ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091404

A PHASE II STUDY OF ENZALUTAMIDE (NSC# 766085) FOR PATIENTS WITH ANDROGEN RECEPTOR POSITIVE SALIVARY CANCERS

Industry-supplied agent(s): Enzalutamide (IND EXEMPT)

ClinicalTrials.gov Identifier: NCT#02749903

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Participating Organizations:
ALLIANCE / Alliance for Clinical Trials in Oncology (lead)
ECOG-ACRIN/ ECOG-ACRIN Cancer Research Group
NRG / NRG Oncology
SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting **http://eapps-ctep.nci.nih.gov/ctepaers/**	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

Protocol Contacts:

A091404 Nursing Contact

[redacted]

A091404 Pharmacy Contact

[redacted]

Alliance Biorepository at Washington University (WUSTL)

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository

CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted], or [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at https://www.ctsu.org.		

A PHASE II STUDY OF ENZALUTAMIDE (NSC# 766085) FOR PATIENTS WITH ANDROGEN RECEPTOR POSITIVE SALIVARY CANCERS

Pre-Registration Eligibility Criteria (see Section 3.2)

Central pathology review and AR testing review form submission

Registration Eligibility Criteria (see Section 3.3)

Histologically proven diagnosis of salivary cancer by central pathology review

AR expression detected by immunohistochemistry by central review.

Measurable disease as defined in Section 11.0

Locally advanced/unresectable (as determined by local surgeon) OR metastatic disease.

No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration.

No prior therapy with Enzalutamide (previous chemotherapy and/or other AR-targeted approaches is allowed.

Not pregnant and not nursing (See Section 3.3.4)

Age ≥ 18 years

ECOG performance status 0 or 1

Any number of prior lines of therapy

No history of the following:

- Prior brain metastases
- Leptomeningeal disease
- Seizures
- Class 3 or 4 congestive heart failure
- Uncontrolled hypertension (systolic BP->170 mmHg or diastolic BP >105 mmHg at screening)
- Major surgery ≤ 4 weeks of registration

No chronic concomitant treatment with strong CYP2c8 inhibitors or CYP3A4 inducers within 14 days of registration.

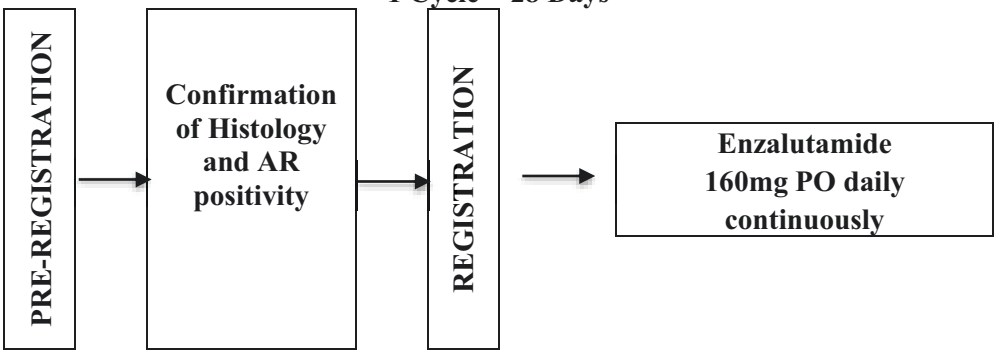
Required Initial Laboratory Values*

Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x ULN
Calc. Creatinine Clearance (see Alliance website)	OR ≥ 30 mL/min
Total Bilirubin	≤ 1.5 x ULN
AST / ALT	≤ 3.0 x ULN

* See Section 3.3.8

Schema

1 Cycle = 28 Days



For patients that are withdrawn from the study for reasons other than radiographic progression, staging scans are to be performed every 3 months (+/- 2 months) until disease progression, for a maximum of 15 months from time of registration. For all patients withdrawn from the study, survival information is required every 6 months until 3 years following registration. **Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.**

Table of Contents

1.0 BACKGROUND

Salivary gland cancers (SGCs) are rare diseases that make up only 5% of all head and neck malignancies[1]. While treatment for locally advanced disease is administered with curative intent, recurrent and/or metastatic SGCs are incurable and commonly treated with palliative chemotherapy. Unfortunately, little prospective trial data is available to guide chemotherapy selection, and there are no FDA-approved or standard therapies. SGCs are a diverse and heterogenous set of disease that the World Health Organization (WHO) divides into more than 20 different histologic types, each with presumably distinct disease biology. Previous phase II SGC trials are difficult to interpret in part because many included all different SGC subtypes[1, 2]. A better understanding of therapeutic targets and the availability of selective, targeted drug therapies provide an opportunity to now design more biology- and target- driven trial concepts that will potentially identify novel therapies and broaden our understanding of these diseases.

1.1 Androgen receptor as a therapeutic target

The androgen receptor (AR) is a therapeutic target that is selectively expressed in a subset of salivary malignancies, but not in normal salivary glands[3]. It is a steroid receptor responsible for sensing and responding to circulating androgens such as testosterone and dihydrotestosterone, which are produced in the testes and adrenal glands[4]. When bound to androgen, AR undergoes a conformational change and translocates from the cytoplasm to the nucleus, where it activates the transcription of AR-dependent target genes. Prostate cancer cells are dependent upon these genes to mediate tumor cell proliferation and survival; suppressing these transcriptional programs via AR-targeting has become a well-established therapeutic strategy for advanced prostate cancer patients. A standard AR-targeted approach for prostate cancer is suppressing gonadal sources of androgen (known as "androgen deprivation therapy" (ADT)) through castration, either surgical (bilateral orchiectomy) or medical (luteinizing-hormone releasing hormone (LHRH) targeting). However, resistant disease can arise ("castration-resistant") since non-gonadal androgen sources (e.g. adrenal glands, intratumoral production) can produce androgen levels sufficient for AR activation. Additionally, tumoral changes in AR biology can make tumors more sensitive to lower levels of circulating androgen, less reliant upon circulating androgens for activation, or newly responsive to a broader spectrum of ligands[5]. Other AR-targeted approaches have been developed to inhibit AR directly and/or better suppress circulating androgen levels. AR-antagonists (also known as "antiandrogens"; e.g. bicalutamide, flutamide, nilutamide, and cyproterone acetate) are drugs that directly bind AR to block ligand engagement (regardless of source), and are often used in combination with castration (known as "combined androgen blockade" (CAB)). Abiraterone acetate is a new generation inhibitor of steroidogenesis that irreversibly binds the p450 enzyme CYP17 to suppress adrenal and tumor intracrine androgen synthesis to therapeutic levels in patients with castration-resistant prostate cancer[6].

