NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-World Characteristics and Treatment Patterns of Patients Treated with Talazoparib + Enzalutamide for Metastatic Castration-Resistant Prostate Cancer in the US Community Oncology Setting
Protocol number	C3441070
Protocol version identifier	2.0
Date	31 May 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000931
Active substance	Talazoparib (L01XK04), Enzalutamide (L02BB04)
Medicinal product	TALZENNA® (talazoparib), XTANDI® (enzalutamide)
Research question and objectives	The research questions for this study are to examine the real-world patient characteristics, HRRm testing and treatment patterns of talazoparib + enzalutamide for metastatic castration-resistant prostate cancer (mCRPC) in the US community oncology setting. Among patients with mCRPC who initiated talazoparib + enzalutamide in the US community oncology setting, the objectives of this study are as follows: <u>Primary objectives</u>: 1. To describe patient demographics and clinical characteristics. 2. To describe the following HRRm testing patterns: a) The count and proportion of patients with documentation of HRRm testing overall and by timing of the first HRRm test relative to metastatic diagnosis and initiation of talazoparib + enzalutamide (i.e., prior to metastatic diagnosis, between metastatic diagnosis and initiation of talazoparib + enzalutamide) b) The count and proportion of patients undergoing subsequent HRRm testing prior to the end of the study observation period overall and by timing of HRRm test (sample size permitting) c) Time to the first documented HRRm testing from metastatic diagnosis and from initiation of talazoparib + enzalutamide d) The distribution of HRRm test results among patients who received HRRm testing, including the count and proportion of patients with BRCA mutation(s), non-BRCA mutations only, or no mutations

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	e) The distribution of testing modality and assay type for the first documented HRRm test among patients who received HRRm testing 3. To describe treatment patterns in the metastatic setting, including: a) Line of therapy (LOT) of initiation of talazoparib + enzalutamide (as defined in **Section 9.3.1**) b) Distribution of treatment regimens received prior to initiation of talazoparib + enzalutamide, including regimens received in the mCSPC and mCRPC settings by LOT (if applicable) c) Distribution of regimens received following initiation of talazoparib + enzalutamide through the end of the follow-up period (as defined in **Section 9.1**) d) Starting dose and dose modifications of talazoparib + enzalutamide e) Reasons for discontinuation of talazoparib + enzalutamide <u>Secondary objectives</u>: 1. To describe real-world clinical outcomes from initiation of talazoparib + enzalutamide, including: a) Real-world time to treatment discontinuation (rwTTD) b) Real-world time to next treatment (rwTTNT) c) Real-world progression-free survival (rwPFS) d) Overall survival (OS) <u>Exploratory Objectives</u>: 1. To describe the availability and distribution of prostate-specific antigen (PSA) and hemoglobin (Hgb) results after initiation of talazoparib + enzalutamide
Country(ies) of study	USA
Author	[redacted] Pfizer Inc.

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1. TABLE OF CONTENTS

1. TABLE OF CONTENTS....4
2. LIST OF ABBREVIATIONS....6
3. RESPONSIBLE PARTIES....8
4. ABSTRACT....9
5. AMENDMENTS AND UPDATES....13
6. MILESTONES....14
7. RATIONALE AND BACKGROUND....15
8. RESEARCH QUESTION AND OBJECTIVES....16
8.1. Primary Objectives....16
8.2. Secondary Objectives....17
8.3. Exploratory Objectives....17
9. RESEARCH METHODS....18
9.1. Study Design....18
9.2. Setting....20
9.2.1. Inclusion Criteria....20
9.2.2. Exclusion Criteria....21
9.2.3. Chart Abstraction Selection....21
9.2.4. Cohorts and Stratifications....22
9.3. Variables....22
9.3.1. Exposure....38
9.3.2. Study Endpoints....40
9.4. Data Sources....41
9.5. Study Size....41
9.6. Data Management....43
9.6.1. Case Report Forms/Data Collection Tools/Electronic Data Record....43
9.6.2. Record Retention....43
9.7. Data Analysis....44
9.7.1. Analysis for addressing primary objective 1 (patient characteristics)....44
9.7.2. Analysis for addressing primary objective 2 (HRRm patterns)....44
9.7.3. Analysis for addressing primary objective 3 (treatment patterns)....45

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

9.7.4. Analysis for addressing secondary objective 1 (clinical outcomes) 45
9.7.5. Analysis for addressing exploratory objective 1 (PSA, Hgb) 45
9.8. Quality Control 46
9.9. Strengths and Limitations of the Research Methods 47
9.9.1. Strengths 47
9.9.2. Limitations 47
9.10. Other Aspects 48
10. PROTECTION OF HUMAN PARTICIPANTS 49
10.1. Patient Information 49
10.2. Patient Consent 49
10.3. Institutional Review Board (IRB)/ Ethics Committee (EC) 49
10.4. Ethical Conduct of the Study 50
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 51
11.1. Human Review of Unstructured Data 51
11.2. Structured Data Analysis 52
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 53
13. REFERENCES 54
14. LIST OF TABLES 55
15. LIST OF FIGURES 55
ANNEX 1. LIST OF STANDALONE DOCUMENTS 55
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 55
ANNEX 3. ADDITIONAL INFORMATION 55

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first-line
2L	second-line
ADT	androgen deprivation therapy
ARPi	androgen receptor pathway inhibitor
BMI	body mass index
CI	confidence interval
CRF	case report form
CVP	ClearValuePlus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EHR	electronic health record
Hgb	hemoglobin
HRRm	homologous recombination repair mutations
ICMJE	International Committee of Medical Journal Editors
iKM	iKnowMed
IQR	interquartile range
IRB	Institutional Review Board
LADMF	Limited Access Death Master File
LOT	line of therapy
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer

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mPC	metastatic prostate cancer
NCCN	National Comprehensive Cancer Network
NGS	next-generation sequencing
NOS	not otherwise specified
OS	Overall survival
PARP	poly(ADP-ribose) polymerase
PC	prostate cancer
PS	performance status
PSA	prostate-specific antigen
rwTTD	Real-world time to treatment discontinuation
rwTTNT	Real-world time to next treatment
rwPFS	Real-world progression-free survival
RUCA	Rural-Urban Commuting Area
SD	standard deviation
VUS	variants of unknown significance

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3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]

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4. ABSTRACT

Title	Real-World Characteristics and Treatment Patterns of Patients Treated with Talazoparib + Enzalutamide for Metastatic Castration-Resistant Prostate Cancer in the US Community Oncology Setting, v2.0, 31 May 2026, [redacted]
Rationale and background	Prostate cancer remains one of the most prevalent malignancies among men, and while most cases are diagnosed among patients with localized disease, approximately 8-9% of cases are de novo metastatic, with 5-year survival rates of only 37%. While patients with metastatic prostate cancer (mPC) are often initially responsive to surgical or medical castration to reduce testosterone levels, most patients with mPC eventually develop resistance to treatments such as androgen deprivation therapy (ADT) and are considered to have metastatic castration-resistant prostate cancer (mCRPC). Talazoparib is a poly (ADP-ribose) polymerase inhibitor that was approved in the US in June 2023 in combination with enzalutamide for the treatment of mCRPC with homologous recombination repair mutations (HRRm). However, additional evidence is needed to understand the patient population and treatment patterns of this combination in real-world settings.
Research question and objectives	The research questions for this study are to examine the real-world patient characteristics, HRRm testing and treatment patterns of talazoparib + enzalutamide for metastatic castration-resistant prostate cancer (mCRPC) in the US community oncology setting. Among patients with mCRPC who initiated talazoparib + enzalutamide in the US community oncology setting, the objectives of this study are as follows: <u>Primary objectives</u>: 1. To describe patient demographics and clinical characteristics. 2. To describe the following HRRm testing patterns: a) The count and proportion of patients with documentation of HRRm testing overall and by timing of the first HRRm test relative to metastatic diagnosis and initiation of talazoparib + enzalutamide (i.e., prior to metastatic diagnosis, between metastatic diagnosis and initiation of talazoparib + enzalutamide) b) The count and proportion of patients undergoing subsequent HRRm testing prior to the end of the study observation period overall and by timing of HRRm test (sample size permitting) c) Time to the first documented HRRm testing from metastatic diagnosis and from initiation of talazoparib + enzalutamide d) The distribution of HRRm test results among patients who received HRRm testing, including the count and proportion of patients with BRCA mutation(s), non-BRCA mutations[1] only, or no mutations e) The distribution of testing modality and assay type for the first documented HRRm test among patients who received HRRm testing

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

	3. To describe treatment patterns in the metastatic setting, including: a) Line of therapy (LOT) of initiation of talazoparib + enzalutamide (as defined in **Section 9.3.1**) b) Distribution of treatment regimens received prior to initiation of talazoparib + enzalutamide, including regimens received in the mCSPC and mCRPC settings by LOT (if applicable) c) Distribution of regimens received following initiation of talazoparib + enzalutamide through the end of the follow-up period (as defined in **Section 9.1**) d) Starting dose and dose modifications of talazoparib + enzalutamide e) Reasons for discontinuation of talazoparib + enzalutamide <u>Secondary objectives</u>: 1. To describe real-world clinical outcomes from initiation of talazoparib + enzalutamide, including: a) Real-world time to treatment discontinuation (rwTTD) b) Real-world time to next treatment (rwTTNT) c) Real-world progression-free survival (rwPFS) d) Overall survival (OS) <u>Exploratory objectives</u>: 1. To describe the availability and distribution of prostate-specific antigen (PSA) and hemoglobin (Hgb) results after initiation of talazoparib + enzalutamide
Study design	This is a retrospective observational cohort study of electronic health record (EHR) data. Phase 1 will assess objectives during the study identification period 20 June 2023 – 31 December 2024 and study-eligible patients will be followed longitudinally until last contact date or date of death on or before 31 March 2025, whichever occurs first. Phase 2 will consist of a data refresh to include additional patients during the study identification period 20 June 2023 – 31 January 2026, provide additional follow-up for existing patients from Phase 1, and assess additional treatment characteristics and clinical outcomes through 30 April 2026. The study time periods may be extended further, and the study results may be updated with the newly available data, up to two additional times.
Population	The study population will consist of patients treated for mCRPC with talazoparib + enzalutamide within The US Oncology Network ("The Network") or non-Network practices during the study identification period (Phase 1: 20 June 2023 – 31 December 2024; Phase 2: 20 June 2023 – 31 January 2026).
Variables	Demographic and clinical characteristics will include age, race, ethnicity, rural/urban, practice location, practice volume (number of patients), body mass index (BMI), height and weight (for BMI calculations), date of initial PC diagnosis, date of mPC diagnosis, time from metastatic diagnosis to index, castration-sensitive and castration-resistant status + dates, disease stage at initial diagnosis, TNM stage, distant metastatic site(s) and type, visceral metastatic site(s), count of metastatic sites, high volume disease status, histology at

