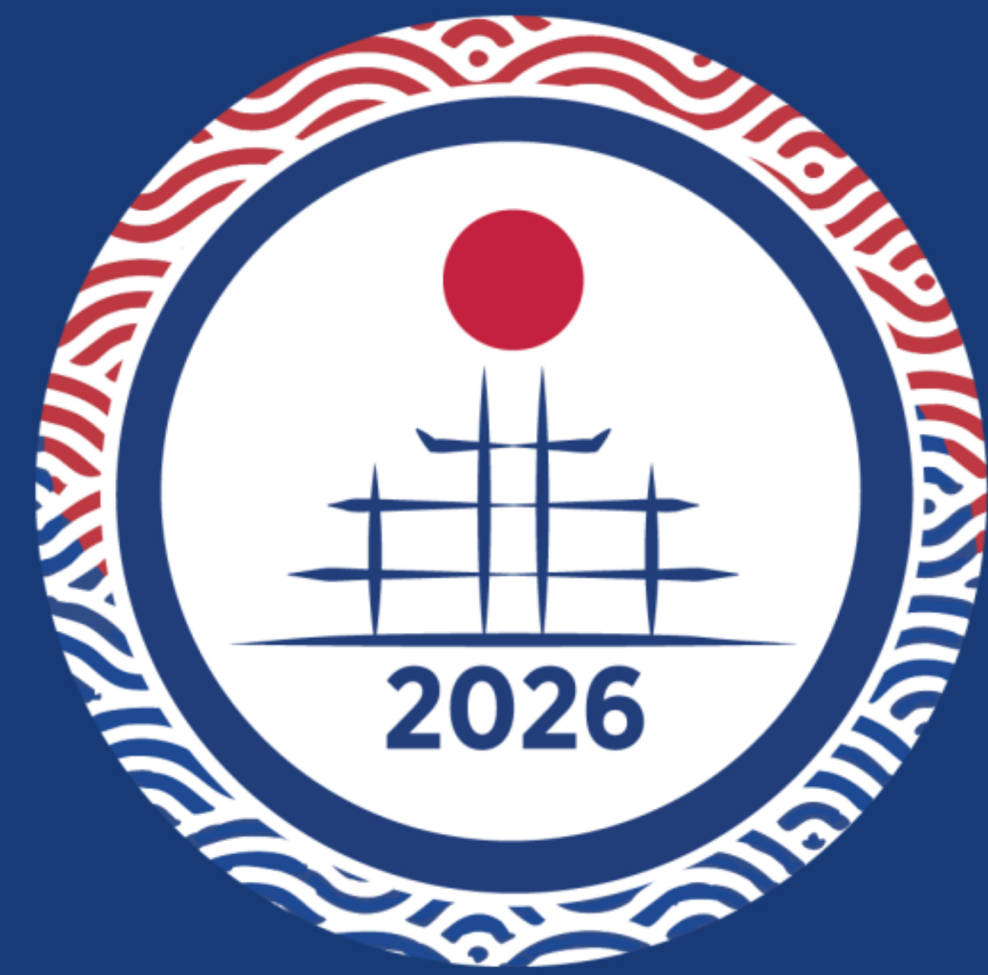




Differential Impact of EGFR Subtype and PD-L1 on EGFR-TKI and Immunotherapy Outcomes in EGFR-Mutant NSCLC



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BACKGROUND

- EGFR tyrosine kinase inhibitors (EGFR-TKIs) are the standard first-line therapy for EGFR-mutant non-small cell lung cancer (NSCLC), yet treatment responses and durability vary substantially across patients.
- PD-L1 expression has been widely studied as a biomarker for immunotherapy; however, its clinical relevance in EGFR-mutant NSCLC remains unclear, particularly regarding outcomes with EGFR-TKI therapy.
- Tumor immune phenotype and EGFR mutation subtype may reflect underlying biological heterogeneity that influences treatment response.
- We therefore investigated the differential impact of EGFR mutation subtype and PD-L1 expression on outcomes with EGFR-TKIs and subsequent immune checkpoint inhibitors (ICIs) using a nationwide Korean registry.

