PD-L1 as a compass for immunotherapy in head and neck cancer

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> Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) remains a clinical challenge, with limited treatment options and poor prognoses. The integration of systemic treatments, particularly immunotherapy, has altered therapeutic approaches, but identifying which patients benefit most from these therapies remains a critical unmet need.1
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> Selecting patients based on programmed death-ligand 1 (PD-L1) expression offers a potential pathway to optimise treatment strategies, moving beyond broad-brush application to a more targeted approach. This precision is essential for improving outcomes in a disease where optimal combinations are still being defined.1

KEY TAKEAWAYS

- The Pivot: PD-L1 expression levels are a key determinant for selecting patients for immunotherapy in recurrent/metastatic HNSCC.
- The Data: High PD-L1 expression (CPS e20) correlates with improved objective response rates and progression-free survival in specific immunotherapy regimens.
- The Action: Clinicians should consider PD-L1 testing to guide treatment decisions for patients with recurrent or metastatic HNSCC, particularly when contemplating immune checkpoint inhibitors.

Head and neck squamous cell carcinoma (HNSCC) represents a diverse group of malignancies, often aggressive and challenging to treat, especially in recurrent or metastatic settings. Historically, platinum-based chemotherapy has formed the backbone of systemic treatment, but survival benefits remain modest. The advent of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis has introduced a new era, offering durable responses for a subset of patients. But, not all patients respond, prompting a search for reliable biomarkers to predict treatment efficacy.2

The integration of radiation therapy (RT) with systemic treatments in head and neck cancers has transformed therapeutic paradigms, yet optimal combinations remain undefined. A study by Becherini, Banini, and Blanchard, published in Radiotherapy and Oncology, aimed to identify priority areas of unmet need in combining RT with systemic treatment in both HNSCC and nasopharyngeal cancer (NPC).1 This expert opinion and roadmap to consensus highlighted the complexity of treatment sequencing and combination strategies, emphasizing the necessity for better patient selection tools. The review emphasized that while ICIs offer promise, their optimal placement within multimodal regimens, especially with RT, requires further elucidation.1

The Role of PD-L1 Expression

PD-L1 expression on tumour cells and immune cells within the tumour microenvironment serves as a critical biomarker for predicting response to PD-1/PD-L1 inhibitors. High PD-L1 expression often indicates a more inflamed tumour environment, making it more susceptible to immune checkpoint blockade. The combined positive score (CPS), which accounts for PD-L1 expression on both tumour cells and tumour-infiltrating immune cells, has emerged as a widely used metric. Different cut-offs (e.g., CPS ≥1, CPS ≥20) define patient populations with varying likelihoods of response.2

Gan, Yang, and Xu, writing in Critical Reviews in Oncology/Hematology, explored the current market and future directions of anti-EGFR therapy combined with immune checkpoint inhibitors in recurrent/metastatic HNSCC.2 Their review emphasized that PD-L1 expression is a key factor in determining the efficacy of ICIs. For instance, pembrolizumab, a PD-1 inhibitor, demonstrated superior overall survival (OS) compared to chemotherapy in patients with recurrent or metastatic HNSCC with PD-L1 CPS ≥1. The benefit was even more pronounced in those with CPS ≥20.2 Patients with PD-L1 CPS ≥20 treated with pembrolizumab as monotherapy achieved an objective response rate (ORR) of 23.3%, compared to 10.1% with chemotherapy. The median OS was 14.9 months vs 10.7 months (HR 0.61; 95% CI, 0.45-0.83). For patients with CPS ≥1, pembrolizumab also improved OS, but the magnitude of benefit was less striking than in the higher PD-L1 expressing group. This data firmly establishes PD-L1 as a critical selection marker.2

Combination Strategies and Unmet Needs

The field continues to explore combination therapies to enhance ICI efficacy, particularly for patients with lower PD-L1 expression or those who progress on monotherapy. Combining ICIs with anti-EGFR agents, such as cetuximab, represents one such strategy. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), has a long-standing role in HNSCC treatment. Preclinical data suggest a synergistic effect between anti-EGFR therapy and ICIs, where EGFR inhibition may modulate the tumour microenvironment, making it more responsive to immunotherapy.2

But, clinical trials evaluating these combinations have yielded mixed results. The Gan, Yang, and Xu review highlighted that while some early phase studies showed promising activity, larger randomised trials are needed to confirm the benefit and identify the optimal patient population for such combinations.2 The challenge lies in balancing enhanced efficacy with increased toxicity, a common concern with multimodal regimens. Clinicians must weigh these factors carefully, especially when considering patients who may already be frail from prior treatments. For a broader understanding of how different systemic treatments are being evaluated in other cancers, our coverage on chemoimmunotherapy in metastatic prostate cancer offers additional context.

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Real-World Evidence and Later-Line Options

Beyond first-line and second-line treatments, patients with recurrent or metastatic HNSCC often face limited options. Real-world data can provide valuable insights into the efficacy and safety of therapies in broader, less selected patient populations. Li, Li, and Li investigated anlotinib as a third-line or later therapy in recurrent or metastatic HNSCC,

publishing their findings in Drug Design, Development and Therapy.3 Anlotinib is a multi-target tyrosine kinase inhibitor (TKI) that inhibits angiogenesis and tumour growth.

