

Do PD-L1 Gene Polymorphisms Influence Efficacy and Toxicity of Pembrolizumab in Advanced Non-Small Cell Lung Cancer?



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INTRODUCTION

Pembrolizumab monotherapy is standard first-line treatment for advanced NSCLC with high PD-L1 expression ($\geq 50\%$), yet clinical outcomes and toxicity profiles remain heterogeneous.

Genetic variability within immune checkpoint pathways — including PD-L1 gene polymorphisms — may influence both treatment efficacy and immune-related toxicity.

Aim:

To evaluate the incidence and spectrum of immune-related adverse events (irAEs) in patients with advanced NSCLC treated with pembrolizumab monotherapy, and to assess the influence of PD-L1 polymorphisms rs4143815 and rs2282055 on treatment efficacy and safety.

METHODS

Design: Retrospective-prospective, single-institution study.

Population: 121 patients with stage IV NSCLC, without EGFR or ALK alterations, PD-L1 expression $\geq 50\%$, who received first-line pembrolizumab monotherapy.

Outcomes: Progression-free survival (PFS) and overall survival (OS); immune-related adverse events (irAEs) recorded and graded by severity throughout treatment.

PD-L1 genotyping: Polymorphisms rs4143815 and rs2282055 analysed from tumor samples by qPCR.

Statistical analysis: Kaplan-Meier method; between-group differences assessed with the Log-rank or Breslow test.

DISCUSSION AND CONCLUSION

Key Conclusions

- irAEs occurred in $\sim 1/3$ of patients on pembrolizumab monotherapy and were associated with significantly longer PFS and OS.
- PD-L1 polymorphism rs4143815 significantly influenced OS (GC vs GG vs CC, $p=0.04$); rs2282055 showed no significant effect on PFS or OS ($p=0.085$).
- Among rs4143815 GG carriers, irAE occurrence was linked to longer OS ($p=0.029$);
- Among rs2282055 TT carriers, irAE occurrence was linked to longer OS ($p=0.040$).

Future Directions

- PD-L1 gene polymorphisms may serve as a low-cost prognostic marker for pembrolizumab efficacy, particularly combined with irAE occurrence.
- Further studies should validate these findings and explore additional polymorphisms of PD-L1 and related immune checkpoint genes.

REFERENCES & ACKNOWLEDGEMENTS

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Scan QR code for the full reference list and extended data.



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RESULTS

121 patients received first-line pembrolizumab monotherapy (median follow-up 44.7 months):

- Median PFS:** 16.82 months (95% CI 12.38–21.27)
- Median OS:** 22.9 months (95% CI 14.21–31.59)
- irAEs:** occurred in 38 patients (31%); grade 3–5 in 12%
- Most frequent toxicities:** dermatologic 12%, arthritis 7%, hepatitis 5%, thyroiditis 5%, colitis 5%, mucositis 4%; pneumonitis, hypophysitis and myositis each in 2 patients
- Fatal irAEs:** recorded in 2 patients: hypophysitis and myocarditis

Table 1. Survival outcomes by irAE occurrence

Outcome	With irAEs	Without irAEs	p
Median PFS (months)	30.06 (14.02–46.10)	12.45 (7.13–17.77)	0.019
Median OS (months)	65.81 (21.00–110.62)	19.15 (12.04–26.26)	0.009