METHODS

- Patients with EGFR-mutant NSCLC who received EGFR-TKIs were identified from the Korean EGFR registry.
- Among them, those who received ICI-based therapy after EGFR-TKI failure were included in the ICI cohort.
- EGFR mutations were categorized as common (exon 19 deletion or L858R) and uncommon (including exon 20 insertion and other rare variants).
- PD-L1 expression was stratified by tumor proportion score (<50% versus ≥50%).
- Outcomes of interest included progression-free survival (PFS) with first-line EGFR-TKI and subsequent ICI.
- Survival curves were estimated using the Kaplan-Meier method and compared with log-rank tests.
- Multivariable Cox proportional hazards models were used to identify independent predictors.

CONCLUSION

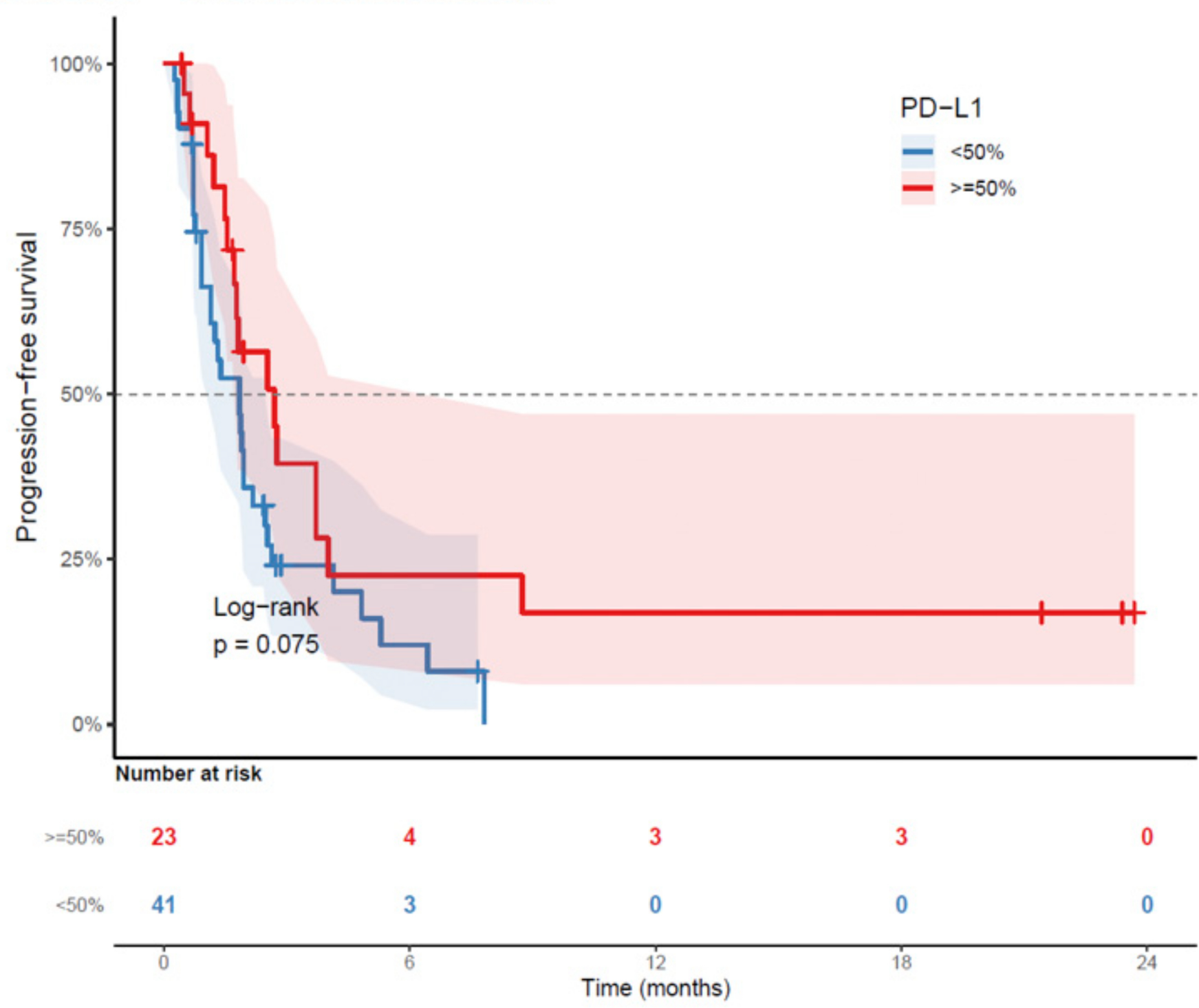
- EGFR subtype and PD-L1 expression exert treatment-phase-specific effects in EGFR-mutant NSCLC.
- While neither EGFR subtype nor PD-L1 expression predicted outcomes with ICI therapy, PD-L1 high tumors demonstrated significantly reduced durability of EGFR-TKI treatment.
- These findings highlight distinct biological roles of EGFR subtype and PD-L1 across treatment phases and may inform therapeutic decision-making in EGFR-mutant NSCLC.

