

Title: Phase 2 study of 9-ING-41, a Glycogen Synthase Kinase-3 Beta (GSK-3 β) inhibitor, plus platinum chemotherapy with or without immunotherapy in patients with advanced, metastatic Salivary Gland Carcinoma

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Carcinoma**

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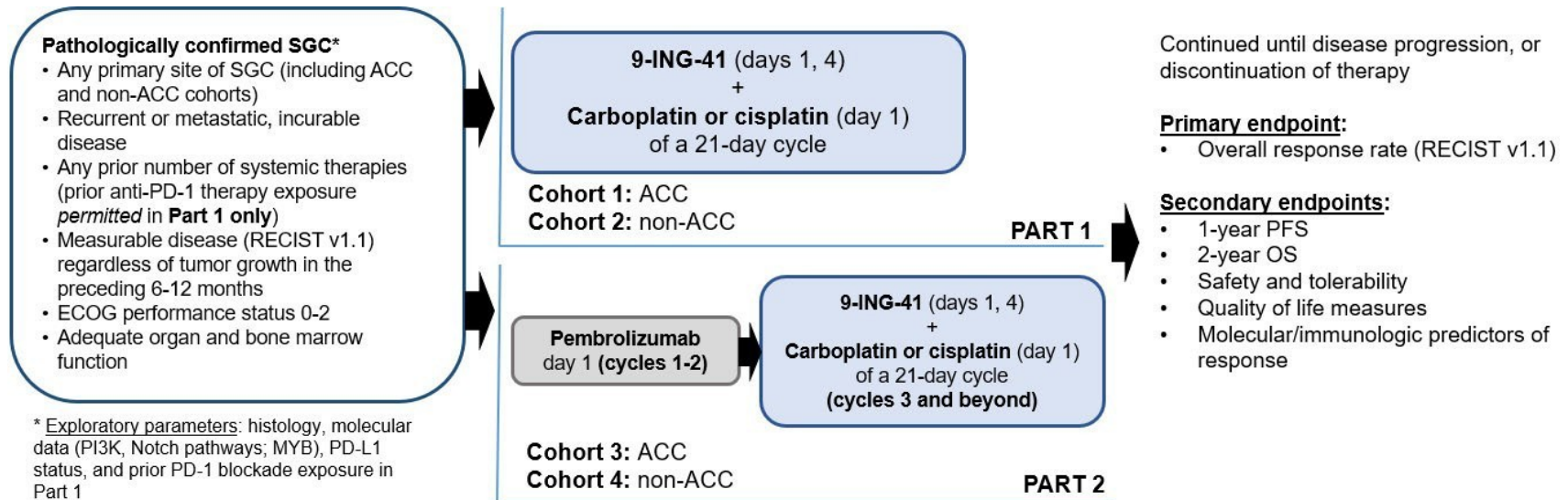


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LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

Abbreviation	Description of Abbreviation
ACC	adenoid cystic carcinoma
AE	adverse event
ANC	absolute neutrophil count
AR	androgen receptor
CAP	cyclophosphamide
CExPA	carcinoma ex-pleomorphic adenoma
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CREB3	cAMP responsive element binding protein
CRF	case report form
CTCAE	NCI Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
DARF	Drug Accountability Record Form
DILI	drug-induced liver injury
DSMC	Data and Safety Monitoring Committee
EOT	End-of-Treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
GCPs	Good Clinical Practices
GSK-3 β	glycogen synthase kinase-3 beta
Gy	Gray
H&E	hematoxylin & eosin
IB	investigator brochure
IHC	immunohistochemistry
IKK β	inhibitor of nuclear factor kappa-B kinase subunit beta
IP	investigational product
MEC	mucoepidermoid carcinoma
NS	Normal saline
NTRK	neurotrophic tyrosine receptor kinase
ODQ	Office of Data Quality
OHRS	Office for Human Research Studies
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed cell death ligand 1

Abbreviation	Description of Abbreviation
PDX	patient derived xenograft
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetics
PKA	protein kinase A
PNI	perineural invasion
PR	partial response
RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
SD	stable disease
SDC	salivary duct carcinoma
SGC	salivary gland carcinomas
TKIs	tyrosine kinase inhibitors
TMB	tumor mutational burden
TNF	tumor necrosis factor
TPS/CPS	tumor proportion or combined proportion score
TRAIL	TNF-related apoptosis-inducing ligand
Vd	volume of distribution
WOCBP	Women of childbearing potential
XIAP	anti-apoptotic protein

1 OBJECTIVES

1.1 Study Design

This is a phase 2, open-label, non-randomized, single institution study investigating the novel glycogen synthase kinase-3 beta (GSK-3 β) inhibitor 9-ING-41 in combination with platinum chemotherapy with or without immunotherapy in patients with incurable, recurrent or metastatic salivary gland carcinomas (SGC). Patients with advanced SGC (including all histologic subtypes and adenoid cystic carcinoma [ACC]) will receive 9-ING-41 intravenously (IV) along with carboplatin or cisplatin IV at standard dosing together on Day 1, and 9-ING-41 alone on Day 4 of a 21-day cycle in Part 1. In Part 2, patients receive two cycles of lead-in pembrolizumab IV at standard dosing on Day 1, followed by the same carboplatin or cisplatin and 9-ING-41 regimen thereafter for cycles 3 and beyond. Accounting for patients who could be registered and classified as ineligible or do not start protocol treatment, up to N=34 patients could be enrolled. Participants will be enrolled to two histologic cohorts (approximately equal numbers into each cohort): Cohort 1 and 3 will be comprised of those with ACC, and Cohort 2 and 4 will include patients with non-ACC SGC (or all other salivary gland cancer histologies). Treatment will continue until progression of disease, death, or discontinuation of therapy for any reason.

The primary aim of the study is to assess the overall response rate (ORR) as defined by RECIST v1.1 in the overall study population (including both Parts and each Cohort). Secondary aims include assessing progression-free survival (PFS), overall survival (OS), determining safety and tolerability, measuring patient-reported quality of life metrics, and correlating efficacy with molecular and immunologic predictors of response.

We hypothesize that the novel combination of a GSK-3 β inhibitor with platinum chemotherapy with and without immunotherapy will result in an ORR of 25% or greater in this critical population where no approved therapies exist.

1.2 Primary Objectives

- To estimate overall response rate (ORR) using RECIST v1.1 from the date of study registration.

1.3 Secondary Objectives

- To estimate PFS from date of study registration
- To estimate OS from date of study registration
- To estimate duration of therapeutic response, and response among patients in Part 1 and Part 2, and among all Cohorts individually
- To evaluate safety and toxicity (CTCAE v5.0)
- To measure quality of life metrics on study treatment (UW-QOL)

- To correlate molecular and immunologic parameters with response and survival outcomes

2 DISEASE BACKGROUND

2.1 Study Disease(s)

Salivary gland carcinomas (SGCs) represent a rare, but unique group of histologically and molecularly distinct malignancies that can occur in the major salivary glands (parotid, submandibular, sublingual) or in minor salivary glands located throughout the head and neck aerodigestive tract.^[1] Despite some variability in prognosis, salivary gland tumors are generally managed with a curative intent surgical approach (the cornerstone of treatment) followed by adjuvant or post-operative radiation in cases at high-risk for locoregional recurrence based on histology, grade, and/or extent of disease. While no randomized clinical trials exist, observational data has indicated that adjuvant radiation improves both locoregional control and survival.^[2] The optimal radiation dose depends on the fractionation scheme, but most doses of 60 to 66 Gray (Gy) are delivered in 2 Gy fractions. The Radiation Therapy Oncology Group (RTOG)/NRG are prospectively investigating the use of weekly cisplatin with radiation in high-risk salivary cancer patients in a phase 2/3 study (RTOG 1008), but these results are not available. Despite aggressive locoregional management, distant metastatic spread is not infrequent among SGCs, particularly among high-risk histologic subtypes.^[3] Histologically, high-grade subtypes include salivary duct carcinoma (SDC), and high-grade mucoepidermoid carcinoma (MEC), carcinoma ex-pleomorphic adenoma (CExPA), as compared with ACC, for example.

ACC is a common malignancy frequently arising in salivary gland tissue, often affecting patients with no identifiable risk factors. Localized disease is generally managed with oncologic resection followed by adjuvant radiotherapy in most cases, given the potential for perineural invasion (PNI) linked with this malignancy^[4,5] – similar to other SGC histologies noted above. Concurrent adjuvant chemoradiotherapy is sometimes offered to mitigate the risk of locoregional recurrence, but no prospective trials have proved that this strategy is beneficial in terms of disease control rates and survival.^[6] Despite initial multimodality therapy in the upfront setting, nearly half of ACC patients develop distant, metastatic spread of disease; but the natural history of such cancers is often reflective of slower growth velocity despite recurrences that involve the lungs, liver, and bones.^[7]

There remain no approved systemic cytotoxic or targeted therapies available for the treatment of SGCs broadly, nor specifically for ACC. While some agents have demonstrated modest disease activity, there has been no overall or progression-free survival advantage observed with any particular agent(s) – therefore the optimal regimen remains unclear.^[8] Cytotoxic chemotherapy combinations using anthracyclines, platinum and fluoropyrimidines, and vinorelbine in some combination may have some benefit in a limited number of patients.^[3,9] While combination therapies result in greater response rates, there is no clear survival advantage to such an approach and they come with toxicity. Although immune checkpoint blockade has revolutionized cancer immunotherapy with the success of PD-1 inhibitors in a host of solid tumors, SGCs do not generally express the ligand of PD-1 (PD-L1) and appears to maintain minimally immunogenic potential.^[10] Early studies investigating PD-1 blockade in SGC patients have been largely disappointing with response rates <15% even among PD-L1 selected tumors.^[11]

