Update #03

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ACTIVATION AMENDMENT TO ALLIANCE A032101

A PHASE 2 TRIAL OF ADT INTERRUPTION IN PATIENTS RESPONDING EXCEPTIONALLY TO AR-PATHWAY INHIBITOR IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC): A-DREAM

X	**Update:**		**Status Change:**
X	Editorial/Administrative changes		Activation
	Eligibility changes		Closure
	Therapy/Dose Modifications/Study Calendar changes		Suspension
	Scientific/Statistical Considerations changes		Reactivation
X	Correlative Science/BioMS changes		
	Informed Consent changes		
X	Other : SAE reporting requirements		

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover page

[redacted] as the primary statistician.

Section 9.3: Expedited Adverse Event Reporting (CTEP-AERS)

- The last paragraph has been revised to refer to Section 9.3.3 for both routine and expedited reporting requirements for deaths.

Section 9.3.3: Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

The last 2 paragraphs under 'Death' have been revised to clarify reporting criteria for deaths during and after study intervention as noted below:

- Deaths during the intervention period and within 30 days of last dose require expedited reporting within 24 hours, regardless of attribution.
- Deaths beyond 30 days require only routine reporting.

Section 13.4

"Gender" has been replaced with "sex" per the NCI mandate.

Section 14.2.1 Optional Tissue Correlative Science study A032102-ST1

- The company name was updated to "Decipher Veracyte, Inc. Biosciences (South San Francisco, CA)" in place of the previous version.
- Corrected spelling: changed "roughing" to "roughly."
- Typo corrected: removed duplicated word "remain" (now reads "treatment-free remains").

Section 14.2.2 ctDNA Genetic Profiling and CfDNA MRD Detection

- Moved "Optional Peripheral Blook Collection for A032101 Biobanking for Future Use" and corresponding information to a separate section.
- Change the section title name to "ctDNA Genetic Profiling and CfDNA MRD Detection"
- Added description of ctDNA-based MRD testing using a Veracyte whole-genome sequencing assay. Included updated analysis plan linking ctDNA results to clinical outcomes. Added statistical methods to assess the predictive value of ctDNA for treatment-free survival.

Section 14.2.3 Optional Peripheral Blood Collection for A032101 Biobanking for Future Use

- Added corresponding information in this new section.

UPDATES TO THE MODEL CONSENT:

No changes were made to the informed consent document.

A replacement protocol document and model consent form have been issued

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ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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ALLIANCE A032101

A PHASE 2 TRIAL OF ADT INTERRUPTION IN PATIENTS RESPONDING EXCEPTIONALLY TO AR-PATHWAY INHIBITOR IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC): A-DREAM

Commercial agents: Abiraterone (NSC 748121), Enzalutamide (NSC766085), Apalutamide (NSC 794776), Darolutamide (NSC 815949), Leuprolide (NSC377526), Goserelin (NSC 606864), Degarelix (NSC 771648), Relugolix (NSC 825960), Triptorelin (NSC 724666)

Study Exempt from IND Requirements per 21 CFR 312.2(b)

ClinicalTrials.gov Identifier: NCT05241860

Study Chair

[redacted]

Co-investigator

[redacted]

Community Oncology Co-chair

[redacted]

Correlative Co-chair

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Health Disparities Champion

[redacted]

Disease Committee Chair

[redacted]

Cancer Care Delivery Research Co-chair

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Correlative Committee Chair

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Health Outcomes Co-Chairs

[redacted]

Health Outcomes Statistician

[redacted]

Primary Statistician

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Secondary Statistician

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Protocol Coordinator

[redacted]

Participating Organizations:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

Study Resources:

Expedited Adverse Event Reporting [redacted]	**Medidata Rave® iMedidata portal** [redacted]
OPEN (Oncology Patient Enrollment Network) [redacted]	**Biospecimen Management System** [redacted]

Protocol Contacts:

A032101 Nursing Contact [redacted]	**A032101 Pharmacy Contact** [redacted]
Alliance Biorepository at Washington University (WUSTL) [redacted]	**IROC** [redacted]

Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions by phone or email: [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

A PHASE 2 TRIAL OF ADT INTERRUPTION IN PATIENTS RESPONDING EXCEPTIONALLY TO AR-PATHWAY INHIBITOR IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC): A-DREAM

Key Eligibility Criteria (see Section 3.0)

Histologic or clinical diagnosis of metastatic prostate cancer
Currently receiving testosterone suppression (TS) and potent ARPI for mHSPC
Evidence of metastatic disease by conventional imaging prior to starting intense ADT
On TS for mHSPC for 540-750 days without breaks; on ARPI for ≥ 360 days with breaks up to 28 days allowed.
Prior intermittent ADT, prior local therapy, prior RT to metastatic sites permitted.
No prior surgical castration, no ARPI prior to mHSPC diagnosis, no experimental treatment for mHSPC.
Age >= 18 years, ECOG 0-2
Not participating in a clinical trial that does not allow for TS or ARPI interruption
No currently active second malignancy

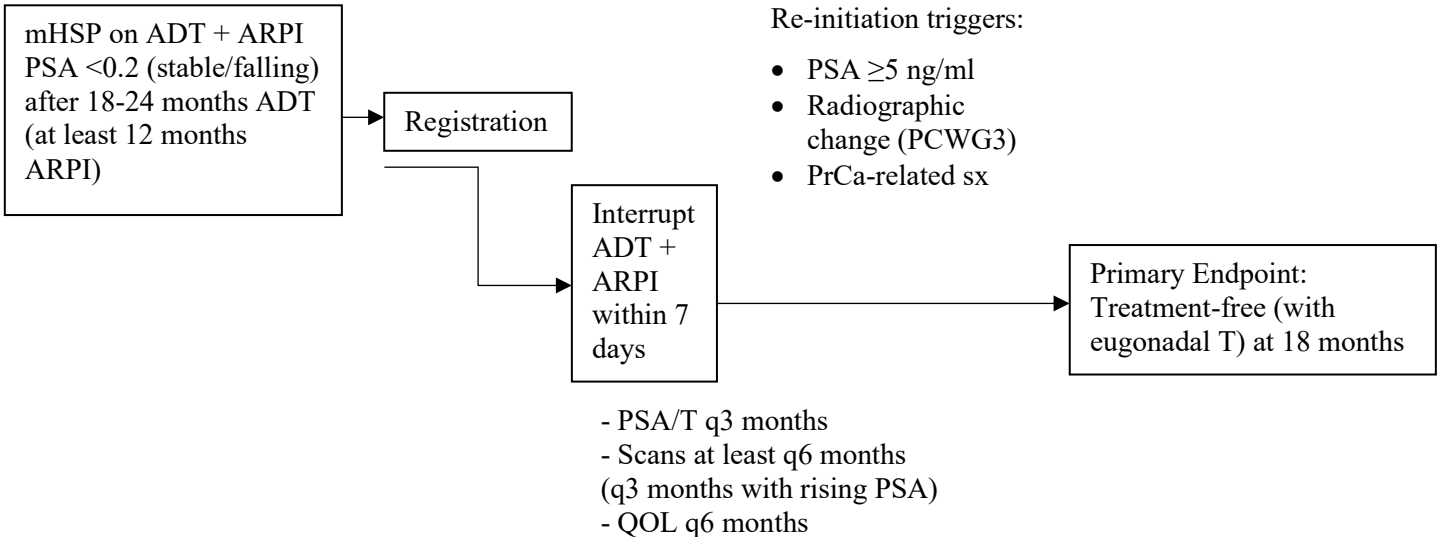
Required Laboratory Values Prior to Initiation of ADT

PSA	≥ 5 ng/ml (does not need to be the most recent value prior to enrollment)
Testosterone	≥ 150 ng/dl or not known to have been hypogonadal (if patient previously received TS, documentation of testosterone ≥ 150 ng/dl is required)

Required Laboratory Values at Enrollment

PSA:	< 0.2 ng/ml (stable or falling for 3 consecutive measurements)
Testosterone:	<50 ng/dl

Schema



Treatment is re-initiated per the pre-specified triggers (PSA increase to ≥ 5 ng/ml, radiographic change [PD on CT/MRI imaging per modified RECIST 1.1 or PDu on bone scintigraphy per PCWG3], or symptoms attributable to prostate cancer). Subsequent management is per physician discretion. Patients undergo protocol assessments until a new treatment is initiated after the initial ARPI is permanently discontinued (i.e. at time to next treatment [TTNT]), and are subsequently followed until withdrawal of consent or death.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