1.2 Androgen receptor in salivary cancers

AR is expressed at high rates in specific histologic subtypes of SGCs, particularly salivary duct carcinomas (SDCs; 43-100%) [7-13]. Other histologies that express AR include adenocarcinoma not otherwise specified (NOS), carcinoma ex pleomorphic adenoma, and basal cell adenocarcinomas[9, 12]. Retrospective and case series studies have suggested that AR-targeted approaches can be clinically efficacious for these AR-positive SGCs. The first documentation of this was a 1994 case report of a patient with a locally advanced parotid adenocarcinoma who experienced a partial response after three months of therapy with an LHRH analogue[14]. Locati and colleagues then published a case in which a patient with AR-positive, relapsed parotid carcinoma experienced a complete clinical response after treatment with the LHRH agonist triptorelin plus the AR-antagonist bicalutamide[15]. The same group later reported a 33% overall

response rate with the combination of bicalutamide and cyproterone acetate (another AR antagonist and suppressor of adrenal biosynthesis) in AR-positive SGCs[16]. In 2011, a Dutch group published in the *Journal of Clinical Oncology* a series of 10 patients with SDCs treated with bicalutamide alone or in combination with an LHRH agonist (only one patient received the combination): 5 patients had clinical benefit with 2 experiencing a partial response and 3 achieving stable disease[17]. Two women were treated with bicalutamide in that series; one experienced a partial response, while the other had progressive disease. The median PFS on the study was 12 months and the treatment was overall well tolerated[17]. Recently, Locati et. al. reported two cases of patients with salivary adenocarcinoma NOS responding to abiraterone after having progressed on combined androgen blockade (one responder's tumor was also Her2 amplified by FISH) [18].

1.3 Rationale for proposed trial

These data strongly suggest that a subset of SGCs are AR-dependent and responsive to AR-targeting. However, the efficacy of AR-targeting must be evaluated in a prospective clinical trial. To this end, we propose to conduct a single arm phase II study of the AR-antagonist enzalutamide in patients with recurrent/metastatic, AR-positive salivary cancers. By focusing upon the molecularly defined subset of AR-positive salivary cancers, we are minimizing the biologic heterogeneity that has made previous salivary trials difficult to interpret.

Enzalutamide is a second-generation AR-antagonist that was rationally designed to be a more potent AR inhibitor based upon structure-activity analysis of the AR crystal structure[19]. Besides possessing 5 to 8 fold greater affinity for AR compared to bicalutamide, preclinical data demonstrated that enzalutamide also abrogates AR signaling by blocking AR nuclear translocation, interfering with the recruitment of transcriptional co-activators, and inducing conformational changes that prevent AR from binding target DNA sequences[20]. Two phase III trials have now demonstrated that enzalutamide (compared to placebo, and in combination with castrate levels of androgen) improves the overall survival of patients with castration-resistant prostate cancer when administered either prior to or after chemotherapy[21, 22]. Another phase II trial demonstrated that enzalutamide monotherapy (with non-castrate levels of testosterone) is efficacious for hormone-naïve prostate cancer patients as well (62/63 (98%) patients had $\geq$ 80% PSA decline; 8/16 (50%) patients with measureable metastatic disease had a complete or partial response) [23].

Assuming that the potency of AR signal abrogation achieved is critical for maximizing clinical efficacy, selecting enzalutamide for this study provides the most rigorous evaluation of the hypothesis that AR-targeting is an efficacious strategy for AR-positive SGCs. We propose to evaluate enzalutamide alone without castration for several reasons. ADT is associated with toxicities (fatigue, hot flashes, decreased libido, etc…) and metabolic adverse effects (decreased bone mineral density, muscle mass loss, insulin resistance, obesity, etc…) that may be diminished with enzalutamide alone[23]. Indeed, European Union guidelines support monotherapy with bicalutamide as an alternative to ADT for locally advanced prostate cancer given evidence of improved quality of life with the former. As described above, enzalutamide alone possesses significant activity against hormone naïve prostate cancer[23]. Single agent activity with the anti-androgen bicalutamide (without ADT) has also been reported in AR-positive SDC patients[17]. These lines of evidence provide the rationale that targeting the androgen receptor alone with enzalutamide without ADT may be clinically efficacious and better tolerated for AR-positive salivary cancer patients.

1.4 Rationale for Correlative Science Study (A091404-ST1)

Pre-clinical and clinical studies now suggest several mechanisms of intrinsic and acquired resistance to AR-targeted therapies in prostate cancer which may be relevant for SGCs. These include AR gene amplification or mutations that sensitizes the tumor to low-level androgen concentrations and/or induces responsiveness to a broader range of ligands (e.g. converting AR antagonists into AR agonists), intratumoral production of androgens, expression of AR variants lacking ligand-binding domains (LBD) leading to ligand-independent signaling, and activation of parallel signaling pathways that cross-talk with AR to facilitate resistance (HER2, PI3K/Akt, Src, etc….)[5]. Recently, a retrospective analysis correlated detection of the AR splice variant 7 (AR-V7) transcript (which lacks the AR LBD) in circulating tumor cells to enzalutamide and abiraterone resistance in castration-resistant prostate cancer patients[24].

Just as the efficacy of enzalutamide in AR-positive salivary cancers remains to be evaluated, little is known regarding the relevant mechanisms of resistance to AR-targeting in these diseases. However, a recent publication from Mitani et. al. provides for the first time an important set of insights into AR biology for salivary duct carcinomas[10]. In this study, AR was detected by immunohistochemistry (IHC) in 27 of 35 tumors analyzed (77%). In addition to full-length, wild-type AR, the investigators also detected several AR variants, the most frequent of which was AR-V7 (13 of 35 tumors). Unlike prostate cancer, AR missense mutations and gene amplifications were not found, though X chromosome gain (AR is located on Xq11-12) was detected in 10 of 27 tumors analyzed (though 3 of the cases were negative for AR expression). Experiments performed on the first AR-positive salivary cancer cell line ever developed (derived from a female patient with metastatic poorly differentiated, mixed malignant tumor) confirmed that tumor cell growth for this line was AR-dependent, but potentially driven in a ligand-independent manner[10].

We propose to conduct correlative tissue studies to broadly explore potential biomarkers of efficacy to test the hypothesis that AR genetic or transcript alterations/variants mediate resistance to enzalutamide therapy and potentially generate new hypotheses regarding tumor biology that contribute to clinical efficacy with enzalutamide.

1.5 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. It will take approximately one minute to complete this measure[25].

1.6 Impact of the trial

SGC is an understudied, orphan disease for which no standard drug therapies currently exist. This phase 2 trial of enzalutamide in patients with AR positive SGC will test the central hypothesis that AR signaling is a critical oncogenic driver for a subset of SGCs. This is one of the first trials dedicated to this histologic subtype of SGCs, and could be among the first to prospectively identify an effective drug for these patients. Both the clinical and tissue correlative data that will be generated will enhance our biologic understanding of this disease and suggest future clinical and scientific research directions.

2.0 OBJECTIVES

2.1 Primary objective (or Co-primary Objectives as appropriate)

To evaluate the rate of best overall response (BOR; by RECIST v1.1) associated with enzalutamide in patients with AR-positive salivary cancers.

