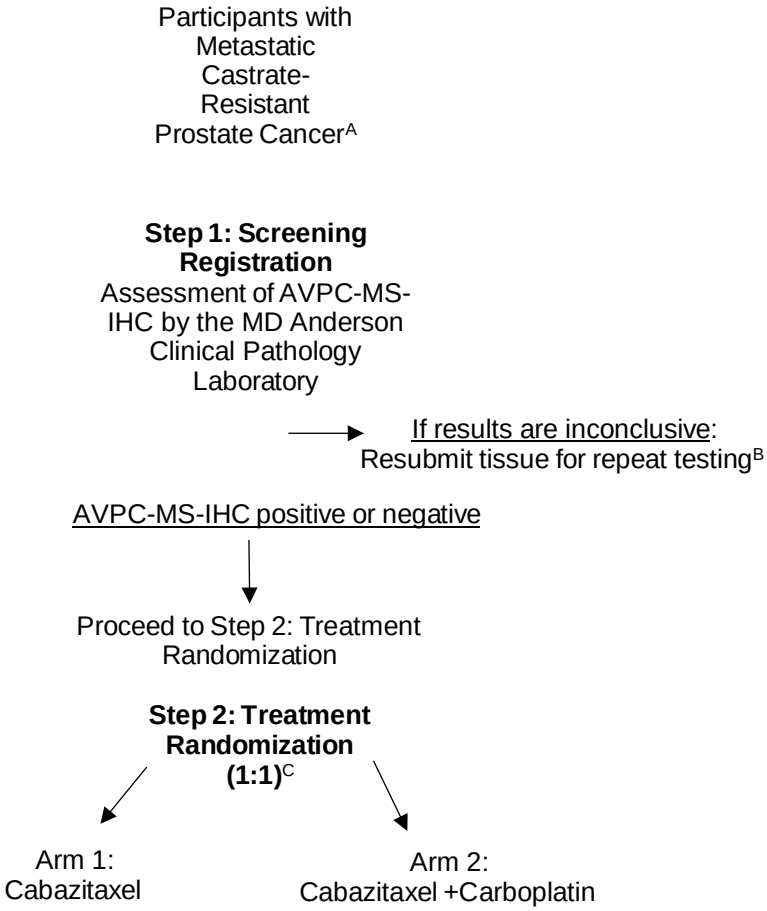
SCHEMA



[A] Participants may have received any prior therapy, but one must be docetaxel or contain docetaxel in either the castrate-sensitive and/or castrate resistant disease state. See Section 5.0 for further eligibility requirements.

[B] See Section 15.1b for additional information.

[C] All participants must have biopsy tissue submitted to MD Anderson Clinical Pathology Laboratory prior to randomization for alteration assessment. See Section 5.1.

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 to by the site, but 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 SDMC in Seattle at 206/652-2267 or GUquestion@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 any of the days in Section 5.0 fall on a weekend or holiday, the limit may be extended to the next working day.**

5.1 STEP 1: Screening Registration

NOTE: All participants must have biopsy tissue submitted to MD Anderson Cancer Center prior to randomization for alteration assessment. Participants must have determination of their AVPC-MS^{IHC} status from central assessment by the MD Anderson Clinical Pathology Laboratory using CLIA certified immunohistochemistry (IHC) assays for TP53, RB1 and PTEN. In addition, while not mandated, CLIA certified NGS of tumor DNA and/or ctDNA assessment of AVPC-MS marker status will be collected from participants for whom it is available (Table 1).

Please see Section 15.1 for details regarding biopsy tissue submission.

a. Disease Related Criteria

1. Participants must have a histologically confirmed diagnosis of prostate cancer at the time of Step 1 Registration.

2. Participants must have castrate-resistant prostate cancer and metastatic disease by bone scan and/or CT/MRI (i.e., soft tissue, visceral, lymph node).

b. Prior/Concurrent Therapy Criteria

1. Participants may have received any prior therapy, but one must be docetaxel or contain docetaxel in either the castrate-sensitive and/or castrate resistant disease state.

c. Clinical/Laboratory Criteria

1. Participants must be ≥ 18 years of age at the time of Step 1 Screening Registration.

d. Specimen Submission Criteria

1. Participants must have solid tumor biopsy material (formalin-fixed paraffin-embedded (FFPE) tissue blocks and/or 10 cut slides on four-micron thick unstained positive charged slides of FFPE tissue) available for submission for alterations in TP53, RB1 and PTEN by IHC using CLIA certified assays in the MD Anderson Clinical Pathology Laboratory. This specimen is required for central assessment of the AVPC-MSIHC regardless of whether the site has already locally evaluated the AVPC-MS status.

