Elraglusib, a Glycogen Synthase Kinase 3β Inhibitor, plus Chemotherapy with or without Immunotherapy in Patients with Recurrent, Metastatic Salivary Gland Carcinoma

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ABSTRACT

Purpose: Glycogen synthase kinase 3β (GSK-3β) is a known therapeutic target in cancer. Aberrant nuclear GSK-3β (nGSK-3β) expression has been shown in some salivary gland cancers. Elraglusib is a small-molecule GSK-3β inhibitor with immunomodulatory potential. We hypothesized that elraglusib plus platinum-based chemotherapy and immunotherapy priming would be a novel treatment approach for salivary gland cancer.

Patients and Methods: This phase II, open-label trial enrolled patients with recurrent or metastatic salivary gland cancer [adenoid cystic carcinoma (ACC) vs. other subtypes] with disease progression in the preceding year. Cohort 1 received elraglusib (15 mg/kg i.v. on days 1 and 4) plus carboplatin (AUC = 5) or cisplatin (75 mg/m^2) every 21 days. Cohort 2 received two cycles of pembrolizumab (200 mg i.v.) every 21 days prior to the same regimen. The primary endpoint included best overall response rate (ORR) by RECIST v1.1 (>5/32 in response to detect 25% ORR).

Results: Thirty-two patients were enrolled, including 15 (47%) with ACC and 17 (53%) with non-ACC. The best ORR was 9.4% [3/32; 95% confidence interval (CI), 2–25; three partial responses, all non-ACC]. Nineteen (59%) patients achieved stable disease. The median duration of response was 6.9 months. Common treatment-related adverse events were anemia (22, 69%), nausea (16, 50%), and neutropenia (14, 44%). At the median follow-up of 18.3 months, the median progression-free survival was 6.4 months (95% CI, 2.3–8.8), and the median overall survival was 18.6 months (95% CI, 9.7–29.4) overall. The median nGSK-3β expression was 50% versus 2% for responders versus nonresponders.

Conclusions: The trial did not meet its primary endpoint, although 18% of patients with non-ACC treated with immune priming followed by cisplatin plus elraglusib achieved a response. Higher nGSK-3β expression was observed in tumor samples obtained from responders.

Introduction

Salivary gland carcinoma is a rare, but histologically and molecularly rich, group of head and neck cancers that are initially managed with curative-intent surgery and adjuvant radiation (1, 2). Despite aggressive locoregional management, recurrence and/or distant spread is not infrequent, particularly among certain high-risk subtypes such as salivary duct carcinoma, high-grade mucoepidermoid carcinoma, and carcinoma ex pleomorphic adenoma. Although not typically high-grade, adenoid cystic carcinoma (ACC) is another subtype with a propensity for perineural invasion and resulting distant metastatic potential, although often yielding a more indolent growth pattern.

Despite decades of research, there are no approved systemic cytotoxic or targeted therapies available for the treatment of advanced salivary gland cancer broadly. Although some treatments have shown modest activity and seem to benefit certain molecular subgroups, such as HER2-overexpressing and androgen receptor (AR)–overexpressing (3, 4) or *NTRK* gene fused tumors (5), most lack actionable therapeutic targets. Cytotoxic chemotherapy agents, including anthracyclines, platinum, and vinorelbine in some combination, may have benefit in a small number of patients (6–8); however, no preferred regimen has been defined, and toxicity remains a concern. Chemotherapy regimens used in salivary gland cancer often combine platinum with a taxane, vinorelbine, or together with doxorubicin and cyclophosphamide (6–8). Furthermore, owing to the scarce immunogenic potential of most salivary gland cancers (9), immunotherapy has shown limited benefit to date. Studies exploring PD-1 blockade have largely been disappointing with low response rates even among patients with PD-L1–positive tumors (10–12). Although tumor genomic profiling data have identified few driver mutations and low somatic mutational burden in ACC, multitargeted VEGFR tyrosine kinase inhibitors demonstrate some antitumor activity (13–16). Taken together, exploring new treatment options and novel therapeutic combinations represents a significant priority in salivary gland cancer.

Glycogen synthase kinase 3β (GSK-3β), a serine/threonine kinase, is a critical member of the NF-κB, Wnt/β-catenin, c-myc, Notch,

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Translational Relevance

There are no approved or preferred systemic therapies to treat advanced, incurable or metastatic salivary gland cancers. Elraglusib (9-ING-41) is a potent, small-molecule glycogen synthase kinase 3β inhibitor with immune-modifying properties that disrupts multiple cellular signaling pathways in cancer cells, leading to inhibition of tumor growth and increased sensitivity to antitumor therapies. This phase II clinical trial evaluated the use of platinum-based chemotherapy plus elraglusib in patients with advanced, metastatic salivary gland cancers (both adenoid cystic carcinoma and other subtypes) and included a cohort treated with sequential, immune checkpoint blockade priming. Some objective clinical responses were observed in elraglusib/cisplatin-treated patients with non–adenoid cystic carcinoma histologic subtypes. Aberrant nuclear glycogen synthase kinase 3β expression was observed in tumor samples obtained from responders.

and other signaling pathways (17, 18). Active GSK-3β has been shown to promote tumor growth and NF-κB–mediated resistance to chemotherapy in various types of cancer (19–22). GSK-3β activity is often elevated in platinum-resistant cancer cells, in which it contributes to cell survival by activating pathways that protect against DNA damage (23, 24). Aberrant nuclear accumulation and overexpression of GSK-3β have recently been demonstrated in some salivary gland cancers, namely, ACC (25). Elraglusib (9-ING-41) is a potent, ATP-competitive small-molecule inhibitor of GSK-3β. Beyond its proposed role in overcoming chemoresistance, elraglusib has also been shown to be immunomodulatory. Anti–PD-1 priming followed by GSK-3β inhibition seems to enhance the cytolytic potential of $CD8^+$ T cells, leading to changes in migratory machinery (26).