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	initial diagnosis, Gleason score, Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance status (PS), baseline PSA, testosterone and hemoglobin (hgb) results + dates, somatic and germline biomarker testing information, BRCA and other non-BRCA HRRm testing and status, HRRm testing status, timing and frequency of the first HRRm test, HRRm testing type (i.e., germline, somatic), somatic HRRm testing collection type, HRRm status, time from HRRm testing to metastatic diagnosis, time from metastatic diagnosis to HRRm testing, and time from HRRm testing to index. Treatment characteristics will include anticancer drug name and start/stop date(s), reason for treatment initiation, reason for treatment discontinuation, baseline treatment dose, treatment dose / dose changes, clinical trial participation and treatment for other primary cancer diagnosis. Last contact date, vital status, hospice status, follow-up time, provider-documented tumor assessments, PSA and Hgb results will be collected at follow-up. Outcomes to be assessed for this study include rwTTD, rwTTNT, rwPFS and OS.
Data sources	This study will leverage data aggregated from several sources, including the iKnowMed (iKM) EHR via Ontada's proprietary data platform, which is refined for completeness and quality to deliver a comprehensive and enhanced view of patient care, including symptoms, diagnosis, treatment choices, therapy cycles, survivorship, and disease progression. It leverages both structured and unstructured data.
Study size	A preliminary feasibility assessment identified 92 patients with mPC who were prescribed talazoparib during the feasibility period, and a subsequent feasibility for Phase 2 extended through January 2026 identified an additional 72 patients. Due to differences in the eligibility criteria used and time period considered, the study patient count may vary from what has been estimated by the feasibility assessment. Therefore, all confirmed eligible patients will complete chart abstraction up to a maximum target sample size of N = 100 (Phase 1). For Phase 2, all confirmed eligible patients from Phase 1 will be reviewed in addition to up to N = 50 new patients that meet eligibility criteria with the extended study periods. Based on estimated rates of ineligibility from Phase 1, approximately 40 new patients are estimated for Phase 2.
Data analysis	For Phase 1, descriptive analyses will be conducted to evaluate demographic and clinical characteristics as well as HRRm testing and treatment patterns. For Phase 2, additional treatment characteristics and clinical outcomes will also be assessed.
Milestones	

Milestone	**Planned Date**
Completion of feasibility assessment	31 January 2025
Start of data collection (Phase 1)	30 April 2025
End of data collection (Phase 1)	31 July 2025

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	Interim report / preliminary results for all planned analyses (Phase 1)	31 October 2025
	Draft study report (Phase 1)	30 November 2025
	Registration in the HMA-EMA Catalogues of RWD studies	15 June 2026
	Start of data collection (Phase 2)	15 June 2026
	End of data collection (Phase 2)	31 August 2026
	Interim report / preliminary results for all planned analyses (Phase 2)	30 September 2026
	Draft study report (Phase 2)	31 October 2026
	Final study report	31 December 2026

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5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	31 May 2026	Substantial	4 (abstract) 8 (objectives) 9.1 (study design) 9.2 (setting) 9.3 (variables) 9.5 (study size) 9.7 (data analysis) 9.9.2 (limitations)	1) Extended study periods 2) Added clinical outcomes, dose changes, reasons for treatment discontinuation, reasons for ineligibility, and subgroup analysis 3) Added clarifications to existing protocol language	1) To include more recent patients and longer follow-up 2) To further describe real-world use of talazoparib + enzalutamide 3) To ensure clarity and transparency
1.0	08 Apr 2025		Original protocol	-	-

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6. MILESTONES

Milestone	Planned Date
Completion of feasibility assessment	31 January 2025
Start of data collection (Phase 1)	30 April 2025
End of data collection (Phase 1)	31 July 2025
Interim report / preliminary results for all planned analyses (Phase 1)	31 October 2025
Draft study report (Phase 1)	30 November 2025
Registration in the HMA-EMA Catalogues of RWD studies	15 June 2026
Start of data collection (Phase 2)	15 June 2026
End of data collection (Phase 2)	31 August 2026
Interim report / preliminary results for all planned analyses (Phase 2)	30 September 2026
Draft study report (Phase 2)	31 October 2026
Final study report	31 December 2026

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7. RATIONALE AND BACKGROUND

Prostate cancer (PC) remains one of the most prevalent malignancies among men, with 299,010 new cases and 35,250 deaths estimated in 2024.[1] Due to enhanced screening protocols, the number of newly diagnosed PC declined sharply from 2007 to 2014, but since 2014 the incidence rate has increased by 3% annually overall, and the burden of prostate cancer is expected to grow with an increasingly aging population.[1-3] While most cases are diagnosed among patients with localized disease, approximately 8-9% of cases are de novo metastatic, with 5-year survival rates of only 37%.[1]

Patients with metastatic PC (mPC) are often initially responsive to surgical or medical castration to reduce testosterone levels, which is the primary driver of PC growth. However, most patients with mPC develop resistance to treatments such as androgen deprivation therapy (ADT) and are considered to have metastatic castration-resistant prostate cancer (mCRPC). The National Comprehensive Cancer Network (NCCN) guidelines recommend several different treatment options for mCRPC, depending on patients' prior history of docetaxel and/or androgen receptor pathway inhibitors (ARPi) such as abiraterone, enzalutamide, darolutamide, or apalutamide.[4] Guidelines also recommend germline (at diagnosis of metastatic, regional, very-high-risk localized, or high-risk localized PC, and/or for patients with a positive family history) and somatic (at mPC diagnosis) multigene tumor testing for alterations in homologous recombination repair genes (HRRm) in patients with mPC, for consideration of targeted therapies which are particularly effective in HRRm-positive tumors.[4]

Talazoparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved in June 2023 in combination with enzalutamide for the treatment of mCRPC with HRRm (BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C).[5] Approval was based on findings from the TALAPRO-2 clinical trial, a randomized, double-blind, phase 3 study comparing talazoparib + enzalutamide vs. placebo + enzalutamide in 399 patients with previously untreated mCRPC with HRRm (Cohort 2). Median follow-up for the primary analysis (data cutoff: October 3, 2022) was 17.5 and 16.8 months for the talazoparib (N=200) and placebo (N=199) cohorts, respectively.[6,7] Talazoparib significantly improved radiographic progression-free survival (rPFS) compared with placebo (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.33 to 0.61; $P < 0.0001$; median not reached at the time of the analysis versus 13.8 months).[6] At an updated data cutoff (September 3, 2024) with a median 44.2 months of follow-up, the median rPFS for the talazoparib and placebo cohorts were 30.7 and 12.3 months, respectively.[8] For overall survival (OS), talazoparib plus enzalutamide resulted in a 38% reduced risk of death vs. enzalutamide plus placebo (HR, 0.622; 95% CI, 0.475 to 0.814; $P = 0.0005$), with a median OS of 45.1 vs. 31.1 months, respectively.[8] The most common adverse events in the talazoparib cohort were anemia, fatigue, neutropenia, thrombocytopenia, nausea and decreased appetite, and there were no treatment-related deaths.[6]

While TALAPRO-2 demonstrated the safety and efficacy of talazoparib + enzalutamide for mCRPC with HRRm, additional evidence is needed to understand the experience in real-world settings. Real-world data plays an important role in understanding the heterogeneity in patient characteristics between controlled trials and clinical practice, and it is important to consider variations in the timing and frequency of monitoring and adherence to treatment. Therefore, the aim of this study is to examine the real-world patient characteristics, HRRm testing and treatment patterns of talazoparib + enzalutamide among patients diagnosed with mCRPC in the US community oncology setting.

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This non interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The research questions for this study are to examine the real-world patient characteristics, HRRm testing and treatment patterns of talazoparib + enzalutamide for metastatic castration-resistant prostate cancer (mCRPC) in the US community oncology setting.

Among patients with mCRPC who initiated talazoparib + enzalutamide in the US community oncology setting, the objectives of this study are as follows:

8.1. Primary Objectives

1. To describe patient demographics and clinical characteristics.

2. To describe the following HRRm testing patterns:
   a) The count and proportion of patients with documentation of HRRm testing overall and by timing of the first HRRm test relative to metastatic diagnosis and initiation of talazoparib + enzalutamide (i.e., prior to metastatic diagnosis, between metastatic diagnosis and initiation of talazoparib + enzalutamide)
   b) The count and proportion of patients undergoing subsequent HRRm testing prior to the end of the study observation period overall and by timing of HRRm test (sample size permitting)
   c) Time to the first documented HRRm testing from metastatic diagnosis and from initiation of talazoparib + enzalutamide
   d) The distribution of HRRm test results among patients who received HRRm testing, including the count and proportion of patients with BRCA mutation(s), non-BRCA mutations[1] only, or no mutations
   e) The distribution of testing modality and assay type for the first documented HRRm test among patients who received HRRm testing

3. To describe treatment patterns in the metastatic setting, including:
   a) Line of therapy (LOT) of initiation of talazoparib + enzalutamide (as defined in **Section 9.3.1**)
   b) Distribution of treatment regimens received prior to initiation of talazoparib + enzalutamide, including regimens received in the mCSPC and mCRPC settings by LOT (if applicable)
   c) Distribution of regimens received following initiation of talazoparib + enzalutamide through the end of the follow-up period (as defined in **Section 9.1**)
   d) Starting dose and dose modifications of talazoparib + enzalutamide
   e) Reasons for discontinuation of talazoparib + enzalutamide

[1] Non-BRCA mutations of interest for this study include ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C.