Novel androgen receptor pathway inhibitors (ARPIs) via extragonadal androgen synthesis inhibition with abiraterone,[1,2] or potent androgen receptor (AR) inhibition with apalutamide,[3] or enzalutamide[4] have been demonstrated to improve overall survival (OS) in first-line treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) in conjunction with testosterone suppression (TS) compared to TS alone. Subsequently, "triplet" therapy with the addition of abiraterone[5] or darolutamide[6] to TS + docetaxel demonstrated OS benefit compared to TS + docetaxel alone. In studies of these agents, TS + ARPI ("intense androgen deprivation therapy [ADT]") was continued indefinitely until radiographic or clinical disease progression or prohibitive toxic effects. However, it is unclear whether all patients who present with mHSPC require continuous treatment with intense ADT for maximal clinical benefit. In long-term follow-up of trials of abiraterone[5,6] and apalutamide,[7] many patients experienced prolonged overall survival with these agents. Clinical guidelines from the National Comprehensive Cancer Network[8] and the European Association of Urology[9] discuss the role of intermittent ADT for mHSPC based on data from an era of TS alone, and do not specifically address discontinuation of ARPIs. We hypothesize that in patients who achieve exceptional response to upfront therapy including a novel ARPI, treatment interruption will allow for a subset of patients to remain treatment-free with testosterone recovery for a prolonged period afterwards. This would in turn lead to improvement in quality of life while saving costs. Thus, we are conducting a single arm Phase 2 study of treatment discontinuation in men with mHSPC 18-24 months after initiation of ADT to characterize kinetics of testosterone recovery, duration off treatment, changes in quality of life, and clinical outcomes.

1.1 Rationale

In the CHAARTED study[10] of TS with or without docetaxel chemotherapy in mHSPC, addition of docetaxel for 18 weeks (six 3-week cycles) led to prolongation of survival by 13.6 months compared to TS alone, demonstrating that the survival benefit to upfront treatment intensification can be much more prolonged than the duration of treatment itself. Subsequent analysis from CHAARTED demonstrated that a favorable PSA nadir of ≤ 0.2 ng/ml at 7 months after initiation of TS was associated with improved survival outcomes both in patients who received TS alone and those who received TS + docetaxel; the addition of docetaxel increased the proportion of patients who achieved PSA ≤ 0.2 ng/ml.[11] In LATITUDE[1]/STAMPEDE[1,2] (abiraterone), TITAN[3] (apalutamide), and ARCHES[12]/ENZAMET[4] (enzalutamide), patients were treated with TS plus ARPI until radiographic or clinical progression or excessive toxicity, but it is not known if the survival benefit to ARPI in mHSPC is based on initial cytoreduction or requires maintenance. In LATITUDE,[13] patients who achieved PSA response to ≤ 0.1 ng/ml at 12 months had improvement in radiographic progression free survival (rPFS; HR 0.24, 95% CI 0.18-0.32) and OS (HR 0.26, 95% CI 0.19-0.36). In TITAN,[14] patients who achieved PSA ≤ 0.2 ng/ml at 3 months demonstrated dramatic improvement in rPFS and OS (HR 0.06 for both). These findings suggest that profound PSA response can identify a favorable subgroup for whom treatment interruption could be considered.

A retrospective analysis of patients simultaneously accrued to the TS + docetaxel and TS + abiraterone/prednisolone cohorts of the multi-arm STAMPEDE study[15] reported that failure-free survival (FFS) was shorter for docetaxel than for abiraterone as expected, given that docetaxel is completed after 18 weeks while abiraterone is maintained continuously. However, in this analysis prostate cancer-specific survival was nearly identical (sub-HR 1.02, 95% CI 0.70–1.49), with a greater number of non-prostate cancer-related deaths seen with abiraterone (19/377 vs. 4/189 for docetaxel, sub-HR 2.33, 95% CI 0.78–6.99), concerning for potential long-term toxicities of continuous abiraterone and prednisolone. These findings demonstrate that continuous ARPI could be associated with life-threatening complications and suggest that patients could benefit with regards to reduction in non-cancer related mortality if an induction

period of ARPI without maintenance is found to be associated with a similar cancer-specific survival as continuous therapy.

There is significant debate in the prostate cancer community on whether treatment interruption in patients with metastatic disease is "safe."[16-18] The largest study of intermittent treatment in mHSPC was SWOG 9346,[19] where patients who achieved PSA ≤ 4 ng/ml after 7 months of induction TS (n=1535 men selected from 3040 men enrolled to the study) were randomized to continuous vs. intermittent TS. In this study, the Hazard Ratio (HR) for death with intermittent vs. continuous treatment was 1.10 (90% CI: 0.99 to 1.23) – this confidence interval exceeded the upper boundary for noninferiority (i.e. could not rule out a 20% greater risk of death with intermittent vs. continuous), but too few events occurred to rule out significant inferiority of intermittent therapy. At 3 months after randomization, intermittent therapy was associated with improved QOL parameters of impotence (P<0.001), mental health (P=0.003) and libido (P=0.04; not meeting prespecified significance level); at 15 months QOL score for physical functioning was higher for intermittent therapy compared to continuous (P=0.04; not meeting prespecified significance level).

However, there are several caveats to applying findings of SWOG 9346 to suggest that intermittent therapy is inferior to continuous therapy in all patients. 1) In this study, patients discontinued TS after only 7 months as long as PSA was ≤ 4 ng/ml at that time point, while now we know that patients with PSA > 0.2 ng/ml at 7 months is a less favorable subgroup. 2) Patients resumed TS when PSA was ≥ 20 ng/ml (or ≥ baseline if baseline PSA < 20, or at time of symptoms), which is a much higher threshold than is commonly used currently. Despite these caveats, this trial was reported as statistically inconclusive as the 90% CI of HR for death overlapped with 1. It is plausible that treating for a longer duration prior to discontinuation, selecting only the most favorable patients (e.g. with PSA ≤ 0.2 ng/ml) for treatment interruption, and resuming treatment at a lower PSA threshold would select for patients likely to benefit from treatment breaks without compromising overall survival compared to continuous treatment.

A useful comparison to SWOG 9346 is the NCIC/PR7 study,[20] where 1386 patients with rising PSA > 3 ng/ml without metastatic disease detected on standard imaging (i.e. biochemical recurrence) greater than 1 year after primary therapy for localized prostate cancer were randomized to intermittent (IAD) vs. continuous androgen deprivation (CAD). At median 6.9 years of follow-up, OS was nearly identical in the 2 arms: 8.8 years (IAD) vs. 9.1 (CAD) (HR: 1.02; 95% CI 0.86 to 1.21). IAD was associated with improved physical function, fatigue, urinary problems, hot flashes, libido, and erectile function. There were fewer deaths from prostate cancer or related causes with CAD (94/696 vs. 120/690 patients) but more non-prostate cancer related deaths (160/696 vs. 148/690), primarily cardiovascular events felt related to long-term TS. Recent studies demonstrate that sites of metastases can be identified in a significant proportion of patients with "biochemical-only" disease using PSMA-based PET imaging[21] – thus the differentiation between "metastatic" disease (as in SWOG 9346) and "biochemically recurrent" disease (as in NCIC/PR7) likely reflects disease burden more than different biology. Moreover, patients with metachronous low volume metastases have a median survival of about 8 years,[22] very similar to patients accrued to NCIC/PR7. Profound cytoreduction of disease burden with intense ADT indicates sensitivity of a patient's cancer to this treatment modality, so if systemic therapy were interrupted, we would expect favorable response to treatment re-initiation without compromising oncologic outcomes. Indeed, similar survival outcomes were reported for metastatic castration-resistant prostate cancer patients treated with enzalutamide who required prolonged treatment breaks for toxicity as those remaining on continuously.[23]

1.2 Importance

The American Society for Clinical Oncology 2018 National Cancer Opinion Survey[24] reported that finances cause anxiety in nearly seven in ten patients and caregivers (69%). When financial concerns ("financial impact on my family" and "paying for treatment") were combined, they were on par with the most common concerns of dying and suffering; "side effects of treatment" was the third most common concern. TS alone can be associated with debilitating side effects with significant reduction in physical and emotional well-being including loss of libido and erectile function, vasomotor symptoms, gynecomastia, muscle and bone loss, and metabolic and cardiovascular complications,[25,26] as well as potentially increased risk of dementia[27] and depression.[28] ARPIs are associated with potential for additional side effects and complications compared to TS alone, with abiraterone plus prednisone primarily associated with hypertension and increased cardiovascular complications,[29] and enzalutamide and apalutamide associated with neurocognitive and neuropsychiatric complications as well as frailty and falls that can at times be associated with life-threatening complications associated with fractures.[30] As such, breaks from intense ADT have the potential for significant benefit to patients with regards to costs as well as short-term and long-term complications of therapy.

