Abstract ID

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Molecular and immune profiling of BRAF-mutated non-small cell lung cancer (NSCLC)

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INTRODUCTION

BRAF mutations occur in 6–7% of NSCLC and comprise biologically distinct classes showing variable therapeutic responses.

While Class 1 benefits from targeted therapy, molecular and immune determinants distinguishing BRAF classes remain incompletely characterized.

Aim: perform comprehensive profiling to identify class-specific biomarkers.

METHODS and

Cohort

51,692 NSCLC specimens (Caris Life Sciences):

BRAF-WT n=48,288 • BRAF-mut n=3,404

Sequencing

DNA 592-gene / WES and/or RNA whole-transcriptome.

BRAF classes

Class 1 (V600E)	n=695
Class 2	n=741
Class 3	n=701
OPV	n=123
VUS	n=936

TME / Survival / Statistics

QuanTIseq for TME deconvolution; OS and IO-OS from insurance claims (Kaplan–Meier from biopsy or IO start). Fisher exact, chi-square, Mann–Whitney U with multiple-comparison correction (P<0.05

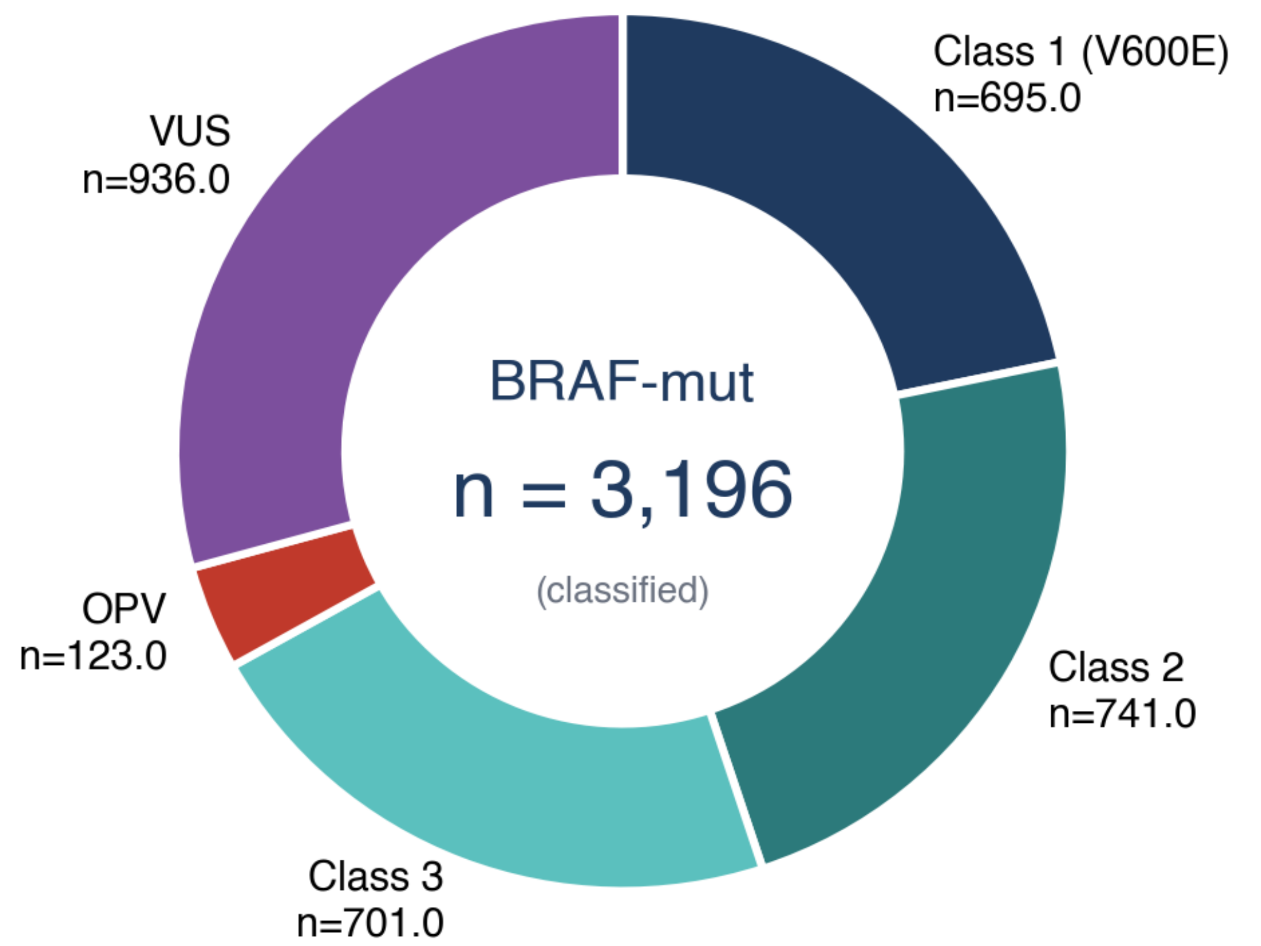

Figure 1. BRAF class distribution (n=3,196 classified).