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8.2. Secondary Objectives

1. To describe real-world clinical outcomes from initiation of talazoparib + enzalutamide, including:
   a) Real-world time to treatment discontinuation (rwTTD)
   b) Real-world time to next treatment (rwTTNT)
   c) Real-world progression-free survival (rwPFS)
   d) Overall survival (OS)

8.3. Exploratory Objectives

1. To describe the availability and distribution of prostate-specific antigen (PSA) and hemoglobin (Hgb) results after initiation of talazoparib + enzalutamide

All analyses will be conducted overall as well as stratified by receipt of prior ARPi and/or docetaxel as described in **Section 9.2.4**.

During Phase 1, only Primary Objectives 1, 2 and 3 a-c are assessed among Phase 1 study patients, and during Phase 2, all Primary Objectives (including 3[d-e]), Secondary and Exploratory Objectives will be assessed among newly identified patients and existing Phase 1 study patients.

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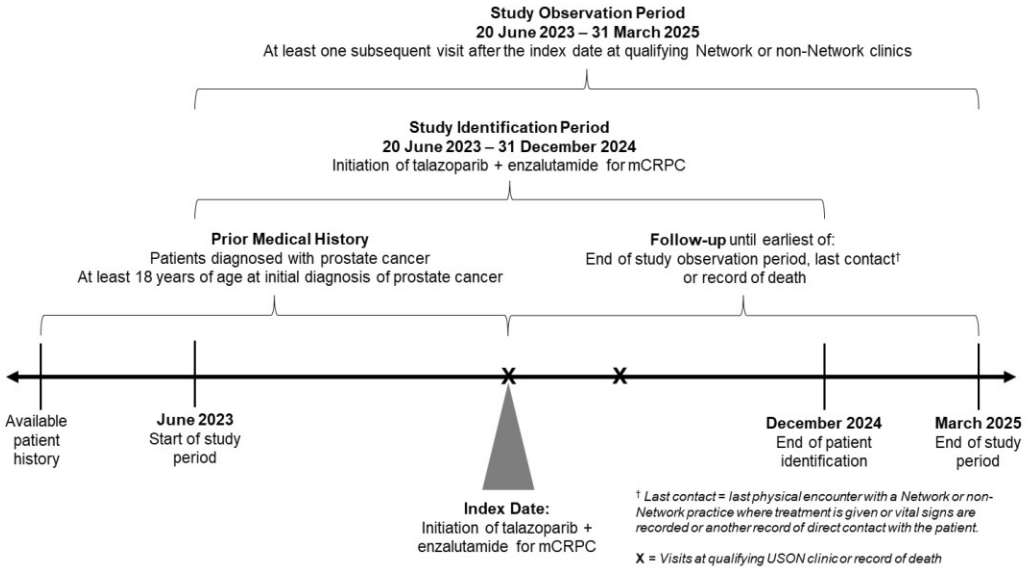
9. RESEARCH METHODS

9.1. Study Design

This is a retrospective observational cohort study of EHR data designed to evaluate patient characteristics, HRRm testing and treatment patterns among patients with mCRPC who initiated talazoparib + enzalutamide within the community oncology setting. A retrospective design was selected to leverage existing real-world clinical data, enabling efficient evaluation of treatment patterns and outcomes in routine clinical practice. Patients who experience an index event, defined as the initiation of talazoparib + enzalutamide for mCRPC during the study identification period (defined below), will be eligible for inclusion in the study (see **Figure 1**). Complete study eligibility criteria and cohort definitions are presented in **Section 9.2**.

Figure 1. Overview of study design

Phase 1:



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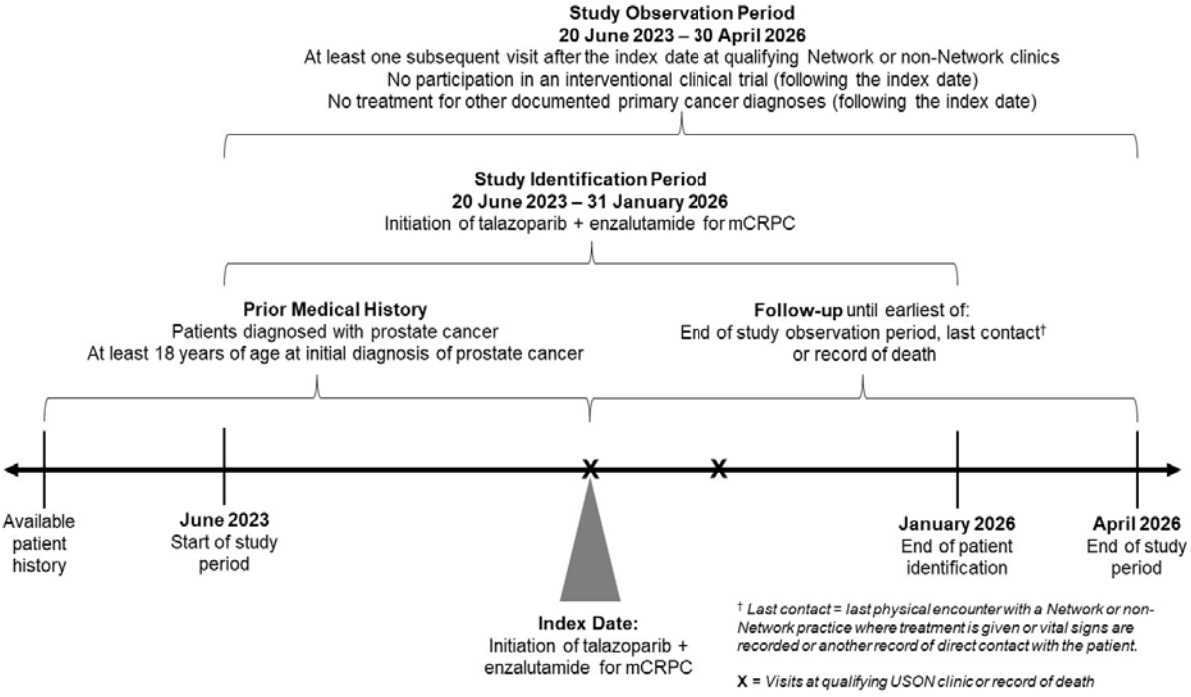
Phase 2:



Phase 1 Study observation period: 20 June 2023 – 31 March 2025

Phase 1 Study identification period: 20 June 2023 – 31 December 2024

Phase 2 Study observation period: 20 June 2023 – 30 April 2026

Phase 2 Study identification period: 20 June 2023 – 31 January 2026

Index date: The index date will be the date of initiation of the talazoparib + enzalutamide regimen for mCRPC. If a combination regimen is used but different initiation dates of talazoparib and enzalutamide are observed, the second initiation date of the two drugs in the regimen will be used as the index date as long as both drugs are active. If the initiation dates are >28 days apart, the treatment received between initiation of the first and second drugs will be considered a separate regimen as described in **Section 9.3.1**.

Baseline: For baseline variables that may change over time, assessments will be performed based on data documented within 60 days before the index date (excluding the index date). If multiple values are available during this assessment window, the closest values before the index date will be prioritized.

Prior medical history: For time-invariant pre-index variables (variables that do not change over time), assessments will be performed based on all available data documented prior to but excluding the index date. Patients' available history in the iKM EHR will vary based on the length of disease and the time within The Network or non-Network practices.

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Follow-up: The follow-up period will begin on the index date and span through the date of death (if the patient died during the study observation period) or the date of last contact on or before the end of the study observation period (if the patient did not die during the study observation period). For analysis, all patients will have a potential follow-up duration of 3 months; however, individual patients will have variable follow-up time periods.

Exposures are defined in **Section 9.3.1**.

9.2. Setting

The study population will consist of patients with mCRPC who initiated talazoparib + enzalutamide within The US Oncology Network ("The Network") or non-Network practices. The US Oncology Network includes over 2,500 affiliated physicians operating in over 600 sites of care across states.[9] Approximately 1.4 million US cancer patients are treated annually in The US Oncology Network.[9] Non-Network practices are independent community-based oncology clinics that have a partnership with Ontada. Approximately 50 non-Network clinics have adopted the iKnowMed EHR and participate in real-world research activities with Ontada.

Phase 1 will assess objectives during the study identification period 20 June 2023 – 31 December 2024 and study-eligible patients will be followed longitudinally until last contact date or date of death on or before 31 March 2025, whichever occurs first. Phase 2 will consist of a data refresh to include additional patients during the study identification period 20 June 2023 – 31 January 2026, provide additional follow-up for existing patients from Phase 1, and assess additional treatment characteristics and clinical outcomes through 30 April 2026. The study time periods may be extended further, and the study results may be updated with the newly available data, up to two additional times.

The inclusion criteria were designed to identify a broad, real-world population of adult patients with mCRPC who initiated talazoparib + enzalutamide in the US community oncology setting and had sufficient follow-up data available to assess study objectives. These criteria support the representativeness and external validity of the study population, and the additional exclusion criteria minimize potential confounding that could independently influence outcomes for Phase 2.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients diagnosed with PC any time prior to the end of the study identification period[2]
2. Patients ≥ 18 years of age at first diagnosis of PC
3. Patients with evidence of mPC any time prior to the end of the study identification period[3]

[2] Diagnoses will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care. International Classification of Diseases (ICD) codes will not be used.

