

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 1 of 13

## CORRELATIVE SCIENCE PROCEDURE MANUAL

### 1. Purpose

This document describes the procedures required for the collection, shipping, and processing of biospecimens from all patients enrolled or registered on A092105. This document also describes the procedures that will be followed subsequent to the receipt of biospecimens by the Alliance Biorepository (i.e. Siteman Cancer Center Tissue Procurement Core at Washington University), prior to their use for protocol-specified and future, unspecified correlative science research studies. This document should be used by staff involved with any aspect of the A092105 biospecimen collection, processing, and submission; including staff at satellite institutions.

### 2. Scope

This document applies to all biospecimens collected specifically for A092105 only. Please refer to the trial protocol-specific language for additional details regarding eligibility, participant enrollment, data submission, and specific procurement procedures. **Please ensure that you are reading the most updated version of this document. This document may experience minor updates, revisions, and clarifications independent of a formal protocol amendment. The most recent version of this document may be found on the Alliance website and CTSU.**

### 3. Definitions

Term	Definition
ABWUSTL	Alliance Biorepository at Washington University in St. Louis
FFPE	Formalin fixed, paraffin embedded
H&E	Hematoxylin and Eosin

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 2 of 13

#### 4. Contact Information

<b>Protocol-related questions may be directed as follows:</b>	
<b>Questions</b>	<b>Contact (via email)</b>
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair: Glenn J. Hanna, M.D. <a href="mailto:glenn_hanna@dfci.harvard.edu">glenn_hanna@dfci.harvard.edu</a>  Nursing Contact: Lisa Kottschade, APRN, MSN, CNP <a href="mailto:kottschade.lisa@mayo.edu">kottschade.lisa@mayo.edu</a>  Protocol Coordinator: Beth Smith <a href="mailto:beth10@bsd.uchicago.edu">beth10@bsd.uchicago.edu</a>  (where applicable) Data Manager: Brandon Bright <a href="mailto:Bright.Brandon@mayo.edu">Bright.Brandon@mayo.edu</a>
Questions related to data submission, RAVE or patient follow-up:	Data Manager: Brandon Bright <a href="mailto:Bright.Brandon@mayo.edu">Bright.Brandon@mayo.edu</a>
Questions regarding the protocol document and model informed consent:	Protocol Coordinator: Beth Smith <a href="mailto:beth10@bsd.uchicago.edu">beth10@bsd.uchicago.edu</a>
Questions related to IRB review	Alliance Regulatory Inbox <a href="mailto:regulatory@allianceNCTN.org">regulatory@allianceNCTN.org</a>
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox <a href="mailto:pharmacovigilance@alliancencn.org">pharmacovigilance@alliancencn.org</a>
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Washington University (WUSTL), <a href="mailto:alliance@email.wustl.edu">alliance@email.wustl.edu</a>
Questions regarding drug supply	PMB: <a href="mailto:PMBAfterHours@mail.nih.gov">PMBAfterHours@mail.nih.gov</a>
Questions regarding drug administration	Pharmacy Contact: Barbara Todaro, Pharm.D. <a href="mailto:barbara.todaro@roswellpark.org">barbara.todaro@roswellpark.org</a>

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 3 of 13

**4.1** For information on using the BiOMS system, please refer to the ‘Help’ links on the BiOMS webpage to access the online user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or [bioms@alliancenctn.org](mailto:bioms@alliancenctn.org). For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or [bioms@alliancenctn.org](mailto:bioms@alliancenctn.org).

**4.2** For all other questions regarding biospecimen procurement and shipping procedures, please contact the Alliance Biorepository Program Manager: 1-314-747-4402 or [alliance@email.wustl.edu](mailto:alliance@email.wustl.edu).

## 5. Site Preparation

**5.1** Please refer to the A092105 protocol document for any specific requirements related to patient enrollment, registration, and regulatory compliance.

**5.2** Please ensure that you have appropriate log on credentials and can successfully access the BiOMS application. The BiOMS application is used for logging the collection and shipment of biospecimens to the Alliance Biorepository at Washington University. For training and assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or [bioms@alliancenctn.org](mailto:bioms@alliancenctn.org).