2.2 Secondary objective(s)

2.2.1 To evaluate the progression-free survival (PFS) of AR-positive salivary cancer patients treated with enzalutamide.

2.2.2 To evaluate the overall survival (OS) of AR-positive salivary cancer patients treated with enzalutamide.

2.2.3 To evaluate the safety/tolerability of enzalutamide for patients with AR-positive salivary cancer.

2.3 Correlative science objective

To identify molecular predictors of response by examining genomic and transcriptional elements of androgen receptor biology.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 1 years.
- Patients who cannot swallow oral formulations of the agent(s).
- Drugs that are metabolized/eliminated by CYP2C9 pathway are to be used with caution while on study, as enzalutamide is a moderate CYP2C9 inducer
- Drugs that are metabolized/eliminated by CYP2C19 pathway are to be used with caution while on study, as enzalutamide is a moderate CYP2C19 inducer.

In addition:

- The effect of enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Subjects receiving enzalutamide are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an enzalutamide study and continuing throughout the course of treatment and for at least three months after enzalutamide is discontinued. Pregnancy reporting is required as per Section 9.3.1.
- SGC histologies that typically express AR at high levels include salivary duct carcinoma, adenocarcinoma, poorly differentiated carcinoma, and high grade carcinoma. Please prioritize considering these SGC histologies for central pathology review to assess AR status, particularly those that have already been noted to be AR positive during routine pathologic investigation. Alternatively, adenoid cystic carcinoma and acinic cell carcinoma are SGC histologies NOT considered to be typically associated with AR expression.

3.2 Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

3.2.1 Central pathology review submission

Patients must have a FFPE tumor block OR 1 representative H&E and 2 unstained SGC tissue slides available for submission to central pathology review and androgen receptor testing (preferably from a metastatic site). This review is mandatory prior to registration to confirm eligibility. See Section 6.2 for details on slide/block submission.

3.2.2 Local Diagnosis

Patients must have a diagnosis by local pathologist of salivary carcinoma. Patients who have had a local androgen receptor testing that is negative are not allowed to participate.

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

___ **3.3.1 Documentation of Disease:**

Histologic Documentation: Histologically proven diagnosis of salivary cancer by central pathology review.

Receptor Status: AR expression detected by immunohistochemistry by central review. See Appendix III for further details.

___ **3.3.2 Disease Status**

Measurable disease, as defined in Section 11.0.

Locally advanced/unresectable (as determined by local surgeon) OR metastatic disease.

___ **3.3.3 Prior Treatment**

- Any number of prior lines of therapy
- No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration.
- No prior therapy with enzalutamide (previous chemotherapy and/or other AR-targeted approaches is allowed).

___ **3.3.4 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.**

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

For women of childbearing potential only, a negative pregnancy test done ≤ 5 days prior to registration is required.

___ **3.3.5 Age ≥ 18 years**

___ **3.3.6 ECOG Performance Status 0 or 1**

___ **3.3.7 No History of the following**

- Prior brain metastases
- Leptomeningeal disease
- Seizures
- Class 3 or 4 congestive heart failure
- Uncontrolled hypertension (systolic BP > 170mmHg or diastolic BP > 105 mmHg) despite optimal medical management
- Major surgery ≤ 4 weeks of registration

___ **3.3.8 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN) **OR**
Calc. Creatinine Clearance	≥ 30 mL/min
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)
AST / ALT	≤ 3.0 x upper limit of normal (ULN)

___ **3.3.9 Concomitant medications**

Chronic concomitant treatment with strong CYP2C8 inhibitors is not allowed. Patients must discontinue the drug ≥ 14 days prior to registration. See Section 7.1 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug ≥ 14 days prior to registration. See Section 7.1 for more information.

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at [redacted].

4.2 CTSU Site Registration Procedures

This study is supported by the NCI CTSU.

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on Protocols in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select Alliance and protocol number A091404;
- Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Checking Your Site's Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on Regulatory at the top of your screen;
- Click on Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.3 Patient Pre-Registration Requirements (Step 0)

- **Informed consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Protected Health Information:** Paraffin Tumor tissues collected for this study will be sent directly to the Memorial Sloan Kettering Cancer Center. These samples will be labeled with patient initials, study ID, and collection date.
- **Central pathology review submission:** Patients who meet the pre-registration eligibility criteria will be pre-registered using the OPEN registration system (see Section 4.6) in order to submit specimens for central pathology review. Once a patient is pre-registered, the diagnostic H&E's and one tissue block should be sent to the Memorial Sloan Kettering Cancer Center along with a completed "Central Pathology Review and AR Testing Results Form", per Section 6.0). **Failure to submit this form with the specimens will delay turnaround time for central pathology review and AR testing.** The specimen will be centrally reviewed to confirm the patient meets the pathology criteria.

4.4 Patient Registration Requirements (Step 1)

- **Confirmation of eligibility by central pathology review and AR testing:** Sites will be notified via e-mail within 5 business days of receipt, whether or not the patient is eligible based on the central pathology review. The results section of the "Central Pathology Review and AR Testing Form" will be completed by the pathologist, scanned and sent via e-mail to the Responsible CRA listed on the form. The form will indicate whether or not the patient is eligible, based on pathologic diagnosis and AR result.
    - Pathology result: The result will indicate that the patient does have SGC or not. If not, the patient is ineligible for the trial. The treating physician should inform the patient and determine next steps.
    - AR result: The result will indicate whether the patient is AR positive or negative. If positive, the patient is eligible, if negative, the patient is ineligible.

  After receiving the results form via e-mail, the institution must forward the form to the Alliance Patient Registration office at [redacted] in order to register the patient. Once the results are confirmed and the Registration-Eligibility Criteria have been met, the patient can be registered using the OPEN system per Section 4.6. Registration must occur within 35 days of specimen submission. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Please contact Alliance Patient Registration office at [redacted] if registration problems occur.

4.5 Patient Pre-Registration/Registration Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at [redacted].

4.6 Registration to Correlative and Companion Studies

4.6.1 Registration to Substudies described in Section 14.0.

There is one substudy within Alliance A091404. This correlative science study must be offered to all patients enrolled on Alliance A091404 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A091404 is:

- DNA and RNA Analysis of Archival and Flash Frozen Tissue From Androgen Receptor-Positive Salivary Gland Cancers- A091404-ST1 (Section 14.1)

If a patient answers "yes" to "I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study (ies) described above." in the model consent, they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A091404-ST1 at the same time they are registered to the treatment trial (A091404). Samples should be submitted per Section 6.2.

4.7 Stratification (or Grouping) Factors-None

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial. One cycle is 28 days.

- To be completed ≤ 14 DAYS before registration: All laboratory studies, with exception of serum or urine HCG.
- To be completed ≤ 28 DAYS before registration: Scans of any type which is to be utilized for tumor measurement per protocol, history and physical, weight/height, vital signs.