More recent approaches to treatment have incorporated molecular and genomic profiling data. While no clear driver mutation is known, these tumors have a low somatic mutation rate when compared with other types of cancer. Multi-targeted tyrosine kinase inhibitors (TKIs) such as sorafenib, and oral therapies targeting c-kit (imatinib, dasatinib) have been investigated with limited objective response rates (<15%).^[12-14] Next-generation sequencing data has suggested frequent alterations in a diverse array of signaling pathways including: epigenetic modifiers, DNA damage and repair signals, Notch pathway, and FGF/IGF/PI3K signaling;^[15] and clinical trials are ongoing to evaluate the anti-tumor effects of drugs aimed at modifying these aberrant signaling cascades in ACC, among other SGC subtypes. One molecular aberration that has been identified in sequenced ACC tumors is the MYB-NFIB fusion oncogene generated by a t(6;9) translocation which occurs in up to 70-90% of ACC tumors. Despite the identification of MYB as an important target in ACC, no MYB inhibitors have been identified. Strong surface expression of HER-2 has been observed in a majority of SDC (upwards of 60-90%) and other high-risk SGCs, as determined by immunohistochemistry (IHC) in the 1-3+ range, even in the absence of HER-2 amplification.^[16] Recent studies have aimed to capitalize on HER-2 directed therapies in this population with favorable response rates,^[17,18] but many SGC tumors don't overexpress this marker, or other targetable receptors like the androgen receptor (AR), or neurotrophic tyrosine receptor kinase (NTRK) fusions.

2.2 IND Agent: 9-ING-41

2.2.1 9-ING-41

2.2.1.1 Mechanism of action and pharmacology

9-ING-41 is a small molecule potent selective GSK-3 β inhibitor with antitumor activity.^[19-21] It acts through downregulation of NF- κ B and decreases the expression NF- κ B target genes cyclin D1, Bcl-2, anti-apoptotic protein (XIAP) and B-cell lymphoma-extra large (Bcl-XL) leading to inhibition of tumor growth in multiple solid tumor cell and lymphoma lines and patient derived xenograft (PDX) models. NF- κ B is constitutively active in cancer cells and promotes anti-apoptotic molecule expression. NF- κ B activation is particularly important in cancer cells that have become chemo- and radioresistant, therefore it is believed that inhibition of GSK-3 β may overcome NF- κ B-mediated chemoresistance in human cancers.

The pharmacokinetics (PK) of 9-ING-41 have been evaluated in cohorts (N=4-7) of patients given 9-ING-41 as IV infusions. Concentrations increased rapidly at all the tested doses, reaching near steady-state levels by 0.25 to 0.5 h into the infusion. Following the end of the infusion, concentrations declined rapidly, decreasing by approximately 30% over the next hour, and approximately 70% by 3 hours post-infusion. The rate of decline in the concentrations slowed after 3 hours post-infusion, dropping just an additional 10% to approximately 20% of the peak concentrations by 7 hours post-infusion. The mean terminal half-lives (over the time interval from 5 to 23 hours post-infusion) ranged from 12 to 20 hours, with no systematic dependence on dose. The systemic exposures, both peak exposure (C_{max}) and total exposure (AUC_{0-72}), were dose proportional (Figure 1), indicating linear pharmacokinetics over the studied dose range. Repeated

dosing of 9-ING-41 at 3 to 4-day intervals resulted in similar PK profiles as were observed with the first dose. Based on these data, a sparse sampling protocol has been specified that identifies the minimum and maximum concentrations associated with a dose of 9-ING-41, and obtains an estimate of total exposure (AUC_{0-72}) by taking advantage of the good correlation ($R^2 = 0.60$) observed between the AUC_{0-72} and the plasma concentration 1 hour after the end of the infusion. This sampling protocol is also anticipated to be able to identify poor metabolizers of 9-ING-41 from the measured pre-dose concentrations in samples collected at the time of the second (and subsequent) dose(s).

2.2.1.2 Preclinical data

Glycogen synthase kinase-3 (GSK-3) is a serine (S)/threonine (T)(ST) kinase initially described as a key regulator of metabolism, specifically glycogen biosynthesis. [22] It has since been shown to play a role in several disease processes including cancer, immune disorders, metabolic disorders, pleural fibrosis and neurological disorders through modulation of a large and diverse number of substrates.[23-28] It is a key regulator of numerous signaling pathways, including cellular responses to Wnt, G protein-coupled receptors and receptor tyrosine kinases. GSK-3 is usually constitutively active in cells and is regulated through inhibition of its activity.

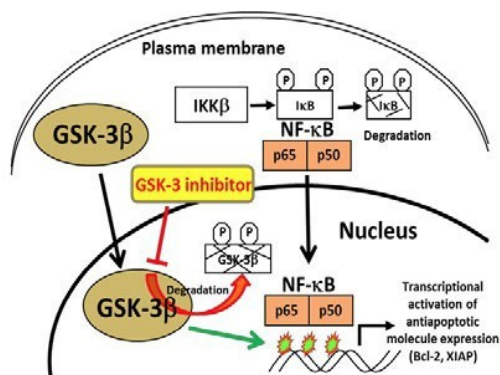
In cancer, much focus has been placed on the role of GSK-3 β in tumor progression and its modulation of oncogenes (beta-catenin, cyclin D1 and c-Myc), cell cycle regulators (e.g., p27^{Kip1}) and mediators of epithelial-mesenchymal transition (e.g., Zinc finger protein SNAI1, Snail) have been extensively described.[29-33] More recently, aberrant overexpression of GSK-3 β has been shown to promote tumor growth and chemotherapy resistance in various solid tumors including pancreatic, ovarian, colon cancer and glioblastoma[34-38] through differential effects on pro-survival nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and c-Myc pathways as well on tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and p53-mediated

apoptotic mechanisms.^[39,40] GSK-3 β is thus a potentially very important therapeutic target in human malignancies.

GSK-3 β was previously described as a potential anticancer target in human pancreatic, colon, bladder and renal cancer cells, and chronic lymphocytic leukemia.^[36,41-45] Recent studies have demonstrated that GSK-3 β is also a promising therapeutic target in glioblastoma, neuroblastoma, thyroid, ovarian, colorectal, lung, and prostate cancer.^[19,38,46-56] The potent maleimide-based GSK-3 β inhibitor, 9-ING-41, was identified as a candidate for targeted therapy in chemoresistant human breast cancer.^[20] Its antiproliferative activity involves G0-G1 and G2-M phase arrest, a mechanism evident from cell-cycle analysis in renal cell carcinoma cell lines.^[19]

NF- κ B is regarded as one of the most important transcription factors and its activation plays an essential role in promoting human cancer progression, metastasis, and chemoresistance.^[57,58] GSK-3 β has been demonstrated to have opposing roles in this context, repressing Wnt/beta-catenin signaling on the one hand but maintaining cell survival and proliferation through the NF- κ B pathway on the other.^[36] Recent data suggests that GSK-3 β positively regulates human cancer cell survival in part through regulation of NF- κ B-mediated expression of anti-apoptotic molecules.^[41] Disruption of the GSK-3 β gene in mice leads to embryonic lethality due to hepatocyte apoptosis and massive liver degeneration, a phenotype that is similar to the disruption of the NF- κ B p65 or inhibitor of nuclear factor kappa-B kinase subunit beta (IKK β) genes.^[59] These findings suggest a link between GSK-3 β and the activation of the NF- κ B pathway and support GSK-3 β as a candidate therapeutic target in human cancer. Studies have also revealed an important role of GSK-3 β in the regulation of histone modifications, which may contribute to NF- κ B p65/p50 binding to promoters and activation of target genes in cancer cells that would lead to increased cancer cell survival.^[45] Nuclear GSK-3 β may well be the primary effector target for GSK-3 inhibition in cancer cells, leading to depletion of GSK-3 β from the nucleus and subsequent inhibition of NF- κ B mediated transcription and decreased cancer cell survival (Figure 2). Nuclear GSK-3 β positively regulates NF- κ B binding to its target gene promoters and NF- κ B transcriptional activity in cancer cells. Preclinical results suggest that GSK-3 β inhibits hypermethylation of histones and thereby GSK-3 β contributes to maintenance of active chromatin at NF- κ B target gene promoters, allowing p65 binding and transcriptional activation.^[45] Inhibition of GSK-3 β resulted in rapid ubiquitin-proteasome degradation of its nuclear pool in cancer cells.^[60]

Figure 2 The Role of GSK-3 β in Cancer Cells



2.2.1.3 Clinical safety

In the 1801 Study Part 1 to date, over 60 patients with advanced solid tumors or lymphoma have received 9-ING-41 on a twice weekly IV schedule at eight dose levels: 1.0, 2.0, 3.3, 5, 7, 9.3, 12.4 and 15 mg/kg. No 9-ING-41-attributable serious adverse events (SAEs) have been observed. Some patients receiving 9-ING-41 reported transient visual symptoms. These usually begin approximately one hour into the infusion. Patient report that lights seem brighter and skin tones darker. These symptoms last for approximately one hour or less in most patients. There are no associated, preceding, or delayed visual symptoms. There are no associated vital sign or biochemical abnormalities. No attendant abnormalities have been demonstrable on retinal or general ocular examinations. These episodes usually occur just once, usually on first 9-ING-41 infusion, but rarely reoccur on a few occasions. Some investigators choose to slow the rate of the 9-ING-41 infusion when these visual symptoms occur – it is not clear if this has any impact on symptom duration. No specific additional tests or precautions are required if these symptoms occur. The dose of 15 mg/kg has been deemed the RP2D based on the volume of fluid given with this dose.

