

Genomic Biomarkers Associated With Suboptimal Outcomes in First-Line EGFR TKI-Treated Patients With Advanced Non-Small-Cell Lung Cancer

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Background

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy is the standard of care first-line therapy for non-small-cell lung cancer (NSCLC) harboring *EGFR*-sensitizing mutations^{1,2}
- Osimertinib-based regimens have considerably improved survival outcomes in this patient population compared with regimens based on earlier generations of EGFR TKIs²⁻⁴
- Evidence suggests that certain subtypes of *EGFR* mutations and concomitant genomic alterations may contribute to primary resistance to EGFR TKI therapy^{5,6}
- This retrospective cohort study aimed to identify potential genomic biomarkers associated with suboptimal clinical outcomes with first-line EGFR TKI therapy in patients with advanced *EGFR*-mutant NSCLC

Methods

Study design and patients

- This study used the US-based deidentified Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic Database (FH-FMI CGDB). Clinical data from the Flatiron Health Research Database⁷ are linked to genomic data, derived from FMI's comprehensive genomic profiling (CGP) tests (FoundationOne, FoundationOne CDx) in the FH-FMI CGDB by deterministic matching, providing a deidentified dataset⁸⁻¹⁰
- The study population included US patients diagnosed with advanced NSCLC harboring at least one *EGFR*-sensitizing mutation who initiated first-line EGFR TKI therapy with erlotinib, gefitinib, afatinib, or osimertinib between January 1, 2011, and January 1, 2024, and underwent comprehensive genomic profiling with treatment-naïve tumor tissue
- The study follow-up period ended December 31, 2024

Real-world outcomes

- Real-world time to next treatment (rwTTNT) was defined as the time from the start date of first-line EGFR TKI to the start date of the next line of therapy or date of death, with censoring at the date of last activity
- Real-world overall survival (rwOS) was defined as the time from the start date of first-line EGFR TKI to death due to any cause, with censoring at the date of last activity

Statistical analyses

- The study population was divided into two groups: patients who had rwTTNT <6 months from first-line EGFR TKI treatment were considered to have suboptimal responses, and those with rwTTNT ≥6 months were considered to have optimal responses
- The prevalence of genomic biomarkers was compared between the optimal response group and the suboptimal response group using multivariate logistic regression adjusted for patient and disease characteristics and multiple comparison
- Genomic biomarkers with significantly different prevalence between the two groups were further validated for their associations with rwTTNT and rwOS using multivariate Cox proportional hazard regression models; HRs with 95% CIs that did not contain 1 were considered statistically significant

Results

Patients

- The study population included 802 patients (Figure 1; Table 1)
- Nearly two-thirds of the study population (66.1%) received first-line osimertinib-containing regimens, followed by erlotinib (18.7%) and afatinib (14.1%); 389 patients (48.5%) initiated second-line treatment
- The suboptimal response group (rwTTNT <6 months) included 229 patients, whereas the optimal response group (rwTTNT ≥6 months) had 573 patients (Figure 1; Table 1)