Given these preclinical findings, we initially hypothesized that combining elraglusib with platinum-based chemotherapy would mitigate chemoresistance. Based on further emerging data, we later added immune priming with upfront anti–PD-1 therapy, as a novel sequential treatment approach to explore in advanced salivary gland cancer.

Patients and Methods

Study oversight

The study protocol (see Supplementary Appendix) was approved by the Institutional Review Board at Dana-Farber Cancer Institute (DF/HCC No. 21-384), and the trial is registered with ClinicalTrials.gov (NCT05010629). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent. Study funding and elraglusib were provided by Actuate Therapeutics, Inc.

Study participants

Patients 18 years or older were eligible if they had advanced unresectable, recurrent, or metastatic salivary gland cancer of any histologic subtype, with at least one site of measurable disease by RECIST v1.1 (27), an Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate organ and marrow function. Sex or gender was captured. Patients were required to have documented clinical or radiographic progressive disease (PD) within 12 months of study registration. Any number of lines of prior systemic therapy for advanced disease was permitted, including prior chemotherapy. Patients with stable or treated central nervous system disease were eligible. Patients with significant autoimmune conditions or those requiring corticosteroids at a dose of 20-mg prednisone daily or equivalent were excluded from the immunotherapy-containing cohort.

Study design and treatment

This single-arm, single-center, nonrandomized, parallel cohort, open-label phase II clinical trial enrolled patients at the Dana-Farber Cancer Institute (Boston, Massachusetts). Following informed consent, patients were first allocated to cohort 1 and received elraglusib (15 mg/kg i.v. on days 1 and 4) plus either carboplatin (AUC = 5 i.v. on day 1) or cisplatin (75 mg/m^2 i.v. on day 1) for each 21-day cycle until the occurrence of disease progression, unacceptable toxicity, withdrawal of consent, or up to 2 years. Platinum agent dosing and schedules were chosen to balance potential benefit with the risk of toxicity with higher dosing when combined with investigational treatment. Patients were enrolled in cohort 1 to two parallel groups, one for patients with ACC tumor histology and another for non-ACC subtypes. Attrition was monitored as part of the study.

The choice of either platinum agent was at the discretion of the treating investigator, accounting for patient age, preexisting medical conditions, and health fitness. Changing from cisplatin to carboplatin was allowed. Prespecified dose adjustments were permitted: up to two dose-reduced levels for both elraglusib (12.4 and 9.3 mg/kg) and for platinum agents (carboplatin: AUC = 4 and 3; cisplatin: 56.25 and 37.5 mg/m^2). Study medications interrupted for more than 12 weeks consecutively could not be reintroduced. Patients who discontinued one of the study drugs for any reason besides disease progression were allowed to continue the other at the discretion of the treating investigator. Patients received standard premedications before platinum therapy that included antiemetics (dexamethasone, 5-HT_3 receptor antagonist, and neurokinin inhibitor), intravenous hydration and electrolyte replacement, and posttreatment G-CSF support after each cycle of chemotherapy if deemed appropriate. Palliative radiation to nontarget lesions was permitted for symptomatic needs.

Following the completion of cohort 1, patients were then sequentially allocated to cohort 2 receiving initial priming with two cycles of single-agent pembrolizumab (200 mg i.v.) every 21 days. Thereafter, they stopped immunotherapy and started the same regimen of elraglusib plus platinum therapy outlined above for cohort 1. Similarly, patients were enrolled in cohort 2 to two parallel groups, separating patients with ACC from those with non-ACC tumors.

Assessments

Routine laboratory assessments were performed with each treatment cycle. Patients underwent imaging assessments (contrast-enhanced CT or MRI of the neck; with CT of the chest, abdomen, and pelvis) at baseline and every 9 weeks or three cycles while on treatment. Following treatment discontinuation, patients were followed every 3 months up to 3 years from trial registration for resolution of toxicity and to document survival.

Adverse events (AE) to assess the safety and side effect profile of treatment were recorded using Common Terminology Criteria for Adverse Events version 5.0. Any grade 4 AE (except for short-term

electrolyte disturbances or cytopenia) and immune-mediated AE were considered unacceptable toxicity, warranting discontinuation of the respective study drug(s). AE were captured up to 30 days after discontinuation of study drugs.

Statistical design

The primary endpoint was best overall response rate (ORR) as determined by RECIST v1.1. A one-stage design was used. When >5 of 32 patients (among cohorts 1 and 2 combined) who were eligible and began protocol treatment had disease in response, there was 84.7% power to rule out a 10% ORR and detect a 25% response rate (using a one-sided exact binomial test, with a type I error rate of 9.4%). Effort was made to enroll equal numbers of patients with ACC and non-ACC in each of the two cohorts. A response rate of 25% was targeted based on published experience with platinum-containing agents and immunotherapy available at the time of trial inception (28) and the desired threshold for response in this disease setting across heterogeneous subpopulations. Secondary endpoints included evaluation of the safety and tolerability of the combination, progression-free survival (PFS) and overall survival (OS), duration of therapeutic response, molecular and immunologic parameters, and quality of life metrics.

The primary efficacy–evaluable population included all eligible patients who began protocol treatment. The response rate was summarized as a proportion with a corresponding exact 95% confidence interval (CI). The distribution of PFS and OS was estimated using the Kaplan–Meier method. Logistic regression and Cox proportional hazard models were used to estimate OR for response and HR for survival, respectively. Two-sided *P* values are reported, if applicable. Data as of March 11, 2025, were analyzed using R (v4.4.0) and GraphPad Prism v10 (RRID: SCR_002798).