A similar approach to treatment de-intensification was tested in the context of high-risk localized prostate cancer where patients were randomized to 18 vs. 36 months of ADT with radiation.[31] In this study, the co-primary endpoints were 5-year OS and QOL. Here, the 5-year OS rates were 91% for 36 months (95% CI 88-95%) and 86% for 18 months (95% CI 83-90%), p=0.07; QOL analysis showed a significant difference ($p<0.001$) in six scales and 13 items favoring 18 months ADT with two of them presenting a clinically relevant difference in mean scores of ≥10 points. While the study was not powered for non-inferiority of OS, this study led to a change in the standard of care in this population for many providers, and now NCCN guidelines include a duration of ADT as short as 18 months with radiation therapy in high-risk localized disease.

Similarly, we hope to demonstrate that treatment interruption in exceptional responders to upfront intense ADT can lead to prolonged treatment-free period. If this is demonstrated to be the case, this could also lead to dramatic system-wide cost reduction in the management of mHSPC by decreasing costs related to continuous ARPI that may not be needed, as well as decreasing costs associated with management of adverse effects and complications of long-term treatment. Another potential benefit to demonstration that a time-delimited course of upfront intense ADT can allow a prolonged treatment-free interval is that this may allay patient and provider concerns regarding cost and long-term adverse effects of continuous treatment that may contribute to low utilization of ARPI upfront and frequent management with TS alone for mHSPC.[32,33] If this is the case, this trial has the potential to improve oncologic outcomes among patients with mHSPC even prior to knowing if they fall into an exceptional responder subgroup.

2.0 OBJECTIVES

2.1 Primary objective

To determine the proportion of men who experience 18-month treatment-free interval from therapy with eugonadal testosterone (to ≥ 150 ng/ml) after treatment interruption.

2.2 Secondary objectives

2.2.1 To determine time to eugonadal testosterone (> 150 ng/dl)

2.2.2 To determine duration off-treatment

2.2.3 To assess changes in quality of life as follows:

2.2.3.1 To assess changes in patient-reported quality of life as assessed by the FACT-P total score from baseline to 24 months after treatment interruption.

2.2.3.2 To assess changes in the FACT-P subscales (i.e., physical well-being, social and family well-being, emotional well-being, functional well-being, and prostate cancer subscale) from baseline to 24 months after treatment interruption.

2.2.3.3 To assess changes in the FACT-P total score and subscales (i.e., physical well-being, social and family well-being, emotional well-being, functional well-being, and prostate cancer subscale) from baseline to the remaining post-baseline time points (i.e., 6, 12, and 18 months) after treatment interruption.

2.3 Exploratory objectives

2.3.1 To evaluate radiographic PFS (rPFS), time to next treatment (TTNT)

2.3.2 To evaluate overall survival (OS), Cancer-specific survival (CSS), Non-cancer specific survival (NCSS)

2.3.3 To estimate cost-savings (total drug cost, out-of-pocket costs to patient)

2.3.4 To correlate tissue and blood-based biomarkers with clinical endpoints (duration off-treatment, rPFS, TTNT and OS)

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Concern for inadequate cytoreduction of disease burden despite PSA < 0.2 ng/ml (such as concern for non PSA-producing sites of disease progression, continued bulky disease on imaging studies or ongoing symptoms related to tumor burden) for which treatment interruption may not be appropriate.
- Medical condition such as uncontrolled hypertension/cardiac disease or severe dementia which, in the opinion of the treating physician, would render resumption of intense ADT after treatment interruption to be inappropriate.
- Patients who express unwillingness to resume intense ADT at the protocol-defined triggers should not enroll.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease**

Histologic or clinical diagnosis of metastatic prostate cancer

___ **3.2.2 Must have had evidence of metastatic disease by bone scan; or bone, nodal or visceral lesions on CT or MRI prior to starting on intense ADT.**

- If only PET imaging was performed prior to starting on intense ADT, then there must have been evidence of metastatic disease on the CT/MRI component (i.e. sclerotic bone lesion, non-regional lymph node ≥ 15 mm, and/or soft tissue lesion ≥ 10 mm).
- Radiographic evidence of disease is not required at the time of enrollment.
- No metastases to liver or to brain, as these represent aggressive variant disease biology for which intermittent treatment may not be favored.

___ **3.2.3 Prior Treatment**

- **Must currently be receiving intense ADT for metastatic hormone sensitive prostate cancer (mHSPC)**
    - Testosterone suppression (TS) with luteinizing hormone releasing hormone (LHRH)-agonist or LHRH-antagonist AND
    - An approved secondary androgen receptor pathway inhibitor (ARPI) abiraterone, enzalutamide, apalutamide, or darolutamide.
- **Must have remained on testosterone suppression for metastatic disease continuously (without treatment breaks) for 540-750 days (approximately 18 to 24 months)** from time of first dose of LHRH agonist or antagonist by time of registration. A period of anti-androgen treatment prior to LHRH agonist or antagonist initiation is not included in the 540 – 750 days (approximately 18 to 24 months).
- **Must have received treatment with ARPI for at least 360 days** in total by time of A032101 registration. Treatment breaks from the ARPI the patient is currently receiving of up to 60 days are permitted (for example peri-procedural for management of a temporary adverse event or lapse in financial coverage) as long as PSA did not rise while holding therapy and the patient has resumed for at least 30 days (without a dose hold > 72 hours within those 30 days) by time of registration. A break from ARPI longer than 60 days is permitted if a patient needed to discontinue a different ARPI for toxicity, as long as PSA did not rise while holding therapy and the patient has received at least 360 days of ARPI in total.
- **Prior TS in the context of neoadjuvant/concurrent/adjuvant treatment with local therapy is permitted.** Prior course(s) of intermittent TS for biochemical-only recurrence is permitted. However, if the patient previously received TS, metastatic progression for which intense ADT was initiated must have occurred during an off-treatment interval and with testosterone ≥ 150 ng/dL.

- **Prior local therapy for prostate cancer (either before or after diagnosis of metastatic disease) is permitted**. Prior treatment with docetaxel chemotherapy for up to 6 cycles is permitted. Prior radiation therapy to metastatic sites (either for symptom palliation or for ablation of oligometastatic disease) is permitted.
- **No history of surgical castration**.
- **No history of ARPI use prior to diagnosis of mHSPC** for which the patient is currently receiving intense ADT (such as in the neoadjuvant setting with prior local therapy).
- **No current or prior treatment with experimental agents** for metastatic hormone-sensitive prostate cancer.

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status 0-2**

___ **3.2.6 Required Laboratory Values:**

Prior to initiating intense ADT

PSA	≥ 5 ng/ml (does not need to be the most recent value prior to enrollment)
Testosterone	≥ 150 ng/dl. Patients are permitted to enroll if testosterone was not measured prior to initiating intense ADT for mHSPC if they did not previously receive TS and were not known or suspected to be hypogonadal at the time

At time of enrollment to A032101

PSA	< 0.2 ng/ml PSA values (measured in the same laboratory) must be stable or falling for 3 consecutive measurements – i.e. any PSA rise must be followed by a decrease in PSA that is further decreased or stable on a 3rd measurement. Any patient with 2 consecutive rises in PSA values since achieving castrate level of testosterone is not eligible
Testosterone	< 50 ng/dl

___ **3.2.7 No current participation in a clinical study that does not allow for TS or ARPI interruption.**

___ **3.2.8 No patients with a "currently active" second malignancy.**

Patients with non-melanomatous skin cancer, superficial bladder cancer, cancer not needing active therapy for at least 2 years, cancer for which the treating investigator deems the subject to be in remission, or any prior malignancy that was

treated with curative intent (no evidence of disease for at least 3 years) are also permitted to enroll.

Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register andwith their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] Investigators and clinical site staff who are significant contributors to research must register in the [redacted] The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;

- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the [redacted] for additional information. For questions, please contact the **RCR Help Desk** by email at [redacted]

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the [redacted] application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website. See Section 4.2.2.

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;

- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Protocol-specific Requirements for A032101 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted] Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted]
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select Alliance, and protocol number *A032101*.
- Click on *Documents, Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] or [redacted] to receive further instruction and support.

