S1605 - Phase II Trial of Atezolizumab in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer

Frequently Asked Questions (FAQ) for Staff Use Only

1. **Is this a FDA registration trial?**
   Answer: Yes

2. **Is there protocol training required for site staff in order to enroll per CTSU Site registrations?**
   Answer: Yes, required training for sites is listed in the protocol, Section 13. Participating institutions are required to have at least one person view the S1605 training module before enrolling patients to the study. The training is available at: https://swog.org/Members/Training/S1605/S1605Training.asp. To obtain credit for completing the training, after viewing the presentation please complete the short form at the bottom of the page on the website, then print the acknowledgement page and submit to CTSU via the Regulatory Submission Portal.

3. **When should TX begin after registration? Will it be a deviation if treatment is delayed for more than protocol-specific guidelines?**
   Answer: Refer to Section 13.1. Patients must be registered no more than five working days prior to the planned start of treatment. If there is a delay (e.g. shipment delay of drug), please document this on the appropriate forms so we have knowledge of the delay. Since it should be "planned" that treatment will begin no more than five working days after registration, you will not get penalized if there is an unplanned delay.

4. **Is the one urine cytology slide required at baseline for the Central Pathology Review?**
   Answer: Per Section 12.E, urine cytology is not required at baseline. For patients with CIS disease, the slide must be submitted at Week 13 and Week 25 Disease Assessments.

5. **Is there a recommended or required postal service for shipping specimens for this study?**
   Answer: No. Whatever shipping service is used should include the ability to track your shipment.

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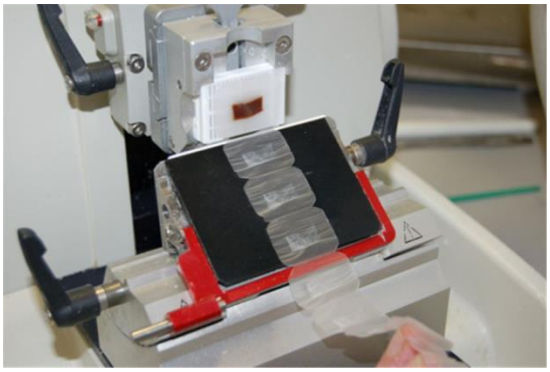
6. **Do you know what the protocol definition of "scroll" is (per section 15)? Does that refer to Paraffin Sections for DNA analysis (TUBE) tissue? If not, can you confirm exactly what kind of sample is needed in the tissue scroll?**

   Answer: When sequential tissue sections are cut from paraffin blocks, they come off loosely attached to each other - like a strip of postage stamps. This strip of tissue sections is called a scroll. It can be rolled and inserted into an Eppendorf tube. This image demonstrates a scroll.



7. **Free T4 and TSH are required at baseline, but there is no timeframe specified.**

   Answer: Free T4 & TSH should be done within the time frame of other labs prior to registration. TSH is to be repeated every 6 weeks at the time of infusion. The H & P is every 3rd infusion by the physician in charge of infusion (Urology or Med Onc).

8. **It states in the protocol that vital signs are required during the first infusion, but it does not specify the frequency.**

   Answer: See Section 7.2. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during, and after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and at the end of the infusion. Vital signs should be collected during the infusion only if clinically indicated.

9. **The eligibility criterion, Section 5.3f, indicates an ECG at baseline; but there are no cardiac parameters that would make the patient ineligible. Does the ECG need to be done?**

   Answer: Per *Section 3.0* of the protocol, there are some rare, unusual cardiac adverse effects from this drug, including pericarditis. For this reason a pre-treatment/baseline EKG is mandated.

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10. Is a patient eligible if (s)he finished induction BCG but could not tolerate any maintenance therapy?

Answer: Only recurrent HG T1 disease is eligible after only induction BCG. All other patients must have at least 2 doses of maintenance BCG or a second induction. BCG intolerance is NOT an inclusion criterion.

11. A patient has completed TURBT 5 weeks prior to registration by the same investigator – will the patient need a repeat cystoscopy within 3 weeks of registration?

Answer: Yes. Patients must have had cystoscopy confirming no visible papillary tumor within 21 days prior to registration. (CIS disease is not expected to have been completely excised).

12. A patient with prior history of muscle invasive bladder cancer treated with bladder preservation (max. TUR or RT) now has BCG unresponsive NMIBC. Is the patient eligible?

Answer: The patient is ineligible for two reasons: prior MIBC and prior RT to bladder for bladder cancer. RT for prostate/cervix/colon is NOT a contraindication.

13. Is a patient with HIV eligible?

Answer: See protocol Section 5.3n. HIV patients can be included if currently on HAART with CD4 count >250.

14. Is a patient with hepatitis eligible?

Answer: Yes. See protocol Section, 5.3m. Patients with past or resolved hepatitis B infection are eligible. Patients must NOT have active hepatitis B or C infection.

15. What if a patient has low grade recurrence?

Answer: The patient continues on protocol. Only high grade recurrences are considered treatment failure.

16. If a patient with CIS has for-cause biopsy after 3 months and it is negative, will the patient be required to have a repeat biopsy at 6 months?

Answer: The patient continues on protocol. If the patient has a normal cystoscopy and normal cytology at 6 months, then no biopsy is required. If the patient has an abnormal cystoscopy and/or cytology, then do a repeat evaluation as per usual clinical routine.

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17. If a patient develops new upper tract disease on follow-up can patient continue on protocol?

Answer: No. Atezolizumab is being administered systemically and upper tract or prostatic urothelial recurrence is considered treatment failure.

18. If infusion is delayed more than 3 doses can the patient go back on the study?

Answer: Criteria for Removal from Protocol Treatment is if t*reatment delay > 42 consecutive days for any reason* - this is equivalent to two dose intervals (6 weeks). See protocol Section 8.2 regarding special conditions. The acceptable length of interruption will be at the discretion of the investigator. Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of delay of three scheduled treatments will be at the discretion of the study PI in consultation with CTEP.

19. Does the investigator have to wait for central review of pathology before determining that a patient has failed study treatment?

Answer: No. Decisions regarding eligibility and attainment of study endpoints are made by the treating physician "real time". Imaging, pathology, and cytology will be reviewed centrally at a later time to ensure patient eligibility (some patients will be deemed ineligible after central review) and to compare endpoint assessment (final endpoint analysis will be based on local interpretation).

20. Can we send FFPE slides or is a block mandatory?

Answer: All translational studies on tissue are based on slides and scrolls. Blocks are not requested or required.

WITHIN 28 DAYS AFTER REGISTRATION (PRESTUDY TURBT)

Positively Charged Unstained Slides:

Number of Slides	Thickness	Type of Testing
Five (5)	5 mcM	IHC

Sections of Scrolls:

Number of Scrolls	Thickness	Type of Testing
Four (4)	5 mcM	RNA-seq
Eleven (11)	10 mcM	Banking for future studies

21. Does surveillance of patients end at the 18 month time point?

Answer: All patients will be followed for recurrence, progression, and survival for 5 years after registration.