



#2873 Concurrent alterations in SMARCA4 truncating mutations versus SMARCA4 non-truncating mutations in lung cancer

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IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

Background

- SMARCA4 is an critical subunit that provides energy from ATP hydrolysis to SWI/SNF complexes which facilitates transcription, cell differentiation, and DNA repair through chromatin remodeling.
- Prior retrospective studies highlight a worse prognosis in SMARCA4-deficient tumors compared to SMARCA4-intact tumors.
- Tumors with SMARCA4 alterations have increased reliance on SMARCA2. Several ongoing phase 1 trials are evaluating SMARCA2 degraders.
- We characterized concurrent alterations within SMARCA4-deficient NSCLC.

Methods

- We queried the AACR GENIE v19.0 database to extract data on SMARCA4 mutations across 39,553 lung cancer samples.
- We characterized the frequency of co-occurring alterations and actionable genomic alterations (AGAs) in non-truncating SMARCA4 mutated lung cancer versus truncating SMARCA4 mutated lung cancer.
- In our analysis, we only included SMARCA4 mutations detected on tissue and classified as oncogenic or likely oncogenic per OncoKB.
- We removed duplicate samples and only analyzed the first specimen that was provided..

Results

Table 1

	TOTAL SMARCA4 MUTATIONS	SMARCA4 TRUNCATING MUTATIONS	SMARCA4 NON-TRUNCATING MUTATIONS
Total Number of Cases, n	1269	1084	185
TP53, n (%)	751 (59.2)	662 (61.1)	89 (48.1)
KEAP1, n (%)	232 (18.3)	197 (18.2)	35 (18.9)
STK11, n (%)	416 (32.8)	362 (33.4)	54 (29.2)
Total AGA, n (%)	348 (27.4)	286 (26.4)	62 (33.5)
KRAS G12C, n(%)	172 (13.5)	150 (13.8)	22 (11.9)
EGFR, n(%)	76 (6.0)	50 (4.6)	26 (14.1)
BRAF, n(%)	49 (3.9)	41 (3.8)	8 (4.3)
HER2, n(%)	20 (1.6)	13 (1.2)	7 (3.8)
MET, n(%)	17 (1.3)	15 (1.4)	2 (1.1)
ALK, n(%)	11 (0.9)	8 (0.7)	3 (1.6)
ROS1, n(%)	11 (0.9)	10 (1.1)	1 (0.5)
RET, n(%)	11 (0.9)	11 (1.0)	0 (0)

- A total of 1,269 lung cancer samples with a SMARCA4 mutation were detected.
 - 85.4% were truncating mutations
 - 14.6% were non-truncating mutations
- Median age at diagnosis was 66 years old. Similar rates between male (48%) vs. female patients (48%) and unknown in (4%).
- Most common reported race/ethnicity was white (69.7%)
- Across all SMARCA4 mutations, 348 (27.4%) had a concurrent AGA. KRAS G12C was the most common alteration (13.5%). EGFR was the second most common alteration (6%)
- Higher rate of EGFR mutations in SMARCA4 non-truncating mutation (14.1%) vs. SMARCA4 truncating mutation (4.6%).
- Higher rate of TP53 mutations in SMARCA4 truncating mutation (61.1%) vs. SMARCA4 non-truncating mutation (48.1%).