The real-world study included 102 patients who had received at least two prior lines of systemic therapy. The objective response rate (ORR) for anlotinib was 13.7%, with a disease control rate (DCR) of 60.8%. The median progression-free survival (PFS) was 3.7 months (95% CI, 2.9-4.5 months), and the median overall survival (OS) was 7.8 months (95% CI, 6.2-9.4 months).3 These numbers, while modest, represent a meaningful outcome for a heavily pretreated population with few alternatives. The most common grade 3 or higher adverse events included hypertension (10.8%), hand-foot skin reaction (7.8%), and fatigue (5.9%).3

The study by Li and colleagues highlights the ongoing need for effective later-line therapies and the potential role of TKIs in this setting.3 While not directly an immunotherapy, anlotinib's mechanism of action, particularly its anti-angiogenic properties, could theoretically influence the tumour microenvironment and potentially interact with immune responses. This opens avenues for future research into combination strategies involving TKIs and ICIs, especially for patients who have exhausted standard immunotherapy options. The complex relationship between cancer and the immune system is a constant area of investigation, and understanding these mechanisms is key to developing new treatments.

The Nuance of PD-L1 Testing

While PD-L1 expression is a valuable biomarker, its assessment is not without challenges. Variability exists in antibody clones, scoring algorithms, and interpretation across different laboratories. This can lead to inconsistencies in patient selection and treatment outcomes. Standardisation of PD-L1 testing methodologies is essential for patient outcomes to ensure reliable and reproducible results, allowing clinicians to make informed decisions with confidence.2

The dynamic nature of PD-L1 expression also presents a challenge. Tumour PD-L1 levels can change over time and in response to treatment, including radiation therapy or chemotherapy. A single biopsy at diagnosis may not fully capture the evolving immune guidelines of the tumour. Serial biopsies or liquid biopsies could offer a more comprehensive picture, but their clinical utility and feasibility in routine practice require further investigation.1

The expert opinion by Becherini, Banini, and Blanchard specifically addressed the integration of radiation therapy with systemic treatments.1 They noted that RT can induce immunogenic cell death, potentially increasing PD-L1 expression and enhancing the efficacy of ICIs. But, the optimal timing and sequencing of RT and ICIs remain a subject of intense debate. Concurrent administration might increase toxicity, while sequential approaches could miss opportunities for synergy. These are complex considerations that require careful clinical judgment and further trial data.1

Where the Data Falls Short

The current body of evidence, while compelling for PD-L1 as a biomarker, still leaves gaps. Many studies, including those reviewed, focus on specific immunotherapy agents or combinations, making direct comparisons across different regimens challenging. The heterogeneity of HNSCC itself, encompassing various subsites and HPV statuses, further complicates generalisability. For example, HPV-driven oropharyngeal cancer often has a different biological profile and prognosis compared to HPV-negative disease, which may influence immunotherapy response.2

The real-world study on anlotinib, while providing valuable insights into later-line therapy, was a single-centre, retrospective analysis.3 Such studies are prone to selection bias and confounding factors, limiting the strength of their conclusions compared to prospective, randomised controlled trials. The relatively small sample size (N=102) also means

that rare adverse events or benefits in specific subgroups might not have been fully captured. These limitations emphasize the need for more robust, multicentre studies to validate real-world observations.3

Still, the emphasis on PD-L1 as a predictive biomarker is clear. Clinicians need to integrate this information into their decision-making process, understanding that higher PD-L1 expression generally translates to a greater likelihood of benefit from immune checkpoint inhibitors. The Oxford Handbook of Oncology provides a concise reference for navigating these complex treatment algorithms.

CLINICAL IMPLICATIONS

The data on PD-L1 expression in recurrent and metastatic HNSCC is not merely academic; it dictates who receives immunotherapy and who does not. For clinicians, this means PD-L1 testing is no longer optional but a fundamental step in treatment planning. Relying solely on clinical judgment without biomarker data risks exposing patients to ineffective treatments or, worse, denying them a potentially life-extending therapy.

The challenge lies in the practicalities of testing and interpretation. Variability in assays and scoring can lead to inconsistent results, which is unacceptable when patient outcomes hang in the balance. We need standardised, robust testing protocols that ensure every patient receives an accurate assessment of their PD-L1 status, regardless of where they are treated.

But, the story does not end with PD-L1. Many patients with low or negative PD-L1 expression still need effective options. The exploration of combination therapies, such as ICIs with anti-EGFR agents or TKIs like anlotinib, points to a future where treatment is tailored not just by one biomarker, but by a more comprehensive understanding of tumour biology. This requires ongoing research and a willingness to move beyond single-agent paradigms.

The goal is to provide every patient with recurrent or metastatic HNSCC the best possible chance at survival and quality of life. PD-L1 is a powerful compass, but it is one tool among many in a complex and evolving therapeutic trial pipeline. We must continue to refine our understanding of tumour immunology to unlock the full potential of immunotherapy for all patients.

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