	Prior to Registration*	Days 1 and 15 of cycle 1, then Day 1 of every cycle *	At PD, withdrawal, or removal**
Tests & Observations			
History and physical, weight, PS	X	X	X
Height	X		
Pulse, Blood Pressure	X	X	
Registration Fatigue/Uniscale Assessment (Ψ)	X		
Adverse Event Assessment (π)	X	X	X
Patient Medication Diary (1)		X	X
Laboratory Studies			
Complete Blood Count, Differential, Platelets	X	X	X
Serum Creatinine	X	X	X
Albumin, glucose	X	X	X
AST, ALT, Alk. Phos., Bili	X	X	X
Serum or Urine HCG	X(2)		
Hormone panel***		X	X
Staging			
Central Pathology review for eligibility (including AR testing)	X(3)		
Radiographic imaging	X(4)	A	X**
Correlative studies: For patients who consent to participate			
Archival Tissue	5		
Tumor tissue biopsy	5#		
Research Blood Sample	5		

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, tests and observations may be obtained +/- 3 days from day 15 cycle 1, and +/- 5 days from day 1 of cycle 2 and beyond. Scans may be obtained +/- 7 days from date due.

** Post treatment follow-up evaluations and blood tests are required 30 days (+/- 5 days) after the end of treatment. For patients that are withdrawn from the study for reasons other than radiographic progression, staging scans are to be performed every 3 months (+/- 2 months) until disease progression, for a maximum of 15 months from time of registration. For all patients

withdrawn from the study, survival information is required every 6 months until 3 years following registration. See also Section 12.0.

*** The hormone panel includes total and free testosterone. The hormone panel will be drawn first after study registration but PRIOR to initiation of study drug, and then Day 1 of every even-numbered cycle starting with cycle 2 times 3 (D1C2, D1C4, D1C6, +/- 7 days), and then at off study (+/- 7 days).

Ψ To be completed after registration and ≤ 21 days prior to treatment, see Section 1.5 and Appendix I.

π Solicited AEs are to be collected starting at baseline until off treatment (See Section 9.1). Routine AEs are to be collected starting after registration. See Section 9.3 for expedited reporting of SAEs.

At baseline (after registration and prior to day 1 cycle 1 of study drug) and after progression (See Section 6.2 for further information).

1 Medication diary should be completed by the patient throughout treatment, and should be collected by site staff at day 1 of every cycle starting with day 1 cycle 2. See Appendix II.

2 For women of childbearing potential (see Section 3.3). Must be done ≤ 5 days prior to registration and ≤ 10 days prior to day 1 cycle 1.

3 See Sections 6.2.

4 Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT performed with both IV and oral contrast, with the CT acquired with 5 mm or less slice thickness (see Section 11.3.2). Supporting documentation is to be submitted, per Section 6.1.1.

5 For patients who consent to submitting archival tumor tissue and research blood samples for correlative tissue analyses and banking, these should be obtained and submitted within 30 days of registration.

A Every 2 cycles for the first 8 cycles (beginning Day 1 Cycle 3) then every 3 cycles (beginning with Day 1 Cycle 9), until evidence of progression or relapse. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0). **Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.**

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted].

6.1.1 Supporting documentation

This study requires supporting documentation for diagnosis, response, and progression. Supporting documentation will include pathology, radiology, and reports. These must be submitted at the following time points:

- Screening: Site will be required to upload the "Central Pathology and AR Testing Results Form" confirming eligibility onto the screening form.
- On study: clinic note, radiology report of baseline study scan only, and local pathology report establishing diagnosis
- Upon partial or complete response: radiology report
- Upon progression: radiology report and pathology report (if applicable)

6.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.3 Specimen collection and submission

For all patients registered to Alliance A091404: real-time histopathology review for AR status will be conducted using the paraffin tumor tissue from a diagnostic biopsy or surgery specimen. **The submission of these samples for histopathology review is required for all patients registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy.**

The central pathology review and AR testing will be performed by [redacted] at Memorial Sloan Kettering Cancer Center.

Typical turn-around time for central pathology review and AR testing is within 5 working days of receipt of the slides and tissue.

For patients registered to substudy A091404-ST1: All participating institutions must ask patients for their consent to participate in the correlative sub-studies planned for Alliance A091404-ST1 (model consent question, "I agree to have my blood and tissue from my previous surgery collected and I agree that my blood and tissue from previous surgery and related information may be used for the laboratory study(ies) described above"), although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, tissue and blood will be collected at the following time points for these studies:

	≤ 30 days of registration	**At disease progression***	**Storage/ Shipping conditions**	**Submit to:**
For patients pre-registered to A091404, submit the following:				
Paraffin block and 1 H&E for histopathology review (preferably from a metastatic site)	X(1)		Ambient temperature/ overnight	MSKCC
For patients registered to A091404-ST1, submit the following:				
Whole Blood (2) (EDTA/lavender top)	1 x 10 mL		Cool pack/ship overnight	WUSTL
Research tumor biopsy (frozen and paraffin-embedded)	X	X	Dry ice/overnight	WUSTL

* Progression samples may be collected and submitted up to 3 months after progression.

1 For patients pre-registered to A091404 and A091404-ST1(described in Section 14.1, (consent question "I agree to have my blood and tissue from my previous surgery collected and I agree that my blood and tissue from previous surgery and related information may be used for the laboratory study(ies) described above.") and/or banking for future research (consent question "My samples and related information may be kept in a Biobank for use in future health research"), 1 H&E and a paraffin block should be submitted. If a Paraffin block is not submitted, , then 30 unstained slides (5 micron thickness) or as many as possible if fewer than 30 slides (but at least 2 slides) should be submitted in the lieu of a paraffin block. After central pathology review and AR testing are performed, the remaining FFPE tissues (after histology review and Androgen Receptor test) will be sent to the Alliance Biorepository at Washington University (WUSTL) by the Memorial Sloan Kettering lab.

For patients who pre-registered to A091404 BUT did not consent to A091404-ST1 (consent question "**I agree to have my blood and tissue from my previous surgery collected and I agree that my blood and tissue from previous surgery and related information may be used for the laboratory study(ies) described above**"), nor banking for future research; please submit 1H&E and 2 unstained slides to MSKCC for central pathology review and AR testing

2 Whole blood to be used for genomic analyses described in Sections 14.1.This whole blood can be collected any time while patient is on study, but preferably prior to the initiation of treatments.

6.3.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted].

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A091404), Alliance patient number, patient's initials, date and type of specimen collected (e.g., whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays.

Tissue samples for histology review, and Androgen Receptor testing should be sent to:

[redacted]

All other specimens (whole blood and research biopsies) should be sent to the following address:

[redacted]

6.3.2 Paraffin block/slide collection and processing for histopathology review

Consistent and accurate assessment of AR status is important for study eligibility. Submission of paraffin blocks or slides from a diagnostic tumor biopsy or surgery is required for all patients enrolled to this study. All tissue will be sent to Memorial Sloan Kettering. All samples should be labeled with institutional surgical pathology number (tumor samples), study number, patient ID number patient initials, sample collection date and time per section 6.2.1.

