# Spatial Profiling of Immune Architecture Reveals APG-157-Induced Anti-Tumor Immune Remodeling in Early Stage and Locally Advanced Head and Neck Cancer

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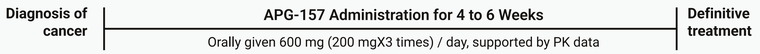
## BACKGROUND

Patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) who are HPV-negative experience the poorest outcomes, especially those with CPS <10 tumors. This subgroup has an immune-cold, suppressive tumor microenvironment (TME) that resists immune activation and responds poorly to peri-operative PD-1 blockade. HPV-positive patients generally fare better, but recurrence and progression remain common, underscoring the need for more effective therapies in both groups.

APG-157 is a nature-inspired, multi-specific drug that synergistically induces apoptosis and reprograms the immune system within the TME.[1] APG-157 functions as an oral, PD-1–independent immunotherapeutic that reprograms the TME by redistributing immune effector cells, collapsing PD-L1⁺ epithelial barriers, enhancing CTL–helper T-cell coordination, and modulating immune suppressor cells including Tregs and M2 macrophages. Its efficacy is independent of PD-L1 combined positive score (CPS). Clinical studies show that APG-157 converts "cold" tumors into immune-active phenotypes in both HPV-positive and HPV-negative cancers, producing durable responses[2] correlated with early ctDNA clearance.

## METHODS

**FIGURE 1: PHASE 2A TRIAL (NCT05312710) SCHEMA**




### TRIAL OBJECTIVES

- Stop tumor growth and/or shrink tumor
- Modulate tumor microenvironment to improve success of definitive treatment
- Reduce post-treatment morbidity and increase survival

### EFFICACY ENDPOINTS

- **Primary Endpoints:** Objective Response Rate (ORR) by RECIST v1.1 and safety
- **Exploratory endpoints:** ctDNA clearance and tumor microenvironment profiling
- **Post-hoc analysis:** Event Free Survival (EFS)

### SPATIAL IMMUNE PROFILING AND ctDNA ANALYSIS

Paired pre/post biopsies were analyzed by CellScape Precise Spatial Proteomics with a 17-marker panel at single-cell resolution. The QuPath Stardist extension was used for segmentation and spatial proximity metrics (20 µm) were quantified for CTLs, other T cell phenotypes, Tregs, macrophages and PD-L1⁺ epithelial cells

Plasma ctDNA was profiled using a 158-probe HNSCC panel (Twist UMI, NovaSeq X Plus); >90 % VAF reduction defined ctDNA clearance correlating with clinical response.

## RESULTS

**TABLE 1: BASELINE CHARACTERISTICS (N=24)**

| | |
|---|---|
| **Sex, n(%)** | |
| Male | 20 (83.3%) |
| Female | 4 (16.7%) |
| **Race, n(%)** | |
| White | 15 (62.5%) |
| Hispanic | 2 (8.3%) |
| African American | 6 (25%) |
| African Indian | 1 (4.2%) |
| **Smoker, n (%)** | |
| Current + Former | 13 (54.1) + 5 (20.8%) |
| Positive | 14 (58.3%) |
| **Primary tumor site, n(%)** | |
| Oral cavity | 13 (54.2%) |
| Oropharynx | 11 (45.3%) |

| | |
|---|---|
| **P16 status** | |
| Negative | 9 (37.5%) |
| Positive | 14 (58.3%) |
| Equivocal | 1 (4.2%) |
| **Clinical T staging** | |
| T1 and T2 | 13 (55%) |
| T3 and T4 | 11 (45%) |
| **Clinical N staging** | |
| N0 | 9 (37.5%) |
| N1 | 11 (45.8%) |
| N2 | 4 (16.7%) |
| **Overall staging** | |
| Stage I or II | 11 (45.8%) |
| Stage III or IVA | 13 (54.2%) |

**TABLE 2: EFFICACY OUTCOME (N=24)**

| | Tumor Site | |
|---|---|---|
| | Oral cavity (n=13) | Oropharynx (n=11) |
| RECIST v1.1 | | |
| CR | 2 (15%) | 0 (0%) |
| PR | 1 (7.7%) | 1 (9.1%) |
| SD | 9 (69.2%) | 10 (90.9%) |
| PD | 1 (7.7%) | 0 (0%) |
| ORR | 23% | 9% |
| DCR | 93% | 100% |

**SAFETY SUMMARY (N=24)**

Oral APG-157 was well tolerated; AEs occurred in 10 patients (33.3%), predominantly Grade 1–2 (43%). Two events were treatment-related (oral dysesthesia, Grade 2; diarrhea, Grade 1), one treatment unrelated Grade 3 tumor bleed led to discontinuation.


