

INTRODUCTION

- The benefit of ICI in oncogene-addicted NSCLC is variable¹, where tumours can be associated with unfavourable tumor microenvironments and low tumor mutational burden².
- Apart from classical alterations (EGFR, ALK), there is a large, heterogeneous cohort of patients with rare driver mutations for which responses to chemo-immunotherapy is unknown
- There is no standardized approach to treating oncogene-addicted NSCLC without an available or approved targeted therapy and this cohort of patients frequently receives chemo-immunotherapy either upfront or sequentially. Responses to ICI-based regimens in this patient population remain poorly characterized and highly variable³.

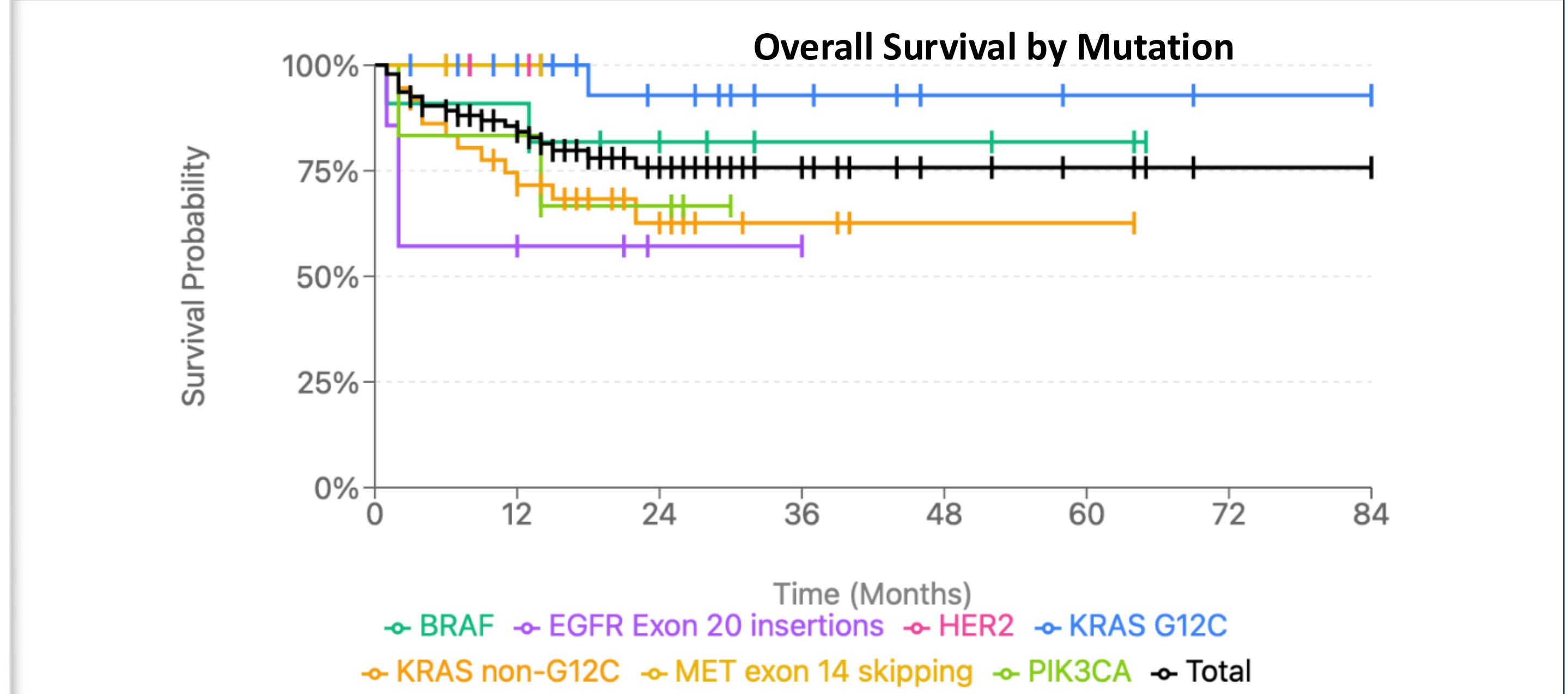
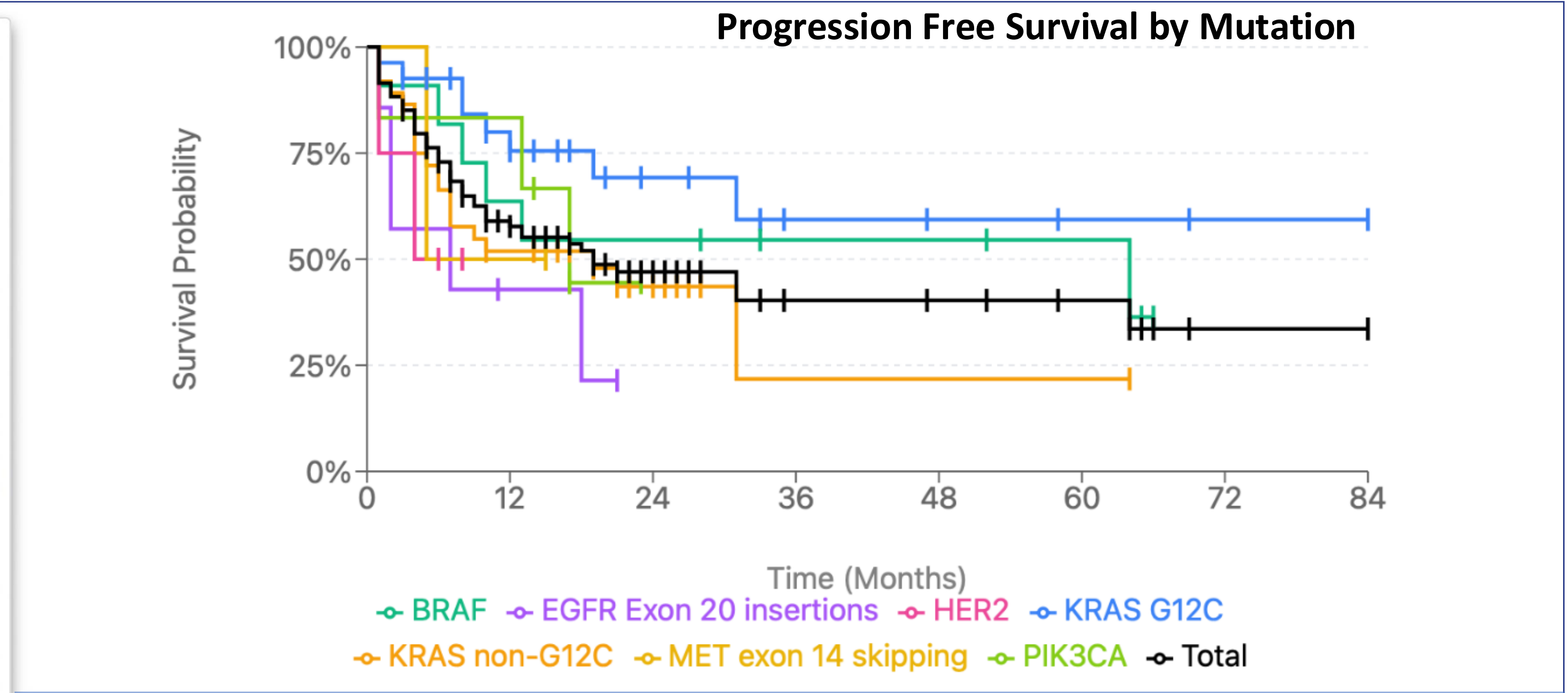
METHODS