In the 1801 Study Part 2 to date, over 170 patients with advanced solid tumors have received 9-ING-41 on a twice weekly schedule at doses of 3.3, 5, 7 or 9.3 mg/kg combined with carboplatin or cisplatin, doxorubicin, gemcitabine, irinotecan, lomustine, carboplatin plus paclitaxel, gemcitabine plus nab-paclitaxel, or carboplatin plus pemetrexed. No 9-ING-41 attributable SAEs or clinically significant adverse events have been observed.

2.2.1.4 Clinical efficacy

Clinical responses including complete response and stable disease has been observed in patients receiving single agent 9-ING-41 at doses of 3.3 mg/kg or higher. The data generated on safety and activity to date support its expansion.

2.3 Other Agent(s): Platinum therapy

2.3.1 Carboplatin

Carboplatin is a platinum compound alkylating agent which covalently binds to DNA, and interferes with the function of DNA by producing interstrand DNA cross-links. Carboplatin is apparently not cell-cycle specific. The volume of distribution (Vd) is 16 L (based on a dose of 300 to 500 mg/m²) into liver, kidney, skin, and tumor tissue. The protein binding of carboplatin is 0% but it irreversibly binds to plasma proteins. Its metabolism is minimally hepatic to aquated and hydroxylated compounds with a half-life elimination of 2.6 to 5.9 hours (based on a dose of 300 to 500 mg/m²) for individuals with a creatinine clearance (CrCl) >60 mL/minute. Carboplatin is primarily excreted in the urine (about 70% as carboplatin within 24 hours; 3% to 5% as platinum within 1 to 4 days).

Cytotoxic chemotherapy combinations using platinum may have some benefit in a limited number of ACC or SGC patients. Limited data suggest that there are differences in chemotherapy sensitivity among the histologic subtypes of salivary gland tumors. Carboplatin is more acutely

myelosuppressive than cisplatin but causes less neurotoxicity, nephrotoxicity, and nausea and vomiting.^[61] Older series have shown that response rates to cisplatin single-agent chemotherapy are 6% in ACC while combining cisplatin with an anthracycline and cyclophosphamide (CAP) increases response rates to 28-83% among all SGCs. Carboplatin has been combined with paclitaxel in two small ACC studies showing a response rate of 20% (2/10), although taxanes are often avoided in ACC in general for limited efficacy noted in retrospective series (Table 1).

2.3.2 Cisplatin

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases and disrupts DNA function; may also bind to proteins; the cis-isomer is 14 times more cytotoxic than the trans-isomer; both forms cross-link DNA but cis-platinum is less easily recognized by cell enzymes and, therefore, not repaired. Cisplatin can also bind two adjacent guanines on the same strand of DNA producing intrastrand cross-linking and breakage. The protein binding of plasma cisplatin is >90%. Its metabolism is non-enzymatic and inactivated by sulfhydryl groups. Half-life of elimination is 20-30 minutes with primary excretion via the kidneys (13-17% within 1 hour).

Table 1. Platinum Therapy Response Rates in Advanced ACC

Chemotherapy	ACC Responses/patient (%)	SGC (non-ACC) Responses/patient (%)	Citation
Cisplatin	2/32 (6%)	1/10 (10%)	De Haan LD, et al. Head Neck 1992 ^[6]
CAP	12/32 (28%)	28/42 (67%)	Licitra L, et al. Cancer 1991 ^[63]
			Licitra L, et al. Ann Oncol 1996 ^[3]
			Dreyfuss AI, et al. Cancer 1987 ^[4]
			Creagan ET, et al. Cancer 1988 ^[5]
			Alberts DS, et al. Cancer 1981 ^[6]
Carboplatin + paclitaxel	2/10 (20%)	1/1 (100%)	Ruzich JC, et al. Head Neck 2002 ^[67]
			Airoldi M, et al. Anticancer Res 2000 ^[8]

2.4 Other Agent(s): Pembrolizumab

2.4.1 Pembrolizumab

Pembrolizumab is a highly selective anti-PD-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling. The volume of distribution is 6L with an elimination half-life of 22 days.

Although immune checkpoint blockade has revolutionized cancer immunotherapy with the success of PD-1 inhibitors in a host of solid tumors, SGCs do not generally express the ligand of PD-1

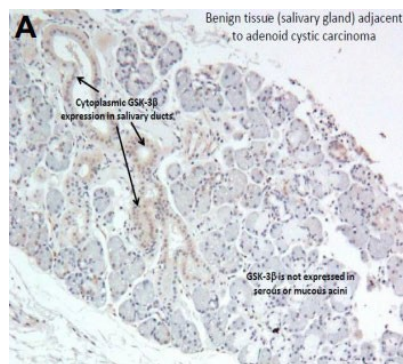
(PD-L1) and appears to maintain minimally immunogenic potential.^[10] Early studies investigating PD-1 blockade as monotherapy in SGC patients have been largely disappointing with response rates <15% even among PD-L1 selected tumors.^[11]

2.5 Rationale

The natural history of metastatic SGC is variable, and some patients remain asymptomatic for protracted periods of time. This is especially true for ACC particularly when metastases are limited to the lung, acinic cell carcinomas, and myoepithelial carcinomas.^[69] Systemic therapy, either with chemotherapy or targeted agents, is offered to SGC patients with an increasing rate of systemic disease progression based on imaging studies, with systemic symptoms, with threatened end-organ dysfunction, and/or with a declined performance status due to progressive disease. Systemic therapy can be administered irrespective of whether local treatments have also been administered, but it may be particularly useful when local treatments are not feasible. There remain no approved systemic cytotoxic or targeted therapies available for the treatment of SGCs broadly, nor specifically for ACC.

Recent preclinical studies evaluating IHC staining of GSK-3 β expression among SGC and other head and neck malignancies have shown aberrant expression patterns among these malignancies. Among 28 malignant head and neck tumors, GSK-3 β overexpression was defined as nuclear accumulation denoted as positive staining among more than 50% of cancer cell nuclei regardless of cytoplasmic staining.^[70] None of the 11 benign, non-salivary head and neck tissues tested showed detectable GSK-3 β expression whereas SGC demonstrated aberrant expression (Figure 3). Of note, among a representative sampling of 5 ACC and 1 mucoepidermoid carcinoma (MEC) (N=6), 60% overexpression of GSK-3 β was observed in the ACC subgroup.

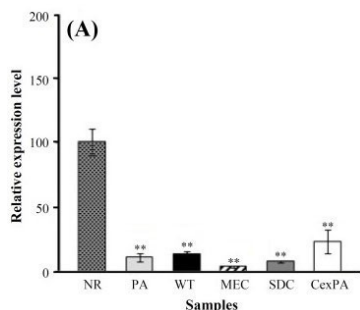
Figure 3 GSK-3 β Expression In Salivary Gland Tissue and ACC



GSK-3 β in the Wnt signaling pathway regulates the amount of β -catenin to moderate cell proliferation. Its inactivation is thought to lead to abnormal levels of β -catenin, inducing tumorigenesis.^[71] Ghahhari and colleagues^[72] have evaluated histologic SGC specimens and shown that GSK-3 β was downregulated in all samples tested (Figure 4), while cAMP responsive element binding protein (CREB3) (also part of the protein kinase A [PKA] signaling pathway) did not show a significant change in mRNA expression outside of MEC and salivary duct carcinoma

subtypes. GSK-3 β down regulation has been reported in many human tumors. These findings taken together suggest that GSK-3 β overexpression among SGC subtypes can be variable and may be important in tumor progression and modulation of oncogenes.

Figure 4 GSK-3 β Expression Among Salivary Cancer Subtypes



GSK-3 is a serine/threonine kinase initially described as a key regulator of metabolism, specifically glycogen biosynthesis. It has a role in diverse disease processes including cancer, immune disorders, metabolic disorders, and neurological disorders through modulation of a large number of substrates. GSK-3 has two ubiquitously expressed and highly conserved isoforms, GSK-3 α and GSK-3 β , with both shared and distinct substrates and functional effects. GSK-3 β is particularly important in tumor progression and modulation of oncogenes (including beta-catenin, cyclin D1 and c-Myc), cell cycle regulators (e.g., p27Kip1) and mediators of epithelial-mesenchymal transition (e.g., zinc finger protein SNAIL, Snail). Aberrant overexpression of GSK-3 β has been shown to promote tumor growth and chemotherapy resistance in various solid tumors including colon, ovarian, and pancreatic cancers and glioblastoma through differential effects on the pro-survival nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and c-Myc pathways as well on tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and p53-mediated apoptotic mechanisms. NF- κ B is one of the most important transcription factors. Its activation is essential in promoting human cancer progression, metastasis, and chemoresistance. Among other relevant activities, GSK-3 β helps maintain malignant cell survival and proliferation, particularly in terms of mediating resistance to standard anti-cancer therapies, through the NF- κ B pathway. GSK-3 β has been established as a potential anticancer target in human bladder, breast, colorectal, glioblastoma, lung, neuroblastoma, ovarian, pancreatic, prostate, renal and thyroid cancers as well as chronic lymphocytic leukemia and lymphomas. GSK-3 β is a potentially very important therapeutic target in human malignancies.