4.2.5 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on *Go*.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision-making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their

Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.5 Registration to substudies and companion studies

4.5.1 Registration to Substudies described in Section 14.0

There are two substudies within Alliance A032101. These correlative science studies must be offered to all patients enrolled on Alliance A032101 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance A032101 are:

- Quality of Life Studies in A032101, Alliance A032101-HO1 (Section 14.1)
- Correlative Science Studies in A032101, Alliance A032101-ST1 (Section 14.2.1)

If a patient answers "yes" to "I choose to take part in the quality of life study and will fill out this form," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.1. Patients registered to HO1 must speak either English or Spanish. The patient should be registered to Alliance A032101-HO1 at the same time they are registered to the treatment trial A032101. Patient questionnaire booklets should be submitted per Section 6.4. Booklets are to be ordered prior to the registration of any patients. Booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A032101 CTSU web site) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendix I which are to be used for reference and IRB submission only. They are not to be used for patient completion. Booklets are available in English and Spanish only.

If a patient answers "yes" to "I agree that my tissue samples and related health information may be used for the laboratory studies described above," Question #2 in the model consent, they have consented to participate in the substudy described in Section 14.2.1. The patient should be registered to Alliance A032101-ST1 at the same time they are registered to the treatment trial (A032101). Samples should be submitted per Section 6.2.

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 42 DAYS before registration: Baseline imaging studies.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

Study Calendar				
	Prior to Registration	**Every 3 months during initial treatment interruption***	**Every 3 months after treatment resumption****	**After TTNT†**
Tests & Observations				
H & P, weight, PS	X	X	X	
Height	X			
Pulse, Blood Pressure	X	X	X	
Adverse Event Assessment		X	X	
Laboratory Studies				
CBC, Differential, Platelets	X	X	X	
Creatinine	X	X	X	
Albumin, glucose	X	X	X	
AST, ALT, Alk. Phos., Bili	X	X	X	
PSA	X	X	X	
Testosterone	X	X	X	
Staging				
CT/MRI chest/abd/pelvis	X	A	B	C
Bone Scan	X	A	B	C
Correlative studies: For patients who consent to participate				
QOL assessment	*See Section 6.3.*			
Tissue and Blood samples	*See Section 6.2.*			

* History and physical, AE assessments, and laboratory studies must be performed every 3 months (+/- 14 days) during initial period of treatment interruption. If any assessments are performed in the interim, these will need to be repeated at the 3-month (+/- 14 day) time point.

** History and physical, AE assessments, and laboratory studies must be performed within 28 days of treatment resumption if not performed already. The 3-month (+/- 14 days) assessments are then timed from resumption of TS or ARPI (whichever is resumed first). Sites should document any cancer-directed treatment received during monitoring on trial and in survival follow-up.

† After permanent discontinuation of initial ARPI and initiation of next systemic therapy, patients are followed at least every 6 months if rPFS endpoint has already been met (or every 3 months otherwise) for 10 years for

documentation of subsequent cancer-directed treatments and survival. QOL assessments continue until 2 years after registration even if TTNT endpoint has already been met.

A Restaging bone scan and CT (or MRI) chest/abd/pelvis must be performed every 6 months (+/- 28 days) during initial period of treatment interruption. Interim assessments are recommended at 3-month intervals during periods of rising PSA. Initial radiographic changes suggestive of disease progression (PD on CT/MRI by modified RECIST 1.1 or PDu on bone scan by PCWG3) should be confirmed on repeat imaging within 6-8 weeks. If restaging studies are performed in the interim (as would be recommended if PSA is rising or the patient is experiencing symptoms, or to confirm progression), restaging will need to be repeated at every 6-month (+/- 28 day) time point if the patient remains off-treatment during this time.

B Restaging imaging must be performed within 28 days of treatment resumption if not performed already. The 6-month (+/- 28 days) imaging studies are then timed from resumption of TS or ARPI (whichever is resumed first). Interim assessments are recommended at 3-month intervals during periods of rising PSA. Initial radiographic changes suggestive of disease progression (PD on CT/MRI by modified RECIST 1.1 or PDu on bone scan by PCWG3) should be confirmed on repeat imaging within 6-8 weeks if rPFS endpoint has not yet been met. Routine imaging per study is not required past 5 years after registration.

C Restaging imaging on study after TTNT endpoint has been met is required only if rPFS endpoint has not yet been met. Initial radiographic changes suggestive of disease progression (PD on CT/MRI by modified RECIST 1.1 or PDu on bone scan by PCWG3) should be confirmed on repeat imaging within 6-8 weeks in this case. Routine imaging per study is not required past 5 years after registration.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning for a study is required and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the *Data Management* section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*).

Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at [redacted]

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis, treatment, progression, and subsequent response. Supporting documentation will include the following and must be submitted at the following time points:

- **Pathology report** documenting prostate adenocarcinoma (submit within 30 days following registration). If the patient has clinical diagnosis of metastatic prostate cancer only (see section 3.2.1), then pathology report is not required.
- **Progress notes or medication records** documenting systemic therapy (TS and ARPI) for metastatic prostate cancer (submit within 30 days following registration)
- **Laboratory reports** of PSA and testosterone values prior to starting intense ADT and at time of enrollment (submit within 30 days following registration). Subsequent laboratory reports of PSA and testosterone values must be submitted within 30 days of the measurement.
- **Imaging reports and progress notes** corresponding to all submissions, including documentation of metastatic disease by bone scan, or nodal or visceral lesions on CT or MRI (but no liver or brain metastases) prior to starting on intense ADT, and documentation of no evidence of disease progression at time of enrollment (submit within 30 days following registration). Subsequent assessments of disease progression and response to treatment re-initiation and "layering on" additional treatments must be submitted within 30 days of the assessment.

Supporting documentation is to be submitted via Medidata Rave.

6.2 Specimen collection and submission

The Alliance A032101 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For patients registered to substudy A032101-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A032101-ST1, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.2.1. For patients who consent to participate, tissue will be collected at the time points listed below for these studies.

For patients consented to biobanking: All participating institutions must ask patients for their consent to participate in biobanking for future research, although patient participation is optional. Biomarker and pharmacogenetic studies will be performed. Rationale for collecting specimens for biobanking are described in Section 14.2.2. For patients who consent to participate, additional blood will be collected at the time points listed below:

	≤60 days after registration	**Prior to treatment interruption**	**6 months and 18 months after treatment interruption***	**Prior to treatment resumption**	**End of treatment ****
For patients registered to A032101-ST1					
Tumor tissue	X				X***
For patients consented to A032101 Biobanking					
Plasma/buffy coat from EDTA lavender top tubes		2 x 10 ml	2 x 10 ml	2 x 10 ml	2 x 10 ml
Serum from Red top tubes		1x10ml	1x10ml	1x10ml	1x10ml

* 6-month and 18-month specimens are only collected if a patient is in the off-treatment interval at the time. If a patient has resumed treatment prior to 6 months or 18 months after treatment interruption, then biospecimens do not need to be collected at these time points. If treatment is resumed within 30 days of the 6 or 18 month collection, then new samples do not need to be collected at the treatment resumption time-point.

** End of treatment samples should be collected between time of permanent discontinuation from ARPI (including day of last dose) and initiation of next systemic therapy. If a new systemic therapy is planned during an off-treatment interval, the end of treatment sample should be collected prior to initiation of next systemic therapy.

*** For patients who undergo a standard of care biopsy at end of treatment, tissue is requested from metastatic site.

6.3 Digital Imaging Therapy Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.1 TRIAD Installations

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted]

6.3.2 Procedures for Data Submission via TRIAD

Imaging Data Submission Methods

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible.

DICOM images uploading is preferred to be submitted using TRIAD, however these methodologies are supported:

- TRIAD-based (a PC with internet access and TRIAD software installation will be needed)
- Web transfer-based (a PC with internet access and a web browser will be needed)
- FTP transfer-based (a PC with internet access and any FTP software will be needed)
- Mail/CD Shipment-based (only if electronic transfer approaches cannot be achieved)

Questions regarding image submissions can be sent to [redacted]

Detailed Steps of Data Submission

Collection of images is required. Images will be collected digitally for central archiving and curation. Imaging studies will be collected digitally of the following time points:

1. Baseline – within 28 days before registration
2. During Treatment Interruption – every 6 months (+/- 28 days), with recommendation of every 3 months during periods of rising PSA
3. After Treatment Resumption – within 28 days of treatment resumption and then every 6 months (+/- 28 days) from the resumption of TS or ARPI, whichever is resumed first, with recommendation of every 3 months during periods of rising PSA
4. After TTNT - every 6 months (+/- 28 days), with recommendation of every 3 months during periods of rising PSA
5. Progression – at suspicion of progression with a confirmatory scan at 6-8 weeks

The complete imaging data set in digital DICOM format will be submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio) within no more than 3 business days upon the image acquisition completeness. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the imaging data is accepted by IROC Ohio

If not using TRIAD, sites need to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g., 112136) and protocol number (e.g., ALLIANCE032101), respectively.

