chemotherapy-naïve (in the CRPC setting), post-ARPI population, which is expected to derive greater benefit than the heavily pre-treated cohort studied to date.

CA244-0021 will randomize participants to iza-bren 2.5 mg/kg IV D1D8 Q3W versus docetaxel 75 mg/m² IV Q3W plus prednisone 5 mg PO BID. Participants must have received prior ARPI therapy (in the castration-sensitive or castration-resistant setting) and be chemotherapy-naïve in the CRPC setting; prior docetaxel for mCSPC is permitted if >12 months have elapsed since completion. The dual primary endpoints are OS and rPFS by blinded independent central review (BICR) per RECIST v1.1 (soft tissue) and PCWG3 (bone) criteria.

OBJECTIVES AND ENDPOINTS

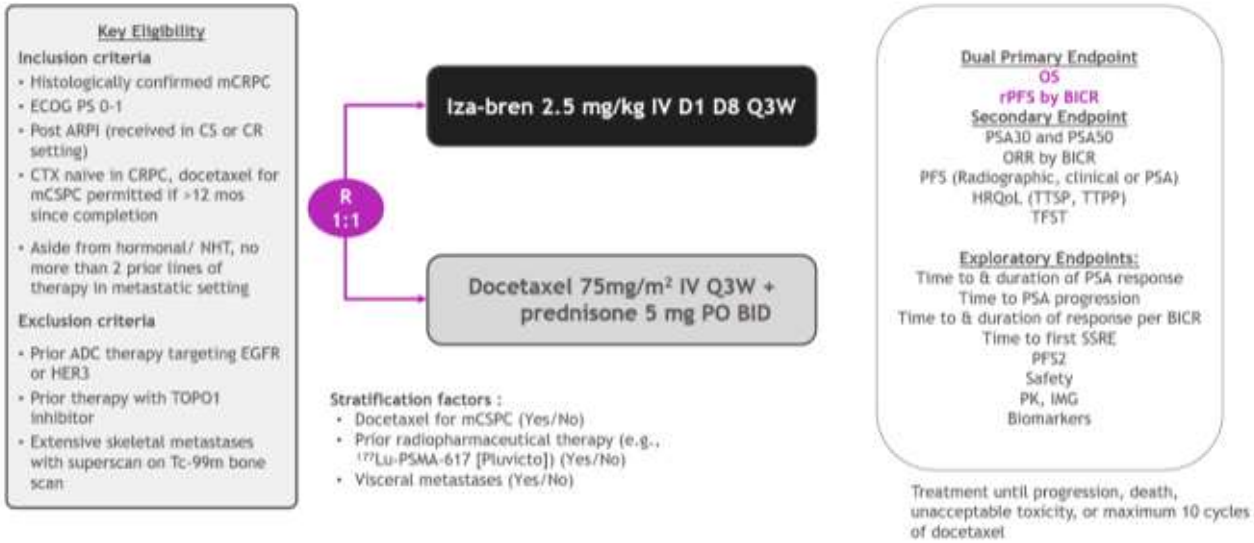
Objectives	Endpoints
Primary	**Primary**
To compare the efficacy of iza-bren vs docetaxel	• Overall Survival • rPFS by BICR using RECIST v1.1 and PCWG3
Secondary	**Secondary**
To further assess the efficacy of iza-bren vs docetaxel	• Confirmed PSA response rate: PSA30 and PSA 50 • Confirmed ORR by BICR in participants with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • PFS (radiographic, clinical, or PSA PFS). Radiographic progression will be assessed by BICR. • Time to Symptomatic Progression (TTSP) and Time to Pain Progression (TTPP) • Time to First Subsequent Therapy (TFST): Time from randomization to initiation of first subsequent anti-cancer therapy or death

Objectives	Endpoints
Exploratory	**Exploratory**
To further characterize the clinical activity, safety, pharmacokinetics, and biomarker profile of iza-bren) in patients with mCRPC	• Time to, and duration of, PSA response • Time from randomization to PSA progression • TTR and DOR as determined by BICR and investigator using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria Time from randomization to first SSRE • Time to second progression (PFS2) • Incidence of TEAEs, SAEs, laboratory abnormalities, and AEs/TRAEs leading to treatment discontinuation, interruption, dose delay, dose reduction and death. • PK/IMG Endpoints TBD • Biomarker Endpoints TBD