Blocks which contain minimal amounts of tissue specimen or that are very thin should not be submitted unless the block is the only representative tissue for the case. A de-identified surgical pathology report should be sent with all specimens. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report. In addition to the pathology report, the institution must complete and submit the "Central Pathology Review Form and AR Testing Form" with the tumor block or slides to Memorial Sloan Kettering Cancer Center. Failure to submit this form with the specimens will delay turnaround time for central pathology review. The top portion of the form must be completed by typing and cannot be handwritten. For Alliance members, the form may be found on the A091404 study page on the Alliance website under the "Supplemental Materials" tab. For non-Alliance institutions, the form can be found under "Miscellaneous" documents section of the CTSU A091404 study page (www.ctsu.org). When shipping blocks and /or FFPE slides, it is important to avoid extreme heat. If environmental conditions indicate, specimens may be shipped in containers containing cold packs. The diagnostic slides must be appropriately packed to prevent damage (e.g. slides should be placed in appropriate slide container) and placed in an individual plastic bag. It is also important that blocks are shipped in appropriately padded and secure containers to avoid physical damage. Do not wrap blocks or slides in tissue or paper toweling that is in direct contact with the paraffin.

The residual material will be forwarded for storage to the Alliance Biorepository at Washington University (WUSTL) by the laboratories performing the central pathology review and AR testing on a yearly basis. Please see Section 6.2.1 for contact information for WUSTL.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent, 30 unstained slides at 5 micron thickness, or as many as possible if fewer than 30 (but at least 2 unstained slides) must be sent.

The goal of the Alliance Biorepository is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the Alliance Biorepository will be vacuum packed to prevent oxidation and will be stored at 4º C to minimize degradation of cellular antigens. For these

reasons it is preferred that the Alliance Biorepository bank the block until the study investigator requests thin sections. Please contact the Alliance Biorepository if additional assurances with your hospital pathology department are required.

6.3.3 Whole Blood submission (for A091404-ST1)

For patients who consent to participate in blood collection, whole blood samples will be used for genomic studies described in Section 14.1. This sample should be collected prior to the initiation of protocol treatment.

Collect 1x10 mL of peripheral venous blood in an EDTA (lavender) tube. The tubes should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository at Washington University. The samples should be labeled with study number, patient ID number patient initials, sample collection date and time and be shipped the same day that the blood is drawn in room temperature with cold pack per Section 6.2.1.

6.3.4 Research tumor biopsies (for A091404-ST1)

For patients who consented to have the research biopsies of A091401-ST1, research tumor biopsies will be performed prior to initiation of enzalutamide and/or at the time of tumor progression (except for those that discontinue therapy for unacceptable toxicities). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores; optimally 4 to 6 cores preferred) is encouraged as long as it is considered reasonably safe for the patient. The tissues will be flash frozen immediately. If sufficient tissue is available, 1-2 core biopsies will also be fixed in formalin and submitted together with the flash frozen tissue. **It is important that samples are frozen or fixed within 30 minutes of removal from the patient.** All samples should be labeled with institutional surgical pathology number (tumor samples), study number, patient ID number patient initials, sample collection date and time, and should be shipped on dry ice with overnight service to the Alliance biorepository at Washington University according per Section 6.2.1.

7.0 TREATMENT PLAN/INTERVENTION

Enzalutamide will be given 160 mg orally once daily (1 cycle= 28 days). Dose interruptions and reductions are detailed in protocol Section 8.2. Patients will remain on therapy until progression of disease or development of unacceptable toxicities or patient or physician withdrawal.

Protocol treatment is to begin ≤ 7 days of registration.

It is acceptable for individual study drug doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

To determine response via RECIST v1.1, patients will undergo radiographic imaging every 2 months (+/- 7 days) treatment for the first 8 cycles (beginning Day 1 Cycle 3) then every 3 cycles (beginning with Day 1 Cycle 9), until evidence of progression or relapse.

Agent	Dose	Route	Schedule
Enzalutamide	160 mg	PO	Daily

Note: If a patient is suspected to be pregnant, enzalutamide should be IMMEDIATELY discontinued and the study physician contacted. A positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patients is not pregnant, the patient may resume dosing with enzalutamide.

7.1 CYP2C8 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP2C8 is not allowed on this trial. The following drug is an EXAMPLE of a strong inhibitor of CYP2C8 and is not allowed during treatment with enzalutamide:

- Gemfibrozil

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP2C8. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts, the FDA, or your local institution's pharmacist.

7.2 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed on this trial. The following drugs are EXAMPLES of a strong inducer of CYP3A4 and are not allowed during treatment with enzalutamide:

Rifampin

Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4 Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts, the FDA, or your local institution's pharmacist.

8.0 DOSE AND TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint. Exception: For patients who were previously treated with a luteinizing hormone-releasing hormone (LH-RH) agonist or antagonist, the LH-RH agonist or antagonist may be continued on this trial at the discretion of the attending physician.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); intermittent use of dexamethasone as an antiemetic or for conditions that are not related to malignancy. Exception: For patients who were previously treated with a luteinizing hormone-releasing hormone (LH-RH) agonist or antagonist, the LH-RH agonist or antagonist may be continued on this trial at the discretion of the attending physician.

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.5 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 Palliative radiation therapy may not be administered during study enrollment.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.7 Surgery: Patients who require surgery during protocol treatment may proceed as such, unless the surgery involves resection of salivary cancer. Study agent should be held prior to and after surgery, for a maximum of 28 days. If the patient requires an interruption of > 28 days, then they will be removed from protocol therapy.

8.1.8 Anticoagulation: Anticoagulation is allowed while on trial. Enzalutamide is a moderate CYP2C9 inducer, and drugs that are metabolized by CYP2C9 should be avoided, which includes warfarin. For patients who require warfarin therapy on trial, INR should be monitored closely while taking study agent. Utilization of other anticoagulation is recommended.

8.1.9 Hypertension: Patients taking enzalutamide should maintain well-controlled blood pressure. The choice of medications used to control blood pressure is at the discretion of the treating physician.

8.1.10 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2015: Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol , 2015.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician. The use of epoetin should follow published guidelines of the American Society of Clinical Oncology 2010 Update of Recommendations on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28(33): 4996-5010, 2010.

Filgrastim (G-CSF), tbo-filgrastim and sargramostim (GM-CSF)

1. Filgrastim (G-CSF)/tbo-filgrastim/pegfilgrastim and sargramostim (GM-CSF) treatment for patients on protocols that do not specify their use is discouraged.
2. Filgrastim/tbo-filgrastim/pegfilgrastim and sargramostim may not be used:
    a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
    b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastimtbo-filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
    c. If filgrastim/tbo-filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.11 Reproductive Considerations

See Sections 3.1 and 3.3.4 for details on teratogenicity of agents and reproductive considerations while on study agent. Please note that patients will need to continue pregnancy prevention for 3 months after discontinuation of study drug.