Correlatives

Exploratory objectives aimed to correlate clinicopathologic, tumor molecular, and immunologic profiling data with response and outcomes. Next-generation tumor sequencing data, PD-L1 scores, HER2 and AR receptor status, and GSK-3β cytoplasmic and nuclear expression were collected. Formalin-fixed, paraffin-embedded tumor samples acquired before treatment were submitted for targeted next-generation sequencing with either the FoundationOne CDx or Caris Molecular Intelligence profile. PD-L1 combined positive score (CPS) was assessed by means of IHC with the use of either the 22C3 or E1L3N clone. IHC for HER2 and AR testing was performed using 4B5 (Ventana) and AR441 (Agilent Dako) clones, respectively. IHC staining for GSK-3β was performed on pretreatment formalin-fixed, paraffin-embedded tumor specimens using the anti–GSK-3β antibody (Cell Signaling Technology; cat. No. 9315, RRID: AB_490890) on the Leica Bond RX platform (Leica Biosystems) and scored (by A. Ugolkov, blinded to clinical outcome data) for GSK-3β cytoplasmic and nuclear expression in cancer cells quantified by percentage.

Results

Administrative summary

Between September 2021 and April 2024, 32 patients enrolled in the trial. All 32 patients began protocol treatment and are included in the analyses (Supplementary Fig. S1).

Study participants

The median age was 65 years (range, 37–85), with most identifying as female at birth (20, 63%; **Table 1**; Supplementary Table S1). Most patients had a primary site of disease arising in the major or minor salivary glands (24, 75%) with the remaining eight (25%) having a primary disease site outside the head and neck; 21 (66%) had distant metastatic disease, and four (13%) had locoregionally recurrent or persistent disease (seven, 22% had both). Fifteen (47%) patients had ACC, and the remaining 17 (53%) had other salivary gland cancer subtypes—including adenocarcinoma (six, 19%), mucoepidermoid carcinoma (five, 16%), acinic cell carcinoma (three, 9%), myoepithelial carcinoma (two, 6%), and carcinoma ex pleomorphic adenoma (one, 3%). Ten (31%) had no prior systemic treatment for recurrent or metastatic disease, but 18 (56%) had received two or more lines of prior therapy.

Response and efficacy

Among 32 evaluable patients, the best ORR was 9.4% (95% CI, 2–25) with three partial responses (PR; **Fig. 1A–C**). An additional 18 (56%) patients achieved stable disease, whereas 10 (31%) experienced PD. All three responders had non-ACC histology, were in the pembrolizumab priming cohort, and received cisplatin with elraglusib. The median time to response was 4.4 months (range, 4.2–9.4), and the median duration of response was 6.9 months (range, 2.2–7.3) with all three responders off-treatment at last follow-up (one after completing >1 year of therapy). No independent clinical or molecular features were statistically significantly associated with response to therapy (Supplementary Table S2).

The primary reason for treatment discontinuation was PD (20, 63%), with two (6%) experiencing unacceptable toxicity (Supplementary Table S3). Patients received a median number of six cycles of treatment (range, <1–18) and remained on study treatment for a median of 3.8 months (range, <1–15.1). The primary reason for coming off study among 21 patients (11 remained on study as of data pull date) was death (19, 91%), with no patients lost to follow-up.

Safety and tolerability

Among all patients, 23 (72%) experienced a grade 3 to 5 AE regardless of treatment attribution. **Table 2** describes the treatment-related AE (TRAE) experienced by >10% of the study cohort or any grade 3 to 5 event. Two (6%) patients had toxicity as the reason for study drug discontinuation (attributable to an infusion-related reaction and peripheral neuropathy), but no treatment-related deaths occurred. The most common TRAE included anemia (22, 69%), nausea (16, 50%), and decreased neutrophil count (14, 44%). Eighteen (56%) patients experienced (at worst) grade 3 TRAE, most commonly anemia (6, 19%) and neutropenia (4, 13%), whereas one (3%) experienced a grade 4 TRAE (neutropenia). Five of 16 (31%) patients in cohort 2 experienced immune-related AE, which included a single patient each with grade 3 pneumonitis and grade 3 hepatitis.

Survival outcomes

At a median follow-up of 18.3 months (range, 2.9–38.0), the median PFS was 6.4 months (95% CI, 2.3–8.8) with 24 (75%) patients experiencing a progression event including three with clinical evidence of PD (**Fig. 2A** and **B**); the 12-month estimated PFS was 26.6% (95% CI, 11.8–44.1). The median OS was 18.6 months (95% CI, 9.7–29.4) for the entire cohort. Nineteen (59%) patients had died at last follow-up (**Fig. 2C** and **D**). The 12- and 24-month estimated OS was 58.1% (95% CI, 39.0–73.1) and 39.7% (95% CI, 20.8–58.1), respectively. No independent clinical or molecular features were statistically significantly associated with OS (Supplementary Table S4). The median PFS was numerically greater for cohort 2 versus 1 and similar among non-ACC versus ACC groups (7.3 vs. 4.3 and 6.6 vs. 4.3 months,

Table 1. Baseline patient characteristics.

