

Salivary gland cancer: Is HER2-low the new HER2-positive?

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Advanced salivary gland carcinoma (SGC) presents a significant therapeutic challenge, with limited systemic treatment options available. Clinicians have long sought targeted therapies, especially for human epidermal growth factor receptor 2 (HER2)-positive disease, but prospective data have remained sparse. This unmet need prompted investigation into trastuzumab rezetecan, a HER2-directed antibody-drug conjugate (ADC), across both HER2-high and HER2-low SGC cohorts.^{1,2}

KEY TAKEAWAYS

- The Pivot: Trastuzumab rezetecan shows activity in advanced salivary gland carcinoma, extending beyond traditional HER2-high definitions.
- The Data: The objective response rate was 50% (95% CI, 33.4-66.6) in the HER2-high cohort and 20% (95% CI, 8.4-38.4) in the HER2-low cohort.
- The Action: Consider HER2 testing for all patients with advanced SGC, as even HER2-low expression may warrant consideration for HER2-directed ADCs.

Systemic treatment for advanced salivary gland carcinoma (SGC) has historically offered limited efficacy, leaving a substantial gap in patient management. The field has lacked robust prospective data for HER2-directed therapies, particularly in the context of HER2-low disease, which represents a larger patient population than traditionally defined HER2-positive cancers. This trial aimed to address that void by evaluating trastuzumab rezetecan (SHR-A1811), an antibody-drug conjugate (ADC) targeting HER2, in a biomarker-stratified Phase II setting.^{1,2}

Investigators enrolled patients with advanced SGC into two prospectively defined cohorts based on HER2 expression: HER2-high (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+) and HER2-low (IHC 1+ or IHC 2+/ISH-). The study design allowed for a clear differentiation of efficacy across the HER2 spectrum, providing valuable insights into the potential utility of ADCs in a broader patient population. Chen and colleagues published these results in the *Journal of Clinical Oncology*.^{1,2}

Efficacy Across HER2 Expression Levels

Trastuzumab rezetecan demonstrated notable antitumor activity in both HER2-high and HER2-low advanced SGC. In the HER2-high cohort (N=24), the objective response rate (ORR) was 50% (95% CI, 33.4-66.6), with 12 patients achieving a confirmed partial response.¹ This level of response is clinically meaningful in a disease with few effective options, suggesting a clear benefit for patients with high HER2 expression.

The HER2-low cohort (N=30) also saw responses, albeit at a lower rate. The ORR in this group was 20% (95% CI,

8.4-38.4), with 6 patients achieving a confirmed partial response.¹ This finding is particularly important because it expands the potential utility of HER2-directed therapy beyond the traditional HER2-positive definition, which typically excludes IHC 1+ and IHC 2+/ISH- tumors. The median duration of response (DoR) was 10.4 months (95% CI, 5.5-not reached) in the HER2-high cohort and 8.3 months (95% CI, 4.2-not reached) in the HER2-low cohort, indicating durable responses in both groups.¹

Median progression-free survival (PFS) was 7.9 months (95% CI, 5.5-11.0) for the HER2-high cohort and 5.5 months (95% CI, 3.7-7.2) for the HER2-low cohort.¹ These PFS numbers, while not directly comparable to a placebo arm due to the single-arm design, represent a significant improvement over historical outcomes for advanced SGC, which often see PFS measured in mere months with conventional chemotherapy. The trial's open-label nature is an obvious caveat, as is the lack of a direct comparator arm, which limits definitive conclusions about superiority to existing treatments. Still, the consistent signal across both cohorts is compelling.

Disease control rates (DCR) further supported the drug's activity. In the HER2-high cohort, the DCR was 91.7% (95% CI, 73.0-99.0), meaning nearly all patients experienced either a response or stable disease.¹ The HER2-low cohort had a DCR of 73.3% (95% CI, 53.8-88.1).¹ These high DCRs suggest that trastuzumab rezetecan can stabilize disease progression for a substantial proportion of patients, even if they do not achieve a full objective response. This broad activity in a difficult-to-treat cancer highlights the potential for ADCs to redefine treatment paradigms, a topic explored in combination oncology therapies more broadly.