[3] To identify patients with metastatic disease status, patients must have at least one of the following indicators: 1) Stage IVB disease; 2) TNM with M value of 1; 3) record of location of metastatic disease; 4) current or prior disease status containing reference to metastatic disease; 5)

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

4. Patients who initiated talazoparib + enzalutamide for mCRPC during the study identification period
5. Patients with at least one subsequent visit[4] within The US Oncology Network or non-Network practices or a record of death during follow-up
6. Patients whose data are accessible for research purposes during the study observation period[5]

9.2.2. Exclusion Criteria

For Phase 1, there are no exclusion criteria. For Phase 2, new and existing patients from Phase 1 meeting any of the following criteria will not be included in the study:

1. Patients who participated in an interventional clinical trial during follow-up
2. Patients who received systemic treatment for other documented primary cancer diagnoses during follow-up

9.2.3. Chart Abstraction Selection

Structured data will be used to screen patients based on the eligibility criteria defined above. Eligible patients will be submitted for targeted chart abstraction. During the course of abstraction, patients' eligibility for the study will be verified and some of these patients may be found to be ineligible. Reasons for ineligibility will be captured and reported in the attrition table. The following inclusion/exclusion criteria will be confirmed during chart abstraction:

1. Patients diagnosed with PC any time prior to the end of the study identification period
2. Patients with evidence of mPC any time prior to the end of the study identification period
3. Patients who initiated talazoparib + enzalutamide for mCRPC during the study identification period
4. Patients who participated in an interventional clinical trial during follow-up [Phase 2 only]
5. Patients who received systemic treatment for other documented primary cancer diagnoses during follow-up [Phase 2 only]

All confirmed eligible patients will complete chart abstraction up to a maximum target sample size of N = 100 (Phase 1). For Phase 2, all confirmed eligible patients from Phase 1 will be reviewed in

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receipt of a numbered line of therapy (LOT) for 2nd line or beyond without reference to metastatic disease; 6) receipt of a LOT with reference to metastatic disease.

[4] Visits are defined as physical encounters with the practice, detected by vital signs records or treatment administration. The second visit must be observed after the index date to demonstrate continuity of care. There is no required time span between the additional visit and the index date.

[5] The health information data used for Ontada's services may vary in accordance with the data rights available to Ontada under agreements with physician practices. Therefore, data from some Network/non-Network practices may not be available for Ontada's services. References to The Network/non-Network practices and the software used by physician practices shall not imply that data from every physician practice in the applicable network will be used for Ontada's services.

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

addition to up to N = 50 new patients that meet eligibility criteria with the extended study periods described in **Section 9.1**.

Additional detail related to the reasons for ineligibility for criterion #3 above will be assessed during Phase 2 for new patients and existing patients from Phase 1 as explicitly recorded in the charts:

a) Denied coverage (i.e., talazoparib + enzalutamide were prescribed but insurance coverage was denied)
b) Monotherapy only (i.e., either talazoparib or enzalutamide were not initiated for other/unspecified reason(s), or talazoparib and enzalutamide were never prescribed as combination therapy)
c) Neither treatment initiated (i.e., both talazoparib and enzalutamide were not initiated for other/unspecified reason(s)
d) Not initiated during the study period (i.e., talazoparib + enzalutamide were initiated before the start or after the end of the study identification period)
e) Other reason(s) (to be collected by free text)

9.2.4. Cohorts and Stratifications

During analysis patients who meet the eligibility criteria described above will be classified into the following:

- Receipt of androgen receptor pathway inhibitor (ARPi; abiraterone, enzalutamide, apalutamide, darolutamide) and/or docetaxel prior to index
  - ARPi and docetaxel
    - ARPi in combination with docetaxel
    - Other sequences of ARPi and docetaxel
  - ARPi only
  - Docetaxel only
- No receipt of ARPi or docetaxel prior to index
  - No prior systemic therapy for mCRPC
  - Prior systemic therapy for mCRPC without ARPi or docetaxel

Each of the tables and figures will be stratified to present results for the subgroups listed above. Sub-categories may be combined if a sufficient sample size (N=5) is not available at the time of the analysis.

Further subgroup analysis by variables of interest (e.g., BRCAm status, LOT of talazoparib+enzalutamide) will be considered for Phase 2 based on a review of sample size.

9.3. Variables

Table 1 presents the study variables and operational definitions. Most data will originate from structured data within the iKM EHR database, although some variables may be derived from these raw data sources (e.g., age from date of birth). Derived and transformed data needed for the analysis

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

are described and presented along with the operational definitions in the table below. Some data elements will be captured from both structured and unstructured (chart abstraction) data within iKM. Since the chart abstraction data are expected to provide a richer source of information, if data are available from both sources for a single patient, then chart abstraction data will supersede what is available in the structured data for the final analysis.

Table 1. Variables and definitions

Variable	Role	Data Source(s)	Period of Measurement	Operational Definition
Demographic characteristics				
Age (continuous + categorical)	Baseline characteristic	iKM structured (derived)	Index	Patient's date of birth as recorded in iKM will be used to calculate patient age and will not be otherwise disclosed during analysis. The patient's age (in years) at the index date will be calculated as the integer part of [(index date – date of birth + 1) / 365.25]. Age categories will be determined pending continuous distribution of age. The following categories will be presented: • < 40 years • ≥ 40 – < 50 years • ≥ 50 – < 60 years • ≥ 60 – < 70 years • ≥ 70 – < 80 years • ≥ 80 years The specific categories to be presented will be confirmed after reviewing sample sizes and the added value to the study with Ontada's Privacy and Compliance team.
Height	Baseline characteristic	iKM structured	Prior medical history	Patient's height in meters will be collected and used for calculations of body mass index (BMI). It will not be separately reported. Since height is generally not expected to change over the course of a patient's treatment, height assessments from prior medical history will be collected. In the case of multiple records, the result closest to index will be used. If multiple measures are reported on the same day, the mean will be used. If height is reported in a different unit (e.g., feet, inches), it will be converted to meters.
Weight	Baseline characteristic	iKM structured	Baseline	Patient's weight in kilograms will be collected and used for calculations of BMI.

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				It will not be separately reported. If weight is reported in a different unit (e.g., pounds), it will be converted to kilograms.
Body mass index (BMI)	Baseline characteristic	iKM structured (derived)	Baseline	Patient's BMI will be collected as recorded in the charts. If BMI is missing, BMI will be derived using the following calculation: BMI = Weight (in kilograms)/ (Height (in meters))^2 Based on the resulting BMI values, patients will be categorized as: • Underweight (BMI < 18.5 kg/m^2) • Normal (18.5 kg/m^2 ≤ BMI < 25 kg/m^2) • Overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) • Obese (BMI ≥ 30 kg/m^2) or • No information (missing height or weight data)
Race	Baseline characteristic	iKM structured	Baseline	Patients will be categorized as: • White • Black or African American • Asian • Other • Not reported The specific categories outside of White and Black/African American will be confirmed after reviewing sample sizes and the added value to the study with Ontada's Privacy and Compliance team.
Ethnicity	Baseline characteristic	iKM structured	Baseline	Patients will be categorized as: • Hispanic or Latino • Not Hispanic or Latino • Not documented The specific categories to be presented will be confirmed after reviewing sample sizes and the added value to the study with Ontada's Privacy and Compliance team.
Rural/urban	Baseline characteristic	iKM structured (derived)	Baseline	The rural/urban status of the clinic where the patient received care for the index visit will be reported. Status will be defined based on the US Department of Agriculture's Rural-Urban Commuting Area (RUCA) codes.[10] Patients will be categorized as urban/rural as

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				recommended by the Federal Office of Rural Health Policy:[11] • Urban (RUCA codes 1-3) • Rural (RUCA codes 4-10)
Practice location	Baseline characteristic	iKM structured (derived)	Index	The US census region of the practice attributed to the patient will be classified as: • Midwest: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota • Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Pennsylvania, New Jersey, and New York • South: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas • West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, California, Oregon, and Washington State Missing clinic values will be captured in a "not documented" category. Some of the regions may need to be collapsed if there are small sample sizes (e.g., South vs. non-South). This determination will be confirmed after reviewing sample sizes and the added value to the study with Ontada's Privacy and Compliance team.
Practice volume (number of patients)	Baseline characteristic	iKM structured (derived)	1/1/2024 – 12/31/2024	The number of patients (cancer or non-cancer) seen at the practice attributed to the patient in the year 2024. Categories will be created based on the distribution observed in the data.
Clinical characteristics				
Date of initial PC diagnosis	Baseline characteristic	iKM structured + chart abstraction	Prior medical history	To assess cancer diagnoses that occurred prior to index, patients' available medical history in iKM will be searched. The completeness of this history will vary based on the length of disease and the time within The US Oncology Network. Records may also be incomplete for patients with an initial diagnosis that

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				occurred outside of The US Oncology Network. Diagnosis will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care (International Classification of Diseases codes will not be used). If no initial diagnosis date is documented, the associated analysis variables will be reported as missing. This date will be used in calculations, not reported separately. Patients without a recorded diagnosis will be excluded from the study.
Date of mPC diagnosis	Baseline characteristic	iKM structured + chart abstraction	Prior medical history	Date of first recorded diagnosis of metastatic disease within the EHR. Patients will be qualified initially based on the date identified in the structured data; this will be confirmed during chart abstraction. Ultimately, the primary source will be chart abstraction data if available. When using structured data, this will be the earliest associated date of any of these criteria: 1. Stage IVB disease (if applicable) 2. TNM with M value of 1 3. Record of location of metastatic disease 4. Current or prior disease status containing reference to metastatic disease 5. A numbered line of therapy (LOT) for second-line or beyond (without reference to metastatic) 6. A LOT with a reference to "metastatic"
Time from metastatic diagnosis to index	Baseline characteristic	iKM structured + chart abstraction (derived)	Prior medical history, index	The duration (in weeks) from the metastatic diagnosis date to the index date will be calculated as the integer part of [(index date – date of metastatic diagnosis + 1) / 7].
Castration-sensitive and castration-resistant status + dates	Baseline characteristic, covariate	iKM structured + unstructured (derived)	All available records	An algorithm which includes provider-documented disease status and/or qualifying treatments for mCSPC and mCRPC will be used. A list of qualifying treatments is presented in **Section 9.3.1**. All patients will be inferred to have mCRPC at index, and mCRPC status will

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				be verified during chart abstraction. Treatment regimens relative to mCSPC will be described in the analysis.
Disease stage at initial diagnosis	Baseline characteristic	iKM structured + chart abstraction	Prior medical history	The patient's disease stage at initial diagnosis of PC will be recorded as available and categorized as: • Stage I • Stage II • Stage III • Stage IVA • Stage IVB • Stage IV NOS • Not documented • Other
TNM stage at initial diagnosis	Baseline characteristic	iKM structured + chart abstraction	Prior medical history	Patients' TNM stage at initial diagnosis of PC will be reported as documented in the iKM EHR.
Distant metastatic site(s)	Baseline characteristic	iKM structured + chart abstraction	Baseline	Baseline distant metastatic location(s) will be identified and categorized as: • Brain/Central Nervous System (CNS) • Head/Neck • Breast • Lung • Chest/Thorax - Other • Liver • Abdomen – Other • Pelvis • Bone(s) • Distant lymph node(s) • Fluid - Pleural/Abdominal • Muscle(s) • Skin • Soft tissue • Other • Not documented Note, "not documented" can indicate that location of metastases was not documented in the chart, not necessarily that patients did not have metastases. Additionally, metastatic location categories are not mutually exclusive, and patients with documented metastases in multiple locations may be included in more than one category.

