UCSF Helen Diller Family Comprehensive Cancer Center

A Phase II study of Sodium thiosulfate (STS) for prevention of ototoxicity in patients with locally advanced squamous cell carcinoma of head and neck (SCCHN) undergoing concurrent chemoradiation with cisplatin

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Protocol Signature Page

Protocol No.: 20208 **Version Date:** 09-09-2022

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	A Phase II study of Sodium thiosulfate (STS) for prevention of ototoxicity in patients with locally advanced squamous cell carcinoma of head and neck (SCCHN) undergoing concurrent chemoradiation with cisplatin
Study Description	This is a phase II study to establish feasibility of using sodium thiosulfate after intravenous cisplatin in head and neck cancer patients undergoing definitive concurrent chemoradiation for prevention of ototoxicity. Hypothesis is that use of intravenous STS would be feasible and safe in patients with locally advanced SCCHN undergoing concurrent chemoradiation with cisplatin. This is a prospective clinical trial for patients getting eitherweekly cisplatin ($40mg/m^2$) or every-3-week cisplatin ($100mg/m^2$). A total of 16 patients will be enrolled and each subject will have baseline and post-treatment (3 months after the completion of concurrent chemoradiation) audiogram to assess hearing loss as defined by NCI CTCAE version 5.0. STS ($10\ g/m^2$ for weekly cisplatin group and $20g/m^2$ for high dose cisplatin group) will be infused 4 hours after each cisplatin infusion is completed. Feasibility will be assessed by successful completion of planned treatment, defined by completion of 5 weekly cisplatin or 2 high dose cisplatin without any extended treatment related delays more than > 7 days.
Phase of Study	Phase II Study
Investigational Products	Sodium thiosulfate (STS)
Study population	Patients with locally advanced SCCHN (oral cavity, oropharynx, hypopharynx, and larynx) eligible for definitive concurrent chemoradiation with cisplatin would be eligible for the study. Patients must be at least 18 years old at the time of enrollment. Women and persons from ethnic minority groups are encouraged to participate the study.
Primary Objective	Primary objective is to establish feasibility of intravenous STS after each dose of concurrent cisplatin in patients with locally advanced head and neck squamous cell carcinoma undergoing definitive radiotherapy.
Secondary Objectives	Secondary objectives are to 1) determine the rate of grade ≥ 2 change of hearing impairment from baseline based on NCI CTCAE version 5.0 with use of STS after concurrent chemoradiation with cisplatin 3 months post-treatment, 2) determine the rate of tinnitus measured by PRO-CTCAE with use of STS 3 months post-treatment, 3) describe patient reported outcomes with STS measured with PRO-CTCAE for selected oral, GI, neurologic and perceptual symptoms 4) describe patient reported outcomes measured with Hearing Handicap Inventory for Adults – Screening (HHIA-S) compared to results from standard NRG Oncology head and neck trials (such as RTOG 1016).
Sample Size	A total of 16 patients are going to be enrolled.

Duration of Study Treatment	Participants may continue study treatment for up to 7 weekly doses or 3 every 21-day doses from the time of initiating treatment.
Duration of Follow up	Participants will be followed up to 3 months post-therapy from the completion of radiation.
Unique Aspects of this Study	This is the first study to evaluate the feasibility of STS in patients with locally advanced head and neck cancer undergoing concurrent chemoradiation therapy with cisplatin.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG/EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLC	free light chain
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Services (UCSF)
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board

List of Abbreviations

IV	intravenous
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

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1 Introduction

1.1 Background on Indication

Most patients with SCCHN present with locally advanced disease which requires multimodality treatment including surgery, radiotherapy and/or chemotherapy. The majority of patients are treated with concurrent chemoradiation with cisplatin and survive the intensive treatment [2]. Especially for HPV positive SCCHN which has excellent prognosis, treatment deintensification has been attempted to save these patients from long term toxicities. Disappointingly, a recent, large randomized clinical trial comparing concurrent cetuximab and cisplatin has suggested that cetuximab may lead to inferior clinical outcome compared to cisplatin [3] and cisplatin remains the standard of care for concurrent chemoradiation in these patients. Cisplatin is a widely used systemic anti-cancer agent, and its toxicities including nephrotoxicity, neuropathy and ototoxicity have been well described. Indeed, in a prospective cohort study, 63% of locally advanced SCCHN patients who were treated with concurrent chemoradiation with cisplatin developed moderate to severe (grade $\geq$ 2 change from baseline (common terminology criteria for adverse events, CTCAE v4.03) ototoxicity with average time to onset of 2.25 months [4]. Furthermore, cisplatin induced ototoxicity seems to be dose-dependent. In testicular cancer patients, every 100mg/m^2 increase in cisplatin dose resulted in a 3.2 dB impairment in the age-adjusted overall hearing threshold[5].

1.2 Background on the Investigational Product(s) and Associated Known Toxicities

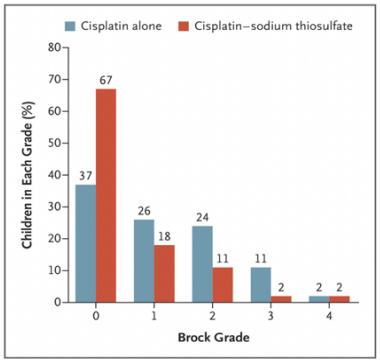
Sodium Thiosulfate (STS) is an inorganic compound which is used widely for gold mining, water treatment, analytic chemistry, development of silver based photographic films and prints, as well as medicine. In medicine, it has been used as an antidote for cyanide poisoning, a topical treatment for certain fungal infections, and a systemic treatment for calciphylaxis in end stage renal disease patients. STS is approved by FDA for use of cyanide poisoning in conjunction with sodium nitrite. Adverse events that have been reported in medical literature include hypotension, headache, disorientation, nausea and vomiting, prolonged bleeding time, salty taste in mouth and warm sensation over body. These adverse events were not reported in the context of controlled trials or with consistent monitoring and reporting methodologies for adverse events.