RESULTS

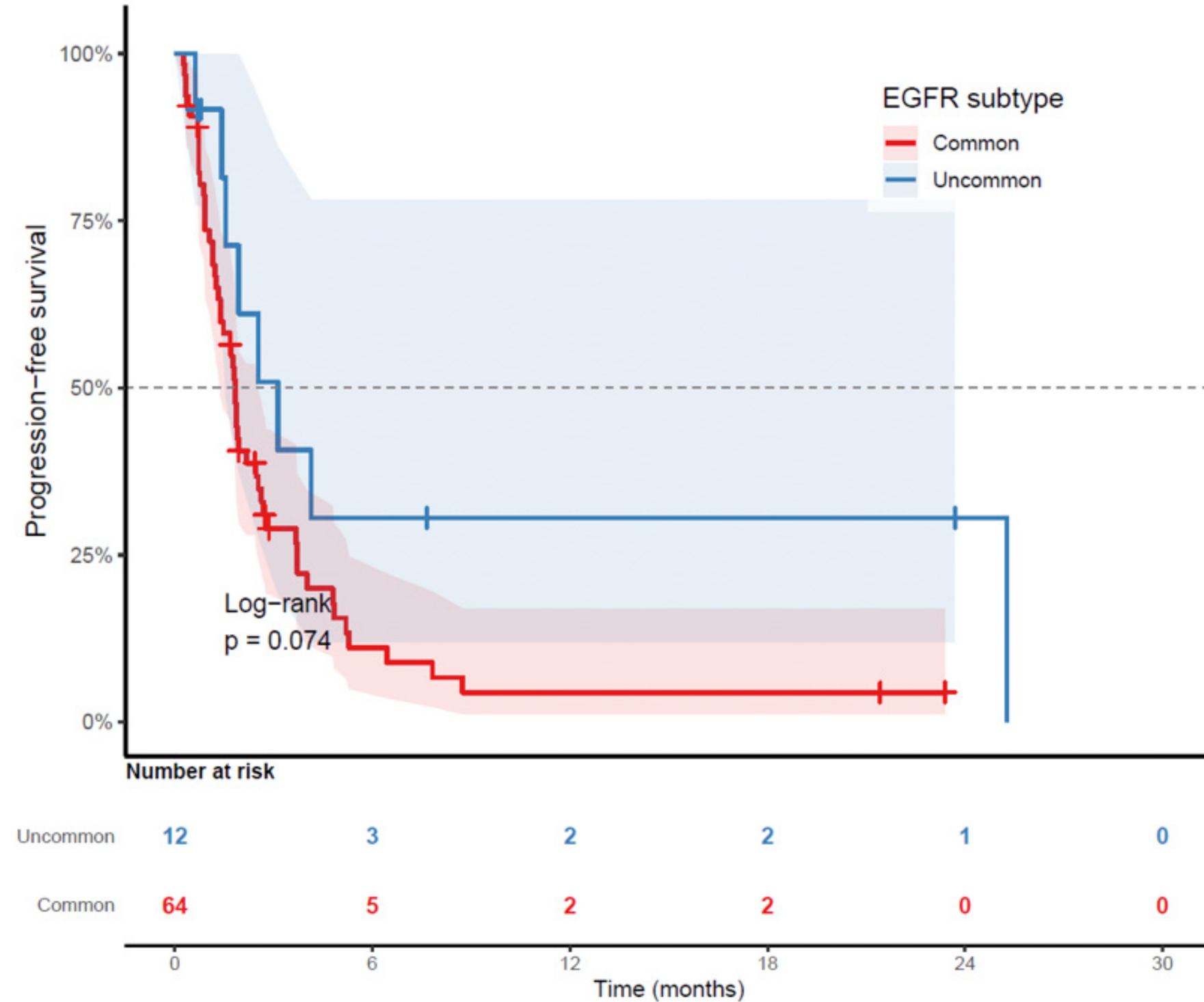
BASELINE CHARACTERISTICS

Characteristic	1L EGFR-TKI n = 1,396	ICI cohort n = 101
Age, median (IQR), years	69 (61–76)	65 (57–70)
Age ≥ 70 years	658 (47.1)	27 (26.7)
Female	839 (60.1)	53 (52.5)
Never-smoker	891 (63.8)	57 (56.4)
ECOG PS 0–1	1,140 (81.7)	93 (92.1)
Adenocarcinoma	1,342 (96.1)	99 (98.0)
≥ 3 metastatic organs	332 (23.8)	22 (21.8)
Brain metastasis	489 (35.0)	35 (34.7)
Liver metastasis	108 (7.7)	9 (8.9)
Bone metastasis	517 (37.0)	40 (39.6)
PD-L1 TPS < 1%	539 (38.6)	28 (27.7)
PD-L1 TPS 1–49%	524 (37.6)	27 (26.7)
PD-L1 TPS ≥ 50%	200 (14.3)	31 (30.7)
EGFR exon 19 deletion	670 (48.0)	42 (41.6)
EGFR L858R	588 (42.1)	45 (44.6)
EGFR uncommon / compound	138 (9.9)	14 (13.9)
1L TKI, 1st generation	197 (14.1)	13 (12.9)
1L TKI, 2nd generation	700 (50.1)	60 (59.4)
1L TKI, 3rd generation	499 (35.7)	26 (25.7)