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

Distant metastatic site type	Baseline characteristic	iKM structured + chart abstraction (derived)	Baseline	Metastatic sites will be categorized by the presence or absence of bone and/or other non-bone sites. • Bone only • Other only • Both bone and other
Visceral metastatic site(s)	Baseline characteristic	iKM structured + chart abstraction (derived)	Baseline	Metastatic sites will also be categorized by the presence or absence of visceral/non-visceral sites. • Visceral (any metastatic site not inclusive of bone or lymph node) only • Non-visceral (bone or lymph node) • Both visceral and non-visceral
Count of metastatic sites	Baseline characteristic	iKM structured (derived)	Baseline	The total count of metastatic site(s) at baseline will be calculated as: • 1 • 2 • 3 • 4+ • Not documented Note: "not documented" does not always mean that patients did not have metastases. It can simply indicate that specific metastatic sites were not documented in the chart.
High volume disease status	Baseline characteristic	Chart abstraction only	Baseline	Patients with explicit document documentation of high volume disease in the charts or documentation of any of the following metastatic sites will be identified: • At least four bone metastases* • At least one bone metastasis outside of the pelvis and vertebral column* • Visceral metastases (any metastatic site not inclusive of bone or lymph node) *Note: documentation of these criteria for high volume disease are expected to be low within the charts.

Histology at initial diagnosis	Baseline characteristic	iKM structured + chart abstraction	Prior medical history	Disease histology will be recorded as available in the data.
				• Adenosquamous
				  ○ Adenocarcinoma
				  ○ Acinar Adenocarcinoma

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				○ Mucinous Carcinoma • Prostatic Duct Adenocarcinoma • Sarcomatoid • Signet Ring • Small Cell • Squamous Cell • Transitional Cell • Undifferentiated carcinoma (NOS) • Other • Not Documented
Gleason score	Baseline characteristic	iKM structured + chart abstraction	Prior medical history	The primary and secondary Gleason score (scale 1-5) as well as the total combined score (scale 6-10) will be recorded as available in the data. If multiple scores are observed on the same date, the higher score will be considered. For the analysis, the total combined score will be reported as: • <8 • ≥8 Gleason score will be reported among patients with any available data prior to index, and in patients with data available during the baseline period (if available).
Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance status (PS)	Baseline characteristic	iKM structured	Baseline (Phase 1) Prior medical history (Phase 2)	The ECOG PS score is a rating of a patient's disease status, daily living activities and quality of life, with low scores indicating greater functioning than high scores. PS will be categorized as: • 0 • 1 • 2 • ≥3 • Not Documented Karnofsky PS is a similar measure and will be converted to ECOG PS using the methodology outlined below. **Karnofsky PS** / **ECOG PS** / **ECOG PS Descr** 100 / 0 / Fully active 80, 90 / 1 / Restricted in phys strenuous activity

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				60, 70 — 2 — Ambulatory and capable of self-care but unable to work 40, 50 — 3 — Capable only of limited self-care 10, 20, 30 — 4 — Completely disabled 0 — 5 — Dead
Baseline Prostate-Specific Antigen (PSA) results + dates	Baseline characteristic	iKM structured + chart abstraction	Baseline	PSA (ng/mL) laboratory results and dates will be collected at baseline. Results will be reported as a continuous variable and categorized as: • ≤4.0 ng/mL[12] • >4.0 ng/mL[12] • Not documented
Testosterone results (continuous + categorical) + dates	Baseline characteristic	iKM structured	Baseline	Testosterone (ng/mL) laboratory results and dates will be collected at baseline. Results will be reported as a continuous variable and categorized as: • <50 ng/mL • ≥50 ng/mL • Not documented
Baseline hemoglobin (Hgb) results + dates	Baseline characteristic	iKM structured	Baseline	Hgb (g/dL) laboratory results and dates will be collected at baseline. Results will be reported as a continuous variable and categorized as: • Mild (≥10 - <13 g/dL) • Moderate (≥8 - <10 g/dL) • Severe (<8 g/dL) • Not documented
Somatic biomarker testing information	Baseline characteristic	Chart abstraction only	All available records	For each biomarker (BRCAm and non-BRCA HRRm) included in the variable list below, collection date(s), result date(s), specimen type(s) (i.e., tissue, blood, other), and assay type (i.e., next-generation sequencing, NGS; etc.) as documented in the charts will be collected for the analysis.
Germline biomarker testing information	Baseline characteristic	Chart abstraction only	All available records	For each biomarker (BRCA and non-BRCA HRRm) included in the variable list below, collection date(s), result date(s), specimen type(s) (i.e., blood, saliva, swab), laboratory name and germline testing panel

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				name as documented in the charts will be collected for the analysis.
BRCA mutation testing and status	Baseline characteristic	iKM structured + chart abstraction	All available records	The count and proportion of patients who received BRCAm testing will be reported as follows: • Both BRCA1 and BRCA2 tested • Neither BRCA1 nor BRCA2 tested • BRCA1 tested only (if applicable) • BRCA2 tested only (if applicable) BRCA mutation status will be reported as follows: • BRCA1 or BRCA2 mutation • BRCA1 and BRCA2 mutations • VUS only • Wild-type (if both genes were tested) • No mutation found, but not all genes tested • Testing not documented BRCA1 results will be collected for all available records. Results will be categorized as: • Germline mutation • Somatic mutation • Wild-type • VUS • Tested, result not documented • Testing not documented BRCA2 results will be collected for all available records. Results will be categorized as: • Germline mutation • Somatic mutation • Wild-type • VUS • Tested, result not documented • Testing not documented
Other HRRm testing and status	Baseline characteristic	iKM structured + chart abstraction (derived)	All available records	The following non-BRCA HRR genes mutations will be captured if available: • ATM • ATR • CDK12 • CHEK2 • FANCA • MLH1 • MRE11A • NBN

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				• PALB2 • RAD51C The count and proportion of patients who received non-BRCA HRRm testing will be reported as follows: • Testing for all genes of interest • At least one but not all genes tested • Testing not documented for any gene Other HRRm status will be reported as follows: • Mutation to one non-BRCA gene • Mutations to two or more non-BRCA genes • VUS only • Wild-type (if all genes were tested) • No mutation found, but not all genes tested • Testing not documented Results will also be reported for other individual HRR genes as follows: • Germline Mutation • Somatic Mutation • Wild-type • VUS • Tested, result not documented • Testing not documented

HRRm testing status	Baseline characteristic, effect modifier	iKM structured + chart abstraction (derived)	All available records	The count and proportion of patients who received HRRm testing will be reported as follows:
				• Both BRCA and non-BRCA HRR genes tested (full panel)
				  ○ At least one but not all genes of interest
				  ○ All genes of interest
				• Only BRCA tested
				  ○ At least one but not all genes of interest
				  ○ All genes of interest
				• Only non-BRCA HRR tested
				  ○ At least one but not all genes of interest
				  ○ All genes of interest
				• Testing not documented for any HRR gene
				•
				•

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

Timing of the first HRRm test	Baseline characteristic, effect modifier	iKM structured + chart abstraction (derived)	All available records	Timing of the first HRRm test (any gene) will be reported as follows:
				• Prior to metastatic diagnosis
				• Between metastatic diagnosis and index
				  ○ mCSPC
				  ○ mCRPC
				• After index
				• Testing not documented

Frequency of HRRm testing	Baseline characteristic, effect modifier	iKM structured + chart abstraction (derived)	All available records	Frequency of HRRm testing will be reported as follows:
				• One test
				• Two or more tests
				  ○ Single-gene testing followed by full panel or additional gene testing
				  ○ Other (i.e., initial multi-gene testing)
				• Testing not documented

HRRm testing type (i.e., germline, somatic)	Baseline characteristic, effect modifier	iKM structured + chart abstraction (derived)	All available records	Type of HRRm testing will be reported as follows: • Germline and somatic testing • Germline testing only • Somatic testing only • Testing not documented
Somatic HRRm testing collection type	Baseline characteristic, effect modifier	iKM structured + chart abstraction (derived)	All available records	Somatic HRRm testing collection type will be reported as follows: • Tissue only • Blood only • Both tissue and blood (multiple tests) • Other only • Testing not documented

HRRm status	Baseline characteristic, effect modifier	iKM structured + chart abstraction (derived)	All available records	The HRRm status will be derived from the BRCA and non-BRCA HRRm status described above, and will be reported as follows:
				• Mutation
				  ○ BRCA mutation only
				  ○ Non-BRCA HRR mutation only
				  ○ BRCA and non-BRCA HRR mutation
				• VUS only
				• Wild-type (if all genes were tested)
				• No mutation found, but not all genes tested
				• Testing not documented