In humans, rapid administration of concentrated solutions or solutions not freshly prepared, and administration of large doses of sodium thiosulfate have been associated with a higher incidence of nausea and vomiting. However, administration of 0.1 g sodium thiosulfate per pound up to a maximum of 15 g in a 10-15% solution over 10-15 minutes was associated with nausea and vomiting in 7 of 26 patients without concomitant cyanide intoxication. In a series of 11 human subjects, a single intravenous infusion of 50 mL of 50% sodium thiosulfate was associated with increases in clotting time 1-3 days after administration. However, no significant changes were observed in other hematological parameters[6].

It also has been extensively studied as a “cisplatin rescue” agent to maximize dose intensity. Cisplatin favors positively charged platinum species, which possess both antitumor and toxic activities in a low chloride environment such as the intracellular space. Following IV administration, sodium thiosulfate rapidly distributes to extracellular space and reacts with cisplatin to form a covalently bound compound [7]. In a phase 1 study, in which cisplatin 100mg/m^2 was infused with concurrent STS followed by continuous STS infusion for 2-3 hours, the pharmacokinetic properties of cisplatin including elimination rate constant, volume of distribution, or total body clearance did not change significantly [8]. In this clinical trial, reported toxicities included elevated creatinine, myelosuppression, nausea, vomiting and hypomagnesemia, which are consistent with known effects of cisplatin.

1.3 Rationale for the Proposed Study

As patients with HPV positive head and neck cancers have excellent clinical outcome [9], long-term treatment related toxicities such as hearing impairment can significantly impact patients' quality of life. In head and neck cancers, sodium thiosulfate delivered after intra-arterial cisplatin has shown to be associated with decreased risks of hearing loss in previous research [10, 11]. Furthermore, recent clinical trials demonstrated IV sodium thiosulfate after 6 hours of cisplatin infusion can protect pediatric cancer patients from cisplatin induced hearing impairment with an acceptable safety profile [1, 12]. One of the trials also demonstrated that there was no significant difference in oncologic outcome between the STS group and the control group in pediatric patients with hepatoblastoma when STS infusion was given 6 hours after cisplatin dose[1]. Although efficacy and safety of STS has been established in pediatric hepatoblastoma patients receiving 480mg/m^2 (cumulative dose) of single agent cisplatin, no prospective studies exist for STS in locally advanced SCCHN patients undergoing definitive chemoradiation. Once the feasibility and safety of STS infusion are deemed promising in this population based on this phase IIt study, the concept could be easily expanded to a larger study for definitive testing which could be conducted in the head and neck cancer population or a broader population with various cancers which utilize cisplatin-based chemotherapy in NRG Oncology, either as a stand-alone supportive care focused trial or as an adjunctive study to existing or new therapeutic clinical trials.



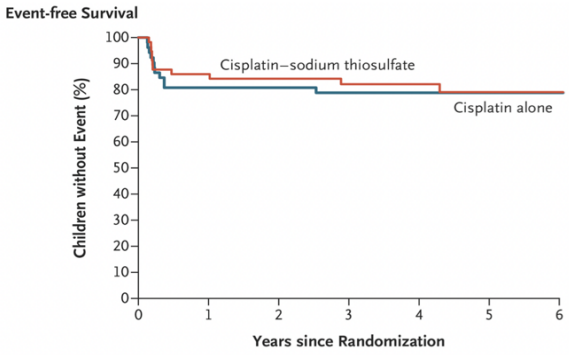


Figure 1. (A) Hearing loss (Brock grade ≧ 1) occurred in 33% in cisplatin-STS group and 63% in cisplatin-alone group (RR 0.52, 95% CI 0.33-0.81) (B) There was no significant difference event-free survival between

1.4 Rationale for the Dose Selection/Regimen

Intravenous STS 10 g/m^2 or 20 g/m^2 will be administered over 1-2 hours, 4 hours after each cisplatin dose is completed, depending on weekly or high dose cisplatin regimen. In recent clinical trials in pediatric cancer patients, STS 20 g/m^2 infused after 6 hours of cisplatin has been well tolerated with little compromise in oncologic outcome. STS can reduce toxicities from cisplatin by quenching reactive oxygen species, preserving the activity of antioxidant enzymes, and forming biologically inactive complexes with cisplatin to effectively reduce the systemic exposure to cisplatin. In pediatric hepatoblastoma study, STS 20 g/m^2 was given after cisplatin 80mg/m^2. For lower dose, weekly cisplatin, 10g/m^2 would be reasonable, as only half dose of cisplatin (40mg/m^2) is given. In animal studies, STS given 4 hours after cisplatin was able to protect rats from ototoxicity with minimal compromise in anti-tumor activity of cisplatin, whereas STS 8 and 12 hours after cisplatin had less and no protective effects at all [13].STS is a FDA approved agent for treatment of cyanide poisoning and it is approved to be given as a single dose of 12.5g after infusion of 300mg of sodium nitrite. In a phase 3 trial for calciphylaxis, STS is given 25 g per day for 3 times a week[14].

2 Study Objectives

2.1 Hypothesis

We hypothesize that use of intravenous STS would be feasible in patients with locally advanced SCCHN undergoing concurrent chemoradiation with cisplatin.

