NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Machine learning prediction of anemia events before and after talazoparib dose modification using TALAPRO-2 phase 3 trial data
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Medicinal product	Talzenna
Research question and objectives	Research question: How well can machine learning models predict anemia events before and after talazoparib dose modification? Primary objectives: 1. Describe patient characteristics, dosing patterns and hemoglobin trajectories with respect to anemia events in talazoparib-treated metastatic castrate-resistant prostate cancer (mCRPC) patients from the TALAPRO-2 trial data. 2. Develop and evaluate machine learning prediction models of anemia risk after treatment initiation and preceding dose modification. 3. Develop and evaluate machine learning prediction models of anemia recovery after dose modification.
Country(ies) of study	United States
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Term
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARPI	Androgen Receptor Pathway Inhibitors
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BRCA	BReast CAncer gene
BUN	Blood Urea Nitrogen
Ca	Calcium
CDARS	Clinical Data Analysis and Reporting System
Cl	Chloride
CCI	Charlson Comorbidity Index
CK	Creatine Kinase
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated Glomerular Filtration Rate
EMBRACA	Elucidating the Efficacy and Safety of Talazoparib in Advanced Breast Cancer
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EPO	Erythropoietin
EU	European Union
FDA	Food And Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCO3	Bicarbonate
HCT	Hematocrit
Hgb	Hemoglobin
HRR	Homologous Recombination Repair
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LASSO	Least Absolute Shrinkage and Selection Operator

Abbreviation	Term
LDH	Lactate Dehydrogenase
mCRPC	Metastatic Castrate-Resistant Prostate Cancer
Mg	Magnesium
ML	Machine Learning
MCV	Mean Corpuscular Volume
NA	Not Applicable
Na	Sodium
NI	Non-Interventional
PARP	Poly (ADP-ribose) polymerase
PLTS	Platelets
PAS	Post-Authorization Studies
PASS	Post-Authorization Safety Study
PSA	Prostate-Specific Antigen
PCWG3	Prostate Cancer Working Group 3
QC	Quality Control
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumors
SAP	Statistical Analysis Plan
SD	Standard Deviation
TALAPRO-2	Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer: a randomized, placebo-controlled, phase 3 trial
US	United States
WBC	White Blood Cell

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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

Title: Machine learning prediction of anemia events before and after talazoparib dose modification using TALAPRO-2 phase 3 trial data

Version 2.0, 12 June 2025

[redacted]

Rationale and background: The risk of anemia due to talazoparib is common and may be a barrier in its utilization and/or lead to premature treatment discontinuation. Successful prediction of this adverse event in patients receiving talazoparib is an important step in understanding and reducing the risk of such toxicities while maintaining patients on treatment through individualized patient-centered approaches such as more vigilant monitoring and early dose management.

Research question and objectives:

How well can machine learning models predict anemia events before and after talazoparib dose modification?

Primary objectives:

1. Describe patient characteristics, dosing patterns and hemoglobin trajectories with respect to anemia events in talazoparib-treated metastatic castrate-resistant prostate cancer (mCRPC) patients from the TALAPRO-2 trial data.
2. Develop and evaluate machine learning prediction models of anemia risk after treatment initiation and preceding dose modification.
3. Develop and evaluate machine learning prediction models of anemia recovery after dose modification.

Exploratory objective:

1. Describe patient characteristics and hemoglobin trajectories with respect to anemia events in control-arm mCRPC patients from the TALAPRO-2 trial data

Study design: This is a non-interventional (NI), observational, retrospective study with secondary data analysis of already existing clinical trial data.

Population: This study will use the existing TALAPRO-2 trial data of metastatic castrate-resistant prostate cancer (mCRPC) patients allocated to the talazoparib + enzalutamide treatment arm and included in the safety analysis. Individuals included in the study were male patients aged ≥18 years (≥20 years in Japan) with mCRPC, enrolled between 07 January 2019, and 17 September 2020 from hospitals, cancer centers and medical centers from 26 countries in North America, Europe, Israel, South America, South Africa, and the Asia-Pacific region, and received talazoparib plus enzalutamide versus placebo plus enzalutamide as a first-line treatment. The trial included two cohorts: Cohort 1, ie, “all-comers” regardless of homologous recombination repair (HRR) gene alteration status, and Cohort 2, ie, “HRR deficient” patients who were enrolled for Cohort 2 plus patients already enrolled in Cohort 1 who were HRR deficient. Non-overlapping patient data from both cohorts will be included in this study. Data cutoff was 16 August 2022 for Cohort 1 and 03 October 2022 for Cohort 2.

Variables: Exposure variables in this study are defined as potential predictors for anemia risk, including demographic characteristics, clinical characteristics, treatment history, talazoparib and enzalutamide starting dosages, medical comorbidities, baseline anemia, and baseline and longitudinal laboratory values. The outcome is anemia, categorized as overall (all grades), mild-to-moderate (grades 1 and 2), and severe (grades 3, 4 and 5), defined based on hemoglobin levels according to Common Terminology Criteria for Adverse Events (CTCAE) classification. Covariates are defined as potential predictors of anemia risk that are considered interventions intended to manage anemia such as dose modification (ie, interruption or reduction) and standard supportive care (e.g. transfusions, erythropoiesis-stimulating agents, iron supplementation).

Data Sources: This study will use the existing TALAPