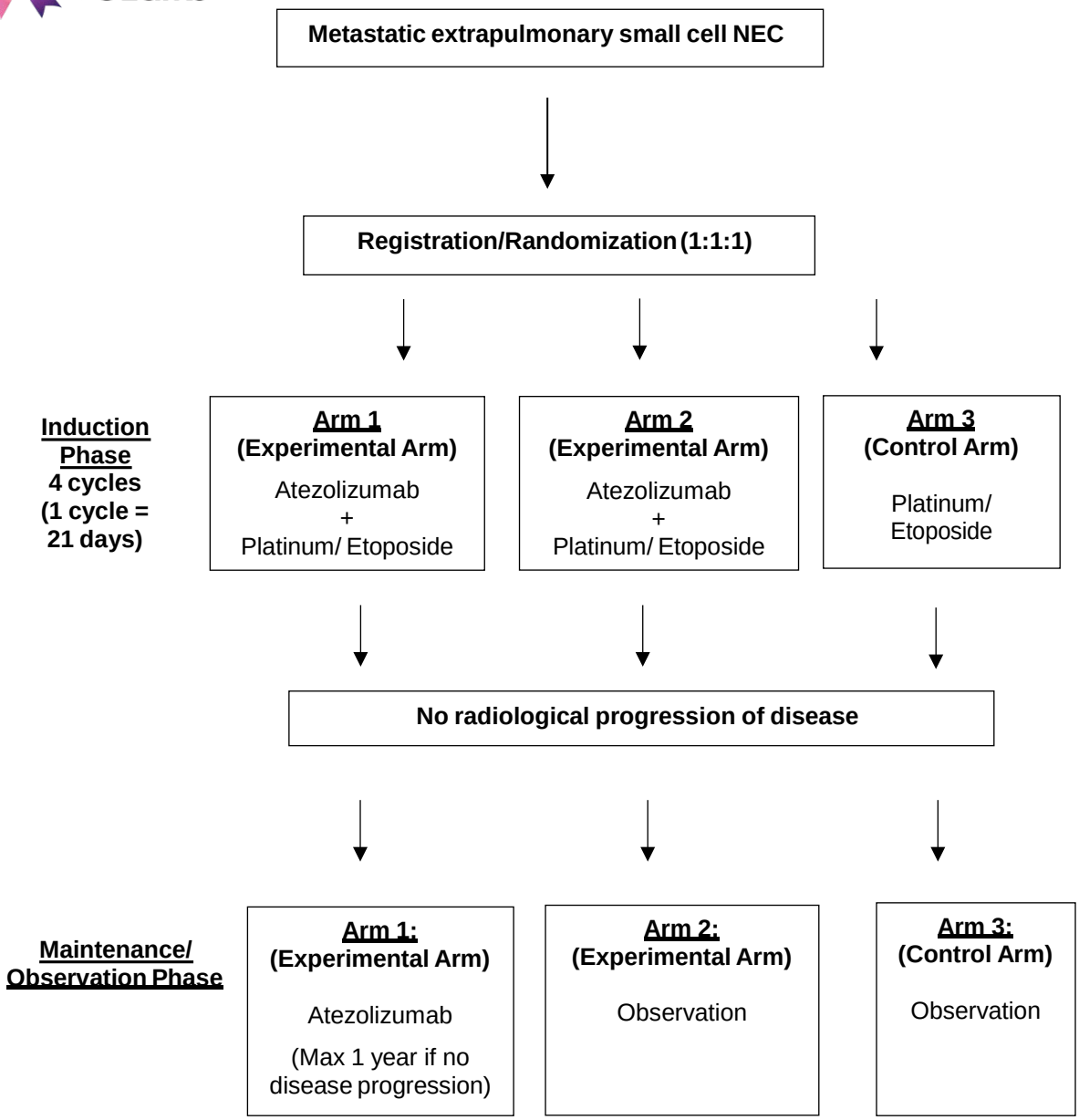
SCHEMA



Randomization Stratification Factors:

- Zubrod Performance Status: 0-1 vs. 2
- Disease origin: Prostate vs. Gastrointestinal vs. Other

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5 may be printed and used by the site, but it is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or: raretumorsquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).**

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines. **If Day 14, 21, 28, or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Participants must have histologically-confirmed (local site pathological confirmation sufficient) extrapulmonary poorly differentiated, small cell neuroendocrine carcinoma (NEC) as defined in Section 4.0 that is metastatic.

b. Participants must have radiologically evaluable disease, measurable or non-measurable, per RECIST 1.1 criteria. All measurable and non-measurable lesions must be assessed by CT scan within 28 days prior to registration. For patients who received one cycle of platinum + etoposide prior to registration, at least 21 days must have elapsed between Day 1 of platinum + etoposide and the pre-registration CT scan. All known sites of disease must be assessed and documented on the Baseline Tumor Assessment Form.

c. Participants must have brain MRI (or CT head with contrast if there is contraindication to MRI brain) within 28 days prior to registration. Participants with asymptomatic central nervous system (CNS) metastases are eligible if one or more of the following apply:

- Participants who have received treatment for brain metastases must have:
  - No evidence of radiological progression (by MRI brain or CT head with contrast if there is contraindication to MRI brain) within 28 days prior to registration
  - Discontinued all corticosteroids at least 14 days prior to registration
- Participants with treatment-naïve brain lesions must have:
  - No lesion measuring >2.0 cm in size in any axis
  - MRI brain or CT head with contrast (if there is contraindication to MRI brain) demonstrating no evidence for mass effect, edema, or other impending neurological compromise within 28 days prior to registration.
  - No evidence of radiological progression (by MRI brain or CT head with contrast if there is contraindication to MRI brain) within 28 days prior to registration
  - No need for >2 mg of dexamethasone (or equivalent of >10 mg prednisone) per day at time of registration.

d. Participants must not have symptomatic central nervous system (CNS) metastases.

e. Participants must not have known or suspected leptomeningeal disease.

f. Participants must not have small cell NEC mixed with urothelial carcinomas.