Safety Profile and Tolerability

Trastuzumab rezetecan demonstrated a manageable safety profile, consistent with other ADCs. The most common treatment-emergent adverse events (TEAEs) of any grade were nausea (61.1%), fatigue (55.6%), alopecia (51.9%), and decreased appetite (48.1%).¹ These are generally expected toxicities for this class of agents, and clinicians are familiar with managing them. The incidence of grade 3 or higher TEAEs was 48.1%.¹

Specific adverse events of interest included interstitial lung disease (ILD), a known risk with HER2-directed ADCs. ILD occurred in 9.3% of patients (5/54), with one grade 5 event.¹ This highlights the importance of vigilant monitoring for respiratory symptoms and prompt intervention, a critical aspect of managing patients on these therapies. Other significant grade 3 or higher TEAEs included neutropenia (14.8%), anemia (11.1%), and thrombocytopenia (7.4%).¹ These hematologic toxicities require careful monitoring of complete blood counts throughout treatment. For clinicians managing complex oncology cases, a comprehensive reference like the Oxford Handbook of Oncology can be invaluable.

Dose reductions due to TEAEs occurred in 25.9% of patients, and treatment discontinuation due to TEAEs occurred in 13.0%.¹ While these rates indicate that some patients struggled with tolerability, the majority were able to continue treatment, suggesting that the benefits generally outweighed the risks for those who responded. The single grade 5 ILD event is a stark reminder of the serious, albeit rare, toxicities associated with ADCs, necessitating careful patient selection and close follow-up. This is a common theme in oncology, where balancing efficacy with toxicity is paramount, as seen in discussions around ICI dissemination challenges.

Implications for Clinical Practice

The data from this Phase II trial provide a strong signal for trastuzumab rezetecan in advanced SGC. The drug's activity in both HER2-high and HER2-low populations suggests that HER2 expression, even at lower levels, can serve as a viable therapeutic target. This expands the potential patient pool for HER2-directed ADCs beyond what was previously considered. Clinicians should consider routine HER2 testing for all patients with advanced SGC, moving beyond the traditional IHC 3+ or IHC 2+/ISH+ criteria. The trial was not powered for direct comparisons between HER2-high and HER2-low groups, but the observed differences in ORR and PFS are consistent with the expected gradient of target expression.

This study also highlights the evolving understanding of HER2 as a target. The concept of HER2-low disease has gained traction in other tumor types, and these SGC data reinforce its relevance. The ability of ADCs to deliver cytotoxic payloads to cells with even modest HER2 expression opens new avenues for treatment. But the relatively small sample size of a Phase II trial means these findings, while encouraging, require confirmation in larger, potentially randomized, studies. The long-term safety profile, particularly regarding ILD, will also need further characterization in broader populations.

The current market for advanced SGC is bleak, with few effective systemic options. Trastuzumab rezetecan offers a new potential strategy, particularly for patients whose tumors express HER2. While not a definitive answer, it provides a much-needed option for a patient population with high unmet need. The next steps will involve further clinical development, likely including comparative trials to firmly establish its place in the treatment algorithm. The ongoing development of novel agents for advanced GIST and other solid tumors reflects this broader push for targeted therapies.

CLINICAL IMPLICATIONS

This trial provides a clear signal: trastuzumab rezetecan works in advanced salivary gland carcinoma, and not just in the traditionally defined HER2-high subset. The 50% ORR in HER2-high disease is compelling, but the 20% ORR in HER2-low patients is arguably more impactful. It forces a re-evaluation of HER2 testing in SGC, pushing clinicians to consider it for all advanced cases, as even lower expression levels may now be actionable.

For oncologists, this means HER2 IHC 1+ and IHC 2+/ISH- tumors are no longer necessarily excluded from targeted therapy discussions. The drug's safety profile, with expected ADC toxicities like nausea and fatigue, and the critical need to monitor for ILD, is manageable. But the single grade 5 ILD event highlights the importance of careful patient selection and proactive management of adverse events.

The pharmaceutical industry will undoubtedly take note. Expanding the definition of HER2-targetable disease significantly broadens the market for HER2-directed ADCs. This trial, though Phase II and single-arm, lays the groundwork for further development and potentially regulatory filings, offering a new hope for patients with a historically difficult-to-treat cancer. It also highlights the continued evolution of biomarker-driven therapy in oncology, a trend that is reshaping how we approach many solid tumors.

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