Characteristic	Total population (%)[a], *N* = 32	Cohort 1[b], number of patients (%)[a], *N* = 16	Cohort 2[b], number of patients (%)[a], *N* = 16
Age, years (median)	65 (37–85)	65 (37–85)	65 (44–77)
Gender			
Male	12 (37)	3 (19)	9 (56)
Female	20 (63)	13 (81)	7 (44)
Race[c]			
White	27 (84)	15 (94)	12 (75)
Black or African American	2 (6)	1 (6)	1 (6)
Asian	1 (3)	0	1 (6)
American Indian	1 (3)	0	1 (6)
Other	1 (3)	0	1 (6)
Ethnicity[c]			
Non-Hispanic	31 (97)	16 (100)	15 (94)
Hispanic	1 (3)	0	1 (6)
ECOG performance status			
0	13 (41)	7 (44)	6 (37)
1	19 (59)	9 (56)	10 (63)
Primary site of disease			
Major salivary gland (parotid, submandibular, and sublingual)	14 (44)	6 (37)	8 (50)
Minor salivary gland	10 (31)	4 (25)	6 (37)
Glands outside the head and neck	8 (25)	6 (37)	2 (13)
Histology			
ACC	15 (47)	9 (56)	6 (38)
Adenocarcinoma	6 (19)	2 (13)	4 (25)
Mucoepidermoid carcinoma	5 (16)	4 (25)	1 (6)
Acinic cell carcinoma	3 (9)	0	3 (19)
Myoepithelial carcinoma	2 (6)	0	2 (13)
Carcinoma ex pleomorphic adenoma	1 (3)	1 (6)	0
Lines of prior systemic therapy for recurrent or metastatic disease			
0	10 (31)	3 (19)	7 (44)
1	4 (13)	2 (13)	2 (13)
2	11 (34)	6 (37)	5 (31)
3 or more	7 (22)	5 (31)	2 (13)
Site(s) of recurrent or metastatic disease			
Local and/or regional	4 (13)	1 (6)	3 (19)
Distant	21 (66)	13 (81)	8 (50)
Both	7 (22)	2 (13)	5 (31)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Values are numbers and percentages, except age, showing range in parentheses.
[b]Cohort 2 patients received two cycles of lead-in pembrolizumab before platinum plus elraglusib treatment.
[c]As classified by the participant.

respectively). The median OS was numerically greater among non-ACC versus ACC groups (27.8 vs. 15.3 months, respectively).

Molecular and immunologic predictors

The median nuclear (n)GSK-3β expression was 5% (range, 0–100) for the subset of all patients (28, 88%) with available tissue for testing, with a median of 50% (range, 20–80) among the three responders and 2% (range, 0–100) among nonresponders (**Fig. 3A–C**). For the patients with nGSK-3β expression above the total median percentage of expression ($N = 9$) versus equal or lower expression, the median PFS was 8.5 (95% CI, 1.9–NA) versus 4.2 months (95% CI, 1.8–12.5), respectively, and the median OS was numerically longer (not reached vs. 18.6 months, respectively).

Tumor PD-L1 status (tumor proportion score or CPS) was known for 27/32 (84%) patients (**Fig. 4A** and **B**). Most (24, 89%) were PD-L1 negative (<1%), whereas three (11%) were positive at a CPS of 1 or greater (two with ACC; one non-ACC). All three responders had tumor PD-L1 scores of <1. The median tumor mutational burden was three mutations/megabase (range, 0–12.2) for the non-ACC subgroup and 1.3 mutations/megabase (range, 0–5) for the ACC subgroup. Among the three patients with baseline molecular profiling results showing *CDKN2A/B* and *MTAP* co-deletion, two were patients with non-ACC who achieved a response (**Fig. 4C** and **D**).

Discussion

This parallel cohort, phase II clinical trial investigated the role of sequential treatment for advanced salivary gland cancer by incorporating immune priming followed by co-administration of