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

Time from HRRm testing to metastatic diagnosis	Baseline characteristic	iKM structured + chart abstraction (derived)	All available records	Among patients who received HRRm testing prior to metastatic diagnosis, the duration (in weeks) from the metastatic diagnosis date to the first HRRm result date will be calculated as the integer of [(metastasis date – date of first HRRm test + 1) / 7] and summarized as a continuous variable.
Time from metastatic diagnosis to HRRm testing	Baseline characteristic	iKM structured + chart abstraction (derived)	All available records	Among patients who received HRRm testing on or after metastatic diagnosis, the duration (in weeks) from the metastatic diagnosis date to the first HRRm testing date will be calculated as the integer part of [(HRRm testing date – date of metastatic diagnosis + 1) / 7] and summarized as a continuous variable.
Time from HRRm testing to index	Baseline characteristic	iKM structured + chart abstraction (derived)	All available records	Among patients who received HRRm testing at or prior to the index date, the duration (in weeks) from the first HRRm result date to the index date will be calculated as the integer part of [(index date – HRRm testing date + 1) / 7] and summarized as a continuous variable.
Treatment characteristics				
Anticancer treatment: drug name and start/stop date(s)	Exposure, outcome, effect modifier	iKM structured + chart abstraction	All available records	The names, start and end date(s), and order of regimens of all anticancer drug treatments for prostate cancer (IV and oral, including ADT) received will be recorded. • Treatment name • Start/stop dates
Anticancer treatment: sequence	Exposure, outcome, effect modifier	iKM structured + chart abstraction	All available records	Treatment sequence will be abstracted. Reviewers will be asked to select sequence as documented in patients' charts. Responses will be categorized as: • Index • Neoadjuvant • Adjuvant • Other sequence
Anticancer treatment: reason for treatment initiation	Exposure, outcome, effect modifier	iKM structured + chart abstraction	All available records	If available, reason for treatment initiation will be abstracted. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. Responses will be categorized as: • Initial diagnosis

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				• Initial diagnosis with unresectable/inoperable disease • Initial diagnosis with metastatic disease • Recurrent or progressive disease • Other reasons; non-progression • Toxicity on previous therapy • Not documented
Anticancer treatment: reason for treatment discontinuation	Exposure, outcome, effect modifier	iKM structured + chart abstraction	All available records	If available, reason for treatment discontinuation will be abstracted. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. Responses will be categorized as: • Completed planned treatment • Progression • Toxicity • Financial/Insurance • Patient preference • Physician preference • Other • Not documented The count and proportion of reasons for treatment discontinuation will be reported during Phase 2 analysis. Reviewers will specify other reasons; these will be reported in the results if any represent >5% of patients.
Baseline treatment dose	Baseline characteristic	iKM structured + chart abstraction	Index	The baseline treatment dose, frequency, duration and cycle length of all talazoparib + enzalutamide prescriptions will be captured and summarized during the analysis.
Treatment dose / dose changes	Outcome	iKM structured + chart abstraction	Follow-up	If applicable, the modified treatment dose for talazoparib + enzalutamide will be captured, as well as any changes to the frequency, duration or cycle length. Reasons for dose change will also be captured, if available. Responses will be categorized as: • Progression • Toxicity • Financial/Insurance • Patient preference • Physician preference • Other

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

				• Not documented
Clinical trial participation	Confounder	iKM structured + chart abstraction	Follow-up	For Phase 1, patients enrolled and participating in interventional clinical trials (not inclusive of observational studies, if applicable) will be captured during the follow-up period and reported as the count and proportion of patients with clinical trial participation (sample size permitting). For Phase 2, patients with clinical trial participation during the follow-up period will be excluded.
Treatment for other primary cancer diagnosis	Confounder	iKM structured + chart abstraction	Follow-up	For Phase 1, systemic treatment for another primary cancer diagnosis during the follow-up period will be captured and reported as the count and proportion of patients with treatment for other primary cancer diagnoses (sample size permitting). For Phase 2, patients with treatment for other primary cancer diagnoses during the follow-up period will be excluded.
Follow-up				
Last contact date	Outcome	iKM structured + chart abstraction	Follow-up	Each patient's last contact date prior to or on the close of the study observation period will be recorded. This date will not be reported separately; it will be used in calculating the patient's available follow-up time. For abstracted data, the last contact date will be defined as the date of the last documented encounter with a facility involving direct contact with a patient or their representative regarding symptoms or events. For structured data, the last contact date will be the most recent visit date, defined as an instance where treatment is administered, or vital signs are recorded.
Vital status	Outcome	iKM structured + chart abstraction + third-party mortality data (derived)	Follow-up	Patient's vital status at the end of the study observation period will be noted as: • Alive • Deceased

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

Hospice status	Outcome	Chart abstraction only	Study observation period	An indicator whether or not the patient was referred/admitted to hospice care before the end of the study observation period will be recorded, in addition to the date of referral/admission. If hospice referral date is not available, the hospice admission date will be used. This date will not be reported separately but will be used in calculations for follow-up and survival analyses.
Follow-up time	Outcome	iKM structured (derived)	Follow-up	The duration of follow-up time (in months) from the index date will be calculated as [(end of follow-up – index date) + 1) / 30.4375]. End of follow-up will be defined as date of death within the study observation period, or among patients without a documented death date, last contact date or end of the study observation period, whichever occurs first.
Provider-documented tumor assessment	Outcome	Chart abstraction only	Follow-up	Provider-documented tumor assessments will be recorded for the treatments during follow-up (excluding baseline scans on the index date). Tumor assessments will not be reported during analysis but will be used during treatment sequencing and LOT assignment as described in **Section 9.3.1**.
Time-to-event outcomes	Outcome	iKM structured + chart abstraction + third-party mortality data (derived)	Follow-up	rwTTD, rwTTNT, rwPFS and OS will be assessed for Phase 2 as described in **Section 9.3.2**.
Follow-up PSA results + dates	Outcome	iKM structured	Follow-up	PSA (ng/mL) laboratory results and dates will be reported at 3, 6, 9, and 12 months post-index using the closest results within 30 days before or after each respective time point. Results will be reported as continuous variables and categorized as: • Above baseline • At or below baseline • Baseline and/or follow-up result not documented The number of PSA tests performed during the follow-up period will be reported as a continuous variable and categorized as: • 0 • 1 • 2

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				• ≥3
Follow-up Hgb results + dates	Outcome	iKM structured	Follow-up	Hgb (g/dL) laboratory results and dates will be reported using the lowest result observed within 4, 8, 12, and 16 weeks post-index. Results will be categorized at each time point as: • Mild (≥10 - <13 g/dL) • Moderate (≥8 - <10 g/dL) • Severe (<8 g/dL) • Not documented

9.3.1. Exposure

The treatment exposure time will be defined as the duration between initiation and discontinuation of talazoparib + enzalutamide for mCRPC. Patients will be followed until the date of death (if the patient died during the study observation period) or the date of last contact on or before the end of the study observation period (if the patient did not die).

The exposure of interest in the current study is talazoparib + enzalutamide. To be considered one regimen, both drugs need to be initiated within 28 days of each other. If different initiation dates of talazoparib and enzalutamide are observed, the second initiation date for either drug will be used as the index date as long as both drugs are active. All patients will be inferred as having mCRPC at index based on the approved indication for talazoparib + enzalutamide at the time of the study. In addition to provider-documented mCSPC and mCRPC diagnosis in iKM, a list of qualifying treatments for mCSPC and mCRPC as presented in **Table 2** which will be used to categorize treatments received prior to talazoparib + enzalutamide (if applicable). Provider documentation of mCSPC/mCRPC will supersede treatment data, if available.

Table 2. Qualifying therapies used to derive mCSPC and mCRPC status in the absence of a provider-documented status

Castration-sensitive patients (mCSPC)	Castration-resistant patients (mCRPC)
Treated with any of the following androgen deprivation therapy (ADT) alone in the metastatic setting: • Goserelin • Leuprolide • Triptorelin • Bicalutamide • Nilutamide • Flutamide • Degarelix • Relugolix	Treated with any of the following in the metastatic setting: • Cabazitaxel • Carboplatin • Cisplatin • Etoposide • Mitoxantrone • Olaparib • Rucaparib • Talazoparib • Niraparib • Pembrolizumab • Sipuleucel-T • Radium-223

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	• Lutetium-177
Treated with any of the following: • Abiraterone • Apalutamide • Darolutamide • Docetaxel • Enzalutamide <u>AND</u> No prior treatment with any of the following ADT in the metastatic setting: • Goserelin • Leuprolide • Triptorelin • Bicalutamide • Nilutamide • Flutamide • Degarelix • Relugolix	Treated with any of the following: • Abiraterone • Apalutamide • Darolutamide • Docetaxel • Enzalutamide <u>AND</u> Prior treatment with any of the following ADT in the metastatic setting: • Goserelin • Leuprolide • Triptorelin • Bicalutamide • Nilutamide • Flutamide • Degarelix • Relugolix

The following treatment patterns will be presented for the entire study population, as well as the subgroups specified in **Section 9.2.4**:

Treatment sequencing

Sequencing of cancer regimens will be described for this study.

During construction of the analytic file, LOT will be assigned based on the provider-documented reason for initiation/discontinuation and start/stop dates of patients' treatment sequence. Patients can receive multiple regimens within a single LOT if they have treatment modification for reasons other than progression and thus do not advance to the next LOT.

Anticancer medication will be grouped into treatment *regimens* as follows:

- All anticancer drugs with a start date that occurs within 28 days from the start of the first anticancer drug will be combined in a single regimen. The regimen combination is the combination of anticancer drugs administered.
- The start date of a regimen will be the start date of the first anticancer drug initiated within the regimen.
- A regimen will be discontinued and/or a new regimen will be started if:
    - There is a gap of 120 days or greater in drug administrations (for non-ADT regimens only); OR

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- A new anticancer drug is added >28 days from the start of the previous anticancer drug.

- The end date of a regimen will be the last order or administration of an anticancer drug within the regimen.
- Continuation and switch of ADT regimens will not be considered as a separate regimen.

Treatment discontinuation for *infused treatments* will be observed on the last administration date of infused treatments or discontinuation date as explicitly documented by providers. Patients without a second infused treatment administration will have a duration of 1 day.

For *oral therapies*, if the date of discontinuation is not recorded, the date of discontinuation will be inferred to be the date of referral to hospice/palliative care, date of death, date of treatment switch or addition of another anticancer regimen, or the last prescription date if the treatment occurred ≥ 120 days before the last contact date, whichever comes first.

Treatment regimens will be assigned into numbered lines for each treatment setting (1L for mCSPC, 1L for mCRPC, 2L for mCRPC, etc.) as follows:

- The first systemic anticancer treatment initiated on or after metastatic diagnosis will be considered the start of 1L.
- Among patients selected for chart abstraction, a new regimen will signal a new LOT if the reason for treatment initiation/discontinuation is provider-documented progression. Additionally, provider-documentation of mCRPC or initiation of a qualifying therapy in **Table 2** will signal a new LOT.
- Continuation and switch of ADT regimens will not advance LOT.

