

INTRODUCTION

- Comprehensive NGS routinely detects concurrent molecular alterations alongside the driver EGFR mutation in NSCLC.
- TP53 and PIK3CA co-mutations have emerged as candidate prognostic biomarkers that may influence response to EGFR-tyrosine kinase inhibitors (TKIs).
- MTAP and BRG1 loss on immunohistochemistry (IHC) are increasingly assessed, but their role in EGFR-mutant disease is not established.

Knowledge gap: despite widespread NGS profiling, how to integrate co-mutation data into EGFR-TKI treatment decisions remains unclear.

Objective: to define the co-mutational landscape of EGFR-mutant NSCLC and test whether any baseline co-alteration predicts EGFR-TKI outcome.

METHODS

Design

Retrospective cohort of patients with EGFR-mutant NSCLC and baseline, pre-treatment NGS. Alterations were summarised at the patient level using a union-based approach across all available baseline assays.

148 patients with EGFR-mutant NSCLC + baseline NGS

109 EGFR-TKI-exposed patients analysed for outcome

Co-alterations of interest

TP53, RB1, PIK3CA, MET amplification, ERBB2 amplification, additional tumour suppressor gene (TSG) alterations, and cell-cycle- and PI3K-pathway alterations.

Protein expression

MTAP and BRG1 expression assessed by IHC.

Endpoints and statistics

- Objective response rate (ORR), by best EGFR-TKI response — Fisher's exact test.
- PFS and OS from TKI initiation — Kaplan–Meier estimates, log-rank test.
- Exploratory subgroups by TKI generation (1st/2nd vs 3rd).

DISCUSSION AND CONCLUSION

Actionable take-away message

- In this real-world EGFR-mutant cohort, baseline co-mutation profiling did not identify a subgroup with differential EGFR-TKI benefit.
- TP53 co-alteration was near-ubiquitous (69.6%), limiting its value as a stand-alone selection biomarker; MTAP and BRG1 loss on IHC were likewise uninformative.

Interpretation and limitations

- Retrospective, single-institution design; heterogeneous NGS assays were combined using a union-based approach.
- The TKI-exposed cohort (n = 109) is modest, leaving analyses underpowered for low-frequency co-alterations and for interaction testing by TKI generation.

Future direction for research

- Larger multicentre cohorts with harmonised NGS panels are needed to establish whether specific co-alterations carry clinically meaningful predictive value.
- Serial and post-progression sequencing, with functional validation of chromatin- and metabolism-related markers, may be more informative than baseline profiling alone.

REFERENCES & ACKNOWLEDGEMENTS

References

- Blakely CM, et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. *Nat Genet.* 2017;49:1693–1704.
- Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. *Nat Rev Cancer.* 2019;19:495–509.
- Canale M, et al. Impact of TP53 mutations on outcome in EGFR-mutated patients treated with first-line TKIs. *Clin Cancer Res.* 2017;23:2195–2202.
- Ramalingam SS, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med.* 2020;382:41–50.

Acknowledgements, funding and disclosures

The authors thank the molecular pathology and clinical research staff at both institutions. No pharmaceutical or biotech funding was received and no industry-sponsored medical writers contributed. The authors declare no relevant conflicts of interest.

Artificial intelligence (AI) use disclosure

The authors disclose that OpenAI ChatGPT assisted with R code drafting for data cleaning and exploratory analysis and with the grammar of the abstract.

All data derive from the authors' original dataset; all analyses, results and interpretations were performed and verified by the authors. No results or conclusions were generated by AI.