**5.3** Identify a reliable source of dry ice for freezing and shipping biospecimens and a -70 to -90 degree Celsius freezer (“ultralow”) in which frozen biospecimens may be stored prior to shipment.

## 6. Collection Schema

The following biospecimens are to be collected at each of the time points. Please refer to biospecimen collection and processing methods and specific shipping procedures below.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 4 of 13

Time Point	Biospecimen	Quantity	Collection / Processing Method	Shipping	Notes
<b>For Patients Consented to A092105 Biobanking</b>					
At Registration	Fixed tissue block	1 block	Fixed tissue block (9.2)	Ambient	1, 2
At Registration	H&E stained slide <b>AND</b> Tumor tissue scrolls	1 H&E stained slide <b>AND</b> 10 x 10 micron scrolls	H&E stained slide <b>AND</b> Fixed tissue sections (9.3)	Ambient	1, 2
At Registration	Whole blood for plasma	6 x 1 ml aliquots	Frozen plasma (10.1)	Dry Ice	1
At Registration	Whole blood for "buffy coat"	2 aliquots	"Buffy Coat" (10.2)	Dry Ice	1, 3
C2D1 (Prior to Treatment)	Whole blood for plasma	6 x 1 ml aliquots	Frozen plasma (10.1)	Dry Ice	1
Progression or End of Treatment	Whole blood for plasma	6 x 1 ml aliquots	Frozen plasma (10.1)	Dry Ice	1

**Notes:**

1. Collection is optional for patients but all sites must ask patients for their consent to participate. Please see protocol-specific consent documents.
2. A representative, archived tumor tissue block from biopsy or surgery should be submitted, if available. If entire tissue block cannot be submitted, one H&E stained slide **AND** ten (10 um) serial tissue scrolls will be accepted as an alternative. If tissue is limited, please submit H&E and as many tissue scrolls as possible. **BLOCK SUBMISSION IS STRONGLY PREFERRED.**
3. Buffy coat only needs to be collected from a single timepoint. Collection of the buffy coat from the "At Registration" timepoint is preferred, but other timepoints are also acceptable.

**7. Biospecimen Collection Kits**

- 7.1** There are no "kits" provided for submission of blood or tissue specimens for this study. Sites are responsible for acquiring materials for collection and shipping of these specimens to the Biorepository.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 5 of 13

## 8. Biospecimen Labeling and Tracking

- 8.1** All research biospecimens (cryovials, and tissue bags) with the exception of surgical pathology blocks and tissue slides **MUST** be labeled with the Alliance patient ID number, patient initials (Last, First, Middle), the date and time (if applicable) of collection, and specimen type (e.g. plasma, “buffy coat”). Specimen labels must match BioMS records.
- 8.2** Surgical pathology tissue blocks should be labeled according to institutional standards, including the institutional surgical pathology number (e.g. “S16-1234”) and the individual block identifier (e.g. “A3”). **Adhesive labels should not be used to cover the institutional label.** If tissue sections are being submitted instead of a block, each slide or tube containing sections should be labeled with the Alliance patient ID number, institutional surgical pathology number (SPN), the block identifier, section thickness, and the serial section number (if applicable).
- 8.3** A **de-identified copy of the surgical pathology report**, labeled with the Alliance patient ID number, is required to accompany **all** tissue submissions. 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 number, and photocopying the report. However, please make sure to **maintain the pathology accession numbers** so the submitted block, slides or tissue sections can be matched directly to the pathology report.
- 8.4** Label all containers and vials with an indelible, solvent-resistant marker when they are at ambient temperature.
- 8.5** Do not affix any labels to vials, slides or tubes. Label the collection containers directly with the marking pen.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 6 of 13

**8.6** All biospecimens that are collected and sent to ABWUSTL must be **logged and tracked in BioMS** under A092105. Do not send samples to the Biorepository in which the patient has not been registered onto the study. The BioMS system is a web-based application that tracks the collection and shipping of biospecimens. Once individual biospecimens are logged and ‘shipped’ in the BioMS system, a packing manifest will be created by the system. **This manifest must be printed out and must accompany all biospecimen shipments.** To become familiar with the BioMS system and for further information about training, access, and use, please contact the BioMS Help desk at: 1-855-55-BIOMS or [bioms@alliancencn.org](mailto:bioms@alliancencn.org).