Figure 1. Study flow diagram

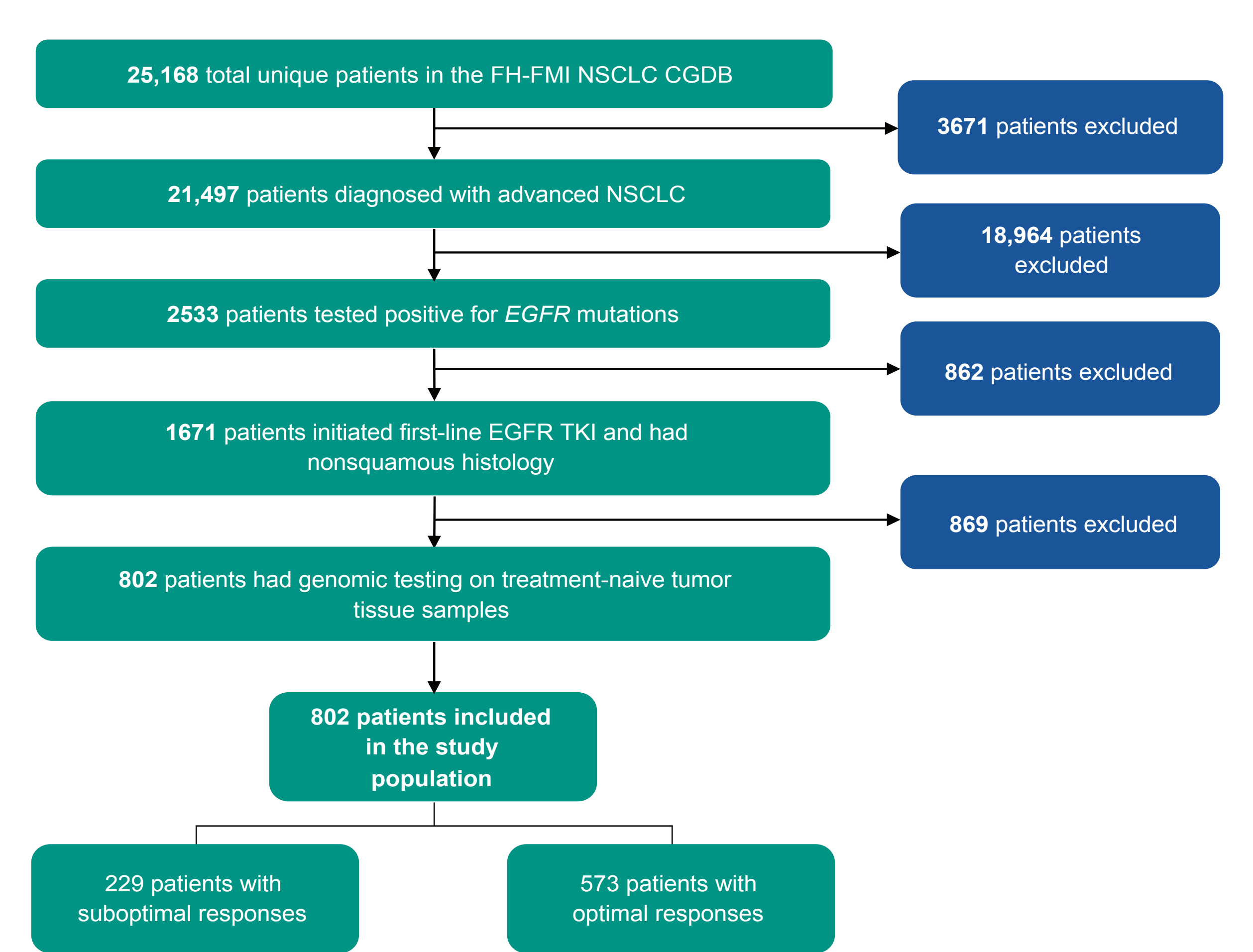


Table 1. Baseline patient and disease characteristics

Characteristic	Suboptimal Response Group (rwTTNT <6 mo) n = 229	Optimal Response Group (rwTTNT ≥6 mo) n = 573	Overall population N = 802
Age at advanced NSCLC diagnosis, median (IQR), y	69.0 (62–78)	68.0 (61–76)	69.0 (61–77)
Female sex	138 (60.3)	393 (68.6)	531 (66.2)
Race			
Asian	25 (10.9)	69 (12.0)	94 (11.7)
Black or African American	10 (4.4)	41 (7.2)	51 (6.4)
White	128 (55.9)	339 (59.2)	467 (58.2)
Other	32 (14.0)	66 (11.5)	98 (12.2)
Missing	34 (14.8)	58 (10.1)	92 (11.5)
History of smoking ^a	118 (51.5)	257 (44.9)	375 (46.8)
Stage at initial diagnosis			
I	9 (3.9)	37 (6.5)	46 (5.7)
II	5 (2.2)	6 (1.0)	11 (1.4)
III	17 (7.4)	31 (5.4)	48 (6.0)
IV	198 (86.5)	493 (86.0)	691 (86.2)
Unknown	0 (0.0)	6 (1.0)	6 (0.7)
ECOG PS			
0	65 (28.4)	210 (36.6)	275 (34.3)
1	103 (45.0)	256 (44.7)	359 (44.8)
≥2	39 (17.0)	76 (13.3)	115 (14.3)
Missing	22 (9.6)	31 (5.4)	53 (6.6)
Most common metastatic sites ^b			
Bone	142 (63.1)	357 (64.3)	499 (64.0)
Pleura	89 (39.6)	259 (46.7)	348 (44.6)
Brain	110 (48.9)	232 (41.8)	342 (43.8)
Lung	72 (32.0)	190 (34.2)	262 (33.6)
Liver	65 (28.9)	125 (22.5)	190 (24.4)
Number of metastatic sites ^b			
1	49 (21.8)	144 (25.9)	193 (24.7)
2	57 (25.3)	146 (26.3)	203 (26.0)
3	57 (25.3)	131 (23.6)	188 (24.1)
≥4	62 (27.6)	134 (24.1)	196 (25.2)

