CORRELATIVE SCIENCE PROCEDURE MANUAL

1. Purpose

This document describes the procedures required for the collection, shipping, and processing of biospecimens that are being submitted for patients enrolled or registered on A171901. This document also describes the procedures that will be followed subsequent to the receipt of biospecimens by the Alliance Biorepository at Mayo Clinic (ABMAYO) or by NCI 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 A171901 biospecimen collection, processing, and submission, including staff at satellite institutions.

2. Scope

This document applies to all biospecimens collected specifically for the A171901 clinical trial study. Please refer to the trial protocol-specific language for additional details regarding eligibility, participant enrollment, and data submission. **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
ABMAYO	Alliance Biorepository at Mayo Clinic
NCI	National Cancer Institute

4. Contact Information

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chairs: Aminah Jatoi, MD jatoi.aminah@mayo.edu Melisa Wong, MD *melisa.wong@ucsf.edu* Nursing Contact: Sherri Homan *Sherrihoman@gmail.com* Protocol Coordinator: Lilli Johnson *lillij@bsd.uchicago.edu* (where applicable) Data Manager: Krista Teske *Teske.Krista@mayo.edu*
Questions related to data submission, RAVE or patient follow-up:	Data Manager: Krista Teske *Teske.Krista@mayo.edu*
Questions regarding the protocol document and model informed consent:	Protocol Coordinator: Lilli Johnson *lillij@bsd.uchicago.edu*
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository (see section 4.2)
Questions regarding drug administration	Pharmacy Contact: Heidi D. Finnes, PharmD, BCOP *finnes.heidi@mayo.edu*

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. 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.

4.2 For all other questions regarding biospecimen procurement and shipping procedures, please contact:

ABMAYO

- Whole blood samples (EDTA):
  Katie Halverson
  Phone: 1-507-293-7147
  Email: halverson.katie@mayo.edu

NCI

- Serum samples:
  Keith T. Schmidt, Pharm.D., Ph.D.
  Phone: 1-240-858-3208
  Email: keith.schmidt@nih.gov

5. Site Preparation

5.1 Please refer to the A171901 protocol document for any specific requirements related to patient enrollment, registration, and regulatory compliance.

5.2 Please ensure that you have the appropriate log-in 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 Mayo Clinic and to NCI. 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.

6. Collection Schema

The following biospecimens are to be collected at each of the time points listed in the table below. Please refer to individual biospecimen collection and processing methods, and specific shipping procedures that are detailed in this manual.

Time Point	Kit (Y/N)	Biospecimen	Quantity	Collection / Processing Method	Shipping / Recipient Lab	Notes
Mandatory for ALL patients registered to A171901; submit the following for A171901-ST1 and A171901-PP1						
Day 1, Cycle 1	N	Whole Blood (EDTA tube)	3 x 10 mL	Whole blood EDTA (9.1)	Cool Pack / ABMAYO (10.3)	1, 3, 5, 6
Day 1, Cycle 1	N	Whole blood for serum	1 x 1 mL aliquot	Frozen serum (9.2)	Dry Ice / NCI (10.4)	1, 4, 5, 6
Day 1, Cycle 2	N	Whole Blood (EDTA tube)	3 x 10 mL	Whole blood EDTA (9.1)	Cool Pack / ABMAYO (10.3)	1, 3, 5, 6,
Day 1, Cycle 2	N	Whole blood for serum	1 x 1 mL aliquot	Frozen serum (9.2)	Dry Ice / NCI (10.4)	1, 4, 5, 6
Day 1, Cycle 3	N	Whole Blood (EDTA tube)	3 x 10 mL	Whole blood EDTA (9.1)	Cool Pack / ABMAYO (10.3)	1, 3, 5, 6, 7
Day 1, Cycle 3	N	Whole blood for serum	1 x 1 mL aliquot	Frozen serum (9.2)	Dry Ice / NCI (10.4)	1, 4, 5, 6
Day 1, Cycle 6	N	Whole blood for serum	1 x 1 mL aliquot	Frozen serum (9.2)	Dry Ice / NCI (10.4)	1, 4, 5, 6
Day 1, Cycle 9	N	Whole blood for serum	1 x 1 mL aliquot	Frozen serum (9.2)	Dry Ice / NCI (10.4)	1, 4, 5, 6
End of Treatment	N	Whole Blood (EDTA tube)	3 x 10 mL	Whole blood EDTA (9.1)	Cool Pack / ABMAYO (10.3)	2, 3, 5
End of Treatment	N	Whole blood for serum	1 x 1 mL aliquot	Frozen serum (9.2)	Dry Ice / NCI (10.4)	2, 4, 5

Notes:

1. Blood will be collected **prior to IV infusion** at all time points except end of treatment.
2. Blood should be collected within 21 days of last day of treatment. Not required for patients who are not scheduled for a visit during this window.
3. Whole blood to be used for biomarker analysis (A171901-ST1).
4. Serum from whole blood to be used for pharmacokinetic analysis (A171901-PP1). Cycle 6 and Cycle 9 samples required only for patients still receiving treatment (to be collected **prior to IV infusion**). If collection of Cycle 9 sample is missed, samples may be collected on Day 1 of Cycle 12 instead. Effective with Update 1, serum samples are being sent to Dr. Cody Peer at the National Cancer Institute (NCI). Serum samples for A171901-PP1 at end of treatment are only required for patients consented following Update 1 to the study.
5. Submission of blood samples for 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. Biomarker and pharmacokinetic studies will be performed. All patients who provide their consent to participate in the main study will have provided their consent to participate in A171901-ST1 and A171901-PP1.