**8.7** In the event that BioMS cannot be accessed, please complete a BioMS Specimen Log and Shipping Manifest form which can be found here- <http://tinyurl.com/alliance-bioms-contingency>.

## 9. Tissue Collection

### 9.1 Overview.

**9.1.1** Please refer to protocol-specific instructions for procedures related to actual tissue procurement from individual participants. The method for tissue procurement (needle core biopsy, sampling of surgically resected tumor, or tumor ‘debulking’) is dependent upon the disease site and the individual patient.

**9.1.2** When procuring tissue biospecimens by any method, when possible, avoid tissue that is grossly necrotic, hemorrhagic, fatty, or fibrous. If in doubt, briefly (1 min or less) place the tissue segment in a sterile specimen cup containing physiologic (normal) saline to rinse the tissue. Necrotic, hemorrhagic, and fatty tissue will generally dissolve or float on the surface while tumor and parenchymal tissue will remain intact and sink to the bottom of the cup.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 7 of 13

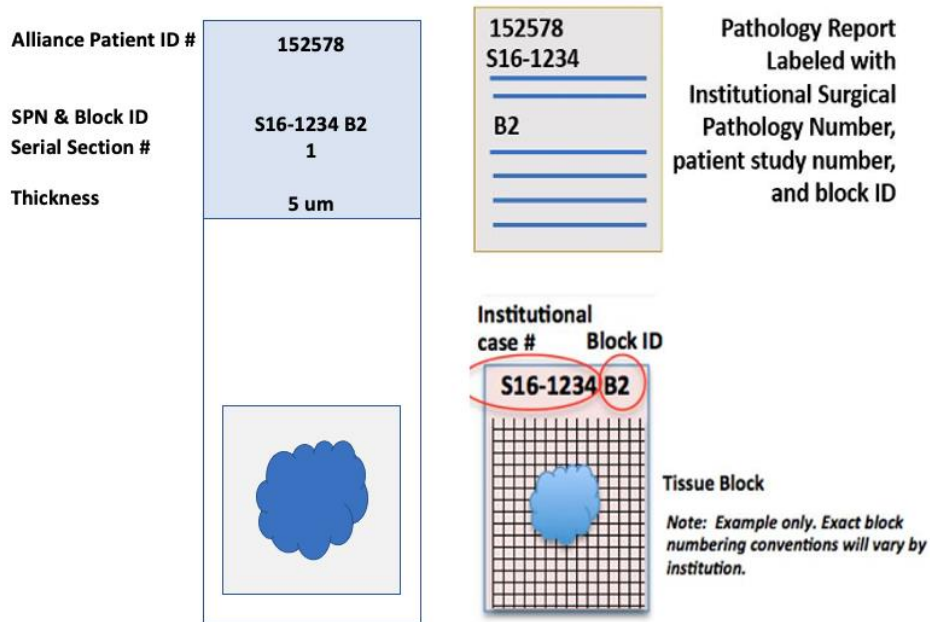
## 9.2 Diagnostic Fixed Tissue Blocks

- 9.2.1** For patients who consent to A092105 biobanking, one archived fixed tissue block is requested.
- 9.2.2** Any clinical surgical pathology block that is submitted for research studies will not be exhausted or rendered unsuitable for future diagnostic use. Any clinical surgical pathology block that is submitted will be returned within ten working days of written request, when needed for clinical management or clinical trial enrollment for a specific patient. Otherwise, all blocks will be returned to the submitting institution when the trial and correlative science study endpoints have been met.
- 9.2.3** In the event that an institution will not release fixed tissue blocks, the institution may instead submit 1 H&E stained slide **AND** 10 (10 um) tissue scrolls as an alternative (see **section 9.3**). **BLOCK SUBMISSION IS STRONGLY PREFERRED.**
- 9.2.4** Include a de-identified copy of the surgical pathology report with all tissue submissions.
- 9.2.5** **During warm weather months, paraffin blocks and slides should be shipped in an insulated container that contains a refrigerant pack, to avoid heat > 25 degrees C (77degrees F) that may melt paraffin and damage the tissue specimens.**