2.2 Primary Objective and Endpoint

Primary Objective	Endpoint	Time Frame
To establish feasibility of intravenous STS after each dose of concurrent cisplatin in patients with locally advanced head and neck squamous cell carcinoma undergoing definitive radiotherapy.	Feasibility measured by successful completion of planned treatment, defined by completion of at least 5 weekly cisplatin or 2 high dose cisplatin administrations without extended treatment related delays more than 7 days.	Occurring up to 7 days after the last dose of STS

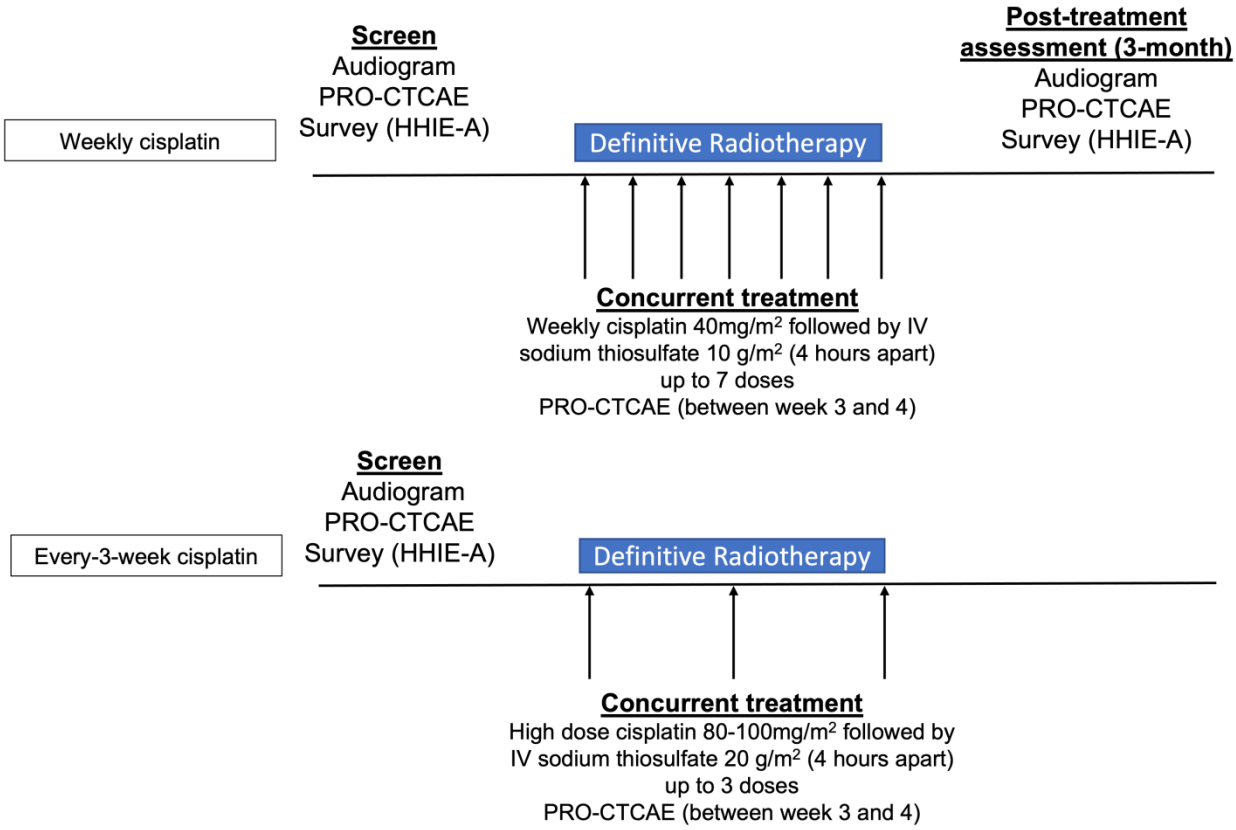
2.3 Secondary Objectives and Endpoints

Secondary Objectives	Endpoints	Time Frame
1. To determine the rate of grade ≥ 2 hearing impairment based on CTCAE version 5 with use of STS after concurrent chemoradiation with cisplatin 3 months post-treatment	Incidence of ototoxicity defined by of grade ≥ 2 hearing impairments based on NCI CTCAE version 5.0 (for patients on a monitoring program) with audiogram in each cohort	3 months after completion of chemoradiation
2. To determine the rate of tinnitus measured by PRO-CTCAE with use of STS 3 months post-treatment	• Incidence of tinnitus using PRO-CTCAE in each cohort	3 months after completion of chemoradiation
3. To describe patient reported outcomes with STS measured with PRO-CTCAE for selected oral, GI, neurologic and perceptual symptoms	• Description of incidence and trend of patient reported outcomes using PRO-CTCAE in each cohort	3 months after completion of chemoradiation
4. To describe patient reported outcomes measured with Hearing Handicap Inventory for Adults – Screening (HHIA-S) compared to results from standard NRG Oncology head and neck trials (such as RTOG 1016)	• Description of incidence and trend of patient reported outcomes using HHIA-S in each cohort	3 months after completion of chemoradiation

3 Study Design

3.1 Characteristics

This is a phase II study to determine feasibility of STS infused 4 hours after each dose of either weekly or every-3-week cisplatin in SCCHN patients undergoing definitive concurrent chemoradiation with cisplatin. Patients with locally advanced SCCHN (oral cavity, oropharynx, hypopharynx, and larynx) eligible for definitive concurrent chemoradiation with cisplatin would be eligible for the study.



3.2 Sample Size

Target accrual is a total of 16 patients, and to account for screen failures and withdrawals, we will consent up to 18 patients. Patients can be enrolled to the and can get concurrent chemoradiation with weekly cisplatin (40 mg/m^2) given once a week or concurrent chemoradiation with high dose cisplatin (80-100 mg/m^2) given every 3 weeks. Participants who do not receive any dose of STS will not be evaluable and will be replaced.