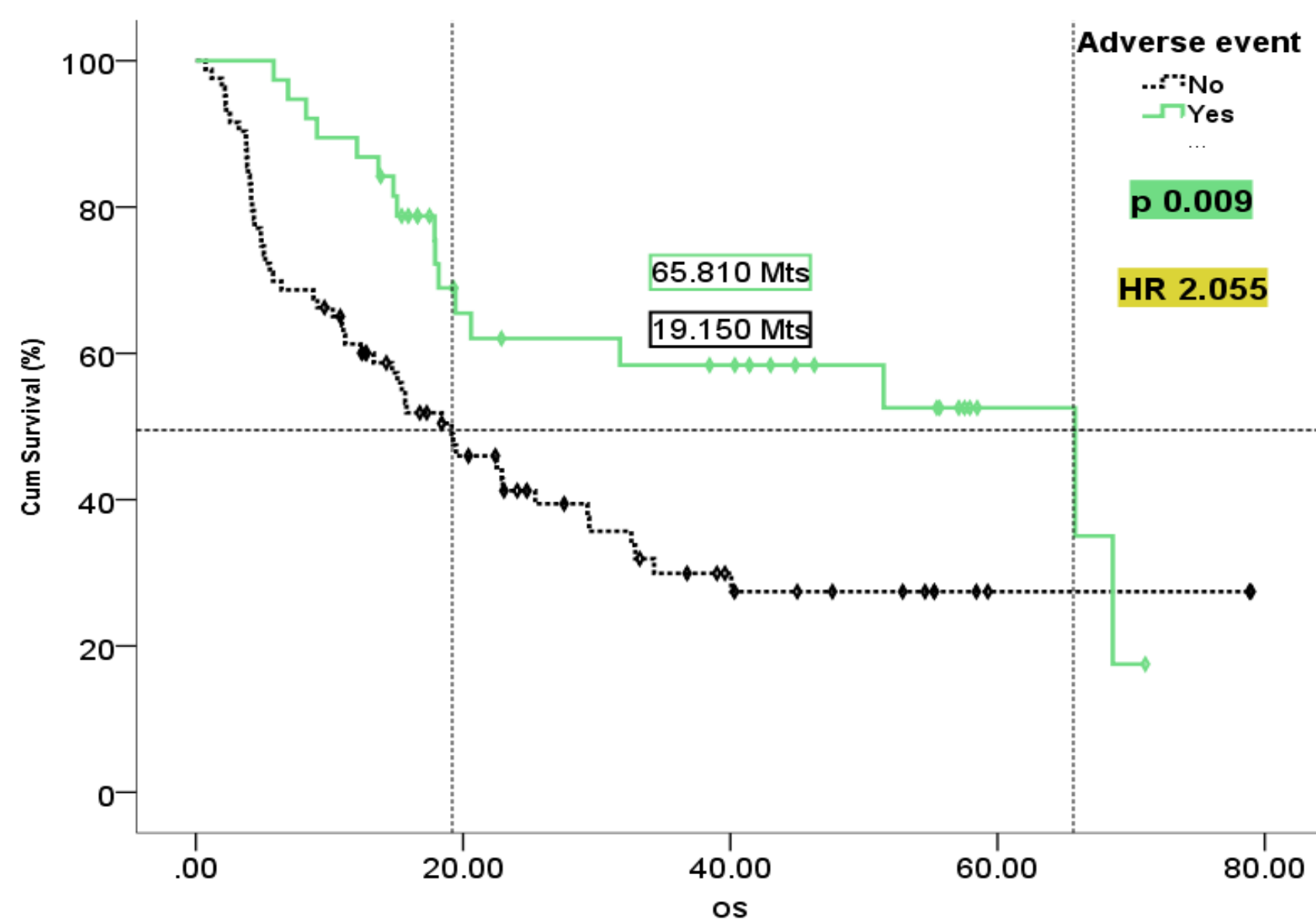
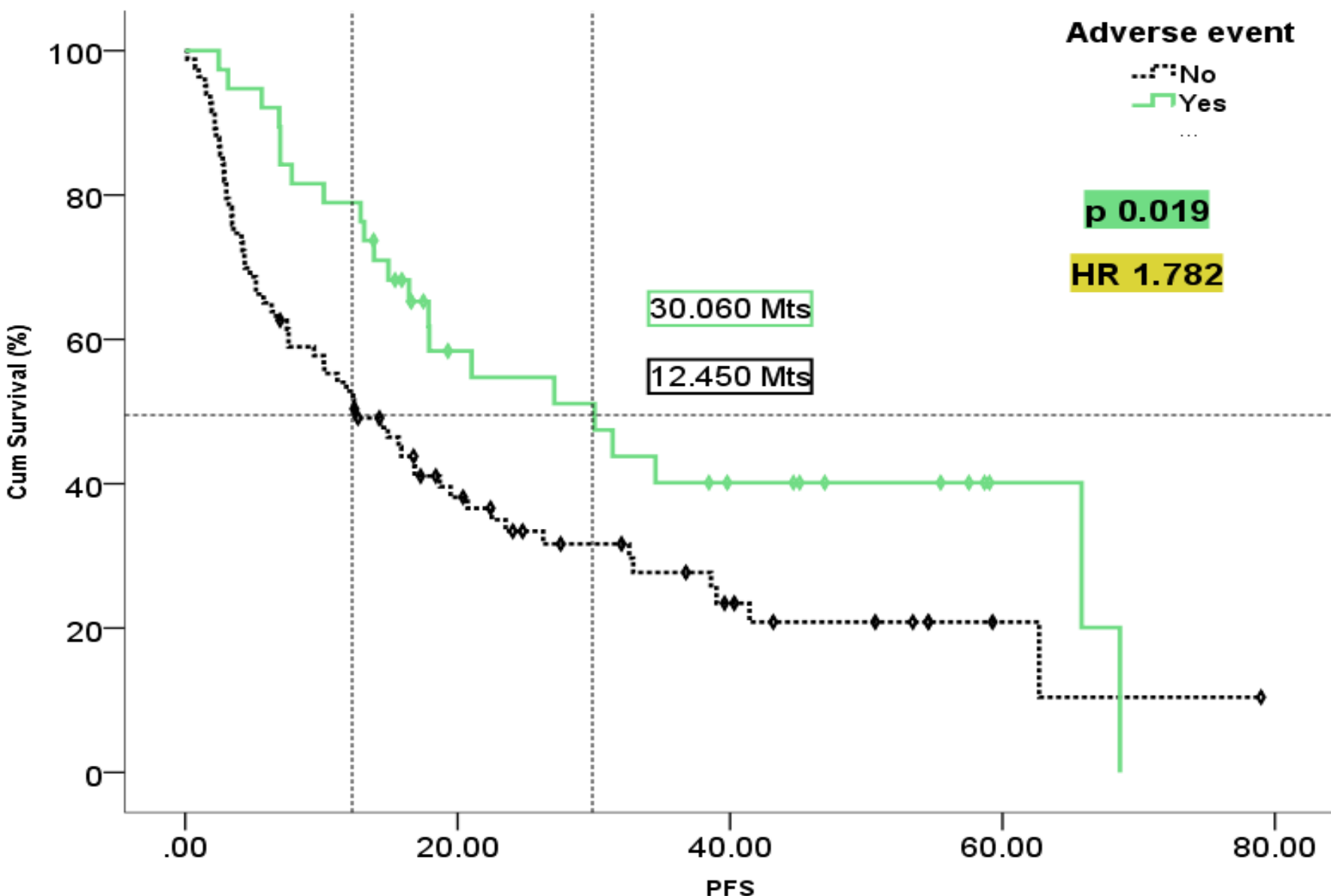
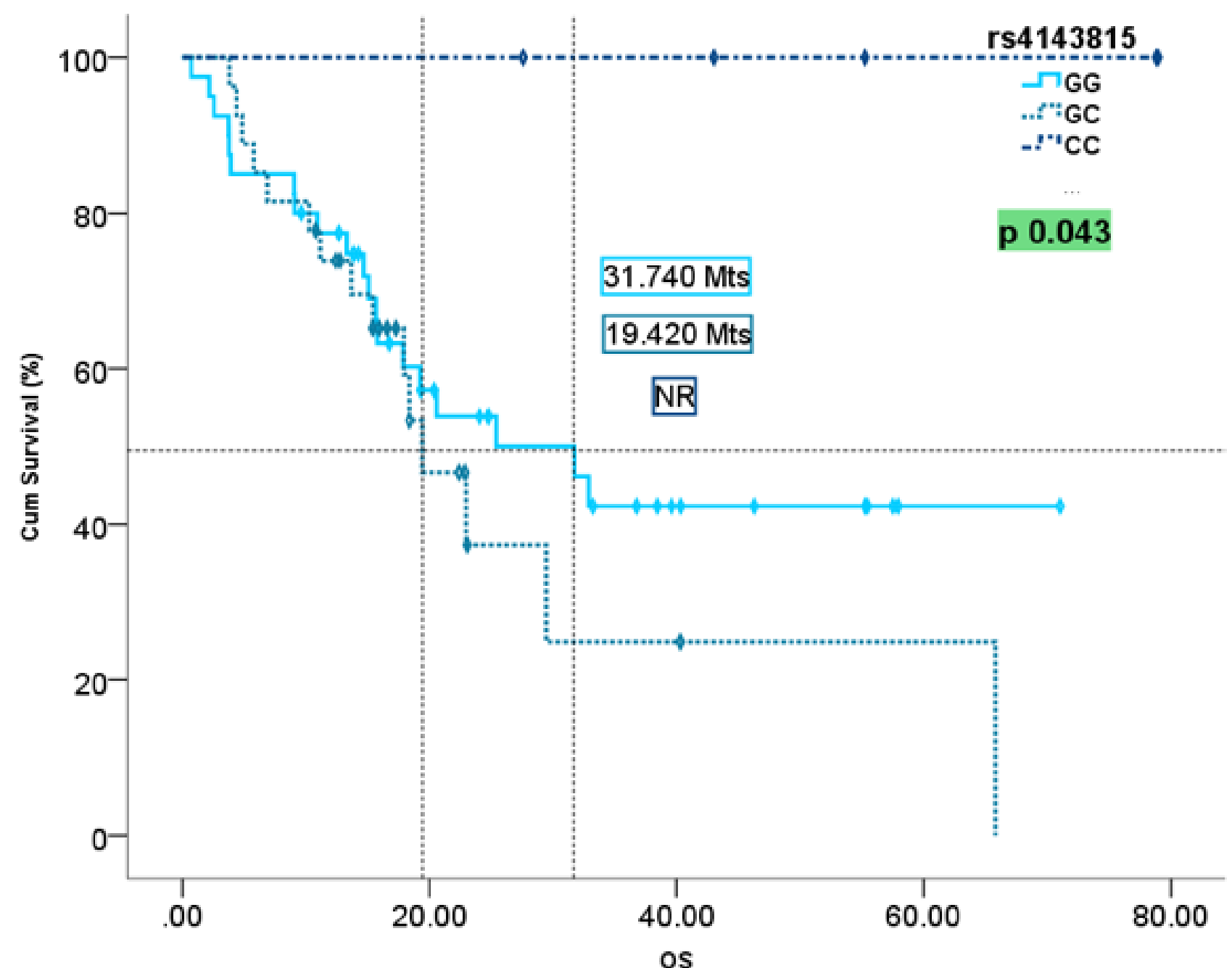


Table 2. PD-L1 polymorphism rs4143815 and overall survival ($p=0.04$)

rs4143815 genotype	Median OS (months)
GC	19.42
GG	31.74
CC	Not reached



- The rs2282055 polymorphism showed **no significant effect** on PFS or OS overall ($p=0.085$).
- No significant association was found between either polymorphism and irAE occurrence in general.
- Among **rs4143815 GG carriers**, **irAE occurrence** was associated with **longer OS** ($p=0.029$).
- Among **rs2282055 TT carriers**, **irAE occurrence** was associated with **longer OS** ($p=0.040$).