## 9.3 H&E Stained Slide and Fixed Tissue Sections

- 9.3.1** In cases where an institution is unwilling or unable to submit a tissue block for biobanking, a single H&E stained slide for references and serial tissue sections (scrolls, ribbons, curls) from the same block may be submitted.
- 9.3.2** Cut and perform routine H&E stain on a single section from the tumor tissue block. See figure below for proper mounting and labeling.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 8 of 13



- 9.3.3** Cut a “ribbon (scroll) of 10 paraffin tissue sections at 10 microns. Place the ribbon of tissue directly into a single microcentrifuge tube or any other suitable container. Do not float the tissue ribbon or sections in a water bath. Label the tube of tissue following the guidelines outlined in **section 8**.
- 9.3.4** Include a de-identified copy of the surgical pathology report with all tissue submissions.
- 9.3.5** During warm weather months, paraffin blocks and slides should be shipped in an insulated container that contains a refrigerant pack, to avoid heat > 25 degrees C (77degrees F) that may melt paraffin and damage the tissue specimens.



<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 9 of 13

## 10 Blood Collection Methods

### 10.1 Plasma Processing

- 10.1.1** Collect 10 ml of whole blood by standard venous phlebotomy technique into each of the purple top (EDTA) tubes. A total of 20 ml of whole blood should be collected into the EDTA tubes (2 x 10 ml). Following collection, invert tubes 10 times.
- 10.1.2** Within 2 hours of collection, spin the vacutainer tubes at room temperature in a clinical centrifuge at 2500 xG for 15 minutes.
- 10.1.3** Carefully remove the plasma layer from each vacutainer tube (~3—5 ml in volume per tube), without touching the white, buffy coat layer, and transfer to new 15 ml conical centrifuge tubes. Keep the vacutainer tubes containing the white, buffy coat layers for white blood cell isolation (**section 10.2**).
- 10.1.4** Spin the centrifuge tubes containing plasma at room temperature in a clinical centrifuge at 2500 xG for 15 minutes.
- 10.1.5** Label 6 cryovials as instructed in **section 8**. Make certain each vial is labeled completely and identically. Please use 2 ml cryovials with threaded caps. Do not use flip-top tubes or cryovials larger than 2 ml.
- 10.1.6** Carefully remove 6 ml of plasma (without touching the pellet) and divide into six (6) 2 ml labeled cryovials. Each aliquot should be between 1—1.5 ml in volume.
- 10.1.7** Freeze plasma containing cryovials on dry ice or a -70 to -90 degree Celsius ultralow freezer. Store at -70 to -90 degrees C until ready for shipment on dry ice. Frozen plasma should be shipped to the Biorepository within 30 days of collection.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 10 of 13

## 10.2 “Buffy Coat” (White Blood Cell) Processing

- 10.2.1** Follow procedures in **section 10.1** for collecting and processing plasma from EDTA tubes.
- 10.2.2** Label 2 cryovials as instructed in **section 8**. Please use 2 ml cryovials with threaded caps. Do not use flip-top tubes or cryovials larger than 2 ml.
- 10.2.3** After removing the plasma, carefully remove the white, “buffy coat” white blood cell layer, avoiding the red blood cell mass as much as possible.
- 10.2.4** Transfer the buffy coat layer (approximately 0.2 – 0.5 ml) from EDTA tubes into the labeled cryovials. Immediately freeze the cryovials of buffy coat on dry ice or in liquid nitrogen vapor. Do NOT freeze buffy coat cells by placing a warm tube in a -70 to -90 degree Celsius ultralow freezer. Once completely frozen, the cryovials containing the buffy coat cells may be stored at -70 to -90 degrees C until ready for shipment on dry ice. Frozen buffy coat should be shipped to the Biorepository within 30 days of collection.