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria

1. Participants must have histologically or cytologically confirmed locoregionally advanced squamous cell carcinomas of mucosal surfaces of head and neck who are being treated with concurrent chemoradiation with cisplatin.

2. Participants must be eligible for cisplatin-based concurrent chemotherapy in conjunction with at least 6 weeks of daily fractionated radiation therapy.

3. Age ≥18 years

4. ECOG performance status ≤ 2 (Karnofsky ≥ 50%, see Appendix 1)

5. Demonstrates adequate organ function as defined below:

   Adequate bone marrow function:

absolute neutrophil count	≥1,000/mcL
platelets	≥100,000/mcL
Adequate hepatic function:	
total bilirubin	within normal institutional limits, unless elevated due to Gilbert's syndrome and direct bilirubin is within normal limits
AST(SGOT)	≤3 X institutional upper limit of normal
ALT(SGPT)	≤3 X institutional upper limit of normal
Adequate renal function:	
creatinine	≤ 1.5 x within institutional upper limit of normal
OR	
creatinine clearance	GFR ≥ 60 mL/min/1.73 m^2,calculated using the Cockcroft-Gault equation, unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m^2

6. Ability to understand a written informed consent document, and the willingness to sign it

7. Individuals with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

8. The effects of sodium thiosulfate (STS) on the developing human fetus are unknown. For this reason and because cisplatin used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception such as hormonal and/or barrier method of birth control for the duration of study participation and for 3 months after last administration of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

   Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 3 months after last administration of study treatment.

3.3.2 Exclusion Criteria

1. Participants that are not eligible for cisplatin-based chemoradiation for reasons such as chronic kidney disease, severe hearing loss, and severe peripheral neuropathy.

2. Uncontrolled inter-current illness or psychiatric illness/social situation that would limit compliance with study requirements

3. Has known hypersensitivity to cisplatin, sodium thiosulfate or any of its excipients.

4. Has profound hearing impairment at baseline and cannot hear a sound below 90 dB

5. Participants with uncompensated congestive heart failure NYHA class 3 or above.

6. Participants who cannot get secure venous access using either a Mediport or a PICC line for safe administration of intravenous sodium thiosulfate.

7. Pregnant women are excluded from this study because cisplatin is a cytotoxic agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cisplatin or sodium thiosulfate, breastfeeding should be discontinued if the mother is treated with either agent.

3.4 Inclusion and Recruitment of Women and Minorities

Individuals of any sex/gender, race, or ethnicity may participate.

3.5 Duration of Treatment

In the absence of treatment delays due to adverse events, treatment may continue for 7 weeks or until:

- Disease progression which requires discontinuation of the study treatment;
- Inter-current illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant decides to withdraw from the study;
- Significant participant non-compliance with protocol;
- If the participant meets an exclusion criterion (either newly developed or not previously; or, recognized) that precludes further study participation
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator.

3.6 Duration of Follow Up

Participants will be followed for 36 months after last treatment or removal from study, or until death, whichever occurs first. Participants removed from study for unacceptable treatment or study related adverse event(s) will be followed until resolution or stabilization (as determined by the investigator) or until initiation of new anti-cancer therapy, whichever occurs first.

3.7 Primary Completion

The expected primary completion is 9 months after the study opens to accrual.

3.8 Study Completion

The expected study completion date is 12 months after the study opens to accrual.

4 Investigational Product

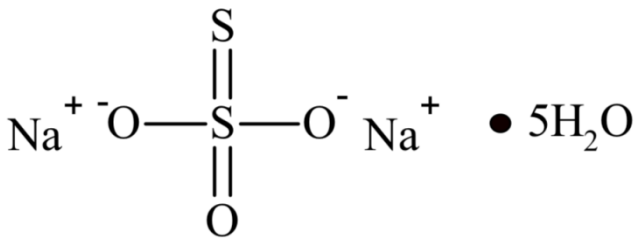
4.1 Description, Supply and Storage of Investigational Product

4.1.1 Sodium Thiosulfate

Classification

Sodium thiosulfate has the chemical name thiosulfuric acid, disodium salt, pentahydrate. The chemical formula is $Na_2S_2O_3 \cdot 5H_2O$ and the molecular weight is 248.17. The structural formula is:

Structure of Sodium Thiosulfate Pentahydrate



Sodium thiosulfate injection is a sterile aqueous solution and is intended for intravenous injection. Each vial contains 12.5 grams of sodium thiosulfate in 50 mL solution (250 mg/mL). Each mL also contains 2.8 mg boric acid and 4.4 mg of potassium chloride. The pH of the solution is adjusted with boric acid and/or sodium hydroxide. Sodium thiosulfate injection is a clear solution with a pH between 7.5 and 9.5.

Mechanism of Action

Sodium thiosulfate can reduce cisplatin-induced toxicity by scavenging reactive oxygen species, preserving the activity of antioxidant enzymes (e.g., SOD), and forming biologically inactive complexes with cisplatin to effectively reduce the systemic exposure to cisplatin. Of the thiol-containing compounds that have been shown to protect against cisplatin-induced ototoxicity, sodium thiosulfate is by far the most nucleophilic and forms complexes with cisplatin faster than any other sulfur-containing otoprotectant. The structural basis for the formation of the Pt–STS complexes has been recently described and a Pt–STS complex has been characterized as a four-coordinate Pt(II) species, $[Pt(S_2O_3)_4]^{6-}$, by the use of X-ray absorption spectroscopy[Metallomics 2016, 8, 1170–117610.1039/C6MT00183A]. In vitro, STS decreases the amount of free cisplatin in human plasma, with 31% of free cisplatin remaining in plasma within 10 min of STS incubation, as compared with 87% with no STS. Furthermore, the free cisplatin remains in human plasma for less than 50 min in the presence of excess STS, as compared with more than 3 h in the absence of STS.

