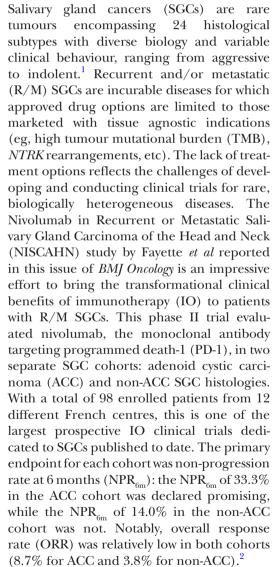
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Nivolumab in salivary gland cancers: confronting the challenges of unlocking the therapeutic benefits of immunotherapy for rare diseases

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Low ORRs (~0–15%) have historically been reported with systemic therapy in patients with R/M ACC.³⁻⁵ This includes recent IO trials using ORR as a primary endpoint with PD-1 inhibitor alone (pembrolizumab; ORR 3.4% in ACCs)⁶ or in combination with cytotoxic T-lymphocyte associated protein 4 (CTLA-4)

(nivolumab-ipilimumab; ORR 3.8% in ACCs). Considering poor correlation between response and overall survival (OS) in IO studies across solid cancers, the NPR_{6m} endpoint may possess greater clinical relevance as a surrogate for OS.8 However, the authors appropriately point out that using NPR_{6m} as a measure of nivolumab clinical activity in a single-arm study is challenging given the indolent natural history of some ACC tumours and lack of reliable historical benchmarks for SGC outcomes. The NISCAHN study adopted the alternative hypothesis of 40% NPR_{6m} for each cohort, which may be a conservative target for clinical benefit given that contemporary SGC trials have reported 6-month PFS rates ranging from 70% to 80%.2 4 5 Notably, we recently published a clinical trial of nivolumab plus the anti-CTLA4 antibody ipilimumab which used ORR as the primary endpoint and was declared negative for the ACC cohort (ORR 6.3%, median PFS 4.4 months), and positive for the non-ACC group (ORR 15.6%, median PFS 2.2 months). 9 Randomised trials would be the most rigorous evaluation of clinical benefit, though such designs would be difficult to justify for early, signal-finding phase II evaluations. As such, our view is that ORR remains a more reliable, though imperfect, efficacy endpoint for single-arm studies until better historical comparators for nonprogression or PFS are available from larger prospective studies.

The inclusion of non-ACC cohorts in clinical trials, as accomplished in NISCAHN, provides the invaluable opportunity to evaluate investigational approaches in SGCs beyond ACC.² The heterogeneity of SGC biology and tumour behaviour requires that the specific histologies enrolled to such cohorts be considered when interpreting



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study outcomes. In NISCAHN, the non-ACC cohort was enriched with adenocarcinoma not otherwise specified (NOS; 53.8%) and mucoepidermoid carcinoma (11.5%) histologies, while salivary duct carcinomas (SDCs) only accounted for 3.8% of cases. In contrast, SDCs was the most common histology enrolled to the non-ACC cohort of the nivolumab plus ipilimumab trial (38%), and appeared to be more susceptible to IO with an ORR of 25%. This clinical result potentially reflects the relatively higher TMB and immune cell infiltration natively present in SDCs compared with other SGC histologies, such as ACC. 100 process of the success of the succ

The NISCAHN investigators also evaluated baseline PD-L1 expression and tumour infiltrating lymphocytes, failing to find evidence that these are predictors of nivolumab benefit, consistent with past studies.^{2 9} While the overall rate of IO benefit in SGC trials appears to be low, the deep and durable tumour regressions that can be achieved among responders reflect the potential for dramatic benefit with these therapies, further incentivising the search for better clinical and/or biological predictors to discern which patients with SGC should receive these agents.

Just as importantly, the NISCAHN study outcomes highlight the pressing need for more clinical trials investigating novel IO agents and strategies to augment and broaden IO benefit to more patients with SGC. Combination approaches have and continue to be explored in patients with SGC, including combining immune checkpoint blockade with radiation therapy, ¹¹ 12 multitargeted kinase inhibitors, ¹³ ¹⁴ histone deacetylase inhibitors ¹⁵ or chemotherapy (NCT03360890 and NCT04895735). In parallel, efforts should be made to collect and analyse trial biospecimens and develop faithful laboratory models to formulate stronger biologic rationales that will aid in identifying opportunities for drug development tailored to SGC biological profiles. The success of the NISCAHN trial illustrates what can be accomplished with a focused commitment and dedication to developmental therapeutics for rare cancer patients, and provides optimism that a multipronged scientific and clinical effort will yield discoveries that meaningfully improve the outcomes of patients with SGCs.

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