2. Tumor samples submitted for analysis must have been collected within 12 months prior to Step 1 Screening Registration. Samples from metastatic lesions collected in the castrate-resistant disease state are preferable but not mandatory. Samples obtained during the hormone-naïve disease state are acceptable if collected within 12 months of Step 1 Screening Registration. If more than one tumor sample exists, the sample obtained closest to the date of registration should be submitted to MDACC for analysis.

NOTE: Sites will receive an email from SWOG Statistics and Data Management Center containing participant results of Aggressive Variant Prostate Cancer Molecular Signature (AVPC-MS) assessment within 5-12 business days after tissue submission to MD Anderson Clinical Pathology Laboratory. The participant's AVPC-MS signature result (Positive or Negative) is required BEFORE randomization on to Step 2. If sites receive a non-evaluable AVPC-MS signature result, SWOG Statistics and Data Management Center will provide instructions for resubmission.

e. Regulatory Criteria

NOTE: As a part of the OPEN registration process (see Section 13.5 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.

1. 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. Documentation of informed consent via remote consent is allowed, as indicated in Section 18.4.

   See Section 18.4 for remote consenting procedures.

For participants with impaired decision-making capabilities, legally authorized representatives may sign and give informed consent on behalf of study participants in accordance with applicable federal, local, and CIRB regulations.

5.2 STEP 2: Randomization

NOTE: Participants must be registered to Step 2 Randomization within 70 days after registration to Step 1. Participants must plan to start protocol therapy no more than 14 days after Step 2 Randomization.

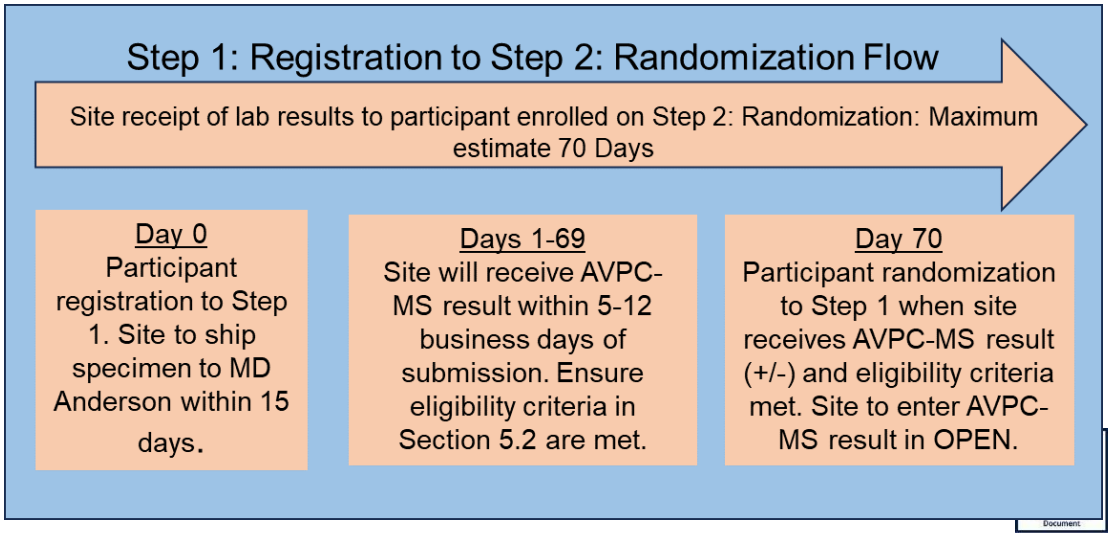
a. Disease Related Criteria

1. Participants must have castrate levels of testosterone with a baseline level < 50ng/dL within 28 days prior to Step 2 Randomization.