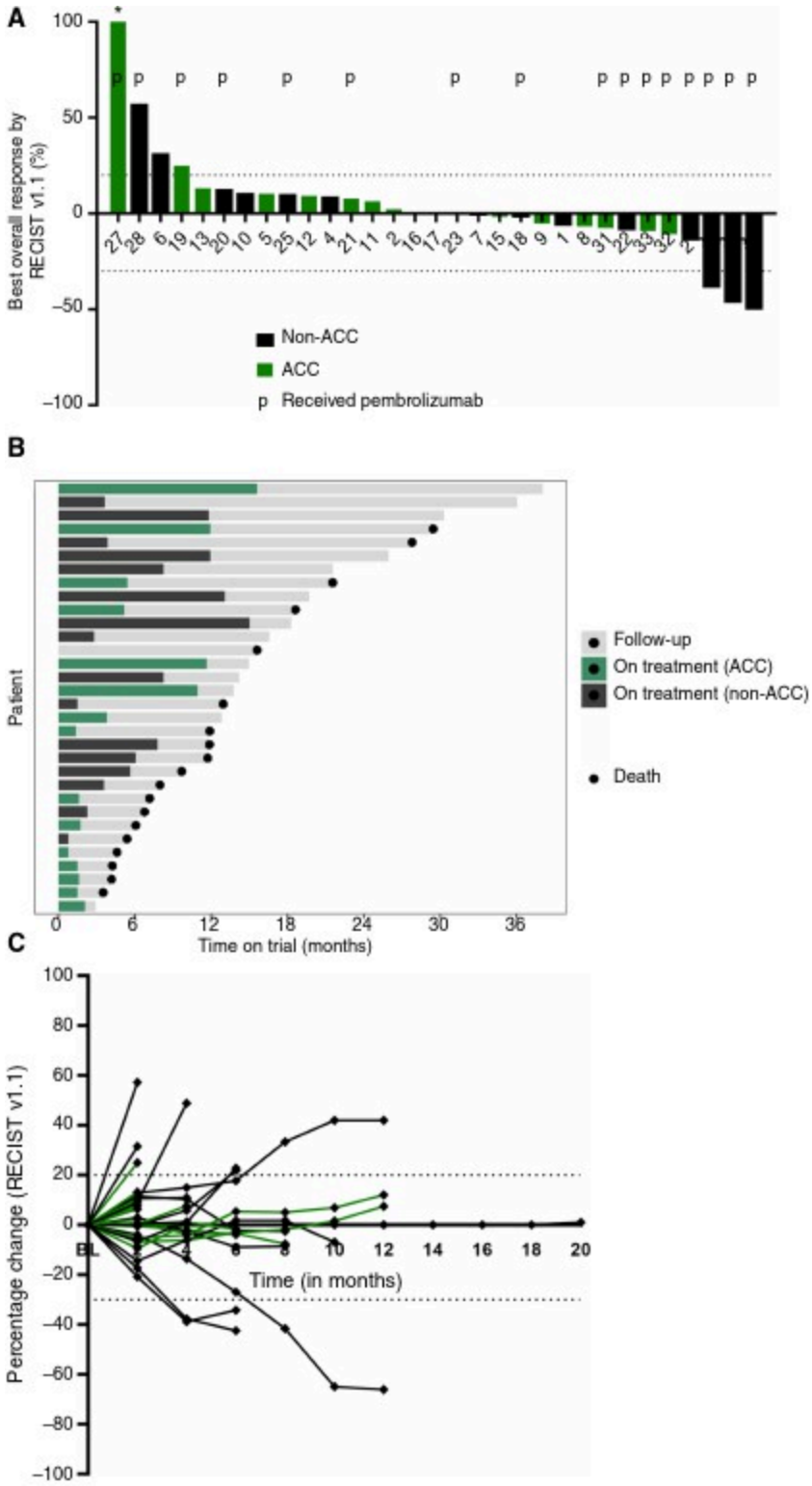

Figure 1.

A, Waterfall plot depicting nadir sum of diameters (RECIST v1.1) from study treatment. Each column represents an individual patient. (*) denotes evidence of clinical progression of disease as best overall response. "p" identifies patients in cohort 2 treated with pembrolizumab. $N = 31$, as one patient was unevaluable. Dotted lines mark the RECIST v1.1 thresholds for response and progression. **B,** Swimmer plot showing time on study treatments and follow-up period; each row represents an individual patient. Salivary cancer groups (ACC vs. non-ACC) are color-coded. **C,** Spider plot showing the percentage change (RECIST v1.1) in tumor measurements over time; each line represents an individual patient. Dotted lines mark the RECIST v1.1 thresholds for response and progression. Salivary cancer groups (ACC vs. non-ACC) are color-coded.

platinum chemotherapy with a novel targeted agent in a rare cancer type with high unmet clinical need. The primary endpoint was not met in the total study population, although we observed an ORR of 18% (three of 17) among the patients with non-ACC treated with immune priming followed by cisplatin plus elraglusib, and three of eight patients who received cisplatin with elraglusib responded.

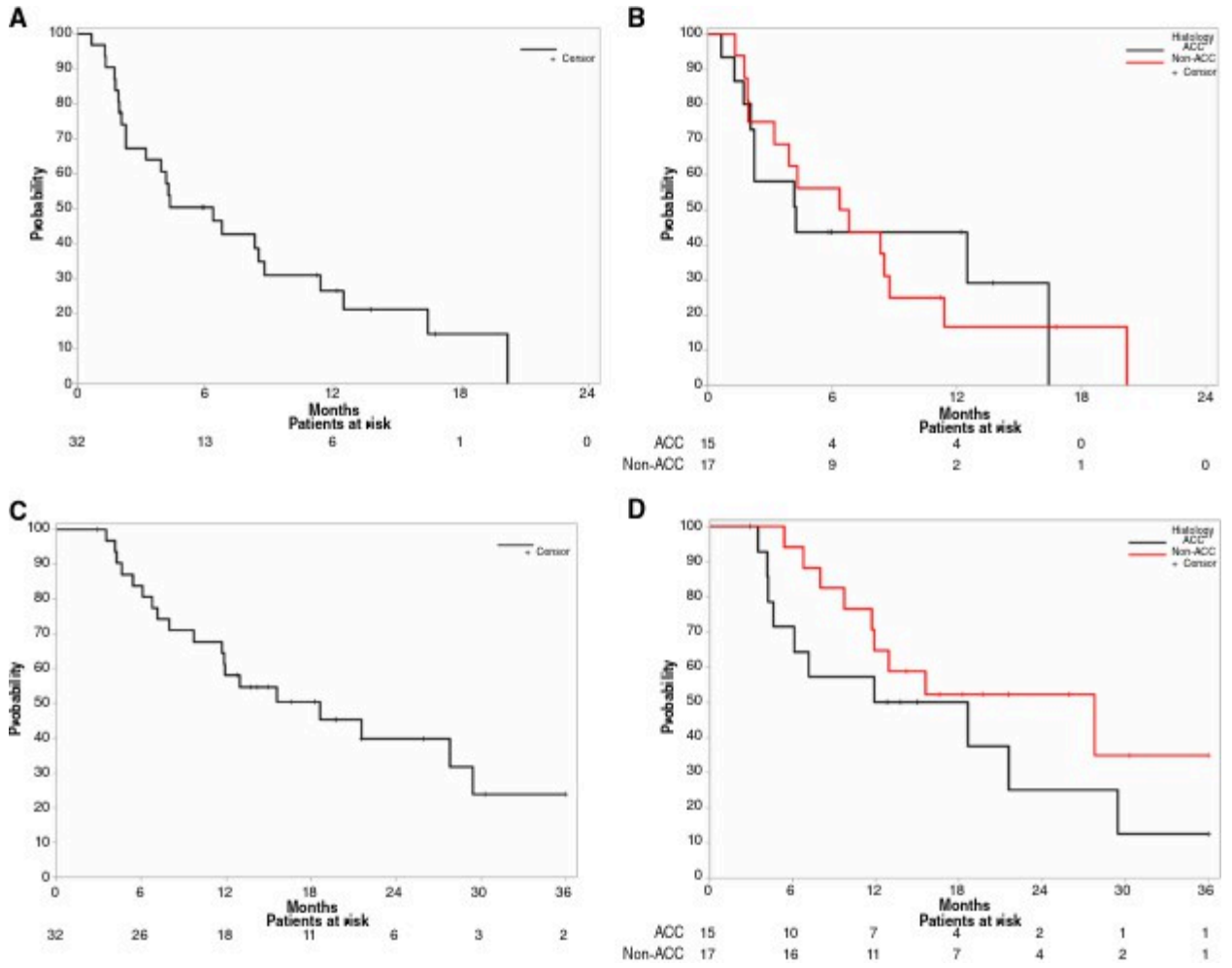

Figure 2.