- Retrospective analysis at Austin Hospital, Australia and Vietnam National Cancer Hospital, Vietnam between June 2018 to July 2025
- Conducted on patients with advanced NSCLC harboring rare non-EGFR/ALK mutations (including KRAS G12C, KRAS non-G12C, BRAF, HER2, EGFR Exon 20 insertions, PIK3CA, and MET skipping).
- Received at least one dose of first-line systemic therapy with chemotherapy, anti-vascular endothelial growth factor (VEGF) therapy and/or ICI.
- Baseline demographics and tumour characteristics were collected. End points of interest included progression-free survival (PFS), overall survival (OS), and overall response rate (ORR).

RESULTS

Patient Demographics		
Total patients: 94		
CHARACTERISTIC	N	%
GENDER		
Male	67	71%
Female	27	29%
SMOKING STATUS		
Never smoker	16	17%
Ex-smoker	64	68%
Current smoker	6	6%
Smoker	8	9%
PD-L1 TPS		
<1%	27	29%
1-49%	20	21%
≥50%	25	27%
Unknown	22	23%
HISTOPATHOLOGY		
Adenocarcinoma	76	81%
Other	18	19%
METASTATIC SITES AT BASELINE		
Liver metastases	9	10%
Brain metastases	21	22%
MUTATIONS		
KRAS G12C	27	29%
KRAS non-G12C	37	39%
BRAF	11	12%
Ex20ins	7	7%
PIK3CA	6	6%
HER2	4	4%
MET skipping	2	2%
Other	4	4%
FIRST LINE THERAPY		
Chemoimmunotherapy	71	76%
Immunotherapy	14	15%
Chemotherapy	3	3%
Chemoimmunotherapy + Anti-VEGF	3	3%
Clinical Trial	3	3%

- A total of 94 patients were identified. Median observed follow-up (time from treatment initiation to last contact or death) was 17 months (range 4–84).
- The overall median PFS was 19 months [95% CI 10.0 – 64.0 months]. Patients with <1% PD-L1 TPS had a median PFS of 10 months (95% CI: 4-31), 1-49% TPS of 19 months (95% CI: 4-NR), and ≥50% TPS of 64 months (95% CI: 31.0-NR). The median OS was not reached in this analysis.
- The ORR for the entire group was 66%. Per mutation, KRAS G12C 78%, KRAS non-G12C 62%, BRAF 82%, Ex20ins 29%, PIK3CA 67%, HER2 50%, MET skipping 100%
- Of the 48 patients who progressed following first-line systemic therapy, 27 (56%) patients went on to receive further anti-cancer treatment
- A multivariable Cox proportional-hazards model was used to identify independent predictors of PFS (Table 1; adjusted for mutation subgroup, PD-L1 TPS, liver metastases at baseline and smoking)



Multivariable Cox proportional-hazards models for progression-free survival: adjusted hazard ratios (95% CI) across the primary model and two sensitivity analyses.			
Predictor (reference)	Primary model (N=94, 48 events)	Complete-case (N=72, 34 events)	Smoking-adjusted (N=94, 48 events)
Mutation subgroup (reference: KRAS G12C)			
KRAS non-G12C	2.68 (1.15–6.21) p 0.022	3.37 (1.11–10.2) p 0.032	2.80 (1.20–6.56) p 0.018
Others	3.13 (1.36–7.20) p 0.007	4.24 (1.33–13.5) p 0.014	3.01 (1.30–6.96) p 0.010
PD-L1 TPS (reference: <1%)			
≥1%	0.46 (0.23–0.92) p 0.028	0.50 (0.25–1.00) p 0.05	0.45 (0.23–0.89) p 0.023
Unknown	1.01 (0.48–2.11) p 0.99	—	0.98 (0.47–2.06) p 0.99
Other covariates			
Liver metastases (yes vs no)	2.08 (0.86–5.01) p 0.10	2.86 (1.03–7.93) p 0.043	2.22 (0.91–5.44) p 0.08
Smoking (ever vs never)	—	—	0.71 (0.32–1.58) p 0.40

CONCLUSION

- Take-Home Message**
- The responses of NSCLC harboring rare oncogenic mutations to chemoimmunotherapy are variable
 - KRAS G12C and PD-L1 TPS ≥1% showed favorable PFS and OS, and were independent predictors of PFS
 - KRAS non-G12C, EGFR Exon 20 insertions, HER2, and PIK3CA mutations were associated with poorer outcomes
- Future Directions**
- As somatic testing becomes increasingly routine, more mutations without approved targeted therapies will be identified, highlighting the need for continued drug development and better understanding of their predictive and prognostic significance.

REFERENCES & ACKNOWLEDGEMENTS

- References:**
- Hendriks, L. E. *Ann. Oncol.* **34**, 358–376 (2023).
 - Negrao, M. V. J. *Immunother. Cancer* **9**, e002891 (2021).
 - Ruge, L. *Front. Oncol.* **16**, 1807704 (2026).
- Artificial Intelligence (AI) Use Disclaimer:** AI was not utilised for data accrual or for statistical analysis. Google AI studio was utilized for the graphical depictions to improve readability and cosmesis.