DICOM tag dates and times cannot be altered prior to submission as they are used to put submissions into context regarding patient treatment. Additional changes to DICOM tags prior to submission impede further technical analysis and should be avoided whenever possible.

Imaging data should be submitted electronically to IROC Ohio via TRIAD, Web Transfer or FTP Transfer:

1. TRIAD based data transfer
   The standard TRIAD based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
2. Web Transfer
   [redacted]
   Any PCs with internet access and web browser (e.g., Chrome, Edge, Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
3. FTP Transfer
   Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
4. Mail/CD Shipment
   Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio.

Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.
Submit these data to:

[redacted]

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email [redacted] to inform that the study has been submitted from the institution. IROC Ohio will notify site and ALLIANCE A032101 imaging committee within 2 business days of the data receipt, and then, within 3 business days following the data receipt, of the quality check report.

Send any questions or problems about the data submission to IROC Ohio email [redacted] for help.

6.4 Submission of Patient Completed Measures

All participating institutions must ask patients for their consent to participate in the Quality-of-Life sub-study planned for Alliance A032101, although patient participation is optional. For patients registered to correlative study A032101-HO1 (model consent question, "I choose to take part in the Quality-of-Life study and will fill out these forms") the quality-of-life evaluations will be performed. For patients who consent to participate, the questionnaires will be completed at the time points listed in the table below (quality of life evaluations should continue in patients who have experienced disease progression and/or resumed treatment after treatment interruption, it may be mailed or e-mailed to patients who do not have a planned clinic visit at the specified QOL time point).

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients who consented to substudy A032101-HO1 (see Section 4.5.1). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient responses into Medidata Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. Booklet administration schedule is provided below.

Note that FACT-P assessments should continue in patients who have experienced disease progression and/or resumed treatment after treatment interruption.

Treatment Arm	At registration*	6 months (+/- 14 days)	12 months (+/- 14 days)	18 months (+/- 14 days)	24 months (+/- 14 days)
For patients registered to A032101-HO1, submit patient-completed questionnaires** at the following time points after initial treatment interruption and even after TTNT endpoint has been reached:					
FACT-P	X	X	X	X	X

* Patients should complete the FACT-P after consent and prior to treatment interruption.

** See Appendix I for FACT-P questionnaires for IRB submission and review only. Patients must complete the questionnaires in booklet format

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

6.4.1 Patient Language Considerations

The FACT-P questionnaire is available in English and Spanish. The translated measures are available on the A032101 CTSU and Alliance study pages. Ad-hoc translation of patient-completed measures is not permitted.

7.0 TREATMENT PLAN/INTERVENTION

Treatment interruption is to begin within 7 days after registration. Thus, patients who are receiving injectable forms of LHRH agonist or antagonist should be registered within 7 days of when the last dose is projected to complete. (The duration of the dose of the last injectable agent should be calculated as 28 days for 1-month depot forms, 84 days for 3-month, 112 days for 4-month and 168 days for 6-month forms.) The last dose of the ARPI should be taken the day the LHRH-A is projected to complete (+/- 7 days). Patients who are receiving abiraterone acetate with a glucocorticoid should then taper off the glucocorticoid per investigator discretion over a maximum of 21 days.

For questions regarding treatment, please see the Study Contacts page.

7.1 Treatment Resumption

Participants should resume both LHRH agonist or antagonist within 28 days of meeting criteria for treatment resumption per protocol: PSA increase to ≥ 5 ng/ml, radiographic change (progressive disease [PD] on CT/MRI by modified RECIST 1.1 criteria or progressive disease – unconfirmed [PDu] on bone scan by PCWG3 criteria), or symptoms attributable to prostate cancer for which the treating investigator feels treatment resumption is indicated. Either the LHRH agonist/antagonist or the ARPI agent can be resumed first. The use of a 1st generation anti-androgen (e.g. bicalutamide) for ≤ 14 days is permitted to prevent testosterone "surge." Patients are required to have restaging imaging within 28 days of treatment resumption.

Management after treatment resumption is per investigator discretion, including allowing for subsequent treatment interruptions. Patients can undergo other cancer-directed interventions after treatment resumption (palliative radiation, SBRT/SABR to oligometastatic sites, "layering on" sipuleucel-T or a radiopharmaceutical) concurrently with TS + ARPI, but these interventions are not permitted prior to intense ADT resumption per protocol except in the case of palliative radiation for an urgent indication.

If a patient is clinically unstable and requires a change in systemic therapy other than protocol-defined treatment resumption (e.g. progression with small cell disease for which chemotherapy is indicated), the patient will meet the time to next treatment (TTNT) endpoint when the new treatment is initiated, and the patient will continue to be followed for the rPFS (if not yet met) and OS endpoints per protocol. QOL assessments will continue every 6 months until 2 years even if the TTNT endpoint has already been reached.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint during the initial off-treatment interval. This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm. Management after treatment resumption is per investigator discretion.

8.1.2 **Patients should receive full supportive care while on this study.** This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the time of initial treatment interruption until 30 days after the TTNT endpoint is reached will be recorded in the medical records.

8.1.3 **Treatment with hormones or other chemotherapeutic agents may not be administered during the off-treatment interval** except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of corticosteroids for indications other than disease control.

8.1.4 **Palliative radiation therapy** may not be administered during the initial off-treatment interval prior to resumption of intense ADT unless the patient is clinically unstable.

8.2 Dose Modifications

Clinical management after resumption of TS + ARPI is per investigator discretion. As such, dose modifications for all prostate cancer-directed treatments should be per the drug label and judgment of the treating physician.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
Fatigue	General disorders and administration site conditions
Hot flashes	Vascular disorders
Erectile dysfunction	Reproductive system and breast disorders
Libido decreased	Psychiatric disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) **Adverse Events CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date, or as part of the Clinical Follow-up Phase or Survival Follow-up Phase.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: Deaths on study meeting the criteria detailed in Section 9.3.3 require both routine and expedited reporting.

9.3.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.3.2 Expedited AE reporting timelines defined

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under an IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

Grade 1-3 erectile dysfunction or gynecomastia and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.

Death

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring during the study intervention (treatment interruption followed by resumption of ADT with the initial ARPI until the TTNT endpoint is met) and within 30 days afterwards, regardless of attribution to the investigational agent/intervention, requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the study intervention is completed requires only routine reporting.

Pregnancy loss and neonatal death

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

A secondary malignancy is a cancer **caused by treatment for a previous malignancy** (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

A second malignancy is one **unrelated to the treatment of a prior malignancy** (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.0 DRUG INFORMATION

10.1 General Considerations:

Management of re-initiation is per physician discretion. Prepare, administer, and store medications according to package insert. Consult the package insert for the most current and complete information.

11.0 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the Prostate Cancer Working Group 3 (PCWG3) modifications[34] (section 11.1.2) to the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the modified

RECIST criteria. Response and progression of osseous disease by bone scintigraphy will be per PCWG3 criteria.[34]

Restaging bone scan and CT (or MRI) chest/abdomen/pelvis must be performed every 6 months (+/- 28 days) during the initial period of treatment interruption. Interim assessments are recommended at 3 month intervals during periods of rising PSA. Initial radiographic changes suggestive of disease progression, i.e. progressive disease (PD) on CT/MRI by modified RECIST 1.1 criteria or progressive disease – unconfirmed (PDu) on bone scan by PCWG3 criteria, should be confirmed on repeat imaging within 6-8 weeks. If restaging studies are performed in the interim (as would be recommended if PSA is rising or the patient is experiencing symptoms, or to confirm progression), restaging will need to be repeated at the every 6-month (+/- 28 day) time point if the patient remains off-treatment during this time.

