

HNSC - Head and Neck Squamous Cell Carcinoma

Subtype	Proliferation	Prognosis	Therapy (Typical / Investigational)	Common Driver Alterations
Classical	High (KEAP1/NFE2L2- driven)	Poor– Intermediate	Radiation + cisplatin; poor response to immune checkpoint blockade; NRF2 pathway inhibitors (experimental)	TP53 , CDKN2A loss; NFE2L2 , KEAP1 , PIK3CA , HRAS mutations
Atypical (HPV+)	Low–Moderate	Best (median OS >5 years)	De-escalated radiation/chemo in trials; high response to PD-1 blockade	PIK3CA , PTEN loss; wild-type TP53 ; HPV E6/E7 expression
Basal	Moderate (EGFR active)	Intermediate	Cetuximab (EGFR inhibitor) + radiation/chemo; PI3K/mTOR and EGFR dual blockade in trials	TP63 , EGFR ampl.; PIK3CA , PTEN , TP53
Mesenchymal	Low–Moderate	Poor	Standard chemoradiation; poor immune response; TGF- β , EMT, or stroma-targeted therapies	NOTCH1 , TP53 ; EMT signature genes (VIM, FN1); TGF- β pathway upregulation