The proportion of patients receiving each regimen relative to initiation of talazoparib + enzalutamide (# regimen(s) prior or after) will be reported.

9.3.2. Study Endpoints

Due to the limited duration of follow-up, clinical endpoints will not be assessed for Phase 1.

For Phase 2, the following endpoints will be assessed in this study. Patients will be followed from index date until end of the study observation period, censoring patients without an event of interest on their last contact date on or prior to end of the study observation period.

- **rwTTD** will be defined as the interval (in months) between the index date and index regimen discontinuation[6] (including death).

[6] Whether the treatment is discontinued or ongoing is recorded during chart abstraction. If treatment is discontinued, the last prescription/administration would be the discontinuation date. If treatment is ongoing (i.e., the treatment end date is missing), the treatment would be censored at the last contact date.

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- **rwTTNT** will be defined as the interval (in months) between the index date and initiation of the next regimen (regardless of progression) or date of death due to any cause.

- **rwPFS** will be defined as the interval (in months) between the index event and the earliest date of provider-documented progression or date of death (any cause).

- **OS** will be defined as the interval (in months) between the index event and the date of death (any cause) as captured from all available sources through the end of the study observation period.

9.4. Data Sources

This study will leverage data aggregated from several sources via Ontada's proprietary data platform, which is refined for completeness and quality to deliver a comprehensive and enhanced view of patient care, including symptoms, diagnosis, treatment choices, therapy cycles, survivorship, and disease progression. It leverages both structured and unstructured data, utilizing human and AI-assisted abstraction to standardize clinical variables; however, data collected solely through AI will not be analyzed for this study. Standardized oncology-specific structured data fields and coding practices are used to support consistent capture of clinical and treatment information. Ontada performs ongoing data quality assessments to evaluate data completeness, consistency, and validity, supporting the use of iKM data for oncology real-world evidence research.

The EHR system of The Network or non-Network practices, iKM. iKM captures outpatient practice encounter histories for patients under community-based care, including but not limited to patient demographics such as age and sex; clinical information such as disease diagnosis, diagnosis stages, performance status information and laboratory testing results; and treatment information within The Network or non-Network practices.

The study will use data from The Network or non-Network practices that utilize the iKM EHR and these data have already been extensively checked and validated through Ontada's quality assurance procedures. Additionally, iKM has been used to evaluate patient characteristics and treatment patterns among patients with mPC and the results have been consistent with other published studies.[13-15]

Mortality data are supplemented with information from commercially-available datasets that contain dates of death sourced from repositories of claims data, obituary records, and the Social Security Administration's Limited Access Death Master File (LADMF).

9.5. Study Size

A preliminary feasibility assessment identified 92 patients with mPC who were prescribed talazoparib during the feasibility period (**Table 3**), and a subsequent feasibility for Phase 2 extended through January 2026 identified an additional 72 patients. Due to differences in the eligibility criteria used and time period considered, the study patient count may vary substantially from what has been estimated by the feasibility assessment. Therefore, all confirmed eligible patients will complete chart abstraction up to a maximum target sample size of N = 100 (Phase 1). For Phase 2, all confirmed eligible patients from Phase 1 will be re-reviewed in addition to up to N = 50 new patients that meet eligibility criteria with the extended study periods. Based on estimated rates of ineligibility from Phase 1, approximately 40 new patients are estimated for Phase 2. As this is a descriptive study with no hypothesis testing, formal sample size calculations are not applicable.

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Table 3: Feasibility Results

Inclusion/Exclusion Criterion	Patient Counts
1. Patients with a diagnosis of prostate cancer	108,800
2. Patients aged ≥18 at initial recorded diagnosis date	108,771
3. Patients with at least 2 vital visits between 1/1/2019–12/31/2024 (feasibility period)	76,031
4. Exclude patients with enrollment in an interventional clinical trial during the feasibility period	75,341
5. Of Line 4, patients with evidence of metastatic disease	30,274
Feasibility for mCRPC	
6. Of Line 5, patients designated as **castrate-resistant** by ClearValuePlus (CVP)	8,803
7. Of Line 5, patients without CVP-designated hormone status	13,942
8a. Of Line 7, patients treated with cabazitaxel, carboplatin, mitoxantrone, olaparib, rucaparib, talazoparib or pembrolizumab	2,276
8b. Of Line 7, patients treated with secondary hormonal therapy of abiraterone, apalutamide, darolutamide, docetaxel or enzalutamide, but only after prior ADT using goserelin, leuprolide, triptorelin, bicalutamide, nilutamide, flutamide, degarelix or relugolix.	9,390
8c. Total unique patients with mCRPC (including transformed patients) [6+8a+8b, minus overlap from 8a/8b]	19,800
Feasibility for Talazoparib (+ Enzalutamide)	
9a. Of Line 5, patients treated with talazoparib	111
9b. Of Line 9a, patients with research rights for chart abstraction	92

9.6. Data Management

The Ontada Biostatisticians will collect the structured iKM data that will be used for analysis. The Biostatistician will begin by generating high-level study sample counts that demonstrate attrition rates of the inclusion/exclusion criteria. The study team will review the attrition count and the Biostatistician will proceed with collecting the remaining data elements detailed in the study protocol.

Data extracts will be generated by authorized personnel (i.e., designated research staff including the Ontada Biostatisticians and Chart Abstraction team who have been granted appropriate permissions to access and extract study data in accordance with organizational data governance, privacy, and security requirements) at pre-specified timepoints following finalization of the study cohort definitions and inclusion/exclusion criteria. The extract will include patient-level structured data elements aligned with study objectives, including but not limited to demographics, clinical characteristics, diagnosis information, treatment exposure, laboratory values, and outcomes, as defined in **Table 1**.

Analyses will be conducted using SAS® (SAS Institute Inc., Cary, NC, US) and/or R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) as appropriate. Other data exploration and analysis tools may be utilized as appropriate.

9.6.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Ontada agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., meeting minutes). The records should be retained by Ontada according to local

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regulations or as specified in the outcomes research services agreement between Ontada and Pfizer (CW2421608), whichever is longer. Ontada must ensure that the records continue to be stored securely for so long as they are retained.

If Ontada becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Ontada and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

Ontada must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

All analyses will be performed by Ontada. The planned analytic strategy is described below. No separate analysis plan will be provided, but the shells for tables and figures will be provided separately after finalization of the protocol. Results will be rounded to the nearest decimal place. No sensitivity analyses are planned. In the case of missing observations, the number and percentage of missing values will be reported. Due to Ontada's Privacy and Compliance policy, categorical variables with small cell size (n<5) may be masked.

Data validation activities will be performed consisting of, but not limited to, quality control checks for appropriate values, logical sequences, and quantity of missing values. Further detail is provided in **Section 9.8**.

9.7.1. Analysis for addressing primary objective 1 (patient characteristics)

Descriptive analysis will be conducted to examine the patient characteristics and treatment patterns. Results will be reported in aggregate. Categorical variables will be reported as patient counts and percentages. Continuous will be described by mean, standard deviation (SD), median, minimum/maximum, and interquartile ranges (IQR, Q3-Q1).

Analyses will be presented overall and for subgroups as defined in **Section 9.2.4**.

9.7.2. Analysis for addressing primary objective 2 (HRRm patterns)

Descriptive analyses will be conducted to examine HRR testing patterns and mutation status. Results will be reported in aggregate. Categorical variables will be reported as patient counts and percentages. Continuous will be described by mean, SD, median, minimum/maximum, and IQR.

Operational definitions for each of the related variables listed below are provided in **Table 1**:

- HRRm testing status
  - BRCA testing status
  - Non-BRCA testing status
- HRRm status
  - BRCA mutation status

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        - BRCA1 mutation status
        - BRCA2 mutation status
    - Non-BRCA mutation status
        - ATM mutation status
        - ATR mutation status
        - CDK12 mutation status
        - CHEK2 mutation status
        - FANCA mutation status
        - MLH1 mutation status
        - MRE11A mutation status
        - NBN mutation status
        - PALB2 mutation status
        - RAD51C mutation status
- Time from HRRm testing to metastatic diagnosis (among patients with testing prior to metastatic diagnosis)
- Time from metastatic diagnosis to HRRm testing (among patients with testing on or after metastatic diagnosis)
- Time from HRRm testing to index (among patients with testing prior to index)
- Frequency of HRRm testing
- HRRm test type (germline and/or somatic)
- HRRm collection type (blood, tissue, other)
- HRRm assay type

9.7.3. Analysis for addressing primary objective 3 (treatment patterns)

Descriptive analysis will be conducted to examine the treatment patterns of the study population. Results will be reported in aggregate. Dose changes and reasons for treatment discontinuation as described in **Table 1** will be reported for talazoparib + enzalutamide only during Phase 2 analysis. Categorical variables will be reported as patient counts and percentages. Continuous variables (will be described by mean, SD, median, minimum/maximum, and interquartile ranges. Treatment sequencing will be presented using tables with frequencies of regimens. Information for talazoparib + enzalutamide will be available for all patients; information for prior or subsequent regimens for metastatic disease will only be presented for the subgroup of patients with prior or subsequent treatment, respectively.

9.7.4. Analysis for addressing secondary objective 1 (clinical outcomes)

Time-to-event outcomes (e.g., OS, rwPFS, rwTTD, rwTTNT) from the start of talazoparib + enzalutamide will be assessed using Kaplan-Meier curves and summary tables with median, 95% CI for median times, IQR, the number of patients at risk, and survival probability at quarterly (3 month) intervals. Further details about these calculations are described in **Section 9.3.2**.

9.7.5. Analysis for addressing exploratory objective 1 (PSA, Hgb)

Descriptive analysis will be conducted to describe the availability and distribution of PSA and Hgb results throughout the follow-up period. PSA results will be described at 3, 6, 9, and 12 months post-index using the closest results within 30 days before or after each respective time point. Hgb results

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will be reported using the lowest result observed within 4, 8, 12, and 16 weeks post-index. Results will be reported in aggregate. Categorical variables will be reported as patient counts and percentages. Continuous variables will be described by mean, SD, median, minimum/maximum, and IQR. Analyses will be presented overall and stratified by prior treatment with ARPi and/or docetaxel.