STUDY DESIGN

CA244-0021 is a Phase III, randomized, open-label, multicenter, multi-regional clinical trial designed to evaluate the efficacy and safety of iza-bren (investigational arm) compared with docetaxel (control arm) in mCRPC patients who have progressed on a prior ARPI therapy. The study schema is depicted in Figure 1**Error! Reference source not found.**. The Schedule of Assessments (SoA) is detailed in Table 8.

Figure 1: Study Schema



This trial will randomize 600 participants in a 1:1 ratio to receive study intervention according to the following treatment arms:

- Arm A: Iza-bren administered IV at 2.5mg/kg D1D8 Q3W.
- Arm B: Docetaxel 75 mg/m2 IV every 3 weeks + prednisone 5 mg PO BID for up to 10 cycles

Mandatory primary granulocyte-colony stimulating factor (G-CSF) prophylaxis is required for participants receiving iza-bren in this experimental arm, whereas primary G-CSF prophylaxis is left at investigator's discretion for participants in the control arm, and will be administered per local SoC.

All participants will be treated until disease progression, intolerable toxicity, or other reasons for discontinuation of dosing (such as withdrawal of informed consent or death), whichever occurs first, or a maximum of 10 cycles of treatment for those participants randomized to the control arm. Cross-over from control to interventional arms will not be allowed prior to final OS endpoint read-out of the iza-bren arm. Treatment beyond BICR confirmed progression will not be allowed.

During the treatment period, safety, efficacy, laboratory, PK (for participants receiving iza-bren only), biomarker, and PRO assessments will be performed. See Table 8 for additional details.

Data Monitoring Committee and Other Committees

Data Monitoring Committee (DMC)

A DMC will be established for the study to provide oversight of safety and efficacy considerations. Additionally, the DMC will provide advice to BMS regarding actions the committee deem necessary for the continuing protection of participants enrolled in the study. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. Complete details regarding the composition, procedures and governance related to DMC will be outlined in a DMC charter.

Study Steering Committee (SSC)

An SSC will be established to provide overall oversight of study conduct and data interpretation. Complete details regarding the composition, procedures and governance related to the SSC will be outlined in an SSC charter.

Blinded Independent Central Review (BICR)

In addition to local tumor assessments, images from this study will undergo a blinded, independent central review to confirm radiographic disease status. The centrally reviewed data will be used in the analyses of PFS, ORR, DoR and TTR. All final determinations on centrally reviewed image-based endpoints will be made based on the independent assessments for a uniform and unbiased assessment of outcome. Details will be outlined in the imaging charter.

Scientific Rationale for Study Design

Rationale for docetaxel control arm

Patients who received docetaxel for metastatic castration-sensitive prostate cancer (mCSPC) prior to enrollment may represent a biologically and clinically distinct subgroup. Prior exposure to taxane chemotherapy may select for more aggressive or treatment-resistant disease at the time of entry into this trial, potentially resulting in lower response rates to subsequent therapies[21]. Furthermore, given that the control arm of CA244-0021 is docetaxel, prior docetaxel use is particularly relevant: patients re-challenged with docetaxel after prior taxane exposure may have meaningfully different response rates and tolerability profiles compared to those who are docetaxel-naïve, potentially affecting outcomes differentially across the two treatment arms. Stratification by this factor therefore ensures that any imbalance in prior taxane exposure does not confound the primary treatment comparison.

2. **Prior radiopharmaceutical therapy (Yes vs No):**

Prior treatment with radiopharmaceutical therapy (RPT), such as ^{177}Lu PSMA-617, may affect subsequent treatment outcomes through several mechanisms. RPT-pretreated patients may exhibit altered PSMA expression, DNA damage repair pathway activation, or a more aggressive, treatment-refractory disease phenotype, all of which may influence response to subsequent systemic therapy, including ADCs such as iza-bren. Additionally, prior RPT is associated with cumulative hematologic toxicity (notably thrombocytopenia and anemia) that may affect tolerability of subsequent cytotoxic therapy[22]. As RPT use in the mCRPC post-ARPI setting continues to increase, ensuring balanced representation of RPT-pretreated patients across treatment arms is important for unbiased assessment of efficacy and safety outcomes.