**References:** 1) Basak SK, et al. Cancer, 2020 Apr 15;126(8):1668-1682. 2) Wang MB, and et al, American Society of Clinical Oncology (ASCO) Annual Meeting, June 2025, Chicago, IL;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## KEY FINDINGS

**FIGURE 2: Event-Free Survival by Disease Risk (N=24): Median Not Reached**

- Consistent benefit across risk groups
- Only one cancer-related event in high-risk patients

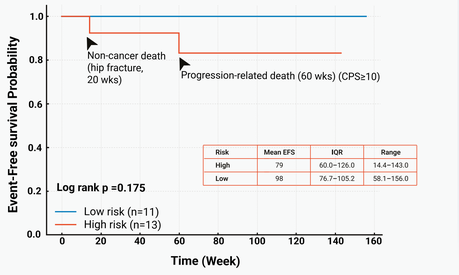


**FIGURE 3: Event-Free Survival by PD-L1 CPS (N=19): Median Not Reached**

- PD-L1 independent durable benefit
- Only one cancer-related event occurred in CPS ≥10

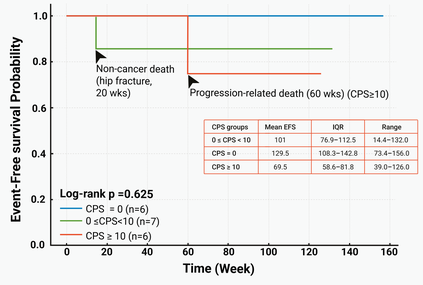


**FIGURE 4: ctDNA: ≥95% clearance by Day 29 (N=21): patient outcomes**

- ≥95% ctDNA clearance in 90% of patients by Day 29 is an early biomarker of APG-157-driven immune remodeling and durable benefit

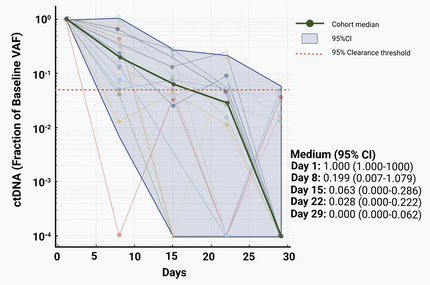


**FIGURE 5: ctDNA: Early Signal for MOA (N=21)**

- Early and rapid ctDNA clearance predicts durable benefit independent of PD-L1 expression

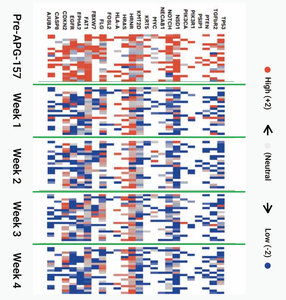


**FIGURE 6: APG-157 Shifts Immune-Cold Tumors Towards an Immune-Engaged State Via Effector T Cell Activation & Modulation Of Suppressor Niches**

(Patient 01-11, Oral cavity, T1N0M0, stable disease at Week 4)

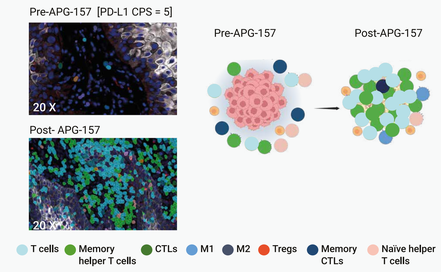


**FIGURE 7: Spatial Profiling In Patient 01-11 Reveals Increased Immune-To-Epithelial Cell Ratio, Coordinated Effector-Helper T-Cell Activity And Reduced Suppressive Niches Post APG-157 Treatment**

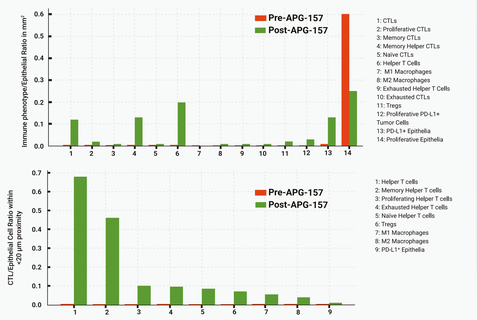


**FIGURE 8: APG-157 Reduced PD-L1+ Epithelial Compartment Expanded CTLs And CTL-Helper Hubs And Suppressor Clusters Yielding An Immune-Engaged "HOT" Tumor Microenvironment**