Metabolism

Thiosulfate taken orally is not systemically absorbed. Most of the thiosulfate is oxidized to sulfate or is incorporated into endogenous sulphur compounds; a small proportion is excreted through the kidneys. Approximately 20-50% of exogenously administered thiosulfate is eliminated unchanged via the kidneys. After an intravenous injection of 1 g sodium thiosulfate in patients, the reported serum thiosulfate half-life was approximately 20 minutes. However, after an intravenous injection of a substantially higher dose of

sodium thiosulfate (150 mg/kg, that is, 9 g for 60 kg body weight) in normal healthy men, the reported elimination half-life was 182 minutes.

Contraindications

None (as per the drug label)

Formulation, Appearance, Packaging, and Labeling

Sodium thiosulfate is supplied as one 50 mL glass vial of 250 mg/mL (containing 12.5 grams of sodium thiosulfate) for intravenous administration.

Availability

Sodium thiosulfate is being obtained as commercial supply.

Storage and handling

Sodium thiosulfate is stored at the UCSF investigational pharmacy at controlled room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted from 15 to 30°C (59 to 86°F). It needs to be protect from direct light. It should not be frozen.

Side Effects

Complete and updated adverse event information is available in product package insert.

4.1.2 Cisplatin

Classification

Cisplatin injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. The active ingredient, cisplatin, is an anti-neoplastic agent, which is yellow to orange crystalline powder with the molecular formula $PtCl_2H_6N_2$, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207° C.

Mechanism of Action

Cisplatin crosslinks with the purine bases on the DNA and interferes with DNA repair mechanisms, causes DNA damage, and subsequently induces apoptosis in cancer cells. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

Metabolism

Plasma concentrations of the parent compound, cisplatin, decay monoexponentially with a half- life of about 20 to 30 minutes following bolus administrations of 50 or 100 mg/m^2 doses. Monoexponential decay and plasma half-lives of about 0.5 hour are also seen following 2-hour or 7-hour infusions of 100 mg/m^2. After the latter, the total-body clearances and volumes of distribution at steady-state for cisplatin are about 15 to 16 L/h/m^2 and 11 to 12 L/m^2.

Due to its unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme- catalyzed metabolism. At physiological pH in the presence of 0.1M NaCl, the predominant molecular species are cisplatin and monohydroxymonochloro *cis*-diammine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids or proteins, accounts for the instability of cisplatin in biological matrices. The ratios of cisplatin to total free (ultrafilterable) platinum in the plasma vary considerably between patients and range from 0.5 to

1.1 after a dose of 100 mg/m^2. Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding. However, the platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins, including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three-hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more.

Following cisplatin doses of 20 to 120 mg/m^2, the concentrations of platinum are highest in liver, prostate, and kidney; somewhat lower in bladder, muscle, testicle, pancreas, and spleen; and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver. Maximum red blood cell concentrations of platinum are reached within 90 to 150 minutes after a 100 mg/m^2 dose of cisplatin and decline in a biphasic manner with a terminal half-life of 36 to 47 days.

Over a dose range of 40 to 140 mg cisplatin/m^2 given as a bolus injection or as infusions varying in length from 1 hour to 24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over five days following administration of 40 to 100 mg/m^2 doses given as rapid, 2- to 3-hour, or 6- to 8-hour infusions, a mean of 35% to 51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14% to 30% of the dose are found following five daily administrations of 20, 30, or 40 mg/m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. Platinum-containing species excreted in the urine are the same as those found following the incubation of cisplatin with urine from healthy subjects, except that the proportions are different. The parent compound, cisplatin, is excreted in the urine and accounts for 13% to 17% of the dose excreted within one hour after administration of 50 mg/m^2. The mean renal clearance of cisplatin exceeds creatinine clearance and is 62 and 50 mL/min/m^2 following administration of 100 mg/m^2 as 2-hour or 6- to 7-hour infusions, respectively.

The renal clearance of free (ultrafilterable) platinum also exceeds the glomerular filtration rate indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

There is a potential for accumulation of ultrafilterable platinum plasma concentrations whenever cisplatin is administered on a daily basis but not when dosed on an intermittent basis.

No significant relationships exist between the renal clearance of either free platinum or cisplatin and creatinine clearance.

Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, the fecal excretion of platinum appears to be insignificant.

Contraindications

Cisplatin is contraindicated in patients with preexisting renal impairment. Cisplatin should not be employed in myelosuppressed patients, or in patients with hearing impairment. Cisplatin is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum-containing compounds.

Formulation, Appearance, Packaging, and Labeling

Cisplatin is supplied as a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL or 100 mL, respectively. Cisplatin injection infusion concentrate must be further diluted prior to intravenous administration.

Availability

Cisplatin is being obtained as commercial supply.

Storage and handling

Cisplatin is stored at the UCSF investigational pharmacy. Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Side Effects

Complete and updated adverse event information is available in the product package insert.

4.2 Accountability Records for Investigational Product(s)

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF.

4.3 Ordering Investigational Product(s)

Cisplatin and sodium thiosulfate will be obtained via commercial supply.