RESULTS

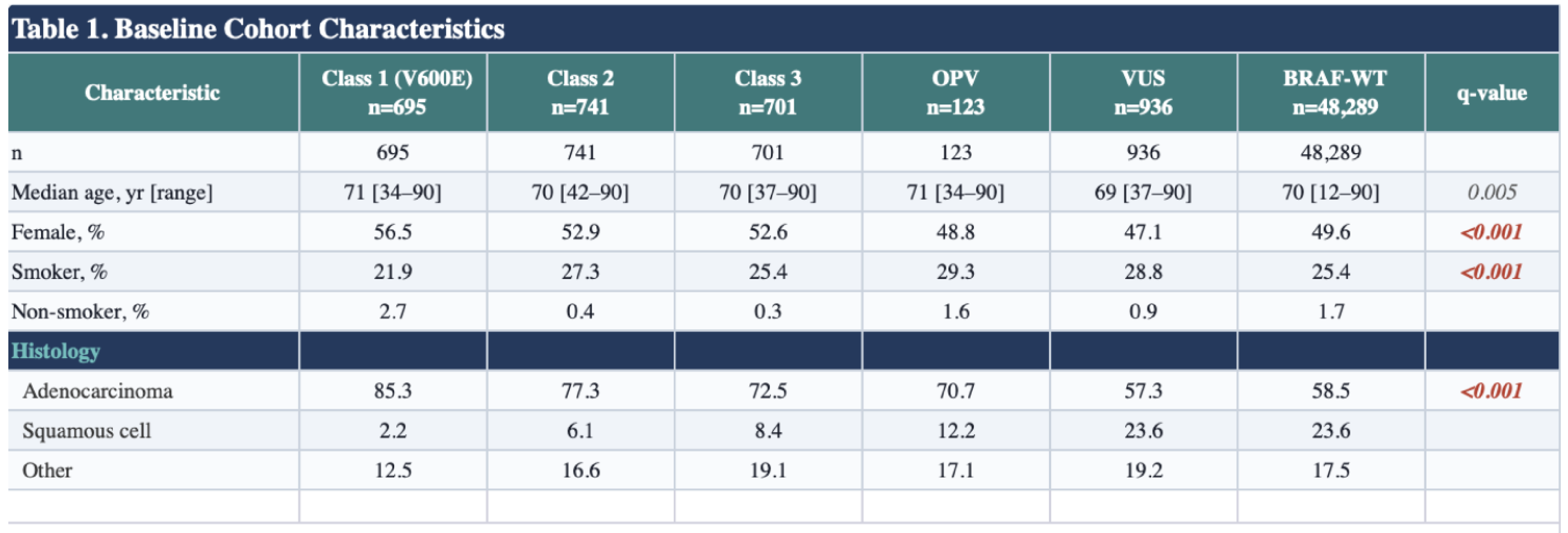

Table 1. Baseline Cohort Characteristics

Characteristic	Class 1 (V600E) n=695	Class 2 n=741	Class 3 n=701	OPV n=123	VUS n=936	BRAF-WT n=48,289	q-value
n	695	741	701	123	936	48,289	
Median age, yr [range]	71 [34–90]	70 [42–90]	70 [37–90]	71 [34–90]	69 [37–90]	70 [12–90]	0.005
Female, %	56.5	52.9	52.6	48.8	47.1	49.6	<0.001
Smoker, %	21.9	27.3	25.4	29.3	28.8	25.4	<0.001
Non-smoker, %	2.7	0.4	0.3	1.6	0.9	1.7	
Histology							
Adenocarcinoma	85.3	77.3	72.5	70.7	57.3	58.5	<0.001
Squamous cell	2.2	6.1	8.4	12.2	23.6	23.6	
Other	12.5	16.6	19.1	17.1	19.2	17.5	

OPV = other pathogenic variants; VUS = variants of unknown significance. Smoking history unknown in ~70–75% across all groups (not shown separately). q-values FDR-corrected.

Molecular feature enrichment (OR vs BRAF-WT)