9.8. Quality Control

For structured data, Ontada's Real World Research team conducts quality assurance checks on all analytics projects. The process includes both technical and clinical quality checks. Technical review of the dataset consists of identifying questionable values (e.g., out of range, illogical), illogical sequences and quantity of missing values. Illogical and missing data will be reported to the study team, which may opt to exclude or impute these values. Clinical review of the data subsequently occurs to ensure aggregate data are aligned within real-world clinical expectations. Final statistical programming code, outputs, and associated documentation will be archived in secure project repositories in accordance with applicable record-retention procedures. Archived materials will be maintained to support reproducibility, quality assurance, and audit readiness.

The quality assurance process includes the following areas:

- Protocol development
- Data extraction and integrity
- Populated tables and study reporting

As results of quality assurance and quality control, the Ontada team can confirm:

- That the source of the data and/or results will be documented, and that results/data can be verified against the source
- The internal consistency of the research data presented
- That the conclusions are objective, balanced and consistent with the study results
- That the format and content of the document are aligned with the agreed-upon template and standards

Quality control and validation of chart abstraction (unstructured) data will occur in multiple phases. Prior to full chart abstraction, a pilot will be conducted with a subset of charts. The Data Quality Lead and the chart abstraction team will review pilot data and address potential problems and questions, including assessment of data completeness, consistency, plausibility, and alignment with the study specifications. If necessary, any issues, questions, or ambiguities identified during this review will be discussed by the Data Quality Lead and chart abstraction team and additional training will be implemented. Once the pilot chart abstraction is complete, the remaining chart abstractions will proceed. During this phase of chart abstraction, the Data Quality Lead will perform source data verification for a pre-specified list of variables on a randomly selected subset of charts. The Quality Control Lead, researcher and study statistical lead will provide additional examination of the dataset by looking for missing or illogical data before preparing it for analyses. Based on extensive experience with chart abstraction of real-world oncology data, the Ontada team has created chart abstraction guidelines to reflect best practices in data collection across a number of disease areas.[16] The intent of this document is to ensure accurate, objective and consistent data capture.

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9.9. Strengths and Limitations of the Research Methods

9.9.1. Strengths

The use of real-world data is advantageous because it reflects community oncology practice trends, as opposed to tightly controlled clinical trials. The study will utilize clinical data from the EHR system of The Network and non-Network practices. Leveraging these data is expected to provide key insights into the patient characteristics, treatment patterns and clinical outcomes among patients with mCRPC who initiated talazoparib + enzalutamide within the community oncology setting. Despite the recent approval, a relatively high number of patients (N>50) is expected to be available for preliminary descriptive analyses. Furthermore, iKM data is updated in real-time to ensure that the results reflect current treatment and testing patterns. This is particularly advantageous for studying newly approved regimens such as talazoparib + enzalutamide. Chart abstraction will also be performed to provide detailed insights into biomarker testing and treatment patterns.

9.9.2. Limitations

Study findings will be interpreted in consideration of the limitations described herein, including their potential impact on the validity, completeness, and generalizability of the results.

Measurement error(s)/misclassification(s)

This retrospective observational study uses iKM EHR data. The iKM database is not primarily collected for research purposes but for clinical practice reasons. As with all administrative databases, iKM data are subject to coding errors of omission and commission. Inadequate or inaccurate codes may introduce some level of misclassification bias of certain diagnoses, events, or procedures of interest in the study. Likewise, some variables of interest may not be complete across the entire population. This may introduce misclassification bias particularly for key variables such as mCSPC and/or progression to mCRPC. While a treatment-based algorithm informed by clinical input was developed to reduce misclassification of mCSPC and mCRPC due to incomplete data, some potential for misclassification remains. In particular, variability in real-world treatment sequencing, timing of ADT initiation relative to ARPi or docetaxel use, and limitations in capturing specific ADT agents may result in patients being misclassified despite application of the algorithm. Because talazoparib + enzalutamide is currently only approved for the treatment of mCRPC, all patients will be inferred to have mCRPC at index though it is possible that patients receive treatment off-label in the real-world setting. Furthermore, because patients with clinical trial participation are not excluded from preliminary Phase 1 analyses, treatment regimens received as part of clinical trials may not be available to assess for these analyses.

The iKM EHR contains information on patients when they are seen by The Network or non-Network providers. Services and procedures provided outside of The Network or non-Network practices as well as a patient's treatment history prior to his/her first encounter at The Network or non-Network practices are not recorded in the iKM EHR and may only be available in progress notes. Drugs received by patients from pharmacies not affiliated with The Network or non-Network are not captured by the database, and these details may only be available in patients' charts which may not be available for all patients included in the study. We cannot rule out the possibility that some patients coded as being tested for HRRm and/or treatment naïve for advanced disease in the iKM EHR had previous testing and/or systemic therapy for advanced disease in healthcare facilities outside The Network or non-Network practices. To better understand the capture of variables recorded outside the

090177e1a6a02796\Approved\Approved On: 24-Jul-2026 12:53 (GMT)

iKM EHR (e.g., testing or treatment from urologist notes), a targeted chart abstraction is being performed to collect key variables of interest that may not be reliably captured in structured fields. With chart abstraction, progress notes and additional free-text fields can be reviewed to provide additional information.

Data may be collected with an intent-to-treat approach, meaning based on when treatment is assigned rather than received. In particular, it will not be possible to determine if oral therapies (i.e., talazoparib, enzalutamide) were dispensed or taken; therefore, we will use an intent-to-treat approach for analysis. However, in the case that these variables are missing or inaccurate, duration of therapy may also not be calculable, though there is still expected to be valuable information available related to testing and treatment patterns among patients who initiated talazoparib + enzalutamide.

Sample size and follow-up

Because this study only includes patients who were prescribed talazoparib + enzalutamide, which was only approved for the treatment of mCRPC with HRRm in June 2023, there may be limited sample size and duration of follow-up for observation of follow-up labs, subsequent treatments, and clinical outcomes. Subsequent data refreshes may provide additional sample size and duration of follow-up, though long-term outcomes such as OS may still require additional follow-up before events are observed.

External validity of study design

Due to the retrospective study design and quickly evolving nature of the oncology treatment landscape, there is potential for bias to be introduced into the calculations of clinical outcome event rates. Specifically, patients who initiated talazoparib + enzalutamide during the patient identification period may be meaningfully different from other patients who initiated therapy prior to or after the study identification period. Not all community oncology practices are included in Network or non-Network practices which utilize the iKM EHR and decision-support technology. Therefore, the results of this study will be most generalizable to other community oncology practices that adhere to evidence-based treatment guidelines. Additionally, patients included in Phase 1 of this study may have received treatment for other primary cancers besides prostate cancer which may limit the generalizability of treatment patterns and outcomes specific to the mCSPC setting.

Results will be stratified based on prior ARPi and/or docetaxel, however there may be patients with non-adenocarcinoma histology for which these regimens would not be recommended based on NCCN guidelines. While the frequency of non-adenocarcinoma is expected to be low, histology will be assessed as an analysis variable to determine the extent of this limitation on the interpretation of results across strata.

9.10. Other Aspects

Not applicable

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10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at Ontada in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Ontada will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Ontada shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

All data will be stored according to Ontada's retention policy. The analysis data will be maintained on a secure data server with appropriate access restrictions. Ontada will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Ontada shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

The Ontada team will submit a request for exemption, waiver of informed consent and authorization to an accredited Institutional Review Board (IRB). This project involves the study of existing data and records; study information will be analyzed by the Ontada study team in such a manner that research participants will not be directly identified. Once exemption status and a waiver of informed consent are met, a waiver of authorization can be approved, allowing the retrospective study to proceed.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

It will be necessary to obtain IRB and Research Compliance approval prior to initiation of the retrospective research study data extraction and analysis. Ontada will submit the appropriate documents, including but not limited to this protocol, to the Ontada Research Compliance department and the IRB for review. Ontada will handle all correspondence with Ontada Research Compliance and the IRB; correspondence will be kept on file at Ontada.

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There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices (GPP).[17]

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report safety events (AEs/SAEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol).

Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE with such causality documented in the medical chart.

The requirements for reporting safety events, as defined below, on the "Non-Interventional Study Adverse Event Report Form for Protocols with Stipulated Active Collection of Adverse Events", herein after referred to as the NIS AEM Report Form are as follows:

- All safety events with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the safety event reporting form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy[(a)], breastfeeding, medication error, overdose, misuse, extravasation, occupational exposure, and off-label use associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

  [(a)] Exposure during pregnancy (EDP) reports are reportable using the NIS AEM Report Form and the EDP Supplemental Form, irrespective of the presence of an associated safety event.

  For exposure during pregnancy in studies exclusively of pregnant people, data on the exposure to any Pfizer drug during pregnancy, are not reportable unless associated with serious or non-serious adverse events. However, if the mother or the fetus experiences any safety event (either serious or non-serious), the event must be reported without the event EDP.

For these safety events with an explicit attribution or scenarios involving exposure to any Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding them. No follow-up will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male...". Other identifiers will have been removed.

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Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current "*Your Reporting Responsibilities (YRR) with Supplemental Topics*" training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer

Adverse events are not expected to be reported from structured data, as the elements required to determine explicit attribution will not be available.

11.2. Structured Data Analysis

This study involves data that exist as structured data by the time of study start.

In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Following completion of the analysis, results will be shared with the study team to collaboratively determine whether it is appropriate to disseminate the findings in the following publications:

- At least one conference abstract
- At least one manuscript
- Final study report

If appropriate, the Ontada study team will collaborate with Pfizer to determine the appropriate conference(s) and journal(s) for submission, following assessment of the study findings.

Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed. Authors will adhere to the ICMJE guidelines: specifically, all authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; (3) approved the version to be published, and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

Table 1. Variables and definitions

Table 2. Qualifying therapies for mCSPC and mCRPC

Table 3: Feasibility Results

15. LIST OF FIGURES

Figure 1. Overview of study design

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	-	30-Oct-2024	List of Pfizer Drugs for AE Reporting

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

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