RESULTS

148
patients with baseline NGS

109
EGFR-TKI-exposed cohort

69.6%
TP53 — most common co-alteration

61.5%
with copy-number alterations

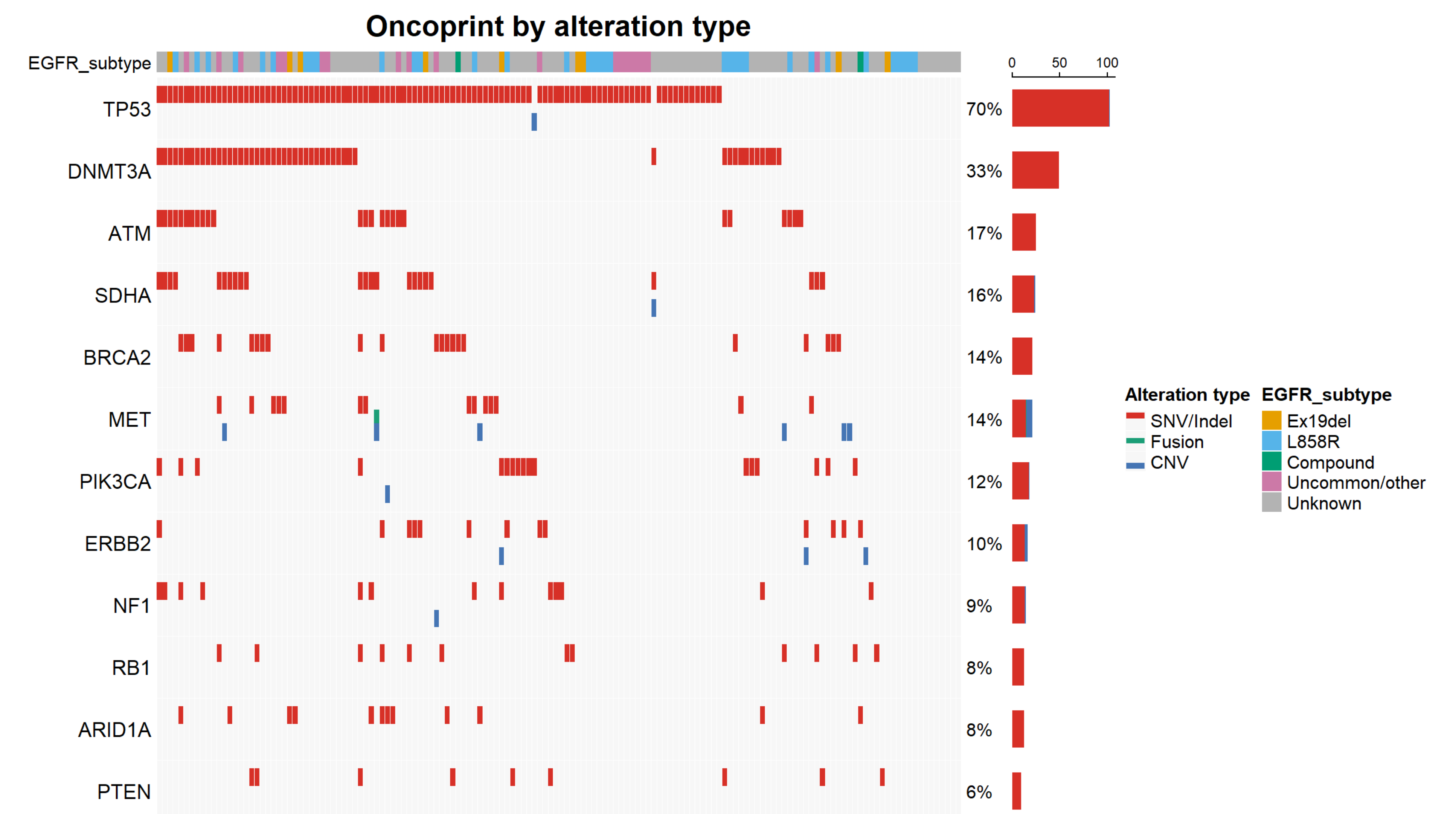


Figure 1. Oncoprint of the 12 most frequently co-altered genes across 148 EGFR-mutant NSCLC tumours, annotated by alteration type (SNV/indel, fusion, CNV) and EGFR subtype. TP53 (70%) and DNMT3A (33%) dominate the landscape.