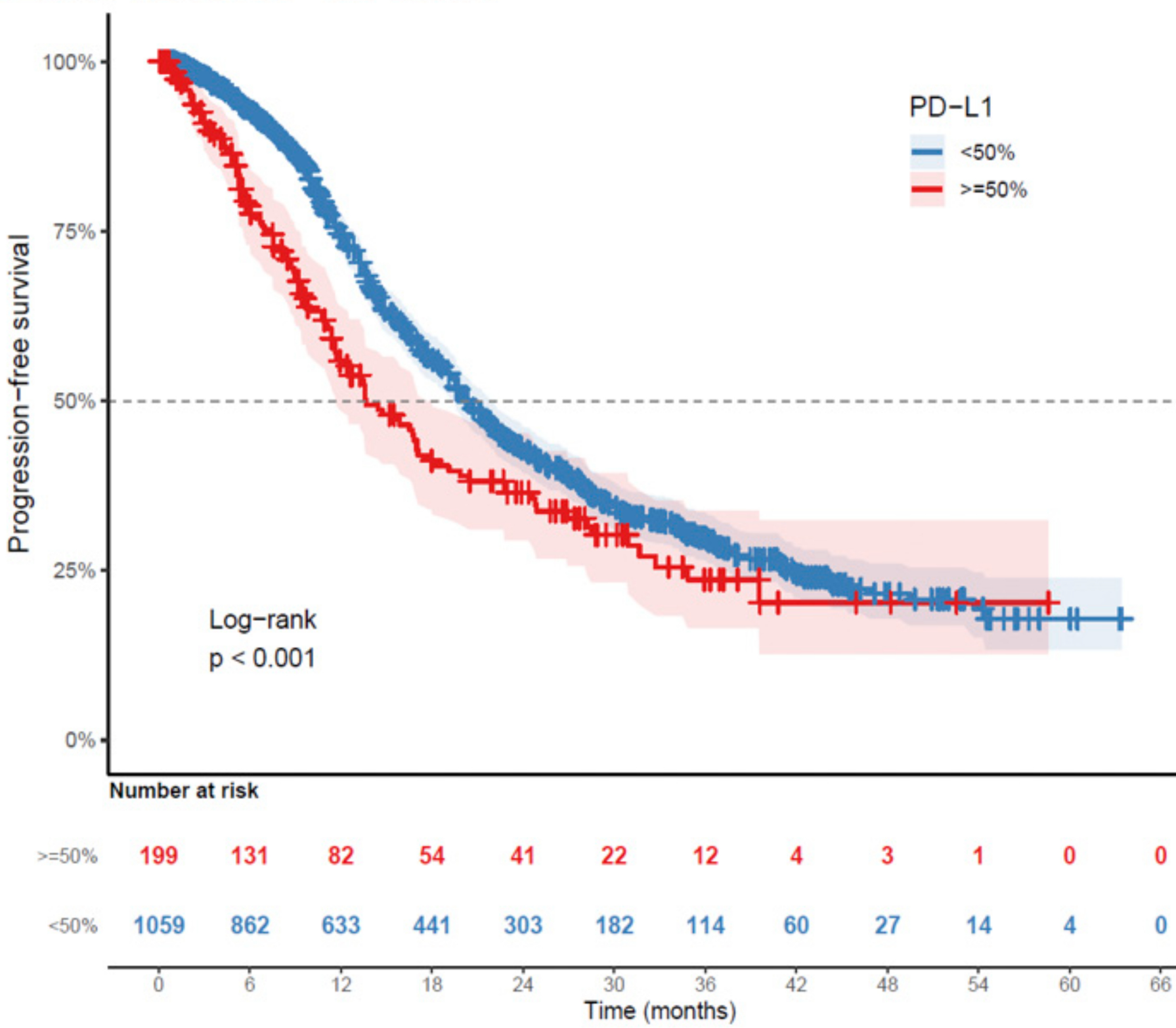
ICI cohort - PFS on immunotherapy



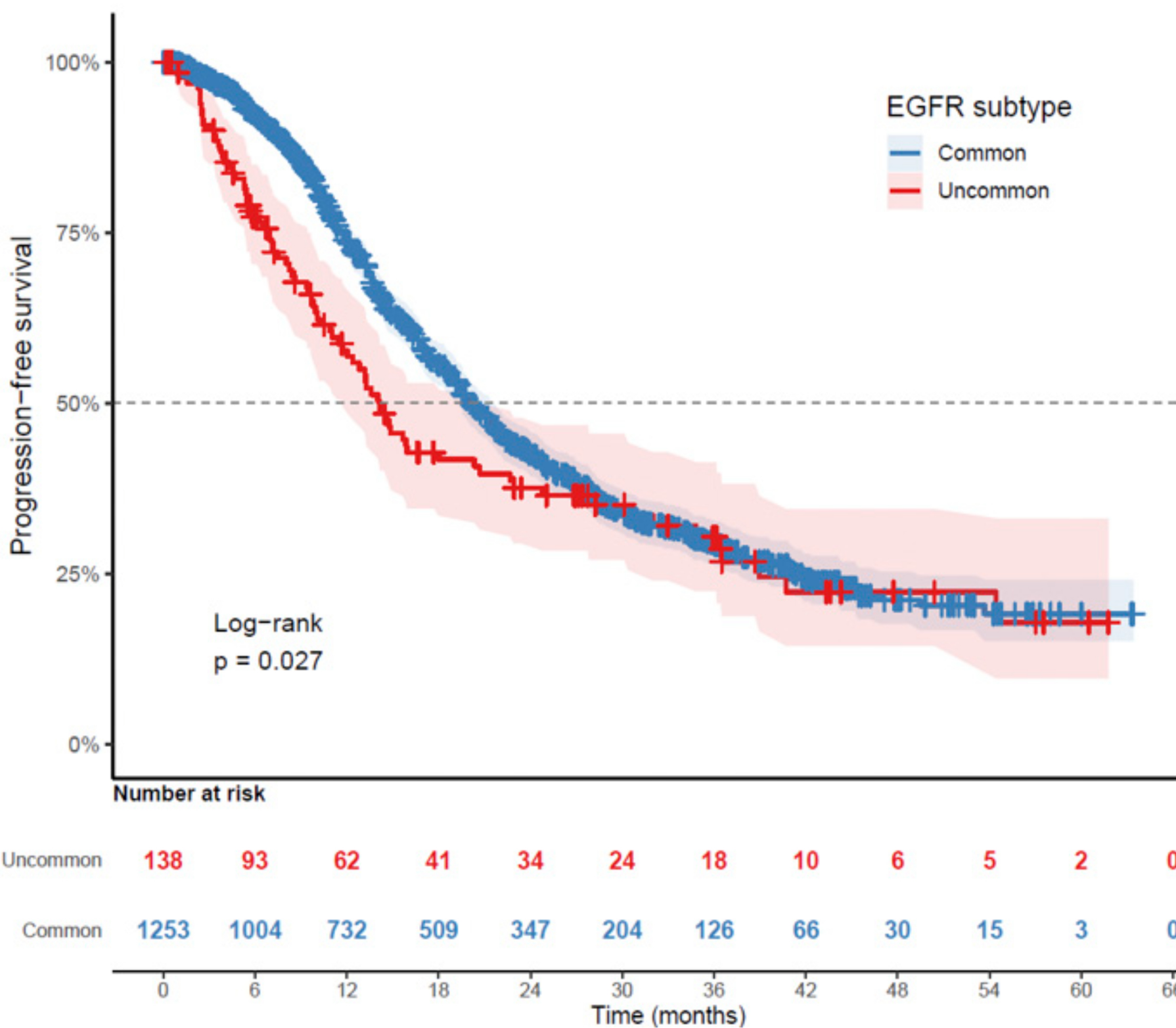
ICI cohort - PFS on immunotherapy



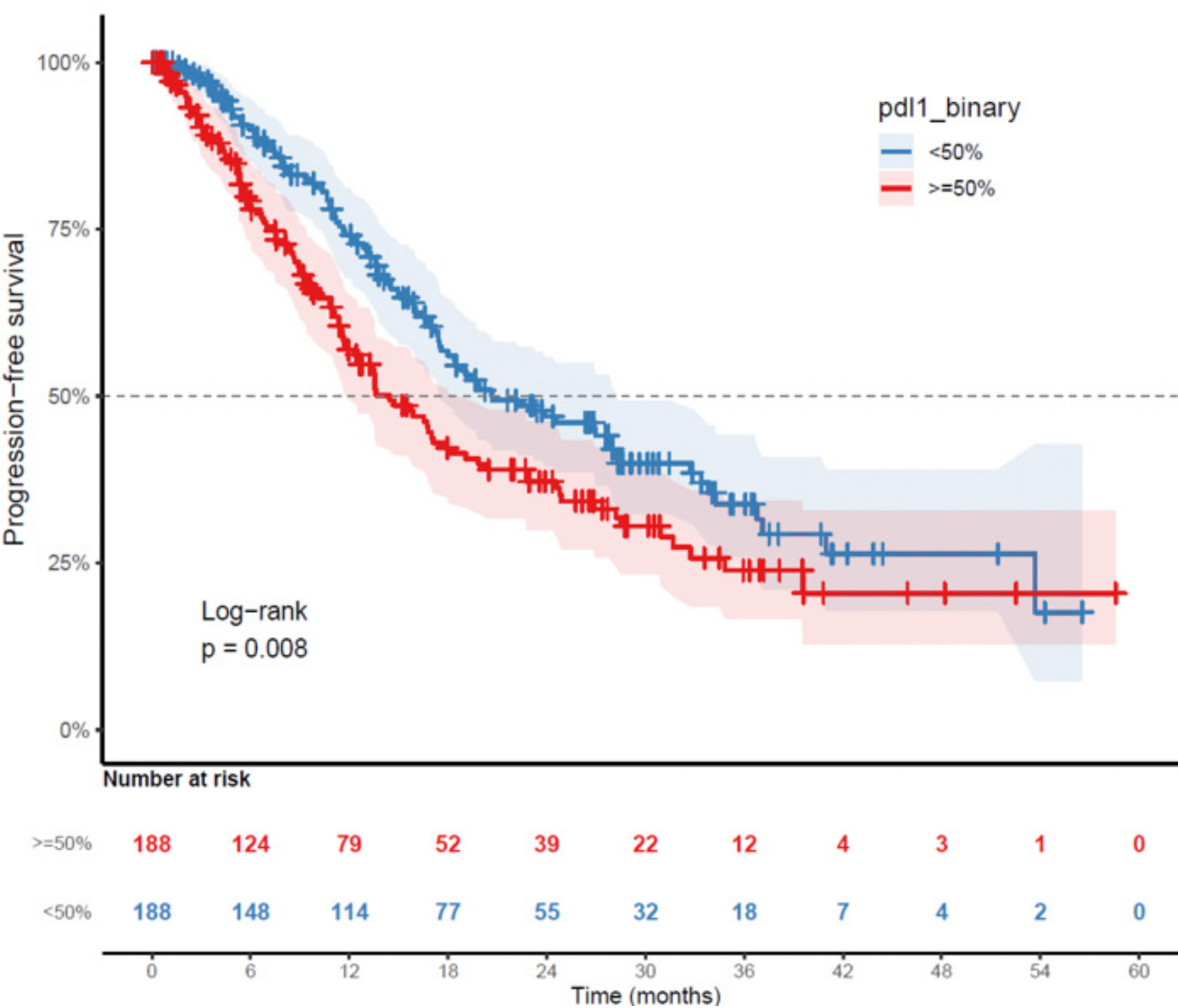
1L EGFR-TKI cohort - full cohort



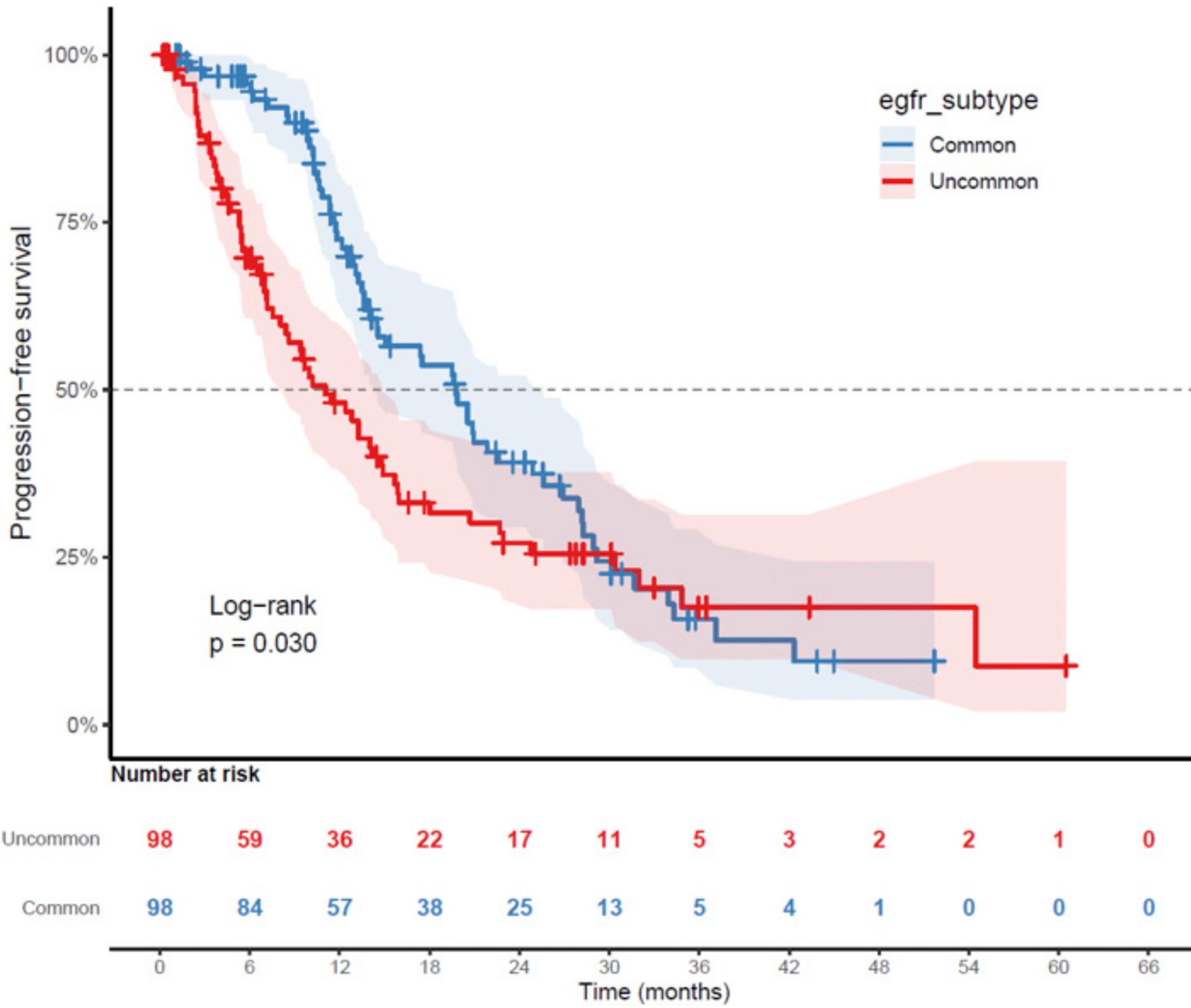
1L EGFR-TKI cohort - full cohort



1L EGFR-TKI cohort 1st - after 1:1 PSM



1L EGFR-TKI cohort - after 1:1 PSM