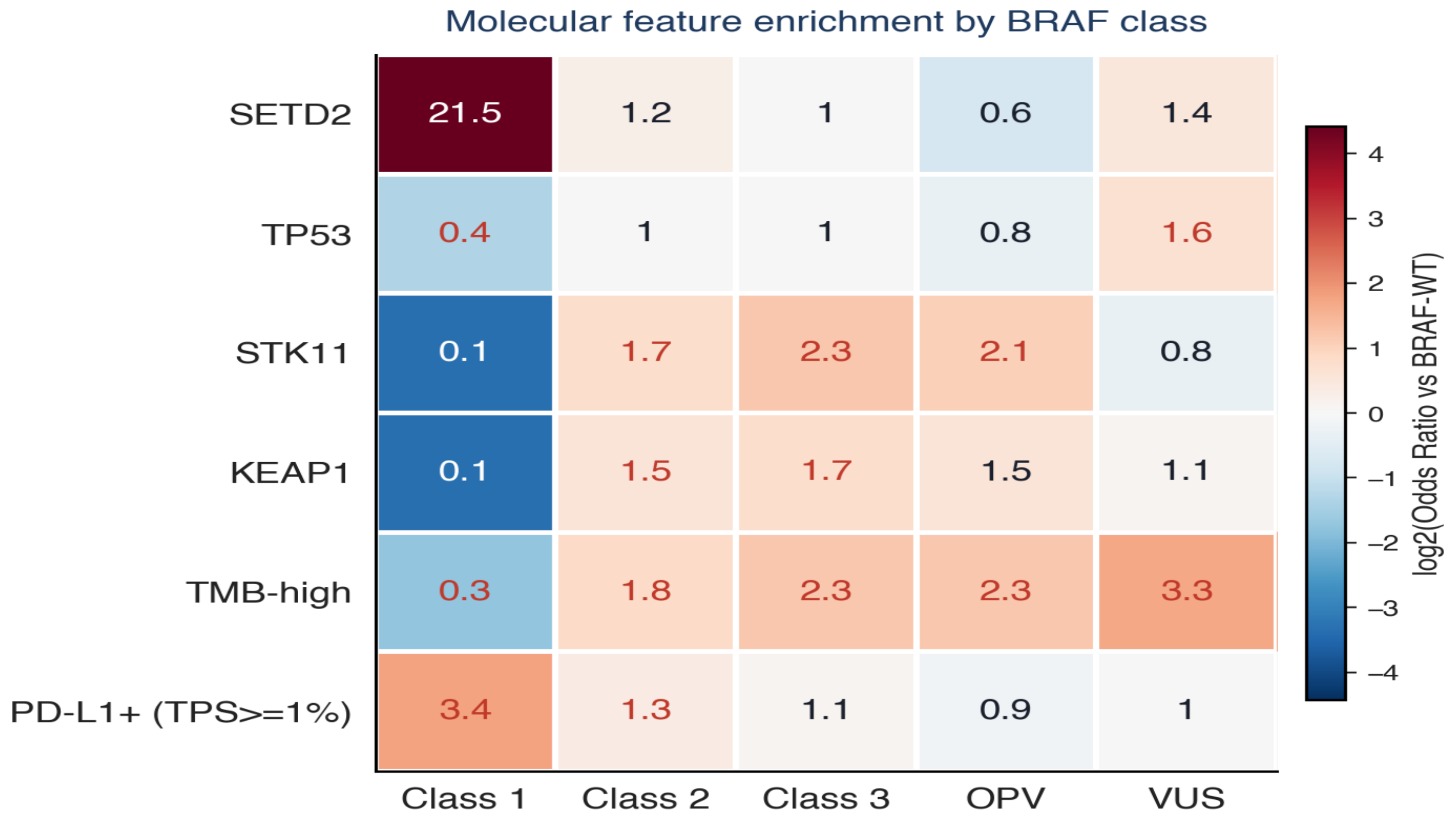

Figure 2. Bold values = P<0.05. See Table 1 for exact ORs.

