

Supplementary Materials: Differential Activation of ERK Signaling in HPV-Related Oropharyngeal Squamous Cell Carcinoma

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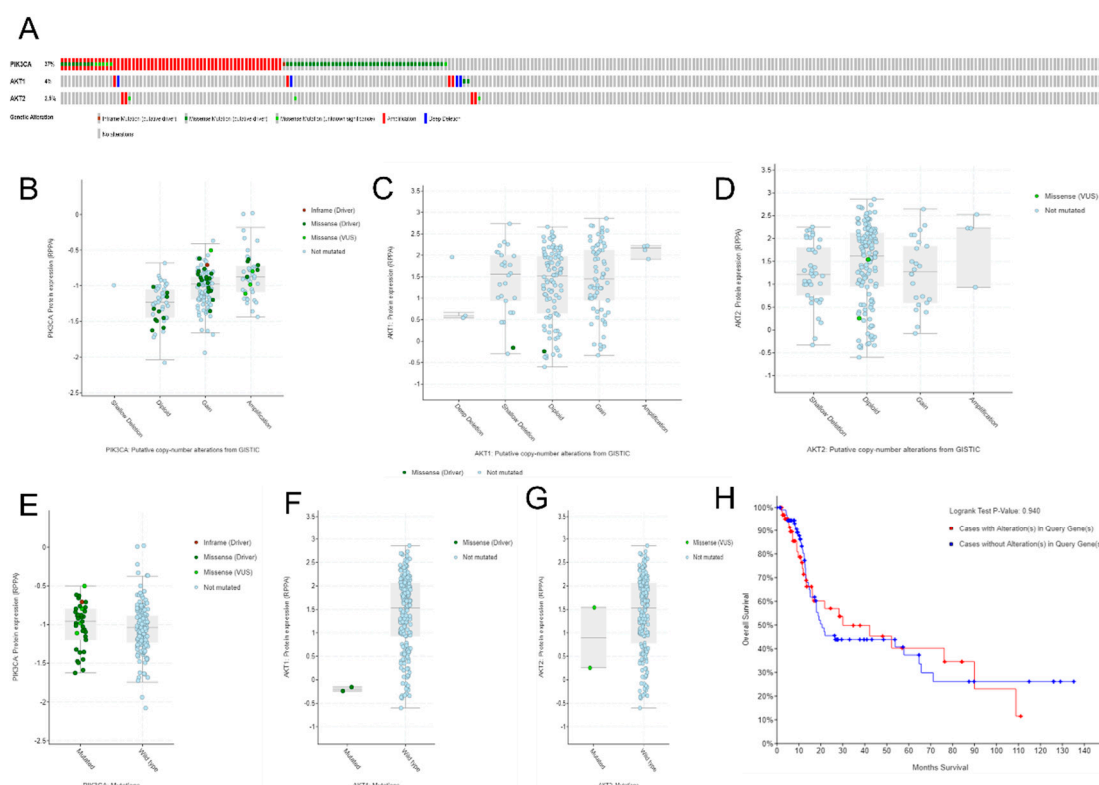


Figure S1. Genomics analysis of PI3k/AKT in HNSCC by the cBio Cancer Genomics Portal. (A) OncoPrint indicates the frequency (%) of alterations for PIK3CA, AKT1 and AKT2 genes in the TCGA-HNC cohort ($n = 191$), based on whole-exome sequencing data (<http://www.cbioportal.org/>). The boxplots show the association of protein levels and copy number variations as well as mutation status in PIK3CA (B,E), AKT1 (C,F) and AKT2 (D,G) genes. Differences in overall survival between subgroups with or without alterations in PIK3CA, AKT1&2 genes are plotted by Kaplan-Meier graph (H).

Table S1. analysis for pERK1/2 and pAKT (Ser473) expression and clinicopathological features ($n = 109$).

Clinicopathological Features	pERK1/2 ^{high}	pAKT ^{high}	Others	p-Value
Age(years)				
<58	19		32	0.494
≥58	18		40	
Gender				
Male	25		56	0.248
Female	12		16	
TNM status				
T1/T2	17		32	0.881
T3/T4	20		40	

N0	7	16	0.689
N+	30	56	
Pathological Grade			
G1/G2	19	38	0.420
G3	10	29	
missing	8	5	
Tobacco			
Never/former	8	20	0.486
Current	29	52	
Alcohol			
Never/former	8	14	0.789
Current	29	58	
HPV			
HPV-	31	51	0.247
HPV+	6	18	
missing		3	
Therapy			
RT	31	65	0.322
Non-RT	6	7	

RT: Radiotherapy.

Table S2. Cox regression analysis of progression-free and disease-specific survival for OPSCC patients ($n = 109$).