Recent preclinical work has also shown that 9-ING-41 blocks the expression of checkpoint molecules to enhance CD8⁺ cytolytic T cell killing in melanoma cells [Shaw G, et al. unpublished 2022]. The study sought to evaluate mouse model B16 melanoma and compare the efficacy of anti-PD-1 therapy both as a single agent and in combination with 9-ING-41. Experiments showed that priming with PD-1 blockade and then exposing the cells to 9-ING-41 enhanced cytolytic CD8⁺ T cell potential and led to changes in migratory and motility machinery, further promoting survival.

Part 1 of the current study aims to evaluate the role of GSK-3 β inhibition among all advanced SGC cancers. This will be explored in combination with standard-dose platinum chemotherapy given its modest single agent activity and tolerance in SGCs, but also given promising data combining GSK-3 β inhibition with cytotoxic agents in solid tumors even when chemoresistance has occurred. Part 2 builds on this notion and adds two doses of lead-in pembrolizumab to try and prime the immune system and stimulate CD8 $^{+}$ T cells after sequential exposure to 9-ING-41 and chemotherapy.

2.6 Correlative Studies Background

As part of the exploratory aims of the study we will request archival biopsy tumor material (or fresh tumor biopsy material when and if clinically indicated) for each patient prior to enrollment as is standard in the management of advanced SGC patients to inform treatment decision-making and evaluate for actionable therapeutic targets. We will utilize existing, standard commercially available tumor next-generation sequencing platforms (FoundationOne[®] CDx, Guardant360 CDx, Tempus, etc.) or our in-house targeted massively parallel sequencing platform Oncopanel to molecularly profile each participant's tumor. As noted above, assessment is typically offered in advanced SGC to detect NTRK gene fusion among secretory tumors, HER-2 and AR expression, among other prognostic and potentially actionable alterations such as aberrations in the Notch, PI3K, and MYB pathways.

Immunotherapy with checkpoint inhibitors has shown limited activity in most patients with salivary gland tumors. The exceptions are: those with SGCs expressing high levels of tumor mutational burden (TMB), for which pembrolizumab has regulatory approval based on the results of KEYNOTE-158 and in the phase 1 KEYNOTE-028 trial of N=26 patients with SGCs expressing programmed cell death ligand 1 (PD-L1) at 1% or greater, after a median follow-up of 20 months, pembrolizumab demonstrated an overall response rate of 12%.^[73] For these reasons, we will explore companion PD-L1 tumor testing among the present cohort should archival or fresh tumor tissue permit (as a tumor proportion or combined proportion score [TPS/CPS]). GSK-3 β is a serine-threonine kinase with the highest number of substrates and multifaceted roles in cell function including immune cells,^[74] thus understanding PD-L1 expression and the association with GSK-3 β inhibition would be of interest.

Paraffin embedded archival tumor tissues will be requested from all enrolling patients and will be analyzed for GSK-3 β expression level and nuclear expression by the sponsor to correlate with study drug response and benefit. Fixed tumor tissue obtained from archival samples may be sequenced in the future to identify mutations and to perform transcriptome analysis to assess gene expression of oncogenes and genes regulated by the GSK-3 β or NF- κ B pathways.

3 PARTICIPANT SELECTION

Participants must meet the following eligibility criteria at the time of screening to be eligible to participate in the study:

3.1 Eligibility Criteria

- 3.1.1 Participants must have histologically confirmed salivary gland carcinoma (any histologic subtype, including ACC) with evidence of recurrent, metastatic or advanced, unresectable disease.
- 3.1.2 Willing to provide tumor tissue from a diagnostic biopsy or prior surgery.
- 3.1.3 Age 18 years or older
- 3.1.4 ECOG performance status 0-2 (see [Appendix A](#))
- 3.1.5 Participant must have organ and marrow function as defined below within 14 days prior to study registration:
 - leukocytes $\geq 3,000/\text{mcL}$
 - absolute neutrophil count $\geq 500/\text{mcL}$
 - hemoglobin $\geq 8.5 \text{ g/dL}$
 - platelets $\geq 75,000/\text{mcL}$
 - total bilirubin $\leq 2.0 \text{ g/dL}$
 - AST(SGOT)/ALT(SGPT) $\leq 2.5 \times$ institutional upper limit of normal
 - creatinine within normal institutional limits
 - OR
 - creatinine clearance $\geq 50 \text{ mL/min/1.73 m}^2$ for participants with creatinine levels above institutional normal
- 3.1.6 Participants must have documentation of a new or progressive lesion on a radiologic imaging study performed *within 12 months* prior to study registration (progression of disease over any interval is allowed) and/or new or worsening disease-related symptoms *within 12 months* prior to study registration. This assessment is performed by the treating investigator. Evidence of progression by RECIST v1.1 criteria not required.
- 3.1.7 Participants must have at least one RECIST v1.1 measurable non-CNS based lesion, as defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) $\geq 1 \text{ cm}$ with CT scans or MR imaging. Prior systemic therapy: At least 2 weeks must

have elapsed since the end of prior chemotherapy, biological agents (3 weeks for anti-cancer monoclonal antibody containing regimens) or any investigational drug product, with adequate recovery of treatment-related toxicity to NCI CTCAE Version 5.0 grade ≤ 1 (or tolerable grade 2) or back to baseline (except for alopecia or neuropathy). Any number of prior therapies for recurrent/metastatic SGC are permitted (including prior platinum chemotherapy or immunotherapy exposure); but prior therapy for recurrent/metastatic SGC is not required for participation.

- 3.1.8 Ability to understand and the willingness to sign a written informed consent document.
- 3.1.9 Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 14 days of study registration. Female subjects of childbearing potential should have a negative urine or serum pregnancy test repeated within 72 hours prior to receiving the first dose of study medication.
- 3.1.10 WOCBP will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product. “Women of childbearing potential (WOCBP)” is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL.
- 3.1.11 Men who are sexually active with WOCBP must agree to use any contraceptive method with a failure rate of less than 1% per year. Men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men) do not require contraception. See [Appendix B](#) for further guidance on contraception.

3.2 Exclusion Criteria

- 3.2.1 Metastatic disease impinging on the spinal cord or threatening spinal cord compression. Patients that have had previous treatment of disease with impinging on the cord with either surgery or radiotherapy with clinical or radiographic evidence of response or stability are eligible.
- 3.2.2 Participant has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at

least four weeks prior to the first dose of trial treatment) and have no evidence of new or enlarging brain metastases.

- 3.2.3 Concurrent administration of other cancer specific therapy or investigational agents during the course of this study is not allowed.
- 3.2.4 Patients on anticoagulants that require INR monitoring (such as warfarin).
- 3.2.5 Uncontrolled intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.
- 3.2.6 Pregnant or lactating women.
- 3.2.7 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include: basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer, and low-risk prostate adenocarcinoma being managed with active surveillance. A history of another separate malignancy in remission without evidence of active disease in the last 2 years is permitted.
- 3.2.8 Existing significant autoimmune conditions. Patients with a history of Hashimoto thyroiditis who are stable on replacement hormone therapy are not excluded. Patients cannot be on long-term (>4 weeks) corticosteroids at doses exceeding prednisone 20 mg daily (or its equivalent) prior to enrollment in Part 2 only.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups, and underrepresented populations are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Eligible participants will be registered in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention (and will occur after surgical resection). Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5 TREATMENT PLAN

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

Eligibility and exclusion criteria are provided in Section 3. These criteria will be assessed 21 days prior to study registration to establish eligibility and baseline values.

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments.

5.1 Treatment Regimen

Patients in **Part 1, Cohort 1** (ACC) and **Cohort 2** (non-ACC) will receive the same study treatment and enroll in parallel and in approximately equal number to the study, based on their differing histologic subtypes of SGC. Patients will receive 9-ING-41 (15 mg/kg IV on Day 1 and Day 4) in addition to either carboplatin (AUC 5 IV on Day 1) or cisplatin (75 mg/m² IV on Day 1) each of a 21-day cycle (± 3 day window) which continues until disease progression, death, or unacceptable toxicity. Treatment duration is at the discretion of the treating investigator.

Patients in **Part 2, Cohort 3** (ACC) and **Cohort 4** (non-ACC) will receive lead-in pembrolizumab (200 mg IV on Day 1) of a 21-day cycle (± 3 day window) for cycles 1 and 2, followed by 9-ING-41 (15 mg/kg IV on Day 1 and Day 4) in addition to either carboplatin (AUC 5 IV on Day 1) or cisplatin (75 mg/m² IV on Day 1) each of a 21-day cycle (± 3 day window) from cycle 3 onward (no specific waiting period required); which continues until disease progression, death, or unacceptable toxicity. Treatment duration is at the discretion of the treating investigator.

The decision to use either carboplatin or cisplatin will be discretionary and determined by the treating investigator, taking into account the age, pre-existing medical conditions, and overall fitness of each individual patient; in addition to considering the differences among side effect profiles for each platinum agent. Note: once a patient starts protocol therapy with either carboplatin or cisplatin, the chemotherapy agent initiated should not change for an individual patient unless discussed with the overall Sponsor-investigator. Moreover, one infrequent scenario would be a change from cisplatin to carboplatin for certain side effects (tinnitus or hearing changes) or laboratory abnormalities (kidney dysfunction), which can be discussed with the overall Sponsor-investigator.

5.2 Pre-Treatment Criteria

On the administration day of Cycle 1, Day 1 with carboplatin or cisplatin patients must have an absolute neutrophil count (ANC) equal to or greater than 500, platelet count equal to or greater than 75,000, a total bilirubin of 2 or less, and a creatinine of 1.6 or less (or a CrCl > 50 mL/min).