IQR, interquartile range.
Data are n (%) unless otherwise specified.
^a1 patient (0.1%) in the optimal response group had unknown/not documented history of smoking.
^bData available for 225 patients in the suboptimal response group and 555 in the optimal response group.

Associations between genomic biomarkers and clinical outcomes

- Non-exon 19 deletion *EGFR* mutations, *TERT* mutations, *TP53* mutations, and high tumor mutational burden (TMB-H) had statistically significantly higher prevalence in the suboptimal response group compared with the optimal response group, after adjustment for underlying patient characteristics and multiple comparisons (Table 2)
- No gene amplifications were found to have significantly different prevalence between the suboptimal and optimal response groups (Table 3)
- In multivariate survival analyses, non-exon 19 deletion *EGFR* mutations and *TP53* mutations were significantly associated with worse rwTTNT and worse rwOS (Figure 2)
- EGFR* amplification was also significantly associated with worse rwOS (Figure 2)

Table 2. Prevalence of select genomic mutations (≥2%) in patients with suboptimal vs optimal responses

Biomarker	Overall population		Suboptimal Response Group		Optimal Response Group		Logistic regression (suboptimal vs optimal) ^a	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	OR	Corrected ^b P value
APC	17/802	2.1 (1.2–3.4)	5/229	2.2 (0.7–5.0)	12/573	2.1 (1.1–3.6)	1.096	0.9251
ATM	17/802	2.1 (1.2–3.4)	4/229	1.7 (0.5–4.4)	13/573	2.3 (1.2–3.8)	0.850	0.8926
CDKN2A	26/802	3.2 (2.1–4.7)	7/229	3.1 (1.2–6.2)	19/573	3.3 (2.0–5.1)	0.840	0.8926
CTNNB1	72/802	9.0 (7.1–11.2)	17/229	7.4 (4.4–11.6)	55/573	9.6 (7.3–12.3)	0.868	0.8926
DNMT3A	44/802	5.5 (4.0–7.3)	9/229	3.9 (1.8–7.3)	35/573	6.1 (4.3–8.4)	0.596	0.3603
EGFR exon 19 del	401/802	50.0 (46.5–53.5)	85/229	37.1 (30.8–43.7)	316/573	55.1 (51.0–59.3)	0.479	0.0001
LRP1B	6/267	2.2 (0.8–4.8)	5/88	5.7 (1.9–12.8)	1/179	0.6 (0.0–3.1)	9.014	0.1590
PIK3CA	60/802	7.5 (5.8–9.5)	21/229	9.2 (5.8–13.7)	39/573	6.8 (4.9–9.2)	1.384	0.4601
PTEN	24/802	3.0 (1.9–4.4)	6/229	2.6 (1.0–5.6)	18/573	3.1 (1.9–4.9)	0.855	0.8926
RB1	52/802	6.5 (4.9–8.4)	20/229	8.7 (5.4–13.2)	32/573	5.6 (3.9–7.8)	1.520	0.3603
RBM10	73/777	9.4 (7.4–11.7)	23/220	10.5 (6.7–15.3)	50/557	9.0 (6.7–11.7)	1.159	0.8926
SMAD4	39/802	4.9 (3.5–6.6)	11/229	4.8 (2.4–8.4)	28/573	4.9 (3.3–7.0)	1.016	0.9651
TERT	18/777	2.3 (1.4–3.6)	11/220	5.0 (2.5–8.8)	7/557	1.3 (0.5–2.6)	3.681	0.0348
TET2	22/802	2.7 (1.7–4.1)	11/229	4.8 (2.4–8.4)	11/573	1.9 (1.0–3.4)	2.308	0.1590
TP53	490/802	61.1 (57.6–64.5)	159/229	69.4 (63.0–75.3)	331/573	57.8 (53.6–61.8)	1.662	0.0146
TMB-H	48/686	7.0 (5.2–9.2)	23/194	11.9 (7.7–17.3)	25/492	5.1 (3.3–7.4)	2.839	0.0083