## 11 Biospecimen Shipping

### 11.1 Overview

- 11.1.1** Place the original, completed copy of the BiOMS packing manifest in the shipment. If sending tissue, include a de-identified copy of the surgical pathology report labeled with the Alliance patient ID number. Do not send specimens without a completed BiOMS Packing Manifest or substitute “BiOMS Downtime Form.” Biospecimens cannot be accepted without this completed form.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 11 of 13

- 11.1.2** Frozen plasma and buffy coat aliquots should be placed in a biohazard bag inside of a Styrofoam cooler and covered with 3 to 4 lbs (2 kg) of commercially-prepared dry ice. Pellets or chunks are preferred. Make sure the box is filled with dry ice and the weight of the dry ice is noted on the dry ice label on the outside of the shipping container. It is the local sites' responsibility to obtain dry ice when shipping frozen specimens. Specimens should be shipped according to IATA guidelines. **Frozen aliquots should be shipped to the Biorepository within 30 days of collection. Batch shipment of frozen aliquots is allowed. If sending specimens from multiple patients within a single shipment, please ensure all specimens are properly labeled and logged in the BioMS system. Specimens from each individual patient should be placed into their own biohazard bag that is clearly labeled with the Alliance patient ID number. The accompanying BioMS manifest should be sealed within each individual bag.**
- 11.1.3** Blocks and slides should be packaged to avoid breakage using a padded envelope or, preferably, a small Styrofoam container. During warm weather months, paraffin blocks, tissue sections, and slides should be shipped in an insulated container that contains a refrigerant pack, to avoid heat >25 degrees C (77 degrees F) that may melt paraffin and damage the tissue specimens.
- 11.1.4** All biospecimens should be shipped within the timeframes indicated above in **section 9** and **10**. If collected biospecimens cannot be shipped within the specified timeframe (e.g. Friday – Saturday or Holiday collections), please contact the Alliance Biorepository Program Manager: 1-314-747-4402 or [alliance@email.wustl.edu](mailto:alliance@email.wustl.edu) for further instructions, at least 24 hours prior to anticipated collection.
- 11.1.5** **Do not ship on Friday, Saturday, Sunday or the day before a nationally recognized holiday.**

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 12 of 13

### 11.2 Shipping to ABWUSTL

Ship container for PRIORITY OVERNIGHT DELIVERY according to IATA guidelines and standard institutional policies and using the preferred vendor.

Ship to:

Alliance Biorepository at Washington University in St. Louis  
c/o Siteman Cancer Center Tissue Procurement Core  
Washington Univ. School of Medicine  
425 S. Euclid Ave.  
Room 5120  
St. Louis, MO  
63110-1005  
Phone: 314-454-7615

## 12 ABWUSTL Biospecimen Receipt and Quality Assurance Measures

- 12.1 Upon receipt, all biospecimens will be accessioned into the TPC informatics system, OpenSpecimen.
- 12.2 All biospecimens will be logged, associated, and tracked by the unique patient biopsy control number.
- 12.3 Each individual biospecimen will receive and be physically labeled with a unique biospecimen identifier, associated with the biopsy control number in the TPC informatics system.
- 12.4 Upon receipt, all physical biospecimens received will be reconciled with what is recorded on the BioMS packing manifest. Any discrepancies noted will be communicated to the Program Manager who will contact the submitting site for reconciliation.

<b>ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY</b>	<b>CORRELATIVE SCIENCE PROCEDURE MANUAL</b> Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients with Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy  Short Title- A092105	Version No: 1.1	Effective Date: 08/15/2023
		Replaces: 1.0	Page 13 of 13

12.5 Upon receipt, any biospecimen received that is not in appropriate physical condition (broken vials, frozen samples that are thawed, ambient samples that are frozen) will be reported to the Program Manager, who will contact the submitting site for reconciliation.

12.6 Aliquoted biofluids will be stored under liquid nitrogen vapor.

12.7 All biospecimens will remain in storage until additional processing or review is requested in writing by the appropriate protocol PI.

### 13 Document History

Version	Description and Justification of Change	Author	Effective Date
1.1	Added contact table, changed 'tissue sections' to 'tissue scrolls' for clarity, added warm weather provisions for shipping	KL	08/15/2023
1.0	New	PAA	05/05/2023