5.2.1 Cycle 1, Day 1 of Therapy

Baseline study evaluations are conducted within 21 days prior to study registration. If screening assessments are 3 days before the start of the study treatment, then they may serve as Cycle 1, Day 1 values. Baseline laboratory testing must be completed within 14 days of study registration.

5.2.2 Subsequent Cycles

Reasonable effort should be made to conduct study visits on the day scheduled (± 3 day window). Any changes from screening clinical evaluation findings that meet the definition of an adverse event (AE) will be recorded on the AE page of the eCRF. The participants ECOG performance status, weight (in kilograms), vital signs, interval history since the last visit, and physical examination are performed at each study visit. Concomitant medications should also be reviewed at each study visit. In addition, the AE grid should be completed at each study visit. All laboratory values should be reviewed before proceeding with an additional cycle of treatment.

5.2.3 End-of-Treatment (EOT) Visit

All subjects will be asked to return to the site for a final, EOT visit, if possible. This visit must be performed within 30 days of final administration of study treatments. EOT assessments will not have to be repeated if the same assessments were performed within 7 days of this planned visit. The subject will be followed for 30 days after the last study intervention for AEs. The reason for the study participant coming off therapy should be clearly documented. For any reason other than for progression of disease, tumor assessments should be performed every 9 weeks if a patient comes off the study drug within 1 year of enrollment. The participants ECOG performance status, weight (in kilograms), vital signs, interval history since the last visit, and physical examination are performed at the end-of-treatment visit. Concomitant medications should also be reviewed at this visit. In addition, the AE grid should be completed at this visit.

5.3 Chemotherapy, 9-ING-41, and Pembrolizumab Administration

5.3.1 9-ING-41 Administration

9-ING-41 will be administered on Day 1 and 4 of each 21-day cycle. On Day 1 of the cycle, 9-ING-41 should be infused 1 hour after platinum therapy has finished. The recommended infusion rate is found in the pharmacy manual. If the prescribing clinician chooses to amend the volume for infusion, this is permitted within recommended concentrations found in the Pharmacy Manual. Infusion is encouraged as an outpatient according to local resources and the requirements of associated monitoring and concomitant chemotherapy. All patients should be weighed within 72 hours prior to dosing for each cycle to ensure they did not experience either a weight loss or gain $>10\%$ from the prior weight used to calculate the dose of 9-ING-41 and concomitant chemotherapy. The decision to recalculate dose(s) according to a change in weight should be in accordance with local practice, however where weight has changed by $>10\%$, dose must be recalculated using the most recent weight recorded.

5.3.2 Platinum Administration

Carboplatin (AUC 5 IV) should be administered following institutional practice guidelines or the FDA package insert. As mentioned above, an every 3-week or 21-day dose is considered a cycle (cycle length: 21 days) and each cycle may be administered with a ± 3 day window. Carboplatin can be given via a peripheral IV or via central venous access. Dosing of carboplatin chemotherapy should infuse over 30-60 minutes if mixed in 250 mL or over 1-2 hours if mixed in at least 500 mL. Appropriate precautions when handling and disposing of chemotherapy is required. When calculating chemotherapy dosing, use the body weight documented at the start of treatment, and the calculated body surface area (BSA) using Dubois formula. Recalculation of dosing or BSA is required for any weight changes of $>10\%$ (or per institutional policy) or more between each 21-day chemotherapy dose.

Cisplatin (75 mg/m² IV) should be administered following institutional practice guidelines or the FDA package insert. As mentioned above, an every 3-week or 21-day dose is considered a cycle (cycle length: 21 days) and each cycle may be administered with a ± 3 day window. Cisplatin can be given via a peripheral IV or via central venous access. Dosing of cisplatin chemotherapy should infuse over 60 minutes if mixed in at least 500 mL. Ensure there is adequate urine output prior to cisplatin infusion. Appropriate precautions when handling and disposing of chemotherapy is required. When calculating chemotherapy dosing, use the body weight documented at the start of treatment, and the calculated body surface area (BSA) using Dubois formula. Recalculation of dosing or BSA is required for any weight changes of $>10\%$ (or per institutional policy) or more between each 21-day chemotherapy dose.

5.3.3 Pembrolizumab Administration

Pembrolizumab (200 mg IV) should be administered following institutional practice guidelines or the FDA package insert. As mentioned above, an every 3-week or 21-day dose is considered a cycle (cycle length: 21 days) and each cycle may be administered with a ± 3 -day window. Pembrolizumab can be given via a peripheral IV or via central venous access. Dosing of pembrolizumab should infuse over 30 minutes as 200 mg in NaCl 0.9% 68 mL IVPB; infuse via a sterile, non-pyrogenic, low protein binding 0.2-5 micron inline or add-on filter. Appropriate precautions when handling and disposing of chemotherapy is required.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Anti-emetics and Pre-medications for Carboplatin

Ondansetron (Zofran) 16 mg may be dosed orally or IV once prior to starting each treatment dose of carboplatin. Dexamethasone (Decadron) 12 mg may be dosed orally or IV once prior to starting each treatment dose (with food to reduce gastrointestinal upset). At the discretion of the treating investigator, a third anti-emetic pre-medication can be dosed: aprepitant (Cinvanti) 130 mg IV administered over 2 minutes once starting 30-120 minutes prior to the start of carboplatin is favored.

Normal saline (NS) can be given at 500 mL/hr IV continuous for 1 hour (1L) prior to carboplatin dosing; but may be held if the patient is well tolerated.

Standard hypersensitivity medications (diphenhydramine, methylprednisolone, meperidine, acetaminophen, famotidine, epinephrine, and albuterol) can be administered per institutional practice guidelines.

5.4.2 Anti-emetics and Pre-medications for Cisplatin

Ondansetron (Zofran) 16 mg may be dosed orally or IV once prior to starting each treatment dose of cisplatin. Dexamethasone (Decadron) 12 mg may be dosed orally or IV once prior to starting each treatment dose (with food to reduce gastrointestinal upset). A third anti-emetic pre-medication can be dosed: aprepitant (Cinvanti) 130 mg IV administered over 2 minutes once starting 30-120 minutes prior to the start of cisplatin.

Normal saline (NS) with or without KCl 20 mEq/L (per investigator discretion) should be given prior cisplatin dosing at 500 mL/hr, starting at treatment start time for 2 hours. Begin prior to chemotherapy. May begin chemotherapy after 1000 mL infused. Ensure adequate urine output prior to beginning cisplatin. Cisplatin-related hydration volume including chemotherapy to total a minimum of 2.5 Liters. Magnesium sulfate IV 2 grams over 60 minutes should start at the treatment start time and begin prior to chemotherapy. It can be administered with the NS and KCl. Additional NS at 500 mL/hr should start 3 hours after the cisplatin start time for a total of 2 hours. Furosemide 20 mg IV can be given as needed once for weight gain greater than 5 pounds since day 1 of the current cycle and/or for the presence of signs/symptoms of fluid overload on day 1. Mannitol 25% in NS (12.5 mg) IV for 30 minutes can be given once as needed per the treating investigator.

Standard hypersensitivity medications (diphenhydramine, methylprednisolone, meperidine, acetaminophen, famotidine, epinephrine, and albuterol) can be administered per institutional practice guidelines.

5.4.3 9-ING-41

No pre-medications are required or suggested prior to dosing. The decision to incorporate pre-medication will be made following discussions between the study medical coordinator and the treating investigator.

For infusion reactions, standard hypersensitivity medications (diphenhydramine, methylprednisolone, meperidine, acetaminophen, famotidine, epinephrine, and albuterol) can be administered per institutional practice guidelines.

5.4.4 CYP3A4 Drug-drug Interactions with 9-ING-41

9-ING-41 has a low potential for interaction with the cytochrome P450 metabolic system within the liver. For FDA designation of drugs with the potential for strong inhibition of

CYP2C19, CYP3A4, and CYP1A2 or strong inducers of CYP3A4 please follow this link: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>

5.4.5 Hematopoietic growth factor support

Primary prophylactic use of granulocyte colony stimulating factors is not permitted during cycle 1 (with chemotherapy), but they may be used to treat treatment emergent neutropenia as indicated by local guidelines and incorporated in cycle 2 and beyond when/if deemed necessary by the treating investigator.

5.4.6 Radiation

Patients who are thought to need palliative radiation (to a non-target lesion or target lesion if another non-radiated target lesion is available for continued response assessment) while on study may temporarily hold 9-ING-41 and platinum chemotherapy while receiving radiation, resuming it after radiation is completed. Study treatments can resume as soon as palliative radiation is completed, if deemed appropriate by the treating investigator.

5.4.7 Prohibited Medications

Anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin and factor Xa inhibitors, anti-platelet agents are permitted). Any other investigational product(s). Immunosuppressive doses of systemic corticosteroids are discouraged but not prohibited.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment with 9-ING-41 and platinum therapy should continue at the discretion of the treating investigator, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), which include **any** of the following:
 - A life-threatening infusion reaction to 9-ING-41, platinum, or pembrolizumab
 - Grade 3 thrombocytopenia >7 days associated with bleeding
 - Grade 4 peripheral neuropathy develops from carboplatin or cisplatin
 - Grade 4 creatinine elevation or acute kidney injury results from cisplatin
 - Any grade 4 adverse event *except*: neutropenia <7 days, lymphopenia or leukopenia, thrombocytopenia, and isolated electrolyte disturbances that resolve in <72 hours
- Participant demonstrates an inability or unwillingness to comply with the medication

regimen and/or documentation requirements

- Patient becomes pregnant
- Patient develops a second primary malignancy that requires treatment which would interfere with conduct of this study
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of the above criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1:

http://www.dfhcc.harvard.edu/crs-resources/DFHCC_Policy_Operation_Library/REGIST-OP-1.pdf.

