Salivary gland cancers (SGCs) are rare tumours encompassing 24 histological subtypes with diverse biology and variable clinical behaviour, ranging from aggressive to indolent. \(^1\) Recurrent and/or metastatic (R/M) SGCs are incurable diseases for which approved drug options are limited to those marketed with tissue agnostic indications (eg, high tumour mutational burden (TMB), NTRK rearrangements, etc). The lack of treatment options reflects the challenges of developing and conducting clinical trials for rare, biologically heterogeneous diseases. The Nivolumab in Recurrent or Metastatic Salivary Gland Carcinoma of the Head and Neck (NISCAHN) study by Fayette et al reported in this issue of BMJ Oncology is an impressive effort to bring the transformational clinical benefits of immunotherapy (IO) to patients with R/M SGCs. This phase II trial evaluated nivolumab, the monoclonal antibody targeting programmed death-l (PD-1), in two separate SGC cohorts: adenoid cystic carcinoma (ACC) and non-ACC SGC histologies. With a total of 98 enrolled patients from 12 different French centres, this is one of the largest prospective IO clinical trials dedicated to SGCs published to date. The primary endpoint for each cohort was non-progression rate at 6 months (NPR\(_{6m}\)); the NPR\(_{6m}\) of 33.3% in the ACC cohort was declared promising, while the NPR\(_{6m}\) of 14.0% in the non-ACC cohort was not. Notably, overall response rate (ORR) was relatively low in both cohorts (8.7% for ACC and 3.8% for non-ACC). \(^2\)

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) inhibition (nivolumab-ipilimumab; ORR 3.8% in ACCs). \(^7\) Considering poor correlation between response and overall survival (OS) in IO studies across solid cancers, \(^8\) the NPR\(_{6m}\) endpoint may possess greater clinical relevance as a surrogate for OS. \(^9\) 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 non-progression 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...
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.

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. 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, multtargeted kinase inhibitors, histone deacetylase inhibitors or chemotherapy (NCT0360890 and NCT04897535). 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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