3. **Visceral Metastases (Present vs Absent):**

The presence of visceral metastases is a well-established adverse prognostic factor in mCRPC, associated with shorter overall survival, higher disease burden, and a phenotype more likely to reflect androgen receptor–independent or aggressive variant disease biology. Patients with visceral disease may respond differently to systemic therapies and are typically underrepresented in clinical trials, making arm balance particularly important for the validity of efficacy assessments[23]. Stratification by visceral metastasis status ensures that this high-risk subgroup is evenly distributed between the iza-bren and docetaxel arms, enabling unconfounded primary endpoint analyses and robust subgroup evaluation.

STUDY POPULATION

Participants are eligible to be included in the study only if all of the following criteria are met:

Key Inclusion Criteria

1) Histologic or cytologic confirmation of adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report and confirmed by the investigator.
2) Current evidence of metastatic disease (M1 per AJCC staging criteria, 8th edition) documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/MRI which can be identified on imaging at screening.
3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

4) Ongoing androgen deprivation with LHRH agonist or antagonist or bilateral orchiectomy, with serum testosterone <50 ng/dL (<1.7 nmol/L) within 28 days before randomization. Participants receiving ADT at study entry should continue to do so throughout the study.
5) Participants with documented progressive mCRPC, as assessed by the treating physician. Progressive disease at study entry is based on at least 1 of the following criteria:
   a) PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the Screening visit should be ≥ 2 ng/mL.
   b) Radiographic disease progression in soft tissue based on RECIST 1.1 criteria.
   c) Radiographic disease progression in bone defined as appearance of 2 or more new bone lesions on bone scan.
6) Participants must be eligible to receive docetaxel.
   a) Have not received taxane-based chemotherapy in the mCRPC setting, and
   b) Prior taxane-based therapy for metastatic castration sensitive prostate cancer (mCSPC) is permitted if completed >12 months prior to randomization.
7) Previous treatment with an androgen receptor pathway inhibitor (ARPI), such as abiraterone, enzalutamide, apalutamide, or darolutamide:
   a) Must have progressed during or after ARPI therapy.
   b) First generation androgen receptor inhibitor therapy (eg, bicalutamide) is allowed but not considered as prior ARPI therapy.
8) Participants who are eligible for PARPi treatment should be offered this treatment whenever available following local labels and guidance. They are eligible for enrollment in trial only if they received prior PARPi, or were deemed ineligible to receive treatment by the investigator, or have refused PARPi treatment.
9) Any toxicity from prior antineoplastic therapy has returned to baseline or Grade ≤ 1 defined by NCI-CTCAE v5.0 (except for Grade 2 neuropathy or asymptomatic laboratory abnormalities and other toxicities that the investigator determines to have no safety risk, for example: alopecia)

Key Exclusion Criteria

Oncologic Medical Conditions

1) Participants with untreated CNS metastases including brain, leptomeningeal and/or spinal cord compression.

   Note: Participants are eligible if CNS metastases have been definitively treated and are clinically stable or have returned to baseline (except for residual effects from treatment).
   Note: Participants must have discontinued corticosteroids or be on a stable/decreasing dose of 10 mg or less of prednisone (or equivalent) daily for at least 2 weeks before initiating treatment.
   Note: Baseline imaging required at screening must be performed 28 days after definitive treatment for CNS metastases is completed. CNS metastases must be radiographically stable.