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Table 5.1 Regimen Description

Investigational Product	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Cisplatin (weekly)	• Cisplatin can be given within 24 hours of radiation therapy. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation resumes. • Prophylactic anti-emetic regimen will be given as per UCSF guidelines. • 1 liter of isotonic fluid will be given intravenously prior to cisplatin infusion	40 mg/m^2	Intravenously	Days 1, 8, 15, 22, 29, 36, and 43	Weekly or every 3 weeks
Cisplatin (every-3-weeks)	• Cisplatin can be given within 24 hours of radiation therapy. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation resumes. • Prophylactic anti-emetic regimen will be given as per UCSF guidelines. • 1 liter of isotonic fluid will be given intravenously prior to cisplatin infusion	80-100 mg/m^2	Intravenously	Days 1, 22, and 43	
*Sodium Thiosulfate (weekly)	No contraindications	10 g/m^2	Intravenously using a Mediport or a PICC line	Between 4-5 hours after each cisplatin infusion sodium thiosulfate will be	

				administered over 1-2 hours	
*Sodium Thiosulfate (every-3-week)	No contraindications	20 g/m^2	Intravenously using a Mediport or a PICC line	Between 4-5 hours after each cisplatin infusion sodium thiosulfate will be administered over 1-2 hours	

*Missed doses of sodium thiosulfate will not be replaced.

5.1.1 Radiation Therapy

Radiation therapy will be delivered according to the standard of care, in daily fractions of 1.8-2.2 Gy per fraction, over at least 6 weeks and no more than 7 weeks.

The maximum radiation dose to the cochlea should not exceed 45 Gy but every effort will be made to constrain the maximum dose to 35 Gy when possible without compromising tumor volume coverage. The maximum point doses and average doses delivered to the right cochlea and left cochlea will be recorded.

5.2 Dose Modifications for Cisplatin

5.2.1 Neutropenia:

If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1000/mm^3, hold the second chemotherapy treatment but not the radiation until ANC ≥ 1000/mm^3, then treat at 100% dose.

5.2.2 Thrombocytopenia:

If on the day of scheduled treatment with cisplatin the platelet count is < 75,000/mm^3, hold the second chemotherapy treatment but not the radiation until platelets are ≥ 75,000/mm^3, then treat at 100% dose.

5.2.3 Renal Adverse Events:

Cisplatin dose should be based on the serum creatinine or creatinine clearance immediately prior to the second cisplatin dose using the following guidelines:

Note: If creatinine is > 1.5 mg/dl, creatinine clearance must be calculated (Cockcroft-Gault) in order to make dose adjustment. The cisplatin dose will be determined as follows:

Serum Creatinine Clearance Cisplatin Dose

- ≤ 1.5 mg/dl or > 50 ml/min full dose
- 1.5 mg/dl and < 50 ml/min Hold drug*
  *Cisplatin should be held (but the RT continued) and the creatinine measured weekly, until it is
- < 1.5 mg/dl or the creatinine clearance is > 50 ml/min, and then the second dose of cisplatin can be given at the reduced dose by 50%.

5.2.4. Nausea and Vomiting:

Maximum supportive therapy will be given, and cisplatin will be continued at full dose for ≤ grade 2 nausea and vomiting.

For grade 3 nausea and vomiting refractory to supportive therapy, cisplatin will be held until recovery to < grade 2. No dose reductions will be made.

5.2.4 Mucositis:

Significant mucositis (grade 3-4, NCI CTCAE, version 45.0) is expected from radiation and cisplatin and should not be a reason for a treatment break, unless it significantly interferes with fluid intake or nutrition. Aggressive supportive care is encouraged.

If a participant experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

5.2.5 Switching to weekly cisplatin from every-3-week cisplatin

If a participant experiences any of the above adverse events requiring dose modification, every-3-week cisplatin can be switched to weekly cisplatin at least 3 weeks after the first dose of every-3-week cisplatin, at the treating physician's discretion. All adverse events should be resolved to baseline or CTCAE grade ≤ 1 before weekly cisplatin can be resumed. If the switching happens, the participant can continue STS infusion at 10mg/m^2 as outline in section 5.1.

5.3 Monitoring after Sodium Thiosulfate infusion

Because of potential hemodynamic instability following STS infusion, participates will be monitored for 30 minutes to 1 hour following completion of STS infusion. If participants manifest symptoms of hypotension (dizziness or orthostasis), IV hydration needs to be initiated following BP measurement, following the current standard of care.

5.4 Stopping Rules

We will use Bayesian decision rules for the study to decide respectively early stop out of safety or feasibility concerns. We expect that at least 75% of patients would receive target cumulative cisplatin dose of 200 mg/m^2 which is similar for both weekly and high dose cisplatin groups[15]. We assume that no more than 25% of patients would fail to receive cumulative cisplatin dose of 200 mg/m^2 in either cisplatin dose stratum. With the Beta prior distribution with parameters 2 and 6, the prior expected rate is set at the targeted rate of 25%, and the prior probability of the risk greater than 25% is 45%. We apply this prior distribution to the observed number of patients experiencing high grade toxicity and compute the posterior (updated) probability of the risk of such toxicities greater than 25%. In each cisplatin dose stratum we will consider stopping treatment any time if the posterior probability is at least .70(Table 1).

Table 1. Stopping rule for safety

Stop, if there are this many patients who do not	2	3	4	5	6

complete cumulative cisplatin dose of 200 mg/m^2					
In this many patients	2-4	5-7	8-10	11-13	14-16

6 Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 6.1.

Screening assessments must be performed within 28 days prior to the first dose of investigational product, unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

Audiogram will be obtained following the institutional standards and will include air-conduction thresholds at (minimally) octave intervals from 0.25 to 8 kHz.