5.2 Prior/ Concurrent Therapy Criteria

a. Participants with prior history of non-metastatic (localized/locally advanced disease) extrapulmonary poorly differentiated small cell NEC may have had prior platinum-based therapy ± radiation ± surgery provided that all therapy was completed ≥ 6 months prior to registration.

b. Participants must discontinue denosumab prior to study registration and plan to replace with a bisphosphonate while on the study.

c. Participants must not have had prior treatment for metastatic disease EXCEPT one cycle of platinum (carboplatin/cisplatin) + etoposide is allowed prior to registration. Other chemotherapy regimens are not allowed.

d. Participants must not have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, CD137 agonists, anti-CTLA-4 agent, or any other immune checkpoint inhibitors for any neuroendocrine neoplasm. Immune checkpoint inhibitors given for other cancer indications are allowed provided last therapy was given at least 12 months prior to study registration.

e. Participants must not have received treatment with systemic immunostimulatory agents including, but not limited to, interferon and interleukin2 [IL-2] within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to registration.

f. Participants must not have had history of known severe allergy, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, including to Chinese hamster ovary cell products or to any component of the atezolizumab formulation, cisplatin, carboplatin, or etoposide.

g. Participants must not be on active systemic therapy for another cancer with the exception of hormonal therapy including androgen deprivation therapy (e.g., gonadotropin-releasing hormone (GnRH) agonists or antagonists), which can be continued while participants are receiving protocol therapy. Use of enzalutamide or apalutamide is permitted after completion of chemotherapy; however, glucocorticoid-containing regimens, including abiraterone, are not permitted.

5.3 Clinical/ Laboratory Criteria

a. Participants must be ≥ 18 years of age.

b. Participants must have a Zubrod Performance Status of ≤ 2 (see Section 10.4) within 28 days prior to registration.

c. Participants must have a complete medical history and physical exam within 28 days prior to registration.

d. Participants must have adequate marrow function as defined below. These results must be obtained within 14 days prior to registration. For participants who received a cycle of chemotherapy prior to registration, at least 21 days must have elapsed between Day 1 of platinum + etoposide and performance of these tests.
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L
- Hemoglobin ≥ 9.0 g/dl
- Platelet count ≥ 100 x 10^9/L

e. Participants must have adequate organ function as defined below. These results must be obtained within 14 days prior to registration. For participants who received a cycle of chemotherapy prior to registration, at least 21 days must have elapsed between Day 1 of platinum + etoposide and performance of these tests.

- Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x institutional upper limit of normal (ULN)
- Serum total bilirubin ≤ 1.5 x ULN
- Measured creatinine clearance (CL) >50 mL/min or Calculated creatinine CL>50 mL/min by the Cockcroft-Gault formula as below (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.

  Cockcroft-Gault formula:
  Calculated Creatinine Clearance = $\frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine}}$ †, *

  Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

f. Participants must not have uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN) within 14 days prior to registration. Participants who have asymptomatic hypercalcemia are eligible provided that medical therapy to treat the hypercalcemia is planned.

g. Participants must not have a diagnosis of immunodeficiency nor be receiving systemic steroid therapy (equivalent of > 20 mg of hydrocortisone per day) or any other form of immunosuppressive therapy within 14 days prior to registration.

h. Participants must not have active or history of autoimmune disease or immune deficiency, including, but not limited to myasthesia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener grandulomatosis, Sjögren syndrome, Guillian-Barré syndrome, or multiple sclerosis with the following exceptions:

- Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
- Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    - Rash must cover < 10% of body surface area
    - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

i. Participants must not have history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. NOTE: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

j. Participants must not have significant cardiovascular disease, such as New York Heart Association Class II or greater cardiac disease (refer to Section 18.2), myocardial infarction within 3 months prior to registration, unstable arrythmias, or unstable angina.

k. Participants must not have had a major surgical procedure other than for diagnosis within 28 days prior to registration. Participant must not plan to receive a major surgical procedure during the course of protocol treatment. NOTE: Patient port placement is not considered a major surgery.

l. Participants must not have severe infections (i.e., CTCAE Grade ≥2) at time of registration, including but not limited to hospitalization for complications for infection, bacteremia, or severe pneumonia.

m. Participants must not have active tuberculosis.

n. Participants with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load, with testing performed as clinically indicated.

o. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. Participants with active HCV infection who are currently on treatment must have an undetectable HCV viral load, with testing performed as clinically indicated.

p. Participants with known HIV-infection must be on effective anti-retroviral therapy at time of registration and have undetectable HIV viral load within 6 months of registration.

q. Participants must not have prior allogeneic bone marrow transplantation or solid organ transplant.

r. Participants must not have received administration of a live, attenuated vaccine (e.g., FluMist®) within 28 days prior to initiation of study treatment, during treatment with atezolizumab, and not plan to receive for 5 months after the last dose of atezolizumab.

s. Participants must not be pregnant due to the possibility of harm to the fetus. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method (with details provided as a part of the consent process) during the treatment period and for 5 months after the final dose of atezolizumab. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

5.4 Specimen Submission Criteria

a. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.1. With participant consent, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.1.

5.5 Regulatory Criteria

a. Participants ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

Note: As a part of the OPEN registration process (see Section 13.0 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.