8.2 Dose Modifications

The following general guidelines apply to all dose modifications listed below

- Doses will not be re-escalated once reduced
- If dose reduction below dose level -2 is required, treatment with the agent will be discontinued.
- If treatment is held for more than four weeks due to toxicity, discontinue protocol therapy
- Each cycle is always 28 days regardless of dose interruption. (i.e., a 7 day interruption of a dose starting on day 15 of a cycle would mean that the dose is restarted on day 22 of the same cycle)
- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

NOTE: AERS reporting may be required for some adverse events (See Section 9.0)

Dose level table for enzalutamide

Dose Level	enzalutamide
0 (starting dose)	160 mg/day
-1	120 mg/day
-2	80 mg/day

8.2.1 Hepatic Toxicity

For ≥ grade 3 ALT or AST or Bilirubin (see Investigations in CTCAE v. 4.0), interrupt enzalutamide. Check liver function labs weekly. Restart enzalutamide at one dose level reduction when ALT, AST, and bilirubin recover to grade 1. Monitor serum transaminases and bilirubin every two weeks for three months and monthly thereafter.

For hepatic failure (see Hepatobiliary Disorders in CTCAE v. 4.0), discontinue enzalutamide.

8.2.2 Neurologic toxicity

Discontinue enzalutamide for any seizure.

8.2.3 Reversible posterior leukoencephalopathy syndrome (RPLS)

For signs and symptoms suggestive of reversible posterior leukoencephalopathy syndrome (RPLS) such as confusion, headache, seizures, and cortical blindness, hold enzalutamide for up to 4 weeks. Suspected RPLS should be investigated with MRI. If diagnosis of RPLS is confirmed, enzalutamide should be permanently discontinued. If RPLS is ruled out via MRI and signs and symptoms attributed to another cause, enzalutamide should resume.

8.2.4 Other Non-Hematologic Grade 3 or 4 Toxicity

For patients on both arms who experience a grade 3 or greater toxicity attributed to enzalutamide, enzalutamide should held for one week or until symptoms improve to ≤ grade 2. Patients may be re-started on enzalutamide at one dose level reduction. If treatment is held for more than 4 weeks, discontinue protocol therapy.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. **However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018.** The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events: Solicited and Adverse Events: Other forms are used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment. Please note that diarrhea will be graded at baseline based on recording number of stools per day.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Fatigue	General disorders
Hot Flashes	Vascular disorders
Diarrhea	Gastrointestinal disorders
Hypertension	Vascular disorders
Dizziness	Nervous system disorders
Seizures	Nervous system disorders
Localized Edema	General disorders
Gynecomastia	Reproductive system and breast disorders
Breast pain	Reproductive system and breast disorders
Weight loss	Investigations

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. 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 beginning April 1, 2018. 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 further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention 1

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3 – 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting

- Grade 3 or 4 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 diarrhea and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 diarrhea does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 fatigue and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 fatigue does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 hot flashes and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 hot flashes does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 edema and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 edema does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 2 or greater posterior reversible leukoencephalopathy syndrome must be reported via AERS.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE v5.0, secondary malignancies may be reported as one of the following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- CTEP-AERS reports should be submitted electronically.
- Pregnancy loss is defined in CTCAE as “Death in utero.” Any Pregnancy loss should be reported expeditiously, as Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, “Death neonatal” under the General disorders and administration SOC.
- Death due to progressive disease should be reported as Grade 5 “Disease progression” in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

10.0 DRUG INFORMATION

10.1 Enzalutamide (Xtandi®)(NSC#766085)

Procurement

Enzalutamide is an investigational agent supplied by Astellas Pharma US, Inc. and distributed by McKesson Specialty Pharmacy. Use the order form on the A091404 Alliance or CTSU webpage to order enzalutamide.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation

Enzalutamide is supplied as 40 mg white to off-white oblong liquid-filled soft gelatin capsules for oral administration. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide and black iron oxide.

Storage and Stability

Store enzalutamide at 20º to 25ºC (68º to 77ºF) in a dry place and keep the container tightly closed. Excursions permitted to 15º to 30ºC (59º to 86º F).

Administration

Enzalutamide is administered orally once daily with or without food. Swallow capsules whole, do not open or crush.

Drug Interactions

Enzalutamide is metabolized by CYP2C8 and CYP3A4. Co-administration of a strong CYP2C8 inhibitor, gemfibrozil) increased the area under the plasma concentration-time curve (AUC) of enzalutamide and N-desmethyl enzalutamide by 2.2-fold in healthy volunteers. Administration of strong CYP2C8 inhibitors is not allowed. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g. rifampin) may alter plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

Co-administration of itraconazole, a strong CYP3A4 inhibitor, increased the AUC of enzalutamide and N-desmethyl enzalutamide by 1.3-fold in healthy volunteers. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concurrent medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

Enzalutamide is a strong CYP3A4 inducer and moderate CYP2C9 and CYP2C19 inducer. Enzalutamide reduced plasma exposure of midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), CYP2C9 (e.g. phenytoin, warfarin), and CYP2C19 (e.g. S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

Pharmacokinetics

Absorption: rapid with time to peak concentration in 1 hour (range 0.5-3 hours). A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide.

Distribution: 110 L; protein binding of parent drug is97-98% to primarily albumin; protein binding of active metabolite is 95% to plasma proteins

Metabolism: Hepatic via CYP2C8 (formation of active metabolite N-desmethyl enzalutamide) and CYP3A4

Excretion: Primarily eliminated by hepatic metabolism. Following single oral administration of 14C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: Urine (71%), feces (14%) primarily as inactive metabolite

T1/2: Enzalutamide: 5.8 days (range 2.8-10.2 days); N-desmethyl enzalutamide: 7.8-8.6 days.

Adverse Events

Common known potential toxicities, > 10%:

Cardiovascular: Peripheral edema, hypertension

Central Nervous System: Fatigue, falling, headache, dizziness

Endocrine & Metabolic: Hot flash, weight loss

Gastrointestinal: Constipation, diarrhea, decreased appetite

Hematologic & Oncologic: Neutropenia

Neuromuscular & Skeletal: Weakness, back pain, arthralgia, musculoskeletal pain

Respiratory: Upper respiratory tract infection, dyspnea

Less common known potential toxicities, 1 to 10%:

Central Nervous System: Myasthenia, insomnia, anxiety, paresthesia, cauda equine syndrome, spinal cord compression, altered mental status, hypoesthesia, hallucination, and restless leg syndrome

Dermatologic: Pruritus, xeroderma

Endocrine & Metabolic: Gynecomastia

Gastrointestinal: Dysgeusia

Genitourinary: Hematuria, pollakiuria

Hematologic & Oncologic: Thrombocytopenia

Hepatic: Increased serum bilirubin

Infection: Infection

Neuromuscular & Skeletal: Bone fracture, stiffness

Respiratory: Lower respiratory tract infection, epistaxis

Rare known potential toxicities, < 1% (Limited to important or life threatening):

Seizure

Reversible Posterior Leukoencephalopathy Syndrome

Please see package insert for further information for enzalutamide.

Nursing Guidelines

- Instruct patients that enzalutamide can be taken either with or without food.
- Assess patient's concurrent medication including over the counter supplements. There are numerous drug-drug interactions as outlined in section 10.1.
- Patients may experience peripheral edema; instruct patients to report any swelling to the study team.
- Warn patients of myalgias. These can be mild to severe. Treat symptomatically and monitor for effectiveness.
- Rarely patients may experience seizures. Warn patients of this and instruct patients to seek out emergency medical attention if they experience a seizure.
- Patients may experience fatigue. Instruct patient in an energy conserving lifestyle, encourage alternating rest and exercise as tolerated.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).[26] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients **should be reevaluated every 8** weeks for the first 8 cycles and every 12 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are not considered measurable disease.