Survival outcomes — Median OS and IO-OS (95% CI) by BRAF class

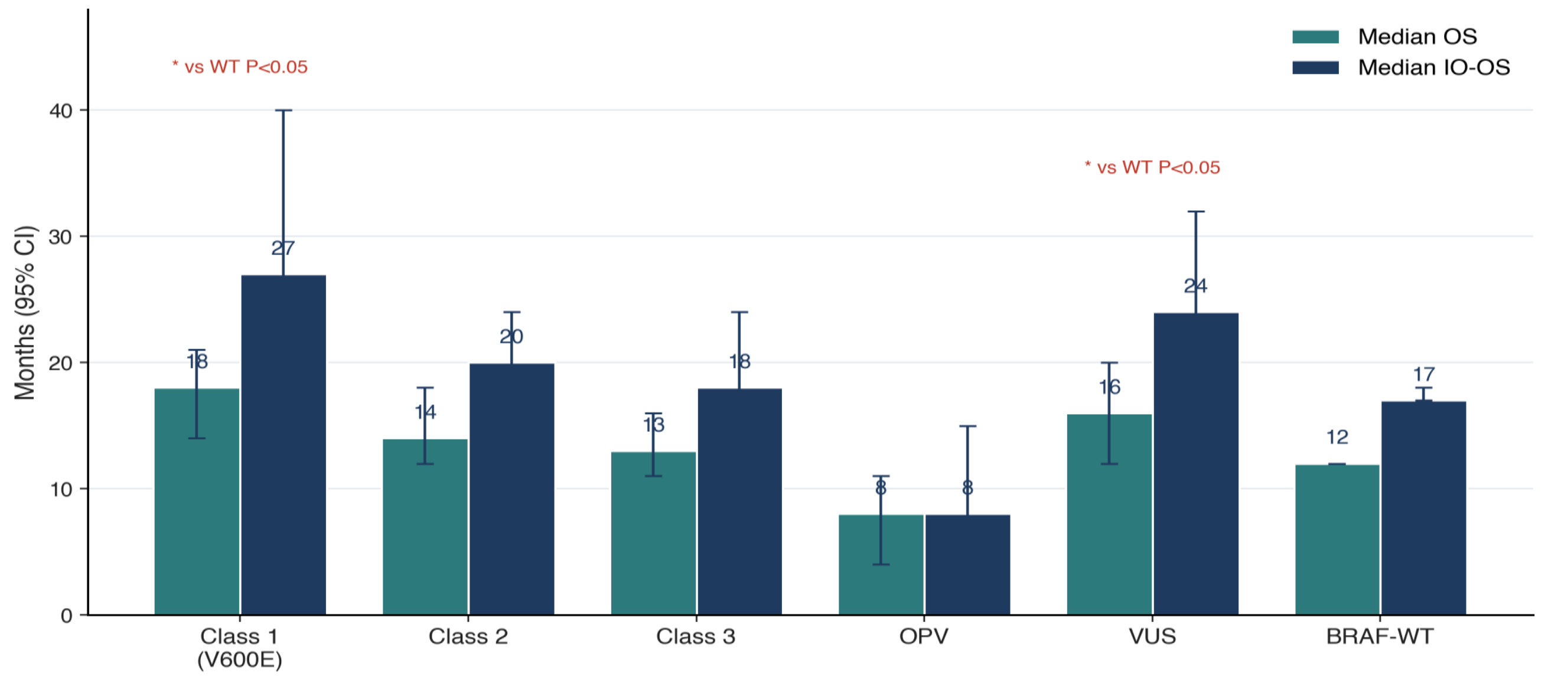

Figure 3. Class 1 and VUS — improved OS/IO-OS vs BRAF-WT (P<0.05). OPV — worst outcomes.

Table 2. Key Molecular Findings — % Prevalence by BRAF Class

Feature	Class 1 (V600E) n=695	Class 2 n=741	Class 3 n=701	OPV n=123	VUS n=936	BRAF-WT n=48,289	q-value
PD-L1+ (TPS ≥1%)	**81.2%***	**62.4%***	59%	54%	55%	**55.5%***	*<0.001*
SETD2	**33.1%***	3%	3%	2%	4%	**2.2%***	*<0.001*
TP53	**41.9%***	67%	67%	62%	**75.8%***	**66.4%***	*<0.001*
STK11	**2.2%***	**20.3%***	**25.2%***	**23.8%***	**10.6%***	**12.7%***	*<0.001*
KEAP1	**1.2%***	**19.1%***	**21.8%***	20%	15%	14%	*<0.001*
TMB-High	**16.1%***	**51.6%***	**57.2%***	**57.0%***	**65.4%***	**36.0%***	*<0.001*

** q<0.05 vs BRAF-WT (Fisher's exact, FDR-corrected). OPV = other pathogenic variants; VUS = variants of unknown significance. PD-L1 highlighted in gold as major differentiator.*

KEY FINDINGS

Molecular

- Class 1 — enriched for SETD2; PD-L1+; low TMB / TP53 / STK11 / KEAP1.
- Class 2/3 — moderately PD-L1+ and TMB-high; enriched in STK11 and KEAP1.
- OPV — enriched in STK11 and TMB-high; not PD-L1+.