COX MODEL - 1L EGFR-TKI PFS

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Female vs male	0.85 (0.73–0.98)	0.025	0.57 (0.36–0.92)	0.021
Ever- vs never-smoker	1.15 (0.99–1.33)	0.062	0.63 (0.38–1.03)	0.068
Squamous vs adeno.	2.62 (1.48–4.65)	<0.001	3.85 (0.50–29.7)	0.196
Poor differentiation	1.42 (1.05–1.91)	0.023	1.45 (1.05–2.00)	0.025
≥ 3 metastatic organs	1.71 (1.46–2.01)	<0.001	0.91 (0.49–1.69)	0.764
Brain metastasis	1.31 (1.13–1.52)	<0.001	1.20 (0.69–2.07)	0.519
Liver metastasis	2.07 (1.63–2.63)	<0.001	1.85 (1.06–3.21)	0.029
Bone metastasis	1.66 (1.44–1.92)	<0.001	1.73 (1.16–2.58)	0.008
PD-L1 ≥ 50% vs < 50%	1.41 (1.15–1.73)	<0.001	1.40 (0.89–2.19)	0.144
Uncommon vs common EGFR	1.29 (1.03–1.63)	0.028	2.95 (1.75–4.98)	<0.001
3G vs 1G/2G TKI	0.68 (0.58–0.80)	<0.001	0.61 (0.42–0.89)	0.011

COX MODEL - ICI PFS

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Female vs male	1.51 (0.90–2.54)	0.118	1.27 (0.53–3.02)	0.591
Ever- vs never-smoker	0.65 (0.38–1.10)	0.108	1.48 (0.59–3.69)	0.402
≥ 3 metastatic organs	2.57 (1.37–4.82)	0.003	1.63 (0.68–3.89)	0.272
Brain metastasis	1.53 (0.91–2.58)	0.106	1.59 (0.83–3.03)	0.164
Liver metastasis	3.75 (1.69–8.29)	0.001	3.23 (1.13–9.24)	0.029
PD-L1 ≥ 50% vs < 50%	0.57 (0.31–1.06)	0.078	1.09 (0.37–3.20)	0.878
Uncommon vs common EGFR	0.49 (0.22–1.09)	0.080	0.33 (0.09–1.20)	0.092
Atezolizumab vs pembro.	2.23 (1.26–3.95)	0.006	2.46 (0.83–7.27)	0.104
≥ 4th vs 2nd line	3.13 (0.74–13.3)	0.122	2.21 (0.46–10.7)	0.323