Elraglusib, a glycogen synthase kinase 3 beta (GSK 3β) inhibitor, plus chemotherapy with or without immunotherapy for advanced salivary gland cancer

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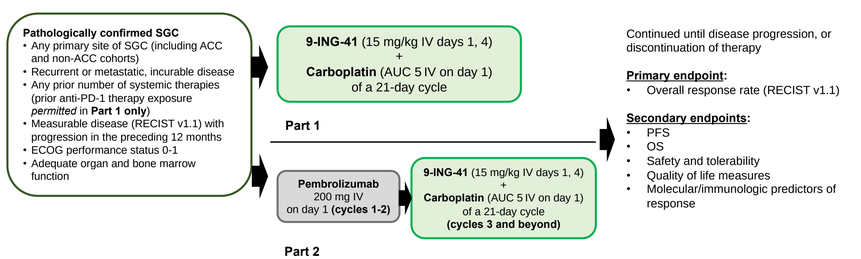
Background & Rationale

- **Salivary gland carcinoma (SGC)** is a rare, but histologically and molecularly rich, group of head and neck cancers.
- **Aberrant overexpression of GSK-3β** has been shown to promote tumor growth and chemotherapy resistance through differential effects on activated NF-κB and cellular apoptosis.
- GSK-3β activity is often elevated in **platinum-resistant** cancer cells, where it contributes to cell survival by activating pathways that protect against DNA damage.
- GSK-3β overexpression or nuclear accumulation has been demonstrated in SGC.
- **Elraglusib (9-ING-41)** is a potent, adenosine triphosphate-competitive small molecule inhibitor of GSK-3β. Beyond its proposed role in overcoming chemoresistance, elraglusib has also been shown to be immunomodulatory.
- We **hypothesized** that combining elraglusib with platinum-based chemotherapy, and immune priming with upfront anti-PD-1 therapy would be a novel sequential treatment approach to explore in advanced SGC.

Kato S, et al. 2015
Domoto T, et al. 2020
Ugolkov AV, et al. 2005
Shakoori A, et al. 2005
Miyashita K, et al. 2009
Liao X, et al. 2003
Tan J, et al. 2005
Ugolkov AV, et al. 2018

Study design

- Single-arm, single center, non-randomized, parallel cohort, open-label phase 2 clinical trial (NCT05010629)



- **Primary endpoint**: best ORR (RECIST 1.1). A one-stage design was utilized. When >5 of 32 patients (among Parts 1 and 2 combined) 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, type I error rate of 9.4%).

KEY POINTS:

While the primary endpoint was not met in the overall study population, **we observed an ORR of 18% among the non-ACC patients treated with immune priming followed by cisplatin plus elraglusib.**

Correlative analyses suggested that pre-treatment tumors from **responders demonstrated higher nuclear GSK-3β expression.**

This trial is one of the first to explore sequential combinatorial treatment incorporating chemotherapy in salivary cancer.

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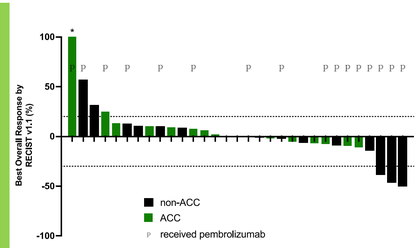
Key Results (n=32)

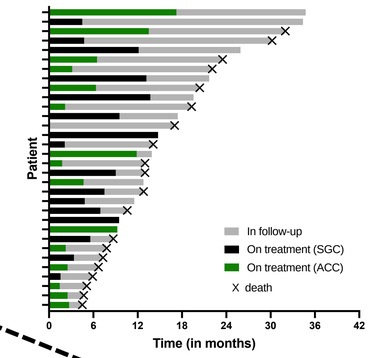
Demographics

- Median age was 65 years (range, 37-85) with most identifying as female at birth (20, 63%). Most patients had a primary site of disease arising in the major or minor salivary glands (24, 75%).

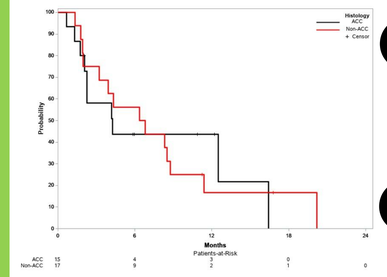
Safety and tolerability

- 23 (72%) had a grade 3-5 AE regardless of treatment attribution. 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.
- Most common TRAEs: anemia (22, 69%), nausea (16, 50%), and decreased neutrophil count (14, 44%).
- 19 (59%) experienced grade 3 TRAEs most commonly anemia (6, 19%), neutropenia (4, 13%), while 1 (3%) experienced a grade 4 TRAE (neutropenia).



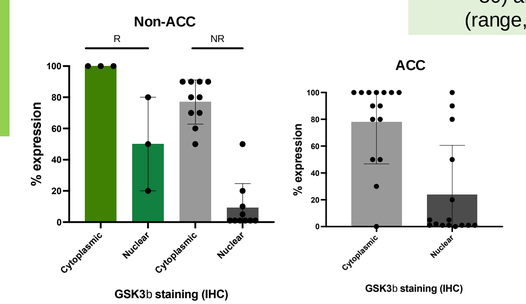


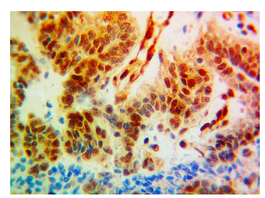
1 **ORR 9.4%** (95% CI, 2-25)
3 PR, 19 SD, 9 PD
Responses only in non-ACC subgroup
Median DoR=6.9 mos (range, 2.2-7.3)



2 Median follow-up: 16.2 months
mPFS 6.4 months (95 CI, 2.3-8.8)
12-month PFS was numerically greater for ACC vs. non-ACC (43.6 vs. 16.7%)

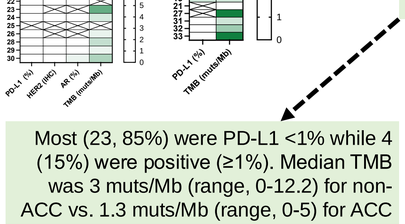
3 Median nuclear (n)GSK-3β expression: 5% (range, 1-100); median of 50% (range, 20-80) among the 3 responders and 2% (range, 1-100) among non-responders

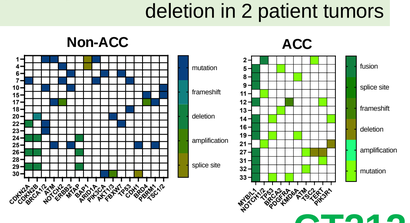




Nuclear GSK3β in tumor cells (40x)

4 Among the 3 non-ACC patients who achieved PR, baseline tumor molecular profiling showed *CDKN2A/B* and *MTAP* co-deletion in 2 patient tumors





Most (23, 85%) were PD-L1 <1% while 4 (15%) were positive (≥1%). Median TMB was 3 muts/Mb (range, 0-12.2) for non-ACC vs. 1.3 muts/Mb (range, 0-5) for ACC

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