Factors	PFS		DSS	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Age(years) ≥58 vs. <58	0.961(0.583–1.583)	0.876	1.064(0.619–1.830)	0.822
Gender male vs. female	1.379(0.746–2.549)	0.305	1.708(0.858–3.403)	0.128
T status T3–4 vs. T1–2	1.881(1.116–3.171)	0.018	2.293(1.272–4.132)	0.006
N status N+ vs. N0	1.384(0.736–2.602)	0.313	2.064(0.971–4.385)	0.060
pathological Grade G3 vs. G1–2	0.742(0.413–1.334)	0.319	0.750(0.393–1.433)	0.384
Tobacco Current vs. Never/former	3.359(1.596–7.072)	0.001	2.861(1.290–6.341)	0.010
Alcohol Current vs. Never/former	1.071(0.558–2.056)	0.837	1.090(0.548–2.171)	0.806
HPV status Driven vs. Non-driven	0.339(0.146–0.789)	0.012	0.423(0.181–0.990)	0.047
Therapy RT vs. Non-RT	1.220(0.555–2.680)	0.620	2.029(0.732–5.626)	0.174
p-AKT ^{high} High vs. Low	1.117(0.673–1.856)	0.668	1.220(0.700–2.124)	0.483
p-ERK1/2 ^{high} p-AKT ^{high} vs. others	1.686(1.009–2.817)	0.046	1.745(1.006–3.028)	0.048

HR, hazard ratio; CI, confidence intervals; Statistically significant values are represented in bold.

Table S3. Multivariate Cox regression analysis of progression-free and disease-specific survival for OPSCC patients ($n = 109$).

Factors	PFS		DSS	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
T status T3–4 vs. T1–2	1.748(1.028–2.973)	0.039	2.114(1.160–3.852)	0.014
Tobacco Current vs. Never/former	2.725(1.276–5.819)	0.010	2.371(1.055–5.327)	0.037
HPV status Driven vs. Non-driven	0.464(0.197–1.097)	0.080	0.577(0.241–1.382)	0.217
p-ERK1/2 ^{high} p-AKT ^{high} vs. others	1.400(0.830–2.362)	0.207	1.338(0.758–2.361)	0.315

HR, hazard ratio; CI, confidence intervals; Statistically significant values are represented in bold.

Table S4. Multivariate Cox regression analysis of progression-free and disease-specific survival for OPSCC patients ($n = 109$).

Factors	PFS		DSS	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
T status T3–4 vs. T1–2	1.826(1.067–3.125)	0.028	2.126(1.158–3.903)	0.015
Tobacco Current vs. Never/former	3.214(1.522–6.787)	0.002	2.620(1.178–5.828)	0.018
p-AKT High vs. Low	1.064(0.630–1.798)	0.816	1.098(0.621–1.942)	0.748
p-ERK1/2 High vs. Low	2.067(1.204–3.550)	0.008	1.855(1.038–3.315)	0.037

HR, hazard ratio; CI, confidence intervals; Statistically significant values are represented in bold.

Table S5. pERK1/2 and pAKT(Ser473) expression distribution in HPV negative and positive OPSCC patients.

Expression Distribution	HPV–		HPV+	
	pERK1/2 ^{low}	pERK1/2 ^{high}	pERK1/2 ^{low}	pERK1/2 ^{high}
pAKT (Ser473) ^{low}	15	22	5	0
pAKT (Ser473) ^{high}	14	31	13	6

Table S6. Descriptive analysis of clinicopathological features of OPSCC cohort, treated between 1990 and 2008 in Heidelberg ($n = 124$).

Clinicopathological Feature	No of Patients (%)
Age(years)	
≥58	58 (46.8)
<58	66 (53.2)
Sex	
Male	93 (75.0)
Female	31 (25.0)
Tobacco use	
Never/Former	32 (25.8)
Current	92 (74.2)
Alcohol use	
Never/Former	29 (23.4)
Current	95 (76.6)
Tumor size (T)	
T1-2	59 (47.6)
T3-4	64 (51.6)

missing	1 (0.8)
Lymph node metastasis (N)	
N0	29 (23.4)
N+	94 (75.8)
missing	1 (0.8)
HPV16	
HPV-non driven	92 (74.2)
HPV-driven	29 (23.4)
n/a (missing)	3 (2.4)
Localization	
Tonsils	60 (48.4)
Tongue base	21 (16.9)
Soft palate/ Uvula/palatoglossal fold	23 (18.5)
Extending several anatomic regions	19 (15.3)
Oropharynx NOS (not otherwise specified)	1 (0.8)
Treatment	
No radiotherapy	16 (12.9)
Radiotherapy	108 (87.1)



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