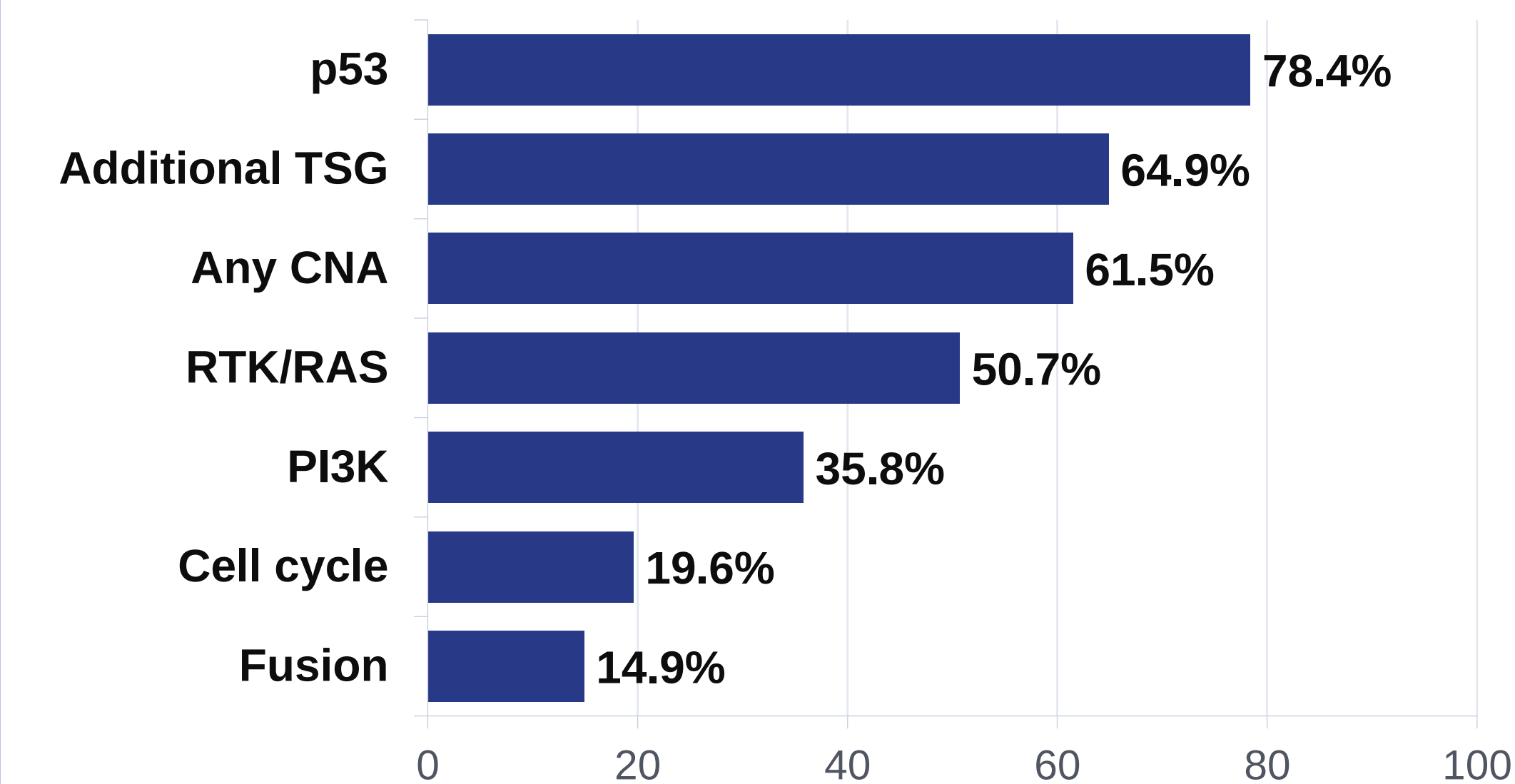


Figure 2. Pathway-level and alteration-class frequencies (n = 148); percentage of patients with ≥1 alteration. TSG, tumour suppressor gene; CNA, copy-number alteration.

Table 1. Biomarker–outcome associations (n = 109)

Biomarker	ORR	PFS	OS
TP53	—	—	—
PIK3CA	—	—	—
RB1	—	—	—
MET amplification	—	—	—
ERBB2 amplification	—	—	—
Additional TSG alteration	—	—	—
Cell-cycle pathway	—	—	—
PI3K pathway	—	—	—
MTAP loss (IHC)	n.s.	n.s.	n.s.
BRG1 loss (IHC)	n.s.	n.s.*	n.s.

— no robust or consistent association across analyses; **n.s.** not statistically significant. *Non-significant numerical trend toward shorter PFS in the strict BRG1-loss group.

Key result: although baseline genomic heterogeneity was considerable, no co-mutation, copy-number event or IHC-defined marker produced a signal strong enough to guide EGFR-TKI selection — including in first/second-versus third-generation subgroup analyses.