi anemia pathway; CP, cell-cycle checkpoint; BER, base excision repair.