Restaging imaging must be performed within 28 days of treatment resumption if not performed already. The every 6 month (+/- 28 days) imaging studies are then timed from resumption of TS or ARPI (whichever is resumed first) until the rPFS endpoint is reached. Interim assessments are recommended at 3-month intervals during periods of rising PSA. Initial radiographic changes suggestive of disease progression (PD on CT/MRI by modified RECIST 1.1 or PDu on bone scan by PCWG3) should be confirmed on repeat imaging within 6-8 weeks if the rPFS endpoint has not yet been met.

Restaging imaging on study after the time to next treatment (TTNT) endpoint has been met is required only if rPFS endpoint has not yet been met. Initial radiographic changes suggestive of disease progression (PD on modified CT/MRI by RECIST 1.1 or PDu on bone scan by PCWG3) should be confirmed on repeat imaging within 6-8 weeks in this case.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan or MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease,

abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a digital measurement tool. All baseline evaluations should be performed within 28 days of registration.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed

as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET CT. ^{18}F-deoxyglucose (FDG), ^{18}F-fluciclovine (Axumin®), ^{68}Ga-PSMA, ^{18}F-DCFPyL (PYLARIFY®) PET imaging modalities are permitted on protocol, but do not take the place of protocol-required CT/MRI and bone scan assessments. A patient should not resume therapy based on changes on PET imaging without meeting other protocol-defined criteria for treatment re-initiation.

11.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Osseous Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Osseous Disease by Bone scintigraphy per PCWG3 criteria[34]

Osseous disease will be monitored by bone scintigraphy. Bone scan progression will be defined as the appearance of at least two new lesions relative to the baseline scan, confirmed on a subsequent scan. Date of progression is the date of the scan that first documents the second lesion (and not the date of the confirmatory scan). Changes in intensity of uptake alone do not constitute either progression or regression.

Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	N/A
CR	Non-CR/Non-PD	No	PR	N/A
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	N/A
PD	Any	Yes or No	PD	Requires confirmatory scan after 6-8 weeks
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Clinical Endpoints

18-month treatment-free with eugonadal testosterone: A patient will be considered to have met this endpoint if testosterone measurement at the 18-month time point is measured at ≥ 150 ng/dl and the patient did not require treatment resumption or other cancer-directed intervention (other than bone protective agent or corticosteroids) prior to the 18 month assessments. Participants who interrupt treatment per protocol but then withdraw, are lost to follow-up or die prior to the 18-month assessments are considered to not meet the primary endpoint of remaining treatment-free.

Time to eugonadal testosterone: Time to eugonadal testosterone is defined as the time from treatment interruption per protocol to first testosterone measurement of ≥ 150 ng/dl, or censored at date last testosterone measurement.

Duration off-treatment: Duration off-treatment is defined as the time from treatment interruption per protocol to date of treatment resumption (first of TS or ARPI initiation) or other cancer-directed intervention (other than bone protective agent or corticosteroids), or censored at date last testosterone measurement. If a 1st generation anti-androgen (e.g. bicalutamide) is used to prevent testosterone "surge," this is not counted towards to the duration off-treatment endpoint.

Radiographic Progression-Free Survival: Radiographic Progression-Free Survival (rPFS) is defined as the time from treatment interruption per protocol to the earlier of radiographic progression by modified RECIST 1.1/PCWG3 criteria[34] (with confirmation on subsequent imaging 6-8 weeks afterwards) or death due to any cause. If radiographic progression is confirmed on subsequent imaging, then the date of progression is the date of the initial imaging studies suggestive of progression (and not the confirmatory scan). If radiographic progression is not confirmed on subsequent imaging (i.e. soft tissue lesions decrease in size, or new lesions seen on bone scintigraphy resolve), then radiographic progression is not confirmed and the rPFS endpoint will not have been met. If a patient is unable to have confirmatory scans within the 6-8 week window (for example due to intercurrent illness or lapse in insurance coverage), then any subsequent scans will be considered for confirming or not confirming progression. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Next Treatment: Time to next treatment (TTNT) is defined as the time from treatment interruption per protocol to the initiation of new systemic therapy after

permanent discontinuation of the initial ARPI, or death due to any cause. After initial TS + ARPI interruption, participants re-initiate intense ADT after meeting the protocol-defined resumption criteria. After treatment resumption, participants can undergo other cancer-directed interventions (palliative radiation, SBRT/SABR to oligometastatic sites, "layering on" sipuleucel-T or a radiopharmaceutical), while continuing the initial ARPI, but these interventions are not considered towards the TTNT endpoint since TTNT is intended to capture when the treating investigator feels that the patient is no longer experiencing benefit from the initial ARPI. The "next treatment" can include an alternate ARPI, chemotherapeutic, radiopharmaceutical, targeted agent, immunotherapeutic, clinical trial drug or any other cancer-directed systemic therapy (excluding bone protective agents or corticosteroids) **after the initial ARPI is permanently discontinued** for whatever reason.

Overall Survival: Overall Survival (OS) is defined as the time from treatment interruption per protocol to death due to any cause, or censored at date last known alive.

Cancer-Specific Survival: Cancer-related survival (CSS) is defined as the time from treatment interruption per protocol to death attributable to cancer or its treatment in the opinion of the treating investigator, or censored at date last known alive.

Non-Cancer Specific Survival: Non-cancer-related survival (NCSS) is defined as the time from treatment interruption per protocol to death NOT attributable to cancer or its treatment in the opinion of the treating investigator, or censored at date last known alive.

PSA Progression-Free Survival (PSA-PFS)

PSA Progression-Free Survival is defined as the time from treatment interruption per protocol to the first PSA failure (two consecutive increases in PSA of 25% and ≥2 ng/mL above nadir) or death, or it is censored at date of last PSA test for participants alive without PSA progression.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Assessments

Protocol assessments are continued until the TTNT endpoint, withdrawal from the study or death due to any cause. Participants are considered to be in follow-up status after the TTNT endpoint is reached and are subsequently followed per the study calendar in Section 5.0.

12.2 Follow-up

12.2.1 Duration of Follow-up

After permanent discontinuation of the initial ARPI, participants are followed for documentation of subsequent cancer-directed interventions and survival status at least every 6 months until rPFS endpoint is met and every 6 months thereafter until 10 years from registration or withdrawal from the study or death.

12.2.2 Follow-up for Specimen and QOL Submission

No further biospecimens are collected after the TTNT endpoint. However, QOL assessments should continue every 6 months until 2 years after initial treatment interruption even if TTNT endpoint has been reached prior to that time point.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue on protocol, management per protocol shall be discontinued. In this event:

- Document the reason(s) for discontinuation from the study on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.4 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for patients deemed ineligible after registering

Patients who are deemed ineligible after registering will be replaced and will not be followed.

Follow-up for patients who are registered, but who never interrupt treatment

Study participants who are registered to the trial but who never interrupt treatment will be followed for overall and progression-free survival.

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample size and power calculation

The primary endpoint of the study is remaining treatment-free with eugonadal testosterone (> 150 mg/dl) 18 months after the start of treatment interruption. A single stage single arm study design will be utilized to evaluate this endpoint in the exceptional responder, metastatic castration-sensitive prostate cancer population. The study will test the hypothesis that the probability of remaining treatment free for 18 months with eugonadal testosterone exceeds 0.30. If it is determined that this probability is exceeded in the patient population, then the investigators will consider a randomized phase 3 clinical trial with either a survival or radiographic progression free survival endpoint.

Seventy-five patients will be accrued for this phase 2 design, which differentiates between the 18-month treatment free rates of 0.30 (null hypothesis) and 0.45 (alternative hypothesis). Anticipating a ~5% dropout rate (e.g. due to finding of castration-resistant PSA rise or radiographic progression between enrollment and planned treatment interruption, or patient/physician decision not to interrupt treatment after enrollment), we anticipate 71 patients to be evaluable for the primary endpoint. At the conclusion of the study, if 27 or more of the 71 patients remain off treatment for 18 months with eugonadal testosterone, then it will be concluded that treatment interruption is beneficial in this patient population. Patients who withdraw from the study after treatment interruption per protocol but prior to the 18-month follow-up period will be counted as not remaining treatment free for 18 months. The study design has a type 1 error equal to 0.10 when the probability of remaining treatment free for 18 months is 0.30 and power equal to 0.90 when this probability increases to 0.45. These calculations were derived from the binomial distribution.

13.2 Analysis plan

At the conclusion of the study, the average duration of time off treatment will be calculated for the study cohort. Kaplan-Meier estimates for the probability of overall survival and radiographic

progression free survival over time will be computed. The cumulative incidence function will be used to compute the probability over time for the following endpoints:

- time to eugonadal testosterone
- time to next treatment
- time to cancer specific death
- time to non-cancer specific death

13.3 Projected accrual rate

It is projected that 6 patients per month will be entered onto this study and accrual will be completed in approximately 13 months.