Kaplan–Meier survival curves plotting the probability of PFS (**A**) among the entire cohort and (**B**) separated by salivary cancer subgroups (ACC vs. non-ACC histology). OS (**C**) among the entire cohort and (**D**) separated by salivary cancer subgroups (ACC vs. non-ACC histology).

Correlative analyses suggested that those few patients with relatively high nGSK-3β expression at baseline responded to treatment. These subgroup findings are, however, exploratory and hypothesis-generating, rather than confirmatory.

In the management of salivary gland cancer, cytotoxic chemotherapy is generally reserved for palliation of advanced disease that is not amenable to local therapies such as surgery and/or radiation. Few studies have prospectively explored the use of chemotherapy in this rare group of histologically diverse and heterogeneous tumors. Outside of clinical trials, many experts use cisplatin with vinorelbine or cisplatin and anthracycline-based combinations based on historical data citing response rates in small cohorts approaching 30% (6, 8, 29–31), but there is no evidence to support single-agent versus combinatorial chemotherapy in this disease. The current trial used carboplatin for its seemingly better tolerance in most participants (72%), but responses were limited to patients with non-ACC (two with acinic cell carcinoma and one adenocarcinoma) receiving cisplatin with elraglusib—despite prior studies reporting cisplatin activity in advanced ACC. Furthermore, all three responders had received 0 to 1 prior lines of systemic therapy in the metastatic setting. The response rate observed in this trial was limited despite the use of sequential, multimodal systemic treatment, and a few (three of eight) patients treated with elraglusib/cisplatin achieved response.

GSK-3, a serine/threonine protein kinase, is an essential positive regulator of NF-κB transcriptional activity and is associated with survival and chemoresistance in cancer cells (22, 32, 33). nGSK-3β plays an important role in regulating histone modifications, which may contribute to NF-κB p65/p50 binding to gene promoters and activating its target genes *Bcl-2* and *XIAP* to promote cancer cell survival (22, 34, 35). In the phase I study of elraglusib exploring monotherapy and chemotherapy in combination, common single-agent toxicity was transient visual change and fatigue, and two patients (with melanoma and acute T-cell leukemia/lymphoma) experienced a response to monotherapy (36). It has been demonstrated that inhibition of GSK-3 activity leads to depletion of nGSK-3β and suppression of NF-κB transcriptional activity, which results in cancer cell death via apoptosis, particularly when used in combination with chemotherapeutic agents in tumors exhibiting

Table 2. TRAE

Event term	Number of patients (%), *N* = 32			
Grade 3–5 AE regardless of attribution	23 (72%)			
AE leading to treatment discontinuation	2 (6%)			
TRAE leading to death	0			
TRAE with a frequency of >10% or any grade 3–5	All	Grade 3	Grade 4	Grade 5
Anemia	22 (69)	6 (19)	0	0
Nausea	16 (50)	1 (3)	0	0
Decreased neutrophil count	14 (44)	4 (13)	1 (3)	0
Temporary color vision changes	13 (41)	0	0	0
Fatigue	13 (41)	0	0	0
Decreased platelet count	13 (41)	1 (3)	0	0
Infusion-related reaction	12 (38)	2 (6)	0	0
Elevated aspartate aminotransferase	8 (25)	1 (3)	0	0
Decreased white blood cell count	5 (16)	1 (3)	0	0
Elevated alkaline phosphatase	5 (16)	0	0	0
Dysgeusia	4 (13)	0	0	0
Vomiting	4 (13)	0	0	0
Elevated creatinine	4 (13)	0	0	0
Hyponatremia	4 (13)	0	0	0
Elevated alanine aminotransferase	3 (9)	1 (3)	0	0
Hypomagnesemia	3 (9)	1 (3)	0	0
Dyspnea	2 (6)	1 (3)	0	0
Febrile neutropenia, sepsis	1 (3)	1 (3)	0	0
Atrial fibrillation or flutter	1 (3)	1 (3)	0	0
Dysphagia	1 (3)	1 (3)	0	0
Acute colitis	1 (3)	1 (3)	0	0
Elevated serum lipase	1 (3)	1 (3)	0	0
Elevated blood glucose	1 (3)	1 (3)	0	0
Elevated uric acid	1 (3)	1 (3)	0	0
Generalized muscle weakness	1 (3)	1 (3)	0	0
Pneumonitis	1 (3)	1 (3)	0	0
Worst degree[a]	31 (97)	18 (56)	1 (3)	0

[a]Worst grade toxicity experienced by a given patient.

chemoresistance (22). Exploratory preclinical studies have shown moderate nGSK-3β expression in some malignant salivary neoplasms as compared with benign tissue (18), whereas higher p-GSK-3 protein expression has been observed in the more indolent subtype of ACC (37). In the present trial, nGSK-3β expression was overall modest across salivary gland cancer subtypes, with only 29% (8/28) of tumors tested showing >10% expression, but median nGSK-3β expression was relatively high among the

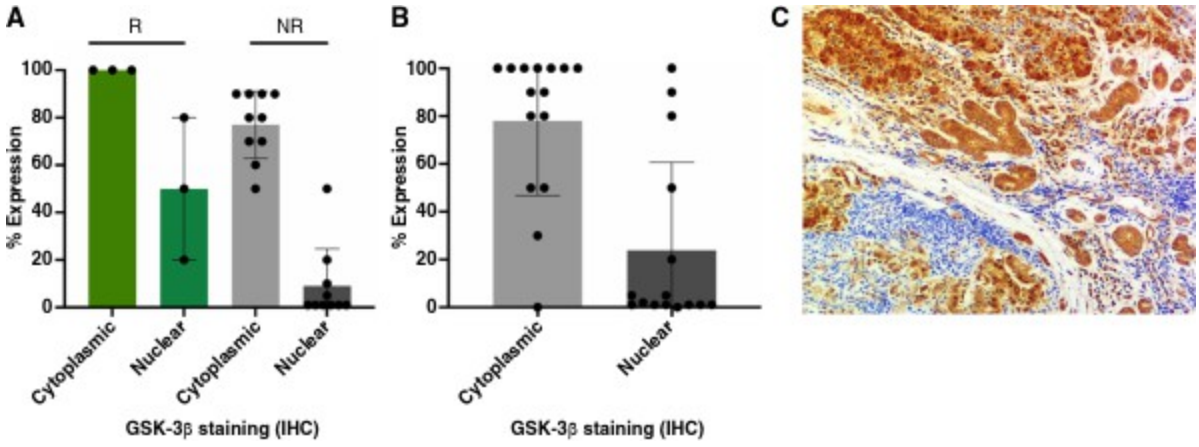

Figure 3.

