PD-L1 isn't just a biomarker for HNSCC, it's a treatment guide

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Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) remains a clinical challenge, often leaving patients with limited treatment options and poor prognoses. The integration of systemic treatments with radiation therapy has transformed therapeutic paradigms, but optimal combinations and patient selection criteria remain undefined.1

Immunotherapy, particularly immune checkpoint inhibitors, has emerged as a critical component of the treatment armamentarium. But identifying which patients will benefit most from these therapies, especially in the context of PD-L1 expression, continues to be a central question for clinicians.2

KEY TAKEAWAYS

- The Pivot: PD-L1 expression levels are critical for stratifying patients who will benefit from anti-PD-1/PD-L1 therapies in recurrent/metastatic HNSCC.
- The Data: High PD-L1 expression (CPS e20) correlates with superior objective response rates and progression-free survival in specific immunotherapy regimens.
- The Action: Clinicians should routinely assess PD-L1 expression using combined positive score (CPS) to guide treatment decisions for patients considering immunotherapy in this setting.

Head and neck squamous cell carcinoma (HNSCC) represents a diverse group of malignancies, often characterised by aggressive local invasion and a high propensity for recurrence and metastasis. Despite advances in surgery, radiation, and chemotherapy, outcomes for patients with recurrent or metastatic disease remain poor. The median overall survival for these patients has historically been dismal, prompting an urgent need for more effective systemic therapies.1

The immune system's role in controlling cancer has led to the development of immune checkpoint inhibitors (ICIs), which block inhibitory pathways like PD-1/PD-L1, thereby unleashing anti-tumor immune responses. These agents have shown efficacy across various solid tumors, including HNSCC. But not all patients respond, and identifying predictive biomarkers is vital for optimising treatment strategies and avoiding unnecessary toxicity and cost for non-responders.2

The Role of PD-L1 Expression

PD-L1 expression on tumor cells and tumor-infiltrating immune cells has emerged as a key biomarker for predicting response to anti-PD-1/PD-L1 therapies. The combined positive score (CPS), which accounts for PD-L1 staining on both tumor cells and immune cells, is a widely accepted method for assessing PD-L1 status in HNSCC. Higher CPS values generally correlate with increased likelihood of response to ICIs. This correlation is particularly relevant in the recurrent or metastatic setting, where treatment options are often limited and the stakes for effective therapy are high.2

The integration of radiation therapy (RT) with systemic treatments in HNSCC has transformed therapeutic paradigms, but optimal combinations remain undefined. Becherini, Banini, and Blanchard, in their 2026 expert opinion and roadmap to consensus published in Radiotherapy and Oncology, highlighted priority areas of unmet need in combining RT with systemic treatment in both HNSCC and nasopharyngeal cancer (NPC).1 This highlights the complexity of treatment decisions, especially when considering the addition of immunotherapy. The relationship between radiation, which can induce immunogenic cell death, and ICIs is an active area of investigation, but clear guidelines for sequencing and combination remain elusive.1

Anti-EGFR Therapy and Immunotherapy Combinations

Beyond single-agent immunotherapy, combinations with other targeted agents, such as anti-EGFR therapies, are under active investigation. Gan, Yang, and Xu reviewed the current market and future directions of anti-EGFR therapy combined with immune checkpoint inhibitors in recurrent/metastatic HNSCC in their 2026 critical review in Critical Reviews in Oncology/Hematology.2 They noted that the integration of these two distinct mechanisms of action holds theoretical promise. EGFR is frequently overexpressed in HNSCC, driving proliferation and survival, while ICIs aim to restore anti-tumor immunity. Combining these approaches could potentially overcome resistance mechanisms and enhance therapeutic efficacy.2

The rationale for combining anti-EGFR agents with ICIs stems from preclinical data suggesting synergistic effects. EGFR inhibition can modulate the tumor microenvironment, potentially increasing the presentation of tumor antigens and enhancing immune cell infiltration. But clinical data supporting this combination in HNSCC are still maturing. The review by Gan and colleagues pointed to several ongoing trials exploring various anti-EGFR and ICI combinations, but definitive efficacy and safety profiles are yet to be fully established.2

One of the challenges in evaluating these combinations is the heterogeneity of HNSCC. Factors such as HPV status, smoking history, and prior treatment exposure can significantly influence treatment response. For instance, HPV-driven oropharyngeal cancer often has a better prognosis and distinct molecular characteristics compared to HPV-negative disease, which may necessitate different therapeutic approaches. The optimal selection of patients for combination therapy, therefore, requires a deeper understanding of these underlying biological differences.2

Real-World Efficacy of Anlotinib

In the context of later-line therapy for recurrent or metastatic HNSCC, novel agents are continually being evaluated. Li, Li, and Li investigated the real-world efficacy and safety outcomes of anlotinib as third-line or later therapy in recurrent or metastatic HNSCC. Their 2026 study, published in Drug Design, Development and Therapy, provides valuable insights into the practical application of this multi-targeted tyrosine kinase inhibitor.3 Anlotinib targets multiple kinases, including VEGFR, FGFR, PDGFR, and c-Kit, which are involved in angiogenesis and tumor growth.3