2. Participants must have evidence for metastatic prostate cancer by bone scan and/or CT/MRI (i.e., soft tissue, visceral, lymph node). Visceral and/or soft-tissue metastases must be ≥1.0 cm in diameter and lymph nodes must be >1.5 cm diameter in the short axis. Scans must be obtained within 28 days prior to randomization.

   NOTE: All disease must be assessed and documented on the Baseline/Pre-Registration Tumor Assessment Form.

3. Participants must have progressive disease (PD) in the opinion of the treating investigator according to any of the following criteria:



i. Progression in measurable disease (RECIST 1.1 criteria). Patient with measurable disease must have at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by computed tomography (CT) [CT scan thickness no greater than 5 mm] or magnetic resonance imaging (MRI). Lymph nodes should be ≥ 15 mm in short axis. Previously irradiated lesions, primary prostate lesion and bone lesions will be considered non-measurable disease.

ii. Progression in bone as evidenced by:

a. Appearance of 2 or more new bone lesions on bone scan (BS). If equivocal, they must be confirmed by other imaging modalities (CT; MRI), and/or repeat BS >4 weeks later.

b. Appearance of a new lytic lesion(s) and/or increasing size of an existing lesion by CT/MRI, since AVPC tumors may produce lytic bone lesions that are not detected on conventional bone scans,.

iii. Rising PSA defined (PCWG2) as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure. In case of progression based on rising PSA only, the first rising PSA (measure 2) must be obtained within 6 months of initiation of AR targeted therapy (≤ 6 months).

iv. Clinical progression. Increasing symptoms unequivocally attributed to disease progression as judged by the treating physician.

b. Prior/Concurrent Therapy Criteria

1. Participants must not have received prior cabazitaxel or carboplatin.

2. Participants must not be receiving treatment on another therapeutic clinical trial at the time of randomization. Chemotherapies, bone targeting therapies, immunotherapies and clinical trial agents must be discontinued ≥21 days prior to randomization. SART (stereotactic radiation) must be discontinued ≥3 days prior to randomization.

3. Participants must not be receiving radiation therapy or kyphoplasty-vertebroplasty within 14 days prior to randomization or major surgery (e.g., open abdominal, pelvic, thoracic, orthopedic or neurosurgery) within 28 days prior to Step 2 randomization.

4. Participants must not have untreated fractures and/or cord compression.

5. Participants must not have symptomatic uncontrolled brain metastases. Properly treated brain metastases (i.e., with stereotactic radiation) within 14 days are allowed.

c. Clinical/Laboratory Criteria

NOTE: The below clinical/laboratory criteria must be confirmed 28 days prior to Step 2 Randomization.

1. Participants must have Zubrod Performance Status of 0 - 2 within 28 days prior to Step 2 randomization (see Section 10.5).

2. Participants must have a complete medical history and physical exam within 28 days prior to Step 2 randomization.

3. Participants must have adequate organ and marrow function as defined below within 28 days prior to Step 2 randomization:

– absolute neutrophil count	≥1.5 x 10^3/uL
– platelets	≥100 x 10^3/uL(unless clinical evidence of bone marrow infiltration by tumor in which case >75 x 10^3/uL are allowed)
– total bilirubin	≤ institutional upper limit of normal (ULN) with the exception of isolated hyperbilirubinemia due to Gilbert's syndrome or if the participant has liver metastases and/or acute tumor-associated illness ≤ 4x ULN.
– AST/ALT	≤ 3 × institutional ULN (or if participant has liver metastases and/or acute tumor-associated illness, ≤ 4x institutional ULN)

4. Participants must have a calculated creatinine clearance ≥ 30 mL/min using the following Cockcroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to Step 2 randomization:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{creatinine}\ *}$$

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

5. Participants with peripheral neuropathy must have ≤ Grade 2 peripheral neuropathy (CTCAE Version 5.0).

6. Participants who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person 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 vasectomy with testing showing no sperm in the semen.

7. Participants must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the treatment regimen.

8. Participants with known human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy at registration and have undetectable viral load test on the most recent test results obtained within 6 months prior to registration.

d. Additional Criteria

1. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.2. With participant consent, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.3.