Cytoplasmic GSK-3β and nGSK-3β expression (percentage of cancer cells) among the (**A**) non-ACC subgroup arranged by responders (R) and nonresponders (NR) and (**B**) for the entire ACC subgroup. **C,** nGSK-3β expression in cancer cells in patient ID No. 29, a responder (original magnification, 50×).

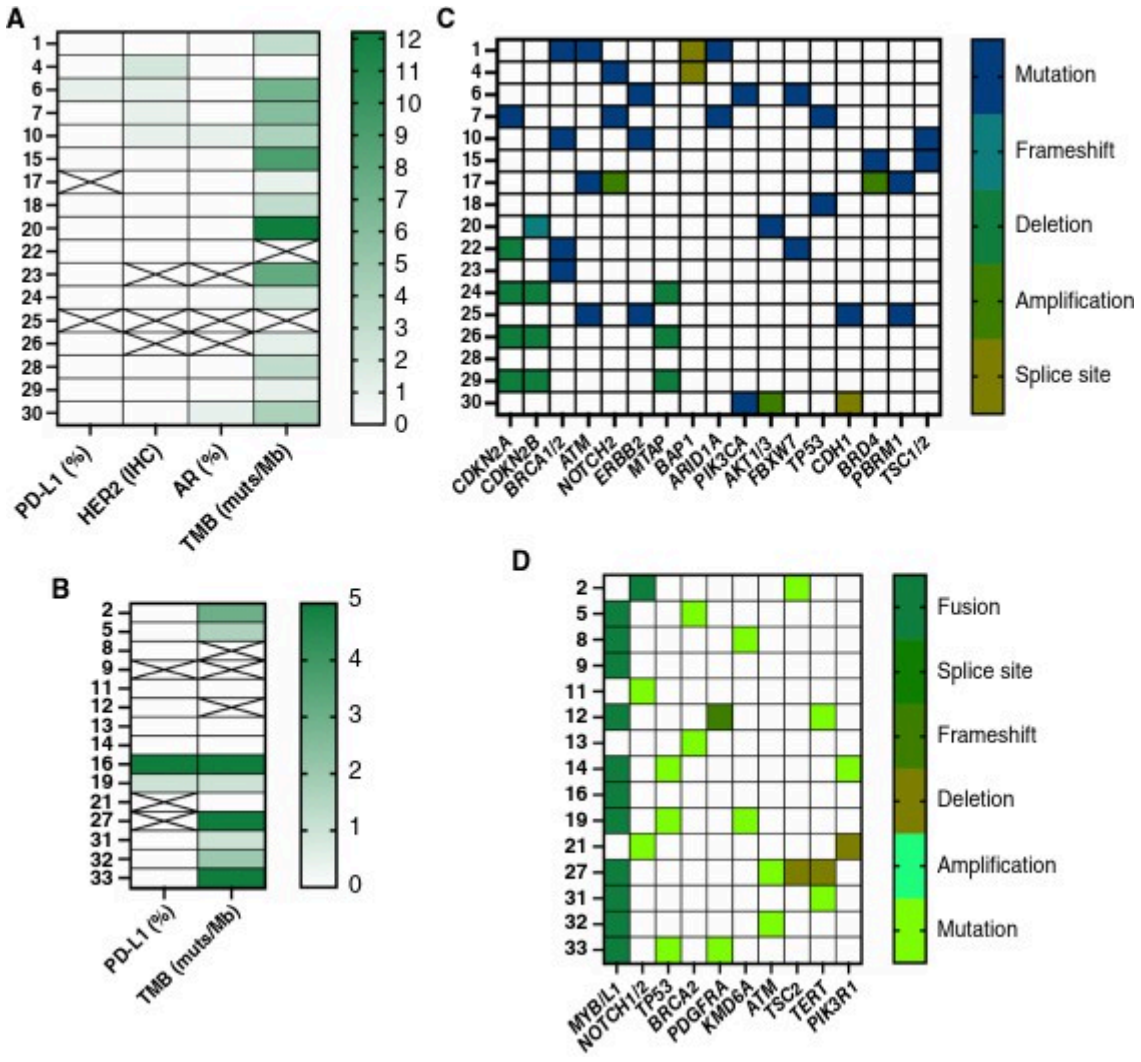

Figure 4.

Pretreatment or baseline tumor mutational burden [TMB, mutations/megabase (muts/Mb)], PD-L1 scores (tumor proportion score or CPS), and AR and HER2 expression testing results arranged in a heatmap and grouped among patients with (**A**) non-ACC and (**B**) ACC. Each row represents an individual patient. The legend reflects higher numerical scores, reflecting darker shading. An "X" in an individual box indicates that the data point was not available. Tumor mutational profiling results displayed in a heatmap and groups among patients with (**C**) non-ACC and (**D**) ACC. Each row represents an individual patient. The legend reflects color coding to indicate the type of mutation event observed.

three responders. However, it is not clear whether the combination of cisplatin plus elraglusib affected response in this scenario, given the reported single-agent activity of cisplatin in this trial and in historical series. However, it is worth noting that two responders continued elraglusib alone after discontinuing cisplatin for peripheral neuropathy, and response durability was maintained for several months. Collectively, tolerability was quite favorable across the study, with some patients remaining on combinatorial therapy for more than a year. Minimal additive toxicity was observed with the addition of elraglusib which is known to primarily cause transient color vision changes that improve with subsequent dosing.