11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  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. The lesions should be measured on the same pulse sequence. 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:** 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.

- **Chest X-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

     1) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

     2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

     3) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.3.3 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 4 weeks (see Section 11.4.4).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.4.3.3.

11.4.3 Response Criteria

11.4.3.1 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.4.3.2 Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.4.3.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3.1

11.4.5 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD will continue on therapy until disease progression, intolerable toxicity, or patient refusal. After treatment is discontinued, patients will be followed per the study calendar in Section 5.0.

12.1.2 Disease Progression: After disease progression, patients should be followed for survival per the study calendar (Section 5.0). Patients will be followed for 3 years after ending treatment.

12.1.3 Discontinuation of study agent: If the patient discontinues enzalutamide, patients should be followed for survival per the study calendar (Section 5.0).

12.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This single arm Phase II trial will assess the best overall response (BOR; by RECIST v1.1) associated with enzalutamide in patients with AR-positive salivary cancers. Given that this will be one of the first prospective studies ever conducted for AR-positive salivary cancers, and there are currently no standard therapies known to be effective for this disease, we will adopt a BOR of 5% as the null hypothesis and BOR of 20% as the alternative hypothesis. In addition to response, this study will also evaluate the progression-free survival (PFS), overall survival (OS), adverse events, and will also try to identify molecular predictors of response by examining genomic and transcriptional elements of androgen receptor biology.

13.2 Primary Endpoint

The primary endpoint for this study is the best overall response rate (BOR; by RECIST v1.1) associated with enzalutamide in patients with AR-positive salivary cancers documented to occur any time during the first 8 cycles (32 weeks). Per RECIST 1.1, responses need to be confirmed (2 consecutive responses at least 4 weeks apart) to count as a response (see Section 11). All eligible patients who are registered and start treatment will be evaluable for response. A Simon's optimal two-stage design will be utilized. In order to detect a difference between an unacceptable BOR of 5% and a desirable BOR of 20% with one-sided type one error of 5% and a power of 90%, at least two responses need to be observed among the 21 patients enrolled in the first stage. If this is achieved, then the study will progress to the second stage in which an additional 20 patients will be accrued. At the end of the trial, at least 5 responses need to be observed among a total of 41 patients enrolled for the drug to be considered worthy of further investigation. The study will be temporarily closed for stage 1 analysis, if necessary (i.e only if 1 or fewer responses have been observed at the time we have 21 evaluable patients enrolled).

13.3 Secondary Endpoints

The following endpoints will be evaluated: progression-free survival, overall survival, and adverse events.

Progression-Free Survival: Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method. The median PFS and 95% confidence interval will be reported.

Overall Survival (OS): OS is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method. The median OS and 95% confidence interval will be reported.

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 4.0. The frequency and percentage of grade 3+ adverse events will be summarized. We will also closely monitor adverse events throughout the study.

13.4 Translational Studies

Due to the limited sample size in this study, the proposed translational studies are considered exploratory and hypothesis generating. Analyses of biomarkers will be summarized by descriptive statistics, including mean, median and standard deviation for continuous biomarker data and frequency (%) for categorical data. Differences in these biomarkers between responders and non-responders will be compared using Fisher's exact tests for categorical biomarker data and Wilcoxon Rank-Sum tests for continuous biomarker data. In addition, a Cox proportional

hazards model will be used to explore the prognostic relationship for these biomarkers measured at baseline and PFS and OS.

13.5 Total Sample Size

A maximum of 41 evaluable patients will be accrued onto this study unless the study is closed early for excessive toxicity or lack of efficacy. We anticipate accruing an additional 10% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 45 patients.

13.6 Expected Accrual and Accrual Duration

The expected accrual during the first 6 months is 1 patient per month as sites are opening the trial, then 2 per month. The total time for study accrual is expected to be around 26 months.

13.7 Anticipated time to study completion

We anticipate that the study will take approximately 36 months to complete. This allows a 6-month follow-up for the final patient enrolled, along with data entry, data clean-up, and analysis.

13.8 AE Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

The study team will have regular toxicity calls to review overall toxicity, along with AERs reports.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following criteria.

- For this study, unacceptable toxicity is defined as: treatment related deaths or seizures. If 1 or more patients out of the first 10 patients enrolled (or subsequently, if more than 10% of all patients) develop unacceptable toxicity, the study will be temporarily suspended until the review of all toxicity data is completed and a decision is made about whether it is safe to resume accrual. This decision will be made by consensus of the study team and CTEP.

In addition, any required reporting to the FDA will be made as per 21 CFR 312.32 by the pharmacovigilance executive officer and Alliance regulatory department.

13.9 Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 1-2 patients per month, it is expected that the study will take around 26 months to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 4 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

13.10 Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting):

The primary endpoint is response rate, as discussed in detail in Section 13.2. The final analysis is expected to take place around 36 months after the study begins, so we expect that the primary endpoint completion time to be around 36 months after study activation.

13.11 Descriptive Factors

Performance Status:
- ECOG 0 vs 1

Histologic Subtypes:
- Salivary duct carcinoma
- Adenocarcinoma not otherwise specified (NOS)
- Carcinoma ex pleomorphic adenoma
- Basal cell adenocarcinomas
- Other

Age:
- <55 years old vs ≥ 55years old

Prior Line of therapy:
- No prior lines of systemic therapy vs 1+ prior lines of systemic therapy

Prior AR-targeted therapy:
- Anti-androgen (bicalutamide, nilutamide, etc…)
- Androgen deprivation therapy (surgical castration, GnRH agonist/antagonist (leuprolide), ketoconazole, abiraterone, etc…)
- Other

Stage at initial diagnosis:
- Stage I or II
- Stage III
- Stage IVa
- Stage IVb
- Stage IVc
- Sites of metastases:
  - Lung metastases only
  - Bone metastases only
  - Other

13.12 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Based on prior studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race and about 40% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	3	4
Not Hispanic or Latino	18	23	41
Ethnic Category: Total of all subjects	19	26	45
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	1	1	2
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	1	1	2
White	15	21	36
Racial Category: Total of all subjects	19	26	45

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one substudy within Alliance A091404. This correlative science study must be offered to all patients enrolled on Alliance A091404 (although patients may opt to not participate). The substudy included within Alliance A091404 is:

14.1 Correlative Science (Alliance A091404-ST1)

14.1.1 Background

There is pre-clinical and clinical evidence regarding mechanisms of intrinsic and acquired resistance to AR-targeted therapies in prostate cancer which may also be relevant for SGCs. These include AR gene amplification or mutations that sensitizes the tumor to low-level androgen concentrations and/or induces responsiveness to a broader range of ligands (e.g. converting AR antagonists into AR agonists), intratumoral production of androgens, expression of AR variants lacking ligand-binding domains (LBD) leading to ligand-independent signaling, and activation of parallel signaling pathways that cross-talk with AR to facilitate resistance (HER2, PI3K/Akt, Src, etc….) [27]. Recently, a retrospective analysis correlated detection of the AR splice variant 7 (AR-V7) transcript (which lacks the AR LBD) in circulating tumor cells to enzalutamide and abiraterone resistance in castration-resistant prostate cancer patients[28].