(Patient 01-05, Oral cavity, T3N0M0, Partial Response at Week 4)

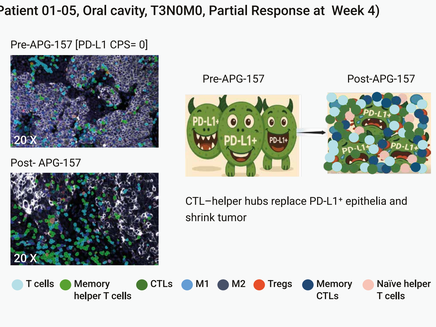


**FIGURE 9: Pre-Post Spatial Profiling For Patient 01-05 Shows A Shift From An Immune-Excluded To Immune-Engaged Tumor Microenvironment with Expansion of CTL-Helper Coordination Hub and Contraction of PD-L1+ Epithelial Barrier Regions**

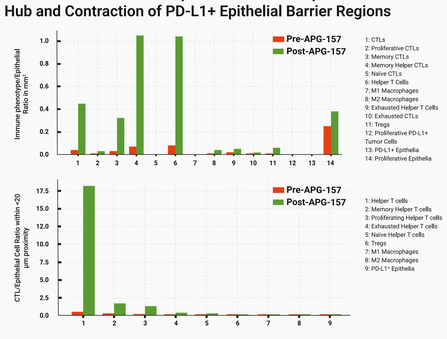


**FIGURE 10: APG-157 Remodeled Tumor Microenvironment: Diminished PD-L1+ Epithelia, Enriched Effector To Epithelial Cell Ratio And Attenuated Suppressor Clustering Consistent With An Immune-engaged State**

(Patient 01-06, oropharyngeal cancer, T3N2M0, Stable Disease at Week 4)

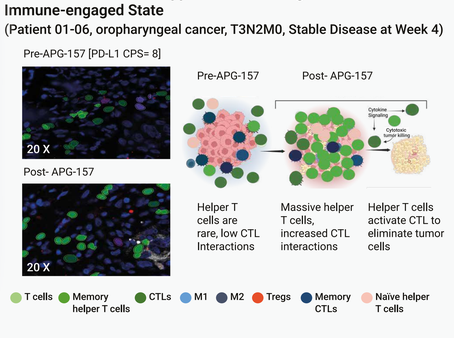


**FIGURE 11: Spatial Modeling Shows Helper Replace Suppressor Proximity As Key Coordinators**


## CONCLUSIONS

**01** **APG-157 remodels immune-cold tumors into immune-engaged states, with ctDNA clearance predicting durable survival**

**Paired pre-post spatial profiling from a total of 12 patients revealed distinct immune remodeling patterns that are aligned with RECIST v1.1 response categories:**

- **Responders (CR n=2, PR n=1):** Naïve CTLs transitioned into effector states with coordinated TME remodeling and strengthened CTL–helper proximity.
- **Stable disease (n=8):** 5/8 achieved clinical-to-pathological downstaging; immune remodeling marked by helper/memory T-cell expansion, suggesting an immune-primed transitional state.
- **Progressive disease (n=1) + upstaging (n=1):** Minimal effector engagement, loss of CTL–APC proximity, consistent with immune exclusion.

**02** **Mechanism of action:** APG-157 induced **de novo T-cell infiltration,** organized **memory CTL hubs,** enhanced **effector–epithelium proximity and M2 to M1 macrophage repolarization,** converting theTME to an immune responsive state.

**03** **Biomarker response:** ~90% achieved **≥95% ctDNA clearance by Week 4,** correlating with **~92% 2-year EFS.**

**04** Early modulation of NF-κB–pathway genes by APG-157 reflects its mechanism of action in suppressing tumor growth; ctDNA became undetectable post-treatment.

**05** **Safety:** APG-157 was well-tolerated, **no Grade ≥3 treatment-related TEAEs,** highlighting a favorable profile compared to PD-1 blockade.

**06** **Overall:** APG-157 drives a **multi-axis immune-engagement mechanism,** distinct from checkpoint inhibition, supporting further clinical development.