Study participants may be treated beyond progression of disease, with approval from the treating investigator, if the participant has limited alternative therapy options and if they are demonstrating ongoing clinical benefit from study therapy.

5.6 Duration of Follow-up

All participants who at least begin protocol therapy (the first dose of 9-ING-41) will be followed until first progression and for survival for 3 years from the time of study registration. Participants removed from protocol therapy for unacceptable adverse event(s) will also be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when **any** of the following criteria apply:

- Patient completed required follow-up
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1:

http://www.dfhcc.harvard.edu/crs-resources/DFHCC_Policy_Operation_Library/REGIST-OP-1.pdf

6 DOSING DELAYS/DOSE MODIFICATIONS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

6.1 Dose Delays and modifications for Platinum chemotherapy

Dose modifications for carboplatin and cisplatin are permitted and should follow institutional standards based on toxicity, with the following suggested modifications:

- When dose reductions in carboplatin or cisplatin occur they should include the appropriate dose level reductions as specified in Table 2 and Table 3 below.
- A maximum of two dose reductions is permitted: if additional reductions are required, the chemotherapy regimen should be discontinued.
- If chemotherapy is delayed or held more than 4 consecutive cycles (12 weeks), it should be discontinued.
- Once a dose has been decreased, it should remain reduced for all subsequent dosing unless dose is further reduced. No dose escalations will be allowed.
- If carboplatin or cisplatin is delayed due to drug-related toxicity during a treatment cycle, 9-ING-41 should be administered at the discretion of the treating investigator; when chemotherapy dosing is resumed, dose reduction should only be applied to the agent that was withheld.

Table 2 Recommended Dose Levels of Carboplatin or Cisplatin

	Carboplatin dose	Cisplatin dose
Starting dose	AUC 5	75 mg/m ²
Dose Level -1	AUC 4 (80%)	56.25 mg/m ² (75%)
Dose Level -2	AUC 3 (60%)	37.5 mg/m ² (50%)

Table 3 Recommended Platinum Dose Modifications for Toxicity

	Carboplatin	Cisplatin
Neutrophils (ANC) <500/mm ³ lasting ≥5 days	Decrease by -1 dose level	Decrease by -1 dose level
Febrile neutropenia (body temperature ≥38.5°C and ANC <1000/mm ³)	Decrease by -1 dose level	Decrease by -1 dose level
Platelets <25,000/mm ³	Decrease by -1 dose level	Decrease by -1 dose level
Platelets <50,000/mm ³ with significant bleeding or requiring transfusion	Decrease by -1 dose level	Decrease by -1 dose level
Grade 4 hemoglobin (<6.5 g/100 mL)	Decrease by -1 dose level	Decrease by -1 dose level
Nausea or emesis ≥ grade 3 despite optimal medical management	Decrease by -1 dose level	Decrease by -1 dose level
Stomatitis ≥ grade 3	Decrease by -1 dose level	Decrease by -1 dose level
Diarrhea ≥ grade 3 despite optimal medical management	Decrease by -1 dose level	Decrease by -1 dose level
Neuropathy (sensory or motor) grade 2 lasting >7 days or grade 3 lasting 7 days or less	Decrease by -1 dose level	Decrease by -1 dose level

Nephrotoxicity (creatinine clearance 50-59 mL/min or grade 3 creatinine elevation)	No modification	75% of previous dose
Nephrotoxicity (creatinine clearance 40-49 mL/min)	No modification	50% of previous dose
Total bilirubin >1.5x ULN	No modification	No modification
Total bilirubin >2.5x ULN	80% of previous dose	No modification
Total bilirubin >4x ULN	60% of previous dose	No modification
Other grade ≥ 3 toxicities (except fatigue or transient arthralgias, myalgias)	Decrease by -1 dose level	Decrease by -1 dose level

6.2 Dose Delays and modifications for 9-ING-41

For mild-to-moderate infusion reactions (characterized by flushing, itching, body aches, fever, chills, gastrointestinal symptoms, chest discomfort, or skin rash) consider slowing the rate of infusion or interrupting the infusion per institutional practice standards. The choice to dose modify 9-ING-41 by one dose level due to an infusion reaction is left to the treating investigator and should follow [Table 4](#) below. In the case of mild-to-moderate infusion related reactions, pre-treatment medication including an antihistamine and antipyretic may be administered prior to subsequent infusions (in the case that the patient is able to continue on treatment).

For severe or grade ≥ 3 infusion reactions, allergic reaction, or anaphylaxis may be a reason for study discontinuation and should be reviewed with the overall study PI.

Dose modifications for 9-ING-41 are permitted (this can occur within a cycle, between cycles, or prior to the next cycle) and should follow the guidelines below:

- When dose reduction in 9-ING-41 occurs it should include the appropriate dose level reduction as specified in [Table 4](#) and [Table 5](#) below.
- A maximum of two dose reductions in 9-ING-41 are permitted: if additional reductions are required, the agent should be discontinued.
- If 9-ING-41 is delayed due to drug-related toxicity during a treatment cycle, platinum chemotherapy can be administered at the discretion of the investigator; when 9-ING-41 is resumed, dose reduction should only be applied to the agent that was withheld.

Table 4 Recommended Dose Levels of 9-ING-41

	9-ING-41 dose
Starting dose	15 mg/kg
Dose Level -1	12.4 mg/kg
Dose Level -2	9.3 mg/kg

Table 5 Recommended Dose Modifications for 9-ING-41 Toxicity

	9-ING-41
Grade 3-4 non-hematologic toxicities (<i>except</i> nausea/vomiting or diarrhea for <72 hours; and <i>except</i> electrolyte disturbances that last <72 hours; <i>except</i> amylase or lipase elevation without symptoms)	Decrease by -1 dose level and resume when recovers to grade 2 or less

Participants with a delay in 9-ING-41 dosing beyond 6 weeks (42 days) should be considered for discontinuation of protocol treatment and discussed with the Principal Investigator.

Permanent discontinuation of chemotherapy and/or 9-ING-41 is recommended if any unacceptable adverse events outlined in Section 5.5 occur.

6.3 Dose Delays and modifications for Pembrolizumab

There are no dose reductions for pembrolizumab permitted. The second dose of pembrolizumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the first treatment in Part 2. Dosing visits are not skipped, but delayed.

Pembrolizumab should be delayed in the event of *any* of the following:

- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
 - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
 - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of pembrolizumab in cycle 2 should be re-evaluated weekly or more frequently if clinically indicated and resume immunotherapy dosing when re-treatment criteria (as described below) are met. Participants with a delay in dosing beyond 10 weeks should be considered for discontinuation of protocol treatment.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Expected Toxicities

Virtually all patients treated with 9-ING-41 and/or platinum therapy may experience some drug-related toxicity, especially fatigue, some degree of cytopenias, limiting gastrointestinal toxicity (diarrhea or nausea and/or emesis), tinnitus related to carboplatin or cisplatin, and mild/limited visual disturbances related to 9-ING-41. These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy. Please see the package insert for carboplatin or cisplatin and the Investigator Brochure (IB) for 9-ING-41.

In the event that visual changes are reported by the patient during 9-ING-41 infusion, the drug infusion can be stopped and/or dropped to half rate at the discretion of the treating investigator. Typically, the infusion can result in altered color tones and changes in interpretation of brightness. If there are no gross visual field defects the infusion may continue as planned. If visual symptoms significantly impact visual acuity or persist beyond the infusion, consider a referral to ophthalmology before re-dosing.

The most common adverse reactions (>20%) related to pembrolizumab include: pruritis or itching, skin rash, elevated blood glucose, elevated serum potassium, a decreased in serum sodium, hypothyroidism, decreased appetite, diarrhea, an increase in serum alanine aminotransferase or alkaline phosphatase, fatigue, headache, joint aches, and/or musculoskeletal pain.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:** AEs for the study agents that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- **Attribution of the AE:**
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the overall study PI. PI must report any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional serious adverse event (SAE) form.

7.3.1 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs. Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

7.3.2 Reporting SAEs

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing. All SAEs should be followed to resolution or stabilization.

Investigators will be notified of all suspected, unexpected serious adverse reactions (SUSARs; 7-/15-Day Safety Reports) that occur during any clinical studies that are using duvelisib. Each site

is responsible for notifying their IRB/IEC/Central Ethics Committee of these additional SUSARs in accordance with local regulations.

7.4 DF/HCC Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2& 3AE Expected	Gr. 2& 3AE Unexpected	Gr. 4 AE Expected	Gr. 4AE Unexpected	Gr. SAE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study <i>or</i> for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6 Reporting to the Actuate

The Table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the **Clinical Trial Serious Adverse Event (SAE) Report Form to Actuate**. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure:

Table 6 Sponsor Adverse Event Reporting Requirements

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Actuate Within 24 Hours of Awareness
SAE	All	Only those attributed to 9-ING-41
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)
Events NOT to be reported as AEs:		

Hospitalization for a routine treatment or monitoring of the disease under study, including hospitalization due to trial-related procedures (e.g., chemotherapy administration), not associated with any deterioration of the patient's status.
 Hospitalization due to the progression of underlying disease and events which are without doubt related to the PD (as assessed by the Investigator).
 Hospitalization due to social reasons, respite care (hospice), and in the absence of a medical condition for the hospital admission.