del, deletion; OR, odds ratio.
Data in bold show genomic biomarkers with higher prevalence in the suboptimal response group vs the optimal response group, except *EGFR* exon 19 deletions, which had a lower prevalence in the suboptimal group.
^aAdjusted for sex, smoking history, and PD-L1 status.
^bCorrected for multiple comparison.

References

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer. Version 6.2026. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450>.
- Hendriks LE, et al. *Ann Oncol*. 2023;34(4):339–357.
- Soria JC, et al. *N Engl J Med*. 2018;378(2):113–125.
- Ramalingam SS, et al. *N Engl J Med*. 2020;382(1):41–50.
- Ferro A, et al. *Crit Rev Oncol Hematol*. 2024;196:104295.
- Felip E, et al. *Ann Oncol*. 2024;35(9):805–816.
- Flatiron Health. Database Characterization Guide. <https://flatiron.com/database-characterization>.
- Singal G, et al. *JAMA*. 2019;321(14):1391–1399.
- Milbury CA, et al. *PLoS One*. 2022;17(3):e0264138.
- Frampton GM, et al. *Nat Biotechnol*. 2013;31(11):1023–1031.

Acknowledgments

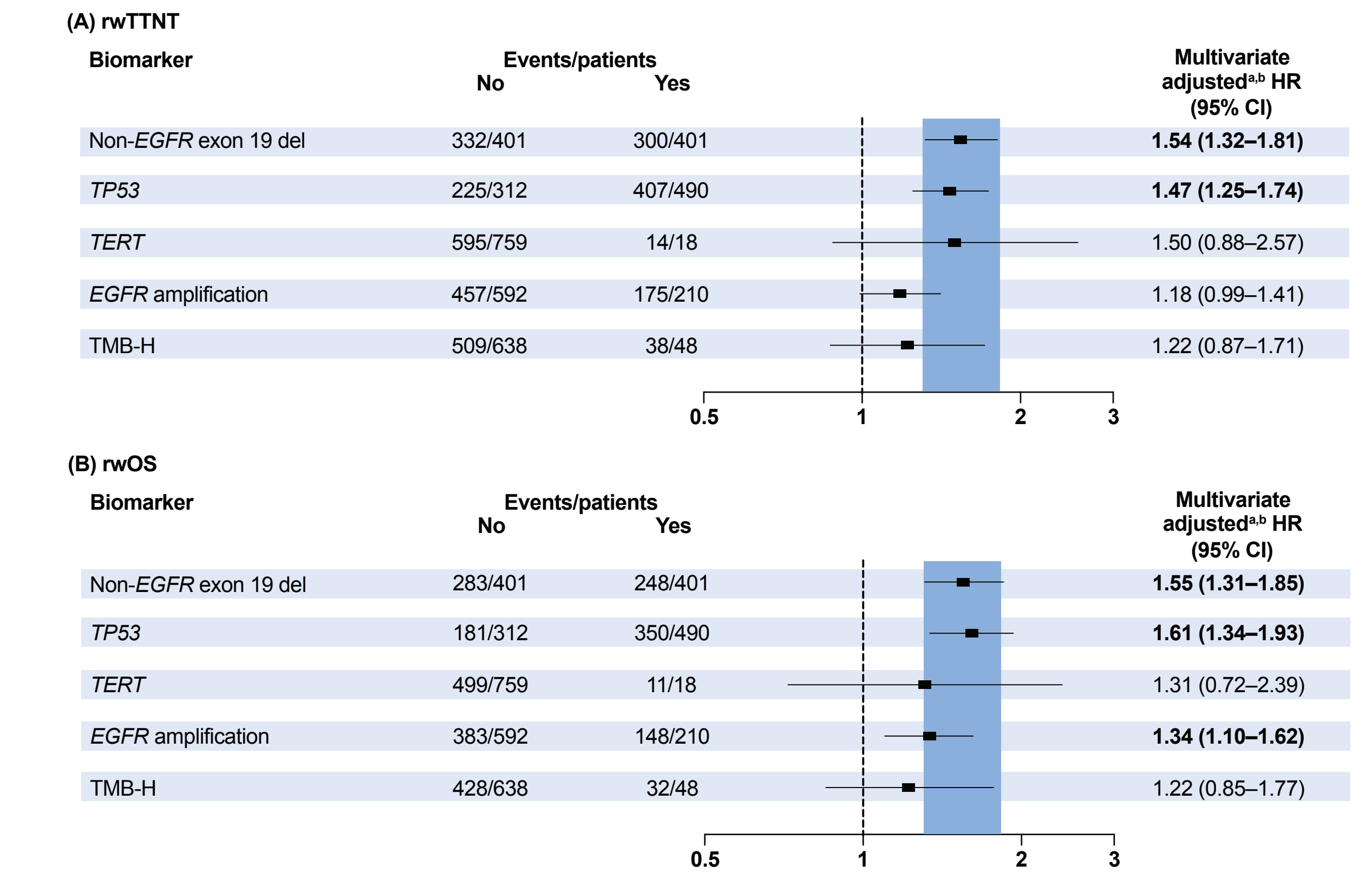
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Table 3. Prevalence of select gene amplifications (≥3%) in patients with suboptimal vs optimal responses