The study enrolled 108 patients with recurrent or metastatic HNSCC who had failed at least two prior lines of systemic therapy. The median age was 59 years, and 72.2% were male. Most patients (81.5%) had received prior platinum-based chemotherapy, and 56.5% had received prior anti-EGFR therapy. This patient population represents a heavily pre-treated group with limited remaining options, making any observed efficacy particularly noteworthy.3

The objective response rate (ORR) for anlotinib was 13.9% (95% CI, 7.8-21.9%), with 15 patients achieving a partial response. The disease control rate (DCR) was 63.0% (95% CI, 53.1-72.1%), indicating that a substantial proportion

of patients experienced stable disease or better. The median progression-free survival (PFS) was 3.7 months (95% CI, 2.8-4.6 months), and the median overall survival (OS) was 7.8 months (95% CI, 6.2-9.4 months). These numbers, while modest, are clinically meaningful in a population with such advanced disease and limited alternatives.3

Safety data from the anlotinib study showed a manageable toxicity profile. The most common grade 3 or higher adverse events included hypertension (15.7%), hand-foot skin reaction (11.1%), and fatigue (7.4%). These adverse events are consistent with the known profile of multi-targeted tyrosine kinase inhibitors. Discontinuation due to adverse events occurred in 9.3% of patients. The real-world setting of this study provides a pragmatic view of anlotinib's tolerability outside of highly controlled clinical trials.3

Limitations and Future Directions

The studies reviewed highlight the ongoing challenges and evolving strategies in managing recurrent and metastatic HNSCC. The expert opinion on radiation and systemic treatments, while providing a roadmap, highlights that optimal integration remains an unmet need.1 This means clinicians are still navigating complex decisions without definitive, large-scale comparative data for many combinations. The heterogeneity of HNSCC and the multitude of potential treatment sequences complicate the design and interpretation of clinical trials.1

The review on anti-EGFR and ICI combinations, while optimistic about synergistic potential, acknowledges the lack of mature clinical data.2 Many of the trials are still in early phases, and robust evidence for improved survival outcomes with these combinations is yet to emerge. The optimal sequencing of these agents, or whether they should be given concurrently, remains an open question. Identifying specific biomarkers beyond PD-L1 that predict response to these combinations is critical for refining patient selection.2

The anlotinib real-world study, while providing valuable data for a heavily pre-treated population, is limited by its retrospective, single-center design.3 The absence of a control arm makes direct comparisons of efficacy challenging, and selection bias cannot be entirely ruled out. Still, the data offer a glimpse into the potential utility of anlotinib in a difficult-to-treat patient group, suggesting it could be a viable option when other standard therapies have failed. For clinicians looking for a concise reference on managing various cancer types, the Oxford Handbook of Oncology can be a useful resource.

The field continues to grapple with the complexities of immunotherapy in HNSCC. While PD-L1 expression offers a guide, it is not a perfect predictor, and a substantial proportion of patients with low PD-L1 expression may still derive some benefit, while some with high expression may not respond. This suggests other, yet-to-be-identified biomarkers or immune-related factors are at play. Future research needs to focus on more comprehensive biomarker panels, including tumor mutational burden, gene expression profiles, and immune cell infiltrates, to better predict response and resistance to ICIs. The integration of these advanced diagnostics, alongside a deeper understanding of the tumor microenvironment, will be essential for personalizing treatment in HNSCC. For instance, understanding why some patients respond to immunotherapy while others do not is a central theme in cancer immunology research. The ongoing efforts to integrate radiation therapy with systemic treatments also require careful consideration of how these modalities interact with the immune system to either enhance or suppress anti-tumor responses.1

CLINICAL IMPLICATIONS

PD-L1 testing is not optional for recurrent and metastatic HNSCC; it is foundational. The data, particularly from trials informing current guidelines, consistently show that patients with higher PD-L1 expression, typically defined by a CPS of 20 or greater, derive more substantial benefits from immune checkpoint inhibitors. Ignoring this biomarker risks exposing patients to ineffective therapy and its associated toxicities.

Clinicians should also temper expectations for combination therapies involving anti-EGFR agents and ICIs. While theoretically appealing, robust clinical evidence for superior outcomes over single-agent or established regimens is still largely absent. The field needs definitive phase 3 data, not just preclinical synergy, before these combinations become standard practice.

Anlotinib's real-world data in heavily pre-treated patients offer a pragmatic option for those who have exhausted standard lines of therapy. A median OS of 7.8 months in this population is not a cure, but it provides a meaningful extension of life for patients with few alternatives. This suggests a role for anlotinib as a salvage therapy, particularly when other targeted agents or immunotherapies have failed.

The persistent challenge remains the significant proportion of patients who do not respond to immunotherapy, even with high PD-L1 expression. This highlights the need for continued research into novel biomarkers and combination strategies. Relying solely on PD-L1, while currently the best available tool, is insufficient for truly personalized medicine in HNSCC.

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