Just as the efficacy of enzalutamide in AR-positive salivary cancers remains to be evaluated, little is known regarding the relevant mechanisms of resistance to AR-targeting in these diseases. However, a recent publication from Mitani et. al. provides the first important set of insights into AR biology for salivary duct carcinomas [29]. In this study, AR was detected by immunohistochemistry (IHC) in 27 of 35 tumors analyzed (77%). In addition to full-length, wild-type AR, the investigators also detected several AR variants, the most frequent of which was AR-V7 (13 of 35 tumors). Unlike prostate cancer, AR missense mutations and gene amplifications were not found, though X chromosome gain (AR is located on Xq11-12) was detected in 10 of 27 tumors analyzed (though 3 of the cases were negative for AR expression). Experiments performed on the first AR-positive salivary cancer cell line ever developed (derived from a female patient with metastatic poorly differentiated, mixed malignant tumor) confirmed that tumor cell growth for this line was AR-dependent, but potentially driven in a ligand-independent manner.

We propose to analyze archival tissue collected in A091404 to investigate how some baseline tumor genetic biomarkers may correlate to clinical efficacy. However, currently available platforms for fixed tissues are limited in the number of genes/exons that may be analyzed, and analysis of a single time point is insufficient for investigating changes in the genetic composition and gene expression program that may occur with therapy. Hence, this companion study also seeks to characterize the genomic landscape of tumors in an unbiased fashion by performing whole exome or whole genome sequencing upon frozen research biopsied tissues. Whole transcriptome shotgun sequencing (RNAseq) will also be done to provide an unbiased evaluation of the RNA transcripts present in the tumor. Performing these analyses in pre-therapy and at the time of progression samples will provide insight into enzalutamide-related changes in the genomic and transcriptomic landscape, including potential acquired mechanisms of therapeutic resistance.

14.1.2 Objectives

We propose to conduct correlative tissue studies to evaluate potential biomarkers of efficacy in an exploratory manner. Archival, fixed tissue samples (submitted block equivalent to > 30 unstained slides or 30 unstained slides) and flash frozen biopsy tissues will be analyzed for 1) full-length AR and AR-V7 mRNA transcripts by RNA in situ

hybridization (ISH) and 2) genetic alterations using an exon capture-based next-generation sequencing of over 300 cancer-related gene exomes.

14.1.3 Methods

RNA in situ hybridization (ISH): RNA ISH will be performed to detect the full-length androgen receptor (AR) and AR-V7 using the ACD (Advanced cell Diagnostics, Hayward, CA) probes and reagents, as previously published [30]. Specifically, the ACD target probes are designed to detect RNA corresponding to exon 1 of the human AR (ACD 401211), or the cryptic AR exon 3 sequence 1,3 that encode human AR-V7 (ACD 401221).

Recognizing that the development of technologies is occurring at a rapid pace, if other approaches for analyzing RNA from archival/fixed tissues (including but not limited to next generation sequencing platforms (such as RNAseq)) those techniques may be used in addition to or in lieu of RNA ISH.

Analysis of tumor genetic alterations: The genomic platform that will be used will be in part determined by the technology available at the time of tissue analysis. As a default, the plan will be to analyze tumors with a next generation sequencing platform focused on select genes/exons. If at the time of tissue analysis the technology has advanced to allow for whole exome or whole genome interrogation of fixed tissues, then those techniques may be used. Comparisons of DNA between tumor and germline sequencing data from normal tissue (from the 10 mL research blood draw) will be performed to identify tumor-specific somatic events. There is no intention to analyze the germline data beyond utilizing it as a normal control for the tumor tissue analysis, and none of this genomic data will not be communicated to the patient.

Research tumor biopsies will be performed prior to initiation of enzalutamide and/or at the time of tumor progression (patients can opt to participate in one or both biopsies). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores; 4-6 would be preferred) can be performed as long as it is considered reasonably safe for the patient. The tissues will be flash frozen: 1 to 2 cores will be fixed if sufficient tissue is available.

DNA and RNA will be extracted from frozen samples and/or paraffin tissue. A research peripheral blood sample will be collected to serve as normal control. DNA will be submitted for whole exome or whole genome sequencing; RNA will be submitted for RNAseq (all done in collaboration with [redacted], Memorial Sloan Kettering Cancer Center). Alternative DNA and RNA analyses may also be considered in addition to or in lieu of the above when appropriate (targeted analysis of select genes/exons, RNA ISH, etc..). There is no intention to analyze the germline data beyond utilizing it as a normal control for the tumor tissue analysis, and generally germline data will not be communicated to the patient.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II: PATIENT MEDICATION DIARY - ENZALUTAMIDE

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **enzalutamide**.
2. You will take your dose of **enzalutamide** daily.
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.
5. Take enzalutamide capsules orally in the morning with or without food. The capsules should be swallowed whole and must not be crushed or broken.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's Signature	Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

APPENDIX III: CENTRAL LABORATORY ANDROGEN RECEPTOR IMMUNOHISTOCHEMISTRY

Paraffin sections will be cut from formalin fixed paraffin embedded blocks and deparaffinized through a xylene-alcohol series following standard procedures. Endogenous peroxidase will be removed by incubation of the sections for 30 min. in 0.08 % hydrogen peroxide in methanol followed by antigen retrieval in citrate buffer pH 6.0 in the microwave.

Immunohistochemistry (IHC) for AR will be performed per the manufacturer's recommendations (clone AR441, monoclonal mouse, dilution 1:100; Dako, Carpinteria, CA). The immunostained slides will be reviewed by our collaborating pathologist at MSKCC, Nora Katabi. The slides will be evaluated for the amount (percentage of staining) and intensity of staining (weak, moderate or strong). AR IHC will be considered positive if there is ≥ 5% positive staining in the tumor cells (with any intensity).

APPENDIX IV: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, enzalutamide. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Enzalutamide interacts with 2 specific enzymes in your liver.

- *The enzymes in question are CYP 2C8 isoenzyme and CYP3A4 isoenzyme, enzalutamide and is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Enzalutamide may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Enzalutamide must be used very carefully with other medicines that use certain liver enzymes to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP 2C8 isoenzyme or CYP3A4 isoenzyme. .

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **enzalutamide.** This clinical trial is sponsored by the NCI.

Enzalutamide may interact with drugs that are processed by your liver]. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Enzalutamide interacts with a specific liver enzymes called CYP2C8 and CYP3A4, and must be used very carefully with other medicines that interact with CYP2C8 and CYP3A4.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP2C8 or CYP3A4.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is

  _____ and can be

  contacted at

  _____.