The combination of elraglusib and gemcitabine/nab-paclitaxel (GnP) has been evaluated as the first-line therapy for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC), and the top-line data demonstrated statistically significant and clinically meaningful improvements in median and 1-year survival in patients treated with elraglusib/GnP compared with GnP alone in an ongoing randomized 1801 part 3B phase II trial (38). In the patients with mPDAC treated with elraglusib/GnP, grade 3 to 4 treatment-induced neutropenia significantly correlated with better survival, whereas grade 4 neutropenia significantly correlated with objective clinical response (39, 40). Among the five patients in our study who developed grade 3+ neutropenia, OS ranged from 11.9 to 38.0 months. Neutropenia was rarely observed in patients with cancer (3%) treated in a phase I study with elraglusib monotherapy (36). Chemotherapeutic drugs can target myeloid progenitor cells leading to neutropenia and a decreased number of myeloid-derived suppressor cells (MDSC) in tumors. MDSC potently suppress T-cell activity and thus contribute to the immune escape of malignant tumors and confer resistance to immune checkpoint inhibitors. Thus, chemotherapy-induced depletion of MDSC can potentially

lead to an increased elraglusib-driven antitumor immune response and improve immune checkpoint inhibitor antitumor effect.

In an effort to explore sequential and combinatorial therapy in the present trial, the second cohort received two doses of immunotherapy before the start of platinum plus elraglusib. A growing literature suggests a multifactorial role for GSK-3β in the tumor immune microenvironment. Specifically, inhibition of GSK-3β has been shown to enhance co-stimulation during antigen presentation, regulate the PD-1/L1 axis in cancer cells interacting with effector T cells, and affect $CD4^+$ Th17 polarization (41). Treatment with elraglusib may lead to an increased antigen presentation through upregulation of MHC-I, downregulation of immune checkpoints such as PD-1, LAG-3 and TIGIT, and increased expansion and infiltration of NK and cytotoxic T cells into tumor (42). In the ongoing randomized phase II study (1801 part 3B), immunophenotyping of paired (pre- and postdose) mPDAC samples demonstrated that the percentage of $CD8^+$ and granzyme B+ cells was significantly increased in postdose tumor samples obtained from elraglusib/GnP-treated patients but not in GnP-treated patients (38). In mPDAC, IL-6 and IL-8 cytokine and soluble receptor expression correlated with survival among patients treated with elraglusib/GnP (43). Sequentially treating with 6 weeks (or two doses) of anti–PD-1 checkpoint blockade was aimed at priming cytotoxic $CD8^+$ T cells for engagement before GSK-3β inhibition and chemotherapy cell death, leading to antigen release. Notably, all three responders in our trial were in this priming cohort despite all three exhibiting tumor PD-L1 scores <1%. First restaging occurred 9 weeks into the start of all treatment, so it is not entirely clear whether the lead-in immunotherapy had much, if any, benefit toward antitumor activity, but this should be further explored. Of 17 patients with molecular profile data, two of three patients with *MTAP* gene loss with co-deletion of *CDKN2A/B* demonstrated a PR, and one of 14 without co-deletion achieved a PR. Some studies suggest that this molecular profile predicts poor chemotherapy and immunotherapy response (44, 45). *MTAP* loss can promote GSK-3β signaling, and therefore, adding elraglusib in this setting might provide added benefit (46). Although intriguing, these observations are exploratory in nature; additional nonresponders may harbor similar alterations.

Beyond measuring antitumor response, the median PFS observed for the total trial population was around 6 months; more than one-fourth of patients were progression-free at 1 year. The median PFS has been estimated around 4 to 9 months for ACC but <6 months for non-ACC (28, 47). Furthermore, the median OS exceeded 12 months and more than one-third of patients were alive at 2 years in the present trial, whereas the median OS for non-ACC patients observed in this study of 27.8 months compares favorably when considering historical data (28, 47). Although the present trial required PD within a year before registration and included higher-grade histologic salivary gland cancer subtypes and heavily pretreated patients, these survival outcomes must be interpreted with caution, as selection bias is still important to consider.

This represents one of the first clinical trials in advanced salivary gland cancer to explore sequential therapy and systemic treatments with varied therapeutic mechanisms in which single-agent approaches have so often yielded limited antitumor activity, and is one of the few modern salivary gland cancer trials evaluating the use of chemotherapy. However, this also represents an important limitation of the present study, as it remains difficult to evaluate the contribution of parts with a limited sample size, and we did not explore platinum doublet or immunotherapy-only combinations. Although our trial included a focused correlative plan, a more expansive and stepwise immune biomarker assessment and first restaging after the immune priming phase and before platinum–elraglusib initiation would have been insightful. It is important to note that following the inception and completion of this trial, the dosing schedule of elraglusib was optimized to favor weekly administration. Furthermore, the lack of a control arm limits interpretability, particularly as cisplatin has known single-agent activity in non-ACC salivary gland cancer. Despite these shortcomings, this trial provides some contemporary support for the use of cisplatin chemotherapy in advanced non-ACC salivary gland cancer. A subsequent study for non-ACC tumors using cisplatin with elraglusib in an nGSK-3β selected population would be of interest. Future trials in advanced salivary gland cancer should continue to prioritize biomarker selection and explore rational combinatorial treatments.

Data Availability

Requests for data are limited to datasets described in this article and are not publicly available because of patient privacy concerns. The data generated from this clinical trial are available upon reasonable request to the corresponding author up to 6 years following publication. Tumor genomic sequencing relied on commercial assay reporting; therefore, raw sequencing data were not available to the investigators.

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Authors' Contributions

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Note

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