Gene	Overall population		Suboptimal Response Group		Optimal Response Group		Logistic regression (suboptimal vs optimal) ^a	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	OR	Corrected ^b P value
<i>ARFRP1</i>	27/802	3.4 (2.2–4.9)	5/229	2.2 (0.7–5.0)	22/573	3.8 (2.4–5.8)	0.567	0.7321
<i>CARD11</i>	58/802	7.2 (5.5–9.2)	15/229	6.6 (3.7–10.6)	43/573	7.5 (5.5–10.0)	0.831	0.8142
<i>CCNE1</i>	38/802	4.7 (3.4–6.4)	7/229	3.1 (1.2–6.2)	31/573	5.4 (3.7–7.6)	0.537	0.7106
<i>CDK4</i>	61/802	7.6 (5.9–9.7)	16/229	7.0 (4.0–11.1)	45/573	7.9 (5.8–10.4)	0.905	0.8835
<i>CEBPA</i>	26/802	3.2 (2.1–4.7)	1/229	0.4 (0.0–2.4)	25/573	4.4 (2.8–6.4)	0.092	0.6352
<i>EGFR</i>	210/802	26.2 (23.2–29.4)	57/229	24.9 (19.4–31.0)	153/573	26.7 (23.1–30.5)	0.893	0.8142
<i>ERBB2</i>	27/802	3.4 (2.2–4.9)	11/229	4.8 (2.4–8.4)	16/573	2.8 (1.6–4.5)	1.733	0.7106
<i>FANCM</i>	13/267	4.9 (2.6–8.2)	4/88	4.5 (1.3–11.2)	9/179	5.0 (2.3–9.3)	0.914	0.9636
<i>FGF10</i>	52/802	6.5 (4.9–8.4)	11/229	4.8 (2.4–8.4)	41/573	7.2 (5.2–9.6)	0.636	0.7106
<i>FRS2</i>	20/244	8.2 (5.1–12.4)	5/79	6.3 (2.1–14.2)	15/165	9.1 (5.2–14.6)	0.639	0.7321
<i>GRM3</i>	26/777	3.3 (2.2–4.9)	9/220	4.1 (1.9–7.6)	17/557	3.1 (1.8–4.8)	1.379	0.7630
<i>HGF</i>	26/802	3.2 (2.1–4.7)	8/229	3.5 (1.5–6.8)	18/573	3.1 (1.9–4.9)	1.210	0.8835
<i>IKZF1</i>	105/802	13.1 (10.8–15.6)	33/229	14.4 (10.1–19.6)	72/573	12.6 (10.0–15.6)	1.216	0.7321
<i>IKZF3</i>	4/105	3.8 (1.0–9.5)	2/25	8.0 (1.0–26.0)	2/80	2.5 (0.3–8.7)	2.752	0.7321
<i>IL7R</i>	24/267	9.0 (5.8–13.1)	7/88	8.0 (3.3–15.7)	17/179	9.5 (5.6–14.8)	0.755	0.8142
<i>INHBA</i>	20/267	7.5 (4.6–11.3)	9/88	10.2 (4.8–18.5)	11/179	6.1 (3.1–10.7)	1.666	0.7321
<i>MAGI2</i>	8/242	3.3 (1.4–6.4)	2/79	2.5 (0.3–8.8)	6/163	3.7 (1.4–7.8)	0.785	0.8844
<i>MCL1</i>	25/802	3.1 (2.0–4.6)	7/229	3.1 (1.2–6.2)	18/573	3.7 (1.9–4.9)	1.005	0.9917
<i>MDM2</i>	80/802	10.0 (8.0–12.3)	17/229	7.4 (4.4–11.6)	63/573	11.0 (8.6–13.8)	0.633	0.7106
<i>MYC</i>	73/802	9.1 (7.2–11.3)	25/229	10.9 (7.2–15.7)	48/573	8.4 (6.2–11.0)	1.468	0.7106
<i>NBN</i>	42/802	5.2 (3.8–7.0)	14/229	6.1 (3.4–10.0)	28/573	4.9 (3.3–7.0)	1.390	0.7321