13.3.1 Data Mapping Utility (DMU)

*For studies assigned **Demography** monitoring **and** enrolling patients via **OPEN**:* Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.4 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race. Expected sizes of racial by sex subsets for patients registered randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	12	0	1	13
White	0	56	0	4	60
More Than One Race	0	0	0	0	0
Total	0	70	0	5	75

14.0 CORRELATIVE AND COMPANION STUDIES

There will be two substudies and all patients are encouraged to participate.

14.1 Quality of Life (Alliance A032101-HO1)

14.1.1 Background

Patients with metastatic prostate cancer experience poorer quality of life (QOL), and higher psychological morbidity compared to men with localized disease and those without cancer.[35,36] Although novel ARPIs in conjunction with TS improve outcomes in first-line treatment of patients with mHSPC,[1-4] these therapeutic advances can exacerbate adverse effects compared to TS alone (i.e. fatigue, hot flashes, loss of libido, erectile dysfunction, emotional and cognitive changes, osteoporosis and pain). Prolonged survival also has the potential to expose patients to symptoms of progression (i.e. bone pain and fractures) and the psychological effects of living with cancer for longer.[36,37] A detailed understanding of QOL associated with varying prostate cancer treatments is critical to high quality patient care and progression of research.

It is unclear whether all patients who present with mHSPC require continuous treatment with intense ADT for maximal clinical benefit. We hypothesize that in patients who achieve exceptional response to upfront therapy including a novel ARPI, treatment interruption will allow for a subset of patients to remain treatment-free with testosterone recovery for a prolonged period, effectively improving QOL. In order to specifically test this hypothesis, the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire will be serially assessed. The information provided by this analysis will be critical to understanding the magnitude, timing, and duration of QOL improvement after cessation of treatment. These data will not only inform clinical decision making, but will directly provide necessary data to design a potential future Phase III randomized trial.

The FACT-P is a well-established, 39-item questionnaire that was developed and validated specifically in patients with advanced prostate cancer.[38,39] The scores for five FACT-P subscales (physical well-being [seven items], social and family well-being [seven items], emotional well-being [six items], functional well-being [seven items], and prostate cancer subscale [12 items]) can be summed to compute the FACT-P total score. The FACT-P total score ranges from 0 to 156. Higher values of the FACT-P total and all subscales indicate a higher QOL. Clinically meaningful changes in the FACT-P total score and subscales have been previously reported on and applied to statistical design.[61]

The FACT-P is expected to take about 10 minutes to complete and will be assessed at baseline and every 6 months up to 24 months.

14.1.2 Objectives

Primary Objective

To assess changes in patient-reported quality of life as assessed by the FACT-P total score from baseline to 24 months after treatment interruption.

Hypothesis: Patient-reported quality of life as assessed by the FACT-P total score will improve from baseline to 24 months after treatment interruption.

Secondary Objectives

To assess changes in the FACT-P subscales (i.e., physical well-being, social and family well-being, emotional well-being, functional well-being, and prostate cancer subscale) from baseline to 24 months after treatment interruption.

Hypothesis: The FACT-P subscales will improve from baseline to 24 months after treatment interruption.

To assess changes in the FACT-P total score and subscales (i.e., physical well-being, social and family well-being, emotional well-being, functional well-being, and prostate cancer subscale) from baseline to the remaining post-baseline time points (i.e., 6, 12, and 18 months) after treatment interruption.

Hypothesis: The FACT-P total score and subscales will improve from baseline to each post-baseline time point (i.e., 6, 12, and 18 months) after treatment interruption.

14.1.3 Methods

For Schedule of Assessments for this QOL study, see Section 6.4. All participating institutions must ask patients for their consent to participate in this quality-of-life study (A032101-HO1), although patient participation is optional. Paper booklets will be used for this study. For information regarding ordering the booklets, see Section 4.5.1. For all patients who consent to participate in this QOL study (A032101-HO1), a booklet will be given to the patient to complete at the specified planned clinic visits before any procedures/tests are initiated at the site visit and prior to any discussion of their status with healthcare personnel at the site. Booklets will be collected at the following time points: during registration and at approximately 6, 12, 18, and 24 months post-randomization. FACT-P assessments should continue in patients who have experienced disease progression and/or resumed treatment after treatment interruption. The booklet contains 39 questions, and it is anticipated that the booklet will take approximately 10 minutes for the patient to complete at each administration time point. We anticipate having booklets available in English and Spanish. Patients who consent to participate in this quality-of-life study (A032101-HO1) may decline to complete a booklet at any time. The primary reason for each missed booklet will be collected on a case report form.

14.1.4 Statistical Considerations

The FACT-P will be scored according to its published scoring algorithm, including recommendations for addressing missing items within a scale. Patients who meet eligibility criteria and complete at least one FACT-P assessment will be included in the analyses. To evaluate change in the FACT-P total score from baseline to 24 months, a mixed model will be estimated for the FACT-P total score at baseline (i.e., treatment discontinuation) and at 6, 12, 18, and 24 months. The mixed model will include a fixed intercept, fixed effect for time, and residual covariance matrix based on the observed covariances. Baseline patient characteristics and prognostic factors may be included in the mixed model as covariates. Estimates from the mixed model will be used to construct 90% confidence intervals for mean changes in the FACT-P total score between baseline and each post-baseline time point (i.e., 24 months as well as 6, 12, and 18 months). For comparison, historical control data was derived from the androgen deprivation therapy plus abiraterone acetate and prednisone arm of the LATITUDE trial and the androgen deprivation therapy plus apalutamide arm of the TITAN trial.[40, 41] In each of these arms, the projected mean change in the FACT-P total score was calculated 24 months following Cycle 19 (1 cycle = 28 days) while assuming linear change over time. The projected mean change in the FACT-P total score 24 months following Cycle 19 was approximately 0.8 points in the LATITUDE trial (indicating slight improvement of quality of life) and -2.1 points in the TITAN trial (indicating slight worsening of quality of life). Based on this historical control data, we will conservatively test whether A032101-HO1 patients experience a 0.8-point or greater mean improvement in the FACT-P total score between

baseline and 24 months from a contrast estimated via the mixed model. This contrast will involve a two-sided *t*-test with a nominal significance level of $\alpha = 0.10$. Independent of statistical significance, a 6-point or greater mean improvement in the FACT-P total score between baseline and 24 months will be considered clinically meaningful based on published literature.[42] If a 6-point or greater mean improvement is not observed in this phase II trial, then treatment interruption will not have demonstrated sufficient quality of life improvement to proceed to a phase III trial based on quality of life. To explore the timing and duration of improvement, estimates from the mixed model will be used to plot the longitudinal mean trajectory of the FACT-P total score.

To evaluate change in the FACT-P subscales (i.e., physical well-being, social and family well-being, emotional well-being, functional well-being, and prostate cancer scores) from baseline to each post-baseline time point (i.e., 6, 12, 18, and 24 months), a mixed model similar to the one described above will be estimated for each subscale. Estimates from the mixed model will be used to construct 90% confidence intervals for mean changes in each subscale between baseline and each post-baseline time point. Each contrast estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = 0.10$. Mean changes in the FACT-P subscales between baseline and 24 months will be compared to clinically meaningful change thresholds summarized by Nussbaum et al.[43] There will be no adjustment for multiplicity for the secondary endpoints, though interpretation will take into consideration that the type I error is strictly controlled for the primary endpoint only. Overall interpretation will also take into consideration consistency of results across analyses. To explore the timing and duration of improvement, estimates from the mixed model will be used to plot the longitudinal mean trajectory of each subscale.

The proportion of, and reported reasons for, missing data will be presented by time point. Correlation analysis and logistic regression analysis will be used to examine whether baseline patient characteristics and prognostic factors predict missingness. The mixed models will provide unbiased parameter estimates under a missing completely at random or missing at random mechanism. However, a sensitivity analysis will be conducted to assess the robustness of the results across various assumptions about the missing data.

Power: To evaluate change in the FACT-P total score from baseline to 24 months, 63 evaluable patients from among the 75 enrolled patients on the parent protocol (i.e., allowing 15% of patients to decline consent or miss booklets for any reason) provide 86% power to detect a mean change in the FACT-P total score based on a two-sided paired *t*-test, nominal significance level of $\alpha = 0.10$, and population standardized mean difference of 0.35 (i.e., between a small and moderate effect size based on Cohen's conventions).[60] The same power calculation applies when evaluating change in all other FACT-P subscales from baseline to each post-baseline time point (i.e., 6, 12, 18, and 24 months).