All on-study visit procedures are allowed **a window of ± 2 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

6.1 Study Calendar

Weekly cisplatin

Period/Procedure	**Screening**	**Cycle 1 and Future Cycles**							**End of Treatment**	**Long Term/Survival Follow-Up[1]**
Study Day/ Visit Day	**-28**	**1 (+/- 2 days)**	**8 (+/- 2 days)**	**15 (+/- 2days)**	**22 (+/- 2 days)**	**29 (+/- 2 days)**	**36 (+/- 2 days)**	**43*[2] (+/- 2 days)**	**133 (+/- 30 days)**	**Every 3 months (+/- 30 days)**
Study Treatment/Drug Administration										
Cisplatin		x	x	x	x	x	x	x		
Sodium Thiosulfate		x	x	x	x	x	x	x		
Clinical Assessments										
Physical exam	x	x	x	x	x	x	x	x	x	
Medical history	x									
Vital signs	x	x	x	x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	
AE assessment		x	x	x	x	x	x	x	x	

[1]Long Term/Survival Follow-up will occur every 3 months via telephone calls up to 36 months.
[2] Day 43 can be omitted at the discretion of treating physician

Period/Procedure	**Screening**	**Cycle 1 and Future Cycles**							**End of Treatment**	**Long Term/Survival Follow-Up[1]**
Study Day/ Visit Day	**-28**	**1 (+/- 2 days)**	**8 (+/- 2 days)**	**15 (+/- 2days)**	**22 (+/- 2 days)**	**29 (+/- 2 days)**	**36 (+/- 2 days)**	**43*[2] (+/- 2 days)**	**133 (+/- 30 days)**	**Every 3 months (+/- 30 days)**
Disease assessment [3]	x									
Performance status	x	x	x	x	x	x	x	x	x	
Audiogram	x								x	
Survival/Long-term Follow-up										x
Questionnaires										
HHIA-S	x				x				x	
*PRO-CTCAE	x				x§[4]				x	
Laboratory Assessments										
Hematology[5]	x	x	x	x	x	x	x	x	x	
Chemistry[6]	x	x	x	x	x	x	x	x	x	

[3] Documentation of disease assessment using AJCC Cancer Staging Manual 8th edition
[4] §PRO-CTCAE can be obtained between days 14 and 23
[5] Including CBC with differential and platelet count
[6] Including alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate

Period/Procedure	**Screening**	**Cycle 1 and Future Cycles**							**End of Treatment**	**Long Term/Survival Follow-Up[1]**
Study Day/ Visit Day	**-28**	**1 (+/- 2 days)**	**8 (+/- 2 days)**	**15 (+/- 2days)**	**22 (+/- 2 days)**	**29 (+/- 2 days)**	**36 (+/- 2 days)**	**43*[2] (+/- 2 days)**	**133 (+/- 30 days)**	**Every 3 months (+/- 30 days)**
Urine pregnancy test[7]	x									

[7] For women of child-bearing potential must have a negative urine pregnancy at screening.

High dose Q3W cisplatin group

Period/Procedure	**Screening**	**Cycle 1 and Future Cycles**							**End of Treatment**	**Long Term/Survival Follow-Up[1]**
Study Day/ Visit Day	**-28**	**1 (+/- 2 days)**	**8 (+/- 2 days)**	**15 (+/- 2 days)**	**22 (+/- 2 days)**	**29 (+/- 2 days)**	**36 (+/- 2 days)**	**43*[2] (+/- 2 days)**	**133 (+/- 30 days)**	**Every 3 months (+/- 30 days)**
Study Treatment/Drug Administration										
Cisplatin		x			x			x		
Sodium Thiosulfate		x			x			x		
Clinical Assessments										
Physical exam	x	x			x			x	x	
Medical history	x									
Vital signs	x	x			x			x	x	
Concomitant medications	x				x			x	x	
AE assessment		x			x			x	x	
Disease assessment [3]	x									

[1] Long Term/Survival Follow-up will occur every 3 months via telephone calls up to 36 months.
[2] Day 43 can be omitted at the discretion of treating physician
[3] Documentation of disease assessment using AJCC Cancer Staging Manual 8th edition

Period/Procedure	**Screening**	**Cycle 1 and Future Cycles**							**End of Treatment**	**Long Term/Survival Follow-Up[1]**
Study Day/ Visit Day	**-28**	**1 (+/- 2 days)**	**8 (+/- 2 days)**	**15 (+/- 2 days)**	**22 (+/- 2 days)**	**29 (+/- 2 days)**	**36 (+/- 2 days)**	**43*[2] (+/- 2 days)**	**133 (+/- 30 days)**	**Every 3 months (+/- 30 days)**
Performance status	x	x			x			x	x	
Audiogram	x								x	
Survival/Long-term Follow-up										x
Questionnaires										
HHIA-S	x				x				x	
*PRO-CTCAE	x				x§[4]				x	
Laboratory Assessments										
Hematology[5]	x	x			x			x	x	
Chemistry[6]	x	x			x			x	x	
Urine pregnancy test[7]	x									

[4] §PRO-CTCAE can be obtained between days 14 and 23
[5] Including CBC with differential and platelet count
[6] Including alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate
[7] For women of child-bearing potential must have a negative urine pregnancy at screening.

6.2 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.3 Schedule of Procedures and Assessments

6.3.1 Pretreatment Period

6.3.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of initiating study treatment.

- Clinical Assessments
    - Documentation of disease assessment using AJCC Cancer Staging Manual 8th edition
    - Physical examination
    - Complete medical history
    - Vital signs
    - Concomitant medication review
    - Performance status
    - Audiologic assessments including audiogram
    - Questionnaires
        - A questionnaire based on PRO-CTCAE for selected oral, GI, neurologic and perceptual symptoms (dry mouth, difficulty swallowing, mouth/throat sores, taste changes, nausea, vomiting, numbness & tingling, and ringing in ears)
        - Hearing Handicap Inventory for Adults – Screening (HHIA-S)
- Laboratory Assessments
    - Hematology labs - CBC with differential and platelet count
    - Blood chemistry assessment, including: Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate
    - Urine Pregnancy Test - For women of child-bearing potential.