Events listed in the Table above that require reporting to Actuate on the CT SAE Report Form within 24 hours of awareness of the event by the investigator are to be reported if the event is determined by the investigator to be related to the investigational product (9-ING-41) under study. In particular if the SAE is fatal or life threatening, notification to Actuate or designee must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE. In addition, the investigator may be requested by Actuate or designee to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Actuate or designee. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (e.g., medical records, CRF, laboratory data) are to be sent to Actuate only upon request.

As part of ongoing safety reviews conducted by Actuate or designee any non-serious AE that is determined by Actuate to be serious will be reported by Actuate as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with this section.

7.7 Routine AE Reporting

All Adverse Events must be reported in routine study data submissions to the PI on the toxicity case report forms. AEs reported through *expedited processes* (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

7.8 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event

that meets the FDA’s criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with 9-ING-41 administered in this study can be found in the Investigator Brochure (IB).

8.1 9-ING-41

8.1.1 Dosage Form and Packaging

8.1.2 Storage and Stability

Please also refer to the Pharmacy Manual. The investigator, or an approved representative (e.g., pharmacist) will ensure that all 9-ING-41, the investigational product (IP), is stored in a secured area with controlled access and in accordance with applicable regulatory requirements. IP should be stored in original containers and in accordance with the labels.

8.1.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.4 Availability

Free of cost, investigational supply of 9-ING-41, will be provided by Actuate Therapeutics.

8.1.5 Reconstitution and Dilution

IP should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, national, state, or institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

After calculating the dose required for the patient, withdraw the appropriate ml of drug from the vial using sterile technique and add to 0.9% Sodium Chloride Injection in the approved infusion container to produce concentrations specified in the Pharmacy Manual.

Upon dilution, infusion contents must equilibrate for 0.25 to 1 hour prior to beginning patient administration. Administer the entire contents of the diluted solution in the infusion container. Complete administration to the patient within 8 hours of making the dilution.

Please reference the recommended infusion rate in the Pharmacy Manual. If the prescribing clinician chooses to amend the volume for infusion, this is permitted within recommended actual (not nominal) concentrations specified in the Pharmacy Manual. Note: Actuate Therapeutics confirmed that there is a typo in the pharmacy manual (version 3), dated July 14, 2021. The following statement in Appendix 2 should read: "On the advice of our CMC group, we recommend that you reduce the 9-ING-41 upper limit **actual**...", not "On the advice of our CMC group, we recommend that you reduce the 9-ING-41 upper limit nominal...".

8.1.6 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage). The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of 9-ING-41 supplies. All IP will be accounted for using a drug accountability form/record.

8.1.7 Destruction and Return

Destruction of unused 9-ING-41 is to take place at the investigator site on approval of the study monitor. The investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Actuate or designee, and all destruction must be adequately documented.

8.2 Carboplatin or Cisplatin

Carboplatin and cisplatin will be stored, prepared, and administered per standard of care or institutional practice standards.

8.3 Pembrolizumab

Pembrolizumab will be stored, prepared, and administered per standard of care or institutional practice standards.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Background information on the pre-clinical and clinical rationale for these investigations is discussed in Section 2.6 above.

9.1 Targeted next-generation sequencing

As part of the exploratory aims of the study we will request archival biopsy tumor material (or fresh tumor biopsy material when and if clinically indicated) for each patient prior to enrollment as is standard in the management of advanced SGC patients. We will utilize existing, standard commercially available tumor next-generation sequencing platforms (FoundationOne[®] CDx, Guardant360 CDx, Tempus, etc.) or our in-house targeted massively parallel sequencing platform Oncopanel to molecularly profile each participant's tumor. As noted previously, assessment is typically offered in advanced SGC for NTRK gene fusion among secretory tumors, HER-2 and AR expression, among other prognostic and potentially actionable alterations such as aberrations in the Notch, PI3K, and MYB pathways. We will descriptively characterize and stratify patients by mutational status and compare response and survival outcomes among these subgroups.

9.2 PD-L1 immunostaining

We will explore companion PD-L1 tumor testing among the present cohort should archival or fresh tumor tissue permit (as a tumor proportion or combined proportion score [TPS/CPS]). GSK-3 β is a serine-threonine kinase with the highest number of substrates and multifaceted roles in cell function including immune cells,^[74] thus understanding PD-L1 expression and the association with GSK-3 β inhibition is of interest. We will quantify PD-L1 scores and compare both continuous and categorical cutoffs (e.g., 1, 10, 20, 50, etc.) to associate immune marker status with response and outcomes.

9.3 GSK-3 β expression and Blood specimens

Formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks will be requested (or 5-10 unstained slides plus one hematoxylin & eosin (H&E) stained slide) from all enrolled patients and will be sent to Actuate Therapeutics to be analyzed for GSK-3 β expression level and nuclear expression to correlate with study drug response and clinical benefit.

FFPE Tissue blocks and/or pathologic slides should be sent to:

10 STUDY CALENDAR

Screening evaluations are to be conducted within 21 days or 3 weeks prior to study registration. Laboratory evaluations do not need to be repeated to meet eligibility criteria on Cycle 1 Day 1, if they were done within 3 days of the first dose of treatment. Laboratory evaluations should be done within 14 days of registration. Scans must be done within 3 weeks (or 21 days) prior to the first treatment dose of study treatments. The cycle length for all study agents is 21 days. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise stated.

Table 8 Study Calendar

	Screening ¹	Day 1 of cycle	Day 4 of cycle	C4D1	End of treatment visit ²	Follow-up ³	EDC Timepoints
9-ING-41		X	X	X			Day 1, 4 of every cycle
Carboplatin or cisplatin		X		X			Day 1 of each cycle
Pembrolizumab (Part 2 only) ⁴	X	X ⁴					Day 1 of each cycle ⁴
Informed consent	X						n/a
Demographics	X						Screening
Medical history	X	X	X	X	X		Screening
Concurrent medications	X	X		X	X		n/a
Physical exam	X	X		X	X		Screening
Vital signs	X	X	X	X	X		Screening
Height and Weight	X	X		X	X		Screening
Performance status ⁵	X	X		X			Screening, Day 1 of every cycle
Hematology labs ⁶	X	X	X	X	X		Screening, day 1 of every cycle, EOT
Serum chemistries ⁷	X	X	X	X	X		Screening, day 1 of every cycle, EOT
TSH or thyroid function testing ⁸	X					X	Screening, f/u
Pregnancy testing ⁹	X						Screening
ECG	X						Screening
Tumor biopsy ¹⁰	X						Screening
Quality of life survey ¹¹	X			X	X		Screening, C4D1, EOT
Adverse event evaluation ¹²		X	X	X	X		All study visits
Tumor measurements ¹³	X			X	X	X	Screening, every 3 cycles

1. Baseline study evaluations are conducted within 21 days prior to study registration. If screening assessments are 3 days before the start of the start of study treatment, then they may serve as C1D1 values.
2. Off protocol treatment visit is to occur within 30 days of final administration of study treatment. End of treatment assessments do not have to be repeated if the same assessments were performed within 7 days prior to the visit.
3. Participants will be followed for development and documentation of first disease progression and for survival every 9 weeks (or 2-3 months) from study registration until 3 years post-study registration. After first progression of disease, patients will be followed every 12 weeks (3 months) for survival (by phone) until death or 3 years from study registration (whichever occurs first).
4. Pembrolizumab is only administered in **Part 2** and as a lead-in dose during cycles 1 and 2.
5. Using ECOG performance status scale of 0-5.
6. Hematology laboratory studies should include: CBC with differential; with coagulation profile (PT/INR and aPTT) only at screening.
7. Serum chemistries should include: a comprehensive metabolic panel with phosphorus and magnesium levels (as appropriate).
8. Thyroid function testing with a TSH and reflex free T4 should be checked at baseline/screening and in follow-up every 3-6 months after the completion of prior head and neck radiation (if relevant), at the discretion of the treating investigator.
9. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 14 days of study registration. Female subjects of childbearing potential should have a negative urine or serum pregnancy test repeated within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Women who could potentially become pregnant while undergoing treatment on this protocol must be willing to use 2 methods of contraception; WOCBP will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product.
10. Archival or fresh tumor biopsy specimens should be procured prior to enrollment and sent for standard next-generation tumor genomic sequencing profiling (using any commercially available or in-house platform). Tumor PD-L1 testing should also be requested from Foundation Medicine or using in-house pathology services. An on-treatment biopsy is not required.
11. The University of Washington Quality of Life Questionnaire (UW-QOL v4.0) will be completed which has 12 items about overall pain, activity level, function, and mental health; along with four general questions. See [Appendix C](#).
12. Adverse event monitoring should utilize CTCAE version 5.0.
13. Radiographic evaluations should include contrast-enhanced CT imaging of the chest, abdomen, and pelvis; contrast-enhanced MR imaging of the neck may replace CT if preferred (at the discretion of the treating physician). CT head or brain imaging is not required. PET-CT imaging can be considered in lieu of CT imaging at any given radiologic assessment, but both studies are often not required. Assessment will be made at baseline/screening and participants will be followed for

development and documentation of disease progression and for survival every 9 weeks (or 2-3 months) until 3 years post-study registration. After first disease progression, patients will be followed every 12 weeks (3 months) for survival (by phone) until death or 3 years from study registration (whichever occurs first).