- VUS — enriched in TP53 and TMB-high; not PD-L1+.

Survival (vs BRAF-WT)

- Class 1 and VUS — improved OS and IO-OS (both P<0.05).
- OPV — shortest OS overall; shorter IO-OS than Class 1 and Class 2 (all P<0.05).
- Class 2 and Class 3 — not significantly different from BRAF-WT.

Tumor immune microenvironment

- Class 1 — highest M1 macrophage and neutrophil infiltration; lowest dendritic cells.
- Class 2 and Class 3 — largely overlapping immune profiles.

KEY TAKEAWAY

27 mo	8 mo	24 mo
Median IO-OS Class 1 (V600E)	Median IO-OS OPV (worst)	Median IO-OS VUS

BRAF-mut classes represent distinct molecular, immune and clinical phenotypes.

CONCLUSIONS

1 Class 1 was significantly enriched for SETD2 mutations (33% vs 2% WT) and strikingly enriched for PDL1+ (81% vs 55% WT; OR 3.4, q<0.001), the largest PD-L1 difference observed across all classes, while showing a lower prevalence of TMB-high (16%), TP53 (42%), STK11 (2%) and KEAP1 (1%) mut (Table).

2 Class 2/3 tumors were moderately PDL1+ (62% and 59%, respectively) and TMB-high (52% and 57%), and enriched for STK11 (20%, 25%) and KEAP1 (19%, 22%) muts (Table).

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