6.3.2 Treatment Period

6.3.2.1 Study Procedures on treatment days

- Clinical Assessments
    - Physical examination
    - Vital signs
    - Concomitant medication review
    - AE assessment
    - Performance status
    - Questionnaires (On Day 22 only)
        - A questionnaire based on PRO-CTCAE for selected oral, GI, neurologic and perceptual symptoms (dry mouth, difficulty swallowing, mouth/throat sores, taste changes, nausea, vomiting, numbness & tingling, and ringing in ears)
        - Hearing Handicap Inventory for Adults – Screening (HHIA-S)
- Laboratory Assessments (Days 1, 8, 15, 22, 29, 36 for subjects getting weekly cisplatin and days 1 and 22 for subjects getting every-3-week cisplatinDay 43 labs will only be collected if treatment occurs that day).
    - Hematology labs - CBC with differential and platelet count
    - Blood chemistry assessment, including: Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate
- Treatment with cisplatin and sodium thiosulfate

6.3.3 Post-treatment/Follow-Up

Participants will be followed at least once around 3 months +/- 2 weeks after discontinuing study treatment. The following procedures will be performed at the Follow Up visit:

- Clinical Assessments
    - Physical examination
    - Vital signs
    - Concomitant medication review
    - AE assessment
    - Performance status
    - Audiologic assessments including audiogram
    - Questionnaires
        - A questionnaire based on PRO-CTCAE for selected oral, GI, neurologic and perceptual symptoms (dry mouth,

difficulty swallowing, mouth/throat sores, taste changes, nausea, vomiting, numbness & tingling, and ringing in ears)

- Hearing Handicap Inventory for Adults – Screening (HHIA-S)

- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Blood chemistry assessment, including: Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate

6.3.4 Long Term/Survival Follow-up

After completing the follow-up period, participants can be contacted by telephone every 3 months (+/- 30 days) up to 3 years to assess for event free survival and overall survival after initiation of treatment to confirm that there is no reduced efficacy of cisplatin when administered prior to sodium thiosulfate (STS) and to assess for survival/anti-cancer therapy status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.4 Use of Concurrent/Concomitant Medications

Participants should receive anti-emetic therapy based on UCSF guidelines at the treating physician's discretion. Use of growth factors is not allowed for patients getting weekly cisplatin , but can be allowed at the treating physician's discretion for patients gettingevery-3-week cisplatin.

7 Reporting and Documentation of Results

7.1 Evaluation of Safety

7.1.1 Definitions

Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with sodium thiosulfate.

7.1.2 Evaluation of Safety

The safety parameters for this study include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by participants.

Toxicity will be assessed according to the NCI CTCAE version 5.0. Safety analyses will be performed for all participants who received at least one dose of sodium thiosulfate.

7.2 Definitions of Adverse Events

7.2.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.2.2 Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.2.3 Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.2.3.1 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some participants exposed to drugs in the angiotensin-converting enzymeinhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.2.3.2 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.2.3.3 Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2.4 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.2.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator, or until the initiation of new anti-cancer therapy, whichever occurs first. For selected adverse events for which administration of the investigational product was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the investigator.

7.2.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.2.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting adverse events: https://irb.ucsf.edu/adverse-event

Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Analysis Plan

Feasibility will be evaluated as the successful completion of 5 weekly cisplatin or 2 every-3-week cisplatin without any extended treatment related delays more than 7 days by at least 75% of patients. Safety will be measured by:

- Frequency of drug related adverse events occurring up to 7 days after the last dose of STS
- Frequency of serious adverse events occurring up to 7 days after the last dose of STS
- Frequency of clinical laboratory test abnormalities by worst toxicity grade using NCI CTCAE version 5.0

8.1 Accrual Estimates

A total of 16 patients are going to be enrolled. Estimated accrual is 2-3 per month. Projected completion of accrual from the activation of the study is 9 months and last patient follow-up will be completed in 12 months from the activation.

8.2 Sample Size Considerations

This is a phase II study that aims to obtain preliminary evidence of feasibility. The proposed sample of n=16 would allow estimating the rates with margins of error of 0.345 at 95% confidence level.

8.3 Interim Analyses and Stopping Rules

There is no plan for interim analyses in this phase II study. Stopping rules are illustrated in section 5.3.

8.4 Analyses Plans

We will report the proportion of patients experiencing high-grade toxicity with exact binomial 95% confidence intervals. We will also describe patient experiences with respect to feasibility as defined above. All other adverse events will be similarly summarized by type and grade.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the FDA has determined that the study is exempt from IND requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materialsrelated to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study specific

procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

9.5 Handling and Documentation of Clinical Supplies

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The PI shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the PI will not allow the investigational product to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the PI and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-

approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

9.8 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the PI shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10 References

1. Brock, P.R., et al., Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. N Engl J Med, 2018. **378**(25): p. 2376-2385.

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Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Data and Safety Monitoring Plan for Phase II or III Institutional Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:
• **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
• **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.

• **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
• **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:
• Death.
• Life-threatening (i.e., results in an immediate risk of death).
• Requires inpatient hospitalization or prolongation of existing hospitalization,
• Permanent or significant disability/incapacity
• Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
• Event occurring in a gene therapy study.
• Event that changes the risk/benefit ratio of a study.
• Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

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DSMP Monitoring Templates (version 12Oct2021)