6. Day 1 samples for these cycles may be collected within 3 days prior to treatment, as long as the exact time and date of collection is recorded on the forms. The exact time and date of infusion start and stop (to assess duration of infusion) will be collected in Rave as well.
7. Day 1 of Cycle 3 sample not required for patients receiving 400 mg pembrolizumab every 42 days.

7. Biospecimen Collection Kits

7.1 Serum Specimens

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

8. Biospecimen Labeling and Tracking

8.1 All research biospecimens MUST be labeled with the Alliance study number (A171901), Alliance patient ID number, patient initials (Last, First, Middle), the date and time of collection and specimen type (i.e. "serum"). Specimen labels must match BioMS records.

8.2 Label all containers and vials with an indelible, solvent-resistant marker when they are at ambient temperature.

8.3 **Do not affix any labels to vials or tubes.** Label the collection containers directly with the marking pen.

8.4 All biospecimens that are collected and sent to ABMAYO and to NCI must be **logged and tracked in BioMS** under A171901. Do not send samples 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@alliancenctn.org.

8.5 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. Blood Collection Methods

9.1 Whole blood (EDTA Tube- no processing)

9.1.1 Collect 3 x10mL of blood into the EDTA tubes using standard venous phlebotomy. Invert tubes 10 times.

9.1.2 Store EDTA tubes with whole blood at ambient temperature until shipping. Do not refrigerate or freeze the tubes. Biospecimens must be received by the recipient lab within 24 hours of collection. If blood must be collected on Friday, it can be shipped on Friday for Saturday delivery. **During warm weather months (i.e. June—August), a refrigerated pack (not frozen) should be included in the shipment to maintain ambient temperature. When shipping during other months of the year, a room temperature pack should be included in the shipment.**

9.2 Serum Processing

9.2.1 Collect 5 mL of whole blood by standard venous phlebotomy technique into the serum-separating tube (SST). Invert tube 10 times.

9.2.2 Place the tube in an upright position and allow the blood to clot for 30 minutes.

9.2.3 Label 1 cryovial as instructed in **section 8.**

9.2.4 Spin blood in vacutainer tube at 4 degrees Celsius in a clinical centrifuge using standard programming for serum separation. Usually this is 1500 xG (actual speed will depend upon the centrifuge) for 10 minutes.

9.2.5 Aliquot 1.0—1.5 mL of serum into the labeled cryovial.

9.2.6 Freeze serum containing cryovial on dry ice or a -70 to -90 degree Celsius ultralow freezer. Store at -70 to -90 degrees Celsius until ready for shipment on dry ice.

10. Biospecimen Shipping

10.1 Place the original, completed copy of the BioMS packing manifest in the shipment. Do not send specimens without a completed BioMS Packing Manifest or substitute "BioMS Downtime Form." Biospecimens cannot be accepted without this completed form.

10.2 All biospecimens collected on the study should be shipped on the same day that they are collected. EDTA whole blood biospecimens must be received by the recipient lab within 24 hours of collection. If biospecimens cannot be shipped on the same day they are collected, please contact appropriate personnel listed in **section 4.3** for further instructions, at least 24 hours prior to anticipated collection.

10.3 Shipping to ABMAYO

Ship container for PRIORITY OVERNIGHT DELIVERY according to IATA guidelines and standard institutional policies and using the preferred vendor. Ship specimens to ABMAYO on Monday through Friday only. Do not ship on Saturdays or on the day before a national holiday.

Ship to:
Alliance Biorepository at Mayo Clinic- BAP Freezer
ST-SL-16
150 Third Street SW
Rochester, MN 55902
Phone: 507-538-0602

10.4 Shipping to NCI

Ship container for PRIORITY OVERNIGHT DELIVERY according to IATA guidelines and standard institutional policies and using the preferred vendor. Ship specimens to NCI on Monday through Thursday only. Do not ship on Fridays, Saturdays or on the day before a national holiday.

Ship to:
Clinical Pharmacology Program
National Cancer Institute
10 Center Dr., Room 5A03
Bethesda, MD 20892
Phone: 240-858-3204

11. ABMAYO Biospecimen Receipt and Quality Assurance Measures

11.1 All biospecimens sent to ABMAYO will be accessioned into the informatics system BioMS, at ABMAYO Research Laboratory Information Management System (RLIMS) which interfaces with BioMS.

11.2 All biospecimens received at the ABMAYO will be logged, associated, and tracked by the Alliance patient ID number.

11.3 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 submitting site for reconciliation.

11.4 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.

11.5 All biospecimens submitted to ABMAYO will remain in storage until exhausted. In the event the patient withdraws consent, the specimens will be disposed/returned according to Alliance Policy and Procedure Chapter 11.

12. Document History

Version	Description and Justification of Change	Author	Effective Date
4.2	Updated contact information for NCI and added contact table	KL	06/26/2023
4.1	Fixed error regarding cryovials no longer being provided	AAW	09/14/2022
4.0	Removed mention of kits supplied by study	AAW	08/02/2022
3.0	Fixed minor grammatical errors and typos Clarified kits provided for serum specimens (cryovials only, if site lacks access)	PAA	04/05/2022
2.4	Updated contact phone number for Katie Halverson Updated serum processing instructions Updated definitions in section 3 Added version number to footer to align with Alliance template	PAA	02/20/2022
2.3	Updated Mayo Clinic contact person	PAA	08/12/2021
2.2	Updated Mayo Clinic contact person	PAA	06/16/2021
2.1	Updated kit policies to align with Mayo practices	PAA	04/07/2021
2.0	Updated serum collection to reflect shipment to NCI Updated kits	PAA	04/06/2021
1.1	Updated EDTA storage to ambient temperature	GLS	12/16/2020
1.0	New	GLS	05/04/2020