Analyses will be coordinated by the Alliance SDMC A032101 Statistician using the dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g., data associated with censoring and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

14.2 Correlative Science

14.2.1 Optional Tissue Correlative Science study A032101-ST1

At the time of enrollment patients can decide whether or not they will have archival FFPE tissue submitted.

In the tissue analysis portion of the study, we plan to assess WES and mRNA profiles at baseline and assess changes compared with post-treatment biopsy when feasible.

Tumor Genomic Profiling

Whole exome sequencing (WES) has become a critical tool across cancer types, and in particularly has shifted the treatment paradigm of advanced prostate cancer.[35-37] Identification of clinically actionable mutations has resulted in advances in molecularly targeted clinical trials and treatment approaches for metastatic castration-resistant prostate cancer, such as CDK12 loss and HRD genomic aberrations.[35-37] Despite some recent genomic characterization in mHSPC patients, further assessments in this population are needed.[38-39] We will thus perform WES on baseline archival tissues and metastatic tissue at end of treatment when available and correlate these findings with responses on trial.

Tumor RNA Profiling

The clinical Decipher assay (Veracyte, Inc.) utilizes a whole-transcriptome microarray assay to measure the expression of 22 RNA markers to generate a genomic classifier score which can be used to predict the probability of metastatic progression.[40,41,45] Recently, the Decipher genomic classifier (GC) score has been shown to further risk stratify men with mHSPC from subset analysis of the CHAARTED,[46] STAMPEDE,[47] and TITAN[48] phase 3 randomized trials. In the present study, we will perform RNA profiling on baseline archival tissues and metastatic tissue at time of progression when available and correlate these findings with responses on trial. In addition to the Decipher GC score, several hundred locked gene expression signatures are automatically generated from the data. These include AR signaling, tumor immune microenvironment and tumor subtyping (e.g. basal/luminal, neuroendocrine) models.[49]

Methods

The Decipher test is a laboratory service provided by Veracyte, Inc. (South San Fransisco, CA). To perform the test, RNA is extracted from the FFPE prostate tissue samples, purified, and reverse-transcribed into cDNA. The cDNA is amplified, labeled, and hybridized to the Decipher GeneChip, a proprietary 1.4 million feature oligonucleotide microarray based on the Affymetrix Human Exon 1.0 ST design (ThermoFisher, Carlsbad, CA). We will be collecting samples during enrollment. The Decipher Biosciences laboratory, located in San Diego, CA, is certified under the Clinical Laboratory Improvement Amendment (CLIA; 05D2055897), accredited by the College of American Pathologists (CAP, 8859006), and licensed by the New York State Department of Health (NYSDOH, 9018). FDA clearance or approval is not required for this assay.

Statistical Considerations

Power: We assume, similarly to the sample size calculation outlined in section 13.1, that the overall rate of remaining treatment-free 18 months after the start of treatment interruption is 45%. We base our power calculation on the logistic regression model for this endpoint with Decipher score as a continuous covariate. With a total sample size of 67 (incorporating an additional 5% sample loss due to poor quality), this regression will have 90% power to detect an odds ratio of 0.758 for every 0.1 increase in Decipher at the 0.10 significance level. Both Decipher risk categories (binarized as Low / Intermediate vs. High-risk) and PAM 50 (predicting basal vs. luminal tumor types) will also be used as covariates in similar logistic regression models. Assuming that roughly 60% of participants are classified as Decipher high risk (similar to observed rates in CHAARTED, STAMPEDE and TITAN), the logistic model will have 90% power at the 0.10 significance level to detect an odds ratio of 0.211 (i.e. rates of remaining treatment-free equal to 67% and 30% in the Decipher Low / Intermediate and High-risk groups, respectively). Similarly, assuming that roughly 50% of participants have basal tumor types (similar to observed rates in

CHAARTED, STAMPEDE and TITAN), this regression model will have 90% power at the 0.10 significance level to detect an odds ratio of 0.217 (i.e. rates of remaining treatment-free equal to 63% and 27% in the luminal and basal subtypes, respectively). The preceding two power calculations are made with the restraint that the overall rate of remaining treatment-free remains equal to 45% in the aggregate.

14.2.2 ctDNA Genetic Profiling and cfDNA MRD Detection

Circulating tumor DNA (ctDNA) analysis has become an increasingly relevant tool across multiple cancer type, and its utility has also been demonstrated in advanced prostate cancer.[51-56] ctDNA and cfDNA MRD are less likely to be detected in patients with mHSPC with ongoing PSA response to therapy. However, even in patients with localized prostate cancer, in whom ctDNA detection is less frequent, detectable levels of ctDNA correlate with an increased likelihood of disease progression.[57] Thus, we collect plasma throughout the study as delineated in Section 6.0 and will monitor ctDNA and cfMRD in our patient cohort, and determine the association with clinical outcomes including the primary endpoint of 18-months treatment-free with eugonadal testosterone (> 150 ng/dl), and secondary endpoints of duration of time off treatment, time-to-next treatment and radiographic PFS.

Methods

The MRD test for this protocol is a laboratory service provided by Veracyte, Inc.(South San Francisco, CA) applying an assay previously reported as C2inform.[57-59] Veracyte's MRD test is a tumor-informed assay, ctDNA-based test using whole-genome sequencing (WGS) that leverages a patient tumor-specific signatures approach to MRD assessment. Use of WGS-based ctDNA assessment enables the potential tracking of tumor evolution as patients progress through treatment paradigms. This approach allows for both the monitoring of disease recurrence and the detection of tumor evolution in longitudinally collected plasma samples. Circulating cell-free DNA will be isolated from banked plasma specimens and undergo whole genome sequencing. Tumor fraction will be estimated based on genome-wide detection of somatic mutations found in the patient's tumor sample (including single nucleotide variants, insertions/deletions, and copy number variants), in conjunction with a proprietary error-suppression model as previously described.[57-59] The technique facilitates the detection of tumor presence in cfDNA and aids in estimating the tumor fraction. FDA clearance or approval is not required for this assay.

Statistical Considerations

<u>Power</u>: We assume, similarly to the sample size calculation outlined in section 13.1, that the overall rate of remaining treatment-free 18 months after the start of treatment interruption is 45%. The MRD test available immediately before interruption will be used for this analysis. As the distribution of tumor fraction and positivity is unknown, we base our power calculation on the logistic regression model for this endpoint with tumor fraction as a continuous covariate (with odds calculated per standard deviation increase) and as a dichotomized variable (split at the median). With a total sample size of 67 (incorporating an additional 5% sample loss due to poor quality), this regression will have 90% power to

detect an odds ratio of 0.487 for every standard deviation increase in tumor fraction at the 0.10 significance level. When dichotomized at the median value, the logistic model will have 90% power at the 0.10 significance level to detect an odds ratio of 0.230 (i.e. rates of remaining treatment-free equal to 62% and 28% in the lower and higher tumor fraction groups, respectively).

14.2.3 Optional Peripheral Blood Collection for A032101 Biobanking for Future Use

NOTE: Additional testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

Future testing of circulating peripheral biomarkers other than ctDNA analysis may include but is not limited to germline genetic profiling, and androgen metabolite evaluation. Rationale for collecting blood for biobanking is summarized here.

Androgen and Metabolite Level Analysis

The use of ADT and multiple AR-targeted agents in advanced prostate cancer impacts the testosterone biosynthesis pathway and has multiple other metabolomics effects,[58] with prior reports of serum metabolites alterations differing depending on the prior duration of ADT.[59] We will thus longitudinally assess various metabolites affected by ADT, including long-chain acyl-carnitines, as well as androsterone sulfate.[59]

Statistical Methods

The data collected from the banked samples, as described above, will be sent using encrypted secure spreadsheets to the Alliance SDMC A032101 Statistician to prepare analysis datasets in conjunction with the clinical/outcome data. The A032101 Statistician will then coordinate the analyses with the A032101 Correlative Science Co-Chair, Melissa Reimers, MD. Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

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APPENDIX I

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some -what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

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APPENDIX II

Patient Information Sheet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains one set of questions:
    a. FACT-P (Version 4)
2. Please follow the directions at the top of this questionnaire.
3. You may choose not to answer any questions that make you feel uncomfortable.
4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.