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect

For the purposes of this study, participants should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).^[75] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonary lymphangitic spread, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 3 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image

quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.1.4 Response Criteria

11.1.5 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.6 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

11.1.7 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.8 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration*.” Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.9 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.10 Time-to-event Endpoint Definitions

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Overall Survival: Overall Survival (OS) is defined as the time from study registration to death due to any cause, or censored at date last known alive.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for phase 2 protocols; response information; audit results, and a summary provided by the study team. Other information (e.g., scans, laboratory values) will be provided upon request.

13 STATISTICAL CONSIDERATIONS

We hypothesize that the combination of 9-ING-41 and platinum chemotherapy with or without pembrolizumab will yield an overall response rate (ORR) >10% (alternative hypothesis) (assuming a historical control 10% ORR rate among most current systemic therapies evaluated for advanced SGCs).

13.1 Study Design/Endpoints

Original design: This was originally designed as a two-stage, non-randomized phase 2 trial utilizing a Simon two-stage optimal design: If >5 patients with disease in response among N=33 eligible patients who began protocol treatment (assuming ≥ 2 with disease in response among N=16 eligible patients who began protocol treatment accrued in the first stage), further testing of this regimen was to be considered. The goal was to accrue equal numbers of patients with ACC and with non-ACC. When >5 responses were confirmed, this design had sufficient power to say that the response rate was >10% and closer to 25%: If the true response rate is 25%, the probability of concluding the regimen is effective is 84.3% (power), if the true response rate is 10%, the probability of concluding the regimen is effective is 9.8% (type I error rate).

Rational for statistical design changes: Since some new data show that the drugs work better after immunotherapy, two cycles of pembrolizumab will be added prior to the original treatment. The original first stage (N=16) will be referred to as “Part 1” (no immunotherapy), and “Part 2” refers to the patients receiving two cycles of pembrolizumab added prior to the original treatment. Given these new data with immunotherapy are preliminary, there is no change in the null or alternative hypothesis. Accrual into Part 2 begins after N=16 are accrued into Part 1. Part 1 will be combined with Part 2 for primary analysis.

Study design after amendment: A one-stage design will be used. Thirty-two eligible patients who begin protocol treatment are planned to be enrolled (N=16 from the original ‘Part 1’ and N=16 in ‘Part 2’) with the continued goal to accrue similar numbers of patients with ACC and non-ACC. If >5 patients with disease in response among 32 eligible patients who began protocol treatment, the trial would have met its primary endpoint. When >5 responses were confirmed, this design had sufficient power to say that the response rate is >10% and closer to 25%: if the true response rate is 25%, the probability of concluding the regimen is effective is 84.7% (power); if the true response rate is 10%, the probability of concluding the regimen is effective is 9.4% (type I error rate). The data would be reviewed and the number of patients with disease in response from Part 1 and from Part 2 as well as the corresponding AE profile would be reviewed prior to making any decisions about further testing. Of note, the use of cisplatin vs. carboplatin does not change our null hypothesis.

13.2 Sample Size, Accrual Rate and Study Duration

To account for patients who register but are classified as ineligible or who do not begin protocol treatment, up to N=34 patients could be enrolled. Assuming accrual of approximately 1-2 eligible patients who begin protocol treatment per month, the first stage could accrue in approximately 10-

15 months. Due to possible delays in initiation of approval at other sites (if applicable) and/or initiation of accrual itself, the accrual period could take longer.

13.3 Stratification Factors

This is a non-randomized trial, and there are no stratification factors.

13.4 Interim Monitoring Plan

Not applicable.

13.5 Analysis of Primary Endpoints

The primary efficacy population includes all eligible patients who begin protocol treatment (the evaluable patient population). Part 1 will be combined with Part 2 for the primary analysis. Best overall response will be summarized as a proportion with a corresponding exact 95% confidence interval (CI).

13.6 Analysis of Secondary Endpoints

For the secondary endpoints, outcome will be summarized within the ACC and non-ACC cohorts, and within Parts 1 and 2 as well. The Kaplan-Meier method will be used to estimate time-to-event endpoints with corresponding 95% confidence intervals for the median or time-specific event time.

Adverse events will be classified and graded according to the CTCAE v.5.0. Frequencies and/or rates of adverse events will be summarized among patients who begin protocol therapy.

Another endpoint is to assess patient-reported quality of life (QOL). QOL will be assessed via self-report questionnaires at the timepoints outlined in the Study Calendar (*Appendix C*). Descriptive statistics from the questionnaires will be summarized across timepoints of assessment. Rates of drop-out/non-response to QOL assessments and corresponding reason will also be summarized across timepoints of assessment.

Molecular and immune correlative studies are also planned for the future. Given the small sample size of this trial, these studies are exploratory. Information on markers such as histology, molecular genomic data, and PD-L1 status from samples will be summarized descriptively.

14 PUBLICATION PLAN

The results of the study will be reported within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study. Dr. Glenn Hanna, as Principal Investigator/PI, will be responsible for reporting the results of the study and will determine all authorship roles for any publications pertaining to the data.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Deceased.

APPENDIX B GUIDANCE ON CONTRACEPTION

Highly Effective Methods of Contraception

Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

At a minimum, subjects must agree to use two highly effective method of contraception as listed below:

For WOCBP, highly effective methods of birth control include the following:

- Progestogen only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, or implants
- Intrauterine devices (IUDs) (hormonal or non-hormonal)
- Intrauterine Hormone-releasing System (IUS)
- Bilateral tubal ligation
- Vasectomy
- Complete abstinence (complete avoidance of heterosexual intercourse)

For male subjects with partners that are WOCBP:

- Condom

All male subjects who have partners who are WOCBP must use condoms as their second method of contraception.

Women of childbearing potential (WOCBP) receiving study drug will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product. Men receiving study treatment and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product.

APPENDIX C UW-QOL QUESTIONNAIRE

**University of Washington Quality of Life Questionnaire
(UW-QOL)**

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by checking one box for each question.

1. Pain. (Check one box: ☒)

- ☐ I have no pain.
- ☐ There is mild pain not needing medication.
- ☐ I have moderate pain - requires regular medication (codeine or nonnarcotic).
- ☐ I have severe pain controlled only by narcotics.
- ☐ I have severe pain, not controlled by medication.

2. Appearance. (Check one box: ☒)

- ☐ There is no change in my appearance.
- ☐ The change in my appearance is minor.
- ☐ My appearance bothers me but I remain active.
- ☐ I feel significantly disfigured and limit my activities due to my appearance.
- ☐ I cannot be with people due to my appearance.

3. Activity. (Check one box: ☒)

- ☐ I am as active as I have ever been.
- ☐ There are times when I can't keep up my old pace, but not often.
- ☐ I am often tired and have slowed down my activities although I still get out.
- ☐ I don't go out because I don't have the strength.
- ☐ I am usually in bed or chair and don't leave home.

4. Recreation. (Check one box: ☒)

- ☐ There are no limitations to recreation at home or away from home.
- ☐ There are a few things I can't do but I still get out and enjoy life.
- ☐ There are many times when I wish I could get out more, but I'm not up to it.
- ☐ There are severe limitations to what I can do, mostly I stay at home and watch TV.
- ☐ I can't do anything enjoyable.

5. Swallowing. (Check one box: ☒)

- ☐ I can swallow as well as ever.
- ☐ I cannot swallow certain solid foods.
- ☐ I can only swallow liquid food.
- ☐ I cannot swallow because it "goes down the wrong way" and chokes me.

6. Chewing. (Check one box: ☒)

- ☐ I can chew as well as ever.
- ☐ I can eat soft solids but cannot chew some foods.
- ☐ I cannot even chew soft solids.

7. Speech. (Check one box: ☒)

- ☐ My speech is the same as always.
- ☐ I have difficulty saying some words but I can be understood over the phone.
- ☐ Only my family and friends can understand me.
- ☐ I cannot be understood.

8. Shoulder. (Check one box: ☒)

- ☐ I have no problem with my shoulder.
- ☐ My shoulder is stiff but it has not affected my activity or strength.
- ☐ Pain or weakness in my shoulder has caused me to change my work.
- ☐ I cannot work due to problems with my shoulder.

9. Taste. (Check one box: ☒)

- ☐ I can taste food normally.
- ☐ I can taste most foods normally.
- ☐ I can taste some foods.
- ☐ I cannot taste any foods.

10. Saliva. (Check one box: ☒)

- ☐ My saliva is of normal consistency.
- ☐ I have less saliva than normal, but it is enough.
- ☐ I have too little saliva.
- ☐ I have no saliva.

11. Mood. (Check one box: ☒)

- ☐ My mood is excellent and unaffected by my cancer.
- ☐ My mood is generally good and only occasionally affected by my cancer.
- ☐ I am neither in a good mood nor depressed about my cancer.
- ☐ I am somewhat depressed about my cancer.
- ☐ I am extremely depressed about my cancer.

12. Anxiety. (Check one box: ☒)

- ☐ I am not anxious about my cancer.
- ☐ I am a little anxious about my cancer.
- ☐ I am anxious about my cancer.
- ☐ I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?

Check ☒ up to 3 boxes.

- | | | |
|-------------------------------------|-------------------------------------|----------------------------------|
| ☐ Pain | ☐ Swallowing | ☐ Taste |
| ☐ Appearance | ☐ Chewing | ☐ Saliva |
| ☐ Activity | ☐ Speech | ☐ Mood |
| ☐ Recreation | ☐ Shoulder | ☐ Anxiety |
-

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life? (check one box: ☒)

- ☐ Much better
- ☐ Somewhat better
- ☐ About the same
- ☐ Somewhat worse
- ☐ Much worse

In general, would you say your **health-related quality of life** during the past 7 days has been:
(check one box: ☒)

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (check one box: ☒)

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).