Figure 1

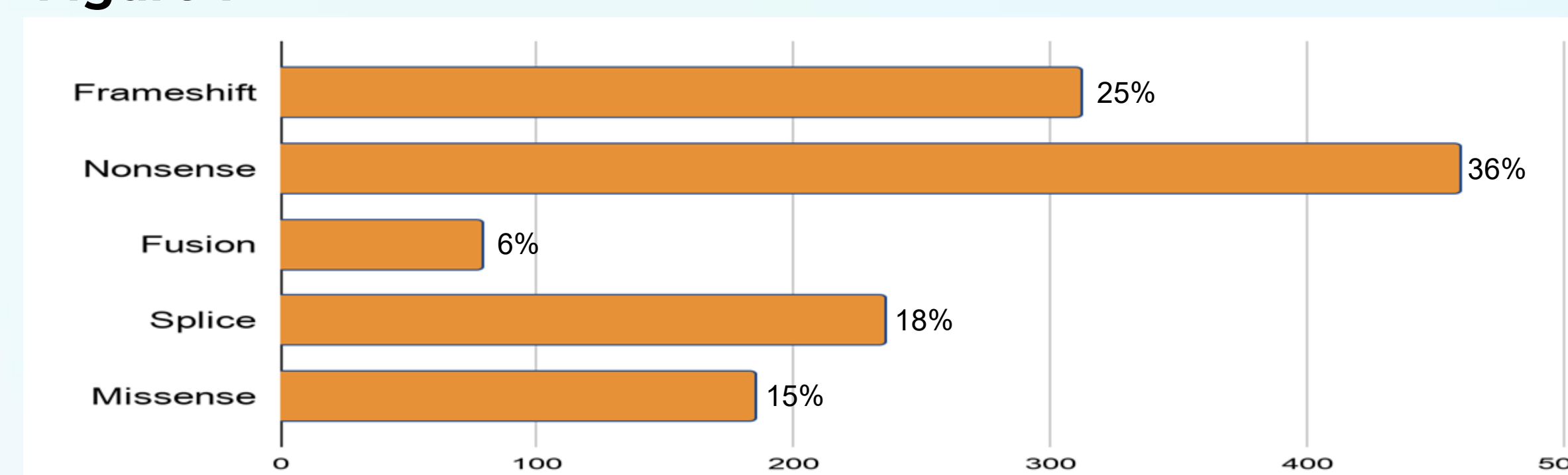
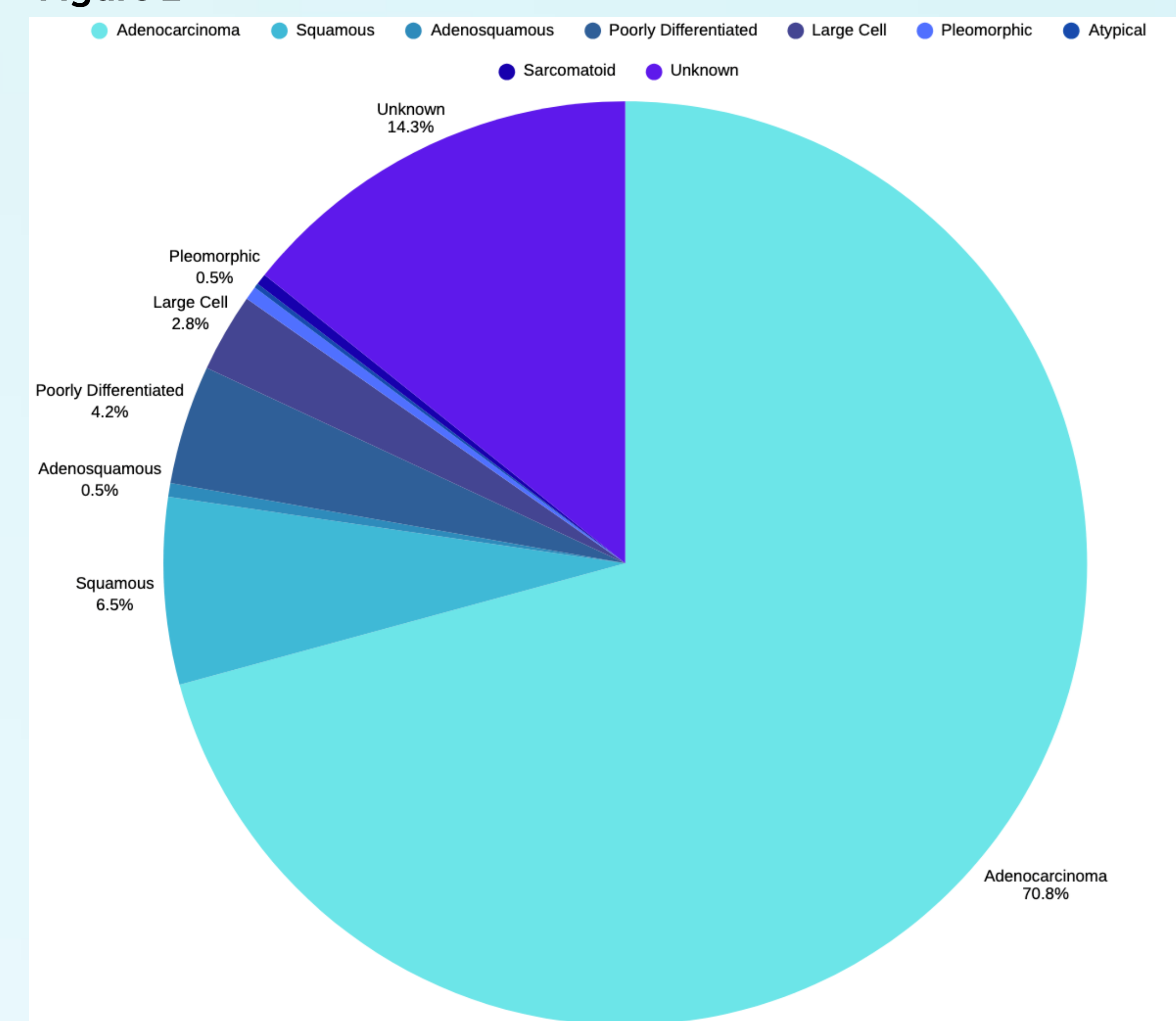


Figure 2



Conclusions

Across all SMARCA4 mutations, 59% had a concurrent TP53 mutation which aligns with prior studies reflecting a worse prognosis. While KRASG12C was the most common AGA identified in lung cancer samples with SMARCA4 truncating mutations, EGFR alterations were the most common AGA in SMARCA4 non-truncating mutations. Further investigation into responses to targeted therapy in the presence of a concurrent SMARCA4 mutation are warranted in addition to combination strategies with SMARCA2 degraders.