<i>NFKBIA</i>	108/802	13.5 (11.2–16.0)	37/229	16.2 (11.6–21.6)	71/573	12.4 (9.8–15.4)	1.342	0.7106
<i>NKX2_1</i>	144/802	18.0 (15.4–20.8)	50/229	21.8 (16.7–27.8)	94/573	16.4 (13.5–19.7)	1.450	0.7106
<i>NUDT1</i>	13/242	5.4 (2.9–9.0)	5/79	6.3 (2.1–14.2)	8/163	4.9 (2.1–9.4)	1.250	0.8835
<i>PMS2</i>	56/802	7.0 (5.3–9.0)	15/229	6.6 (3.7–10.6)	41/573	7.2 (5.2–9.6)	0.879	0.8835
<i>RAC1</i>	77/777	9.9 (7.9–12.2)	22/220	10.0 (6.4–14.7)	55/557	9.9 (7.5–12.7)	0.968	0.9636
<i>RAD21</i>	60/537	11.2 (8.6–14.1)	17/141	12.1 (7.2–18.6)	43/396	10.9 (8.0–14.3)	1.345	0.7321
<i>RICTOR</i>	71/802	8.9 (7.0–11.0)	15/229	6.6 (3.7–10.6)	56/573	9.8 (7.5–12.5)	0.611	0.7106
<i>RUNX1T1</i>	16/267	6.0 (3.5–9.5)	7/88	8.0 (3.3–15.7)	9/179	5.0 (2.3–9.3)	1.720	0.7321
<i>SDHA</i>	110/779	14.1 (11.8–16.8)	32/220	14.5 (10.2–19.9)	78/559	14.0 (11.2–17.1)	1.079	0.8835
<i>SPTA1</i>	9/242	3.7 (1.7–6.9)	2/79	2.5 (0.3–8.8)	7/163	4.3 (1.7–8.6)	0.509	0.7321

^aAdjusted for sex, smoking history, and PD-L1 status.
^bCorrected for multiple comparison.

Figure 2. Association between select genomic biomarkers and rwTTNT and rwOS



Statistically significant associations are bolded.
Data in bold show genomic biomarkers with higher prevalence in the suboptimal response group vs the optimal response group, except *EGFR* exon 19 deletions, which had a lower prevalence in the suboptimal group.
^aNo status served as the reference for all analyses.
^bAdjusted for age at diagnosis of advanced NSCLC, smoking history, and PD-L1 status.

Conclusions

- Non-exon 19 deletion *EGFR* mutations, *TERT* mutations, *TP53* mutations, and TMB-H were enriched in patients who experienced suboptimal responses (rwTTNT of <6 months) to first-line EGFR TKI therapy
- Non-exon 19 deletion *EGFR* mutations and *TP53* mutations were associated with worse rwTTNT and rwOS in this real-world cohort of patients with advanced NSCLC treated with EGFR TKIs
- Our findings inform the identification of subpopulations of patients with NSCLC harboring *EGFR* mutations who may benefit from novel therapeutic agents

Poster presented



<https://bit.ly/4pE0oTa>