Systemic Medical Conditions

2) History of severe heart disease including, but not limited to, any of the following:
   a) History of clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification II to IV, or significant pericardial effusion) within 6 months prior to randomization
   b) Myocardial infarction, uncontrolled angina or stroke/transient ischemic attack within the past 6 months prior to randomization
   c) QTcF prolongation ≥ 470 msec, except for right bundle branch block.
3) Unstable thrombotic events such as deep vein thrombosis, arterial thrombosis, and pulmonary embolism within 2 months prior to randomization that require therapeutic intervention; except for infusion set-related thrombosis. Participants receiving treatment for a thrombotic event, regardless of etiology, need to be on a stable dose of anticoagulant to be eligible and must have tolerated treatment without clinically significant bleeding or other major sequelae.
4) Participants with known bleeding diathesis, including but not limited to hemophilia and von Willebrand disease
5) Participants with known hematologic conditions that may affect bone marrow reserve, including but not limited to myelodysplastic syndrome, unexplained anemia, unexplained thrombocytopenia, or a history of immune thrombocytopenia.
6) Prior history of clinically significant bleeding, or perforation of the gastrointestinal tract within 6 months of randomization
7) Participants with any of the following pulmonary conditions are excluded:
   a) Advanced or clinically significant lung disease (e.g., poorly controlled COPD or asthma, restrictive lung disease, or pulmonary hypertension) within 6 months prior to randomization
   b) Any history of interstitial lung disease (ILD) or pneumonitis requiring systemic corticosteroid treatment (≥ Grade 2)
   c) Current or suspected ILD or pneumonitis at the time of screening
8) Aside from hormonal/ novel hormonal therapy, no more than 2 prior lines of therapy in metastatic setting (eg, taxane-based chemotherapy, radiopharmaceutical therapy, PARP inhibitors).
9) Systemic anticancer therapy or investigational agent within 28 days or 5 half-lives (whichever is shorter) of study intervention. Use of ADT in this timeframe is allowed and not exclusionary.
10) Participants with previous exposure to the following:
   a) Prior treatment with any antibody and/or ADC targeting EGFR and/or HER3 including iza-bren.
   b) Prior treatment with a topoisomerase-1 inhibitor in any setting.
11) Participants with extensive or diffuse skeletal metastases with a superscan on a Tc-99m radionuclide bone scan are not eligible for the study.

    Note: A superscan is defined as a bone scan which demonstrates markedly increased skeletal radioisotope uptake relative to soft tissue in association with absent or faint renal activity (absent kidney sign).

Physical and Laboratory Test Findings

12) Inadequate bone marrow function to undergo treatment
13) Inadequate organ function to undergo treatment

STUDY INTERVENTION(S)

Interventional Arm A:

- Iza-bren will be administered IV at 2.5 mg/kg on Days 1 and 8 every 3 weeks.

Note: The first intravenous infusion duration of iza-bren will be 120 minutes ± 10 minutes; if no infusion reactions occur during the first dose, subsequent infusions can be completed in 60 to 120 minutes.

Note: Participants must be observed for safety purposes for at least 60 minutes following completion of iza-bren infusion after the first dose (Cycle 1 D1) and second dose (Cycle 1 D8). For subsequent doses, participants will be monitored for 30 minutes after the completion of the infusion.

Control Arm B:

- Docetaxel 75 mg/m2 IV every 3 weeks + prednisone 5 mg PO BID for up to 10 cycles.

STATISTICAL CONSIDERATIONS

Sample Size Determination

The dual primary endpoints of this study are OS and rPFS per BICR for comparing Interventional Arm A (iza-bren 2.5 mg/kg) against Control Arm B (docetaxel+prednisone). Approximately 600 participants will be randomized in a 1:1 ratio to Arm A and Arm B in the study. All participants in Phase 3 study are expected to be enrolled in approximately 17 months. A final analysis (FA) for rPFS is planned when approximately 337 rPFS events have occurred. The first interim analysis (IA1) for OS will be triggered by the rPFS FA. The expected number of OS events at the OS IA1 is approximately 190 OS events (55% IF). The second interim analysis (IA2) for OS is planned when approximately 276 OS (80% IF) events have occurred. The OS FA is planned when approximately 345 OS events have occurred. Power for rPFS FA is 97% and power for OS FA is 85%. Details of the assumptions for sample size calculation are provided in (Table 1).

Table 1: Sample Size Assumptions

Description	rPFS	OS
N of randomized participants for 2 arms	600	600
Accrual Time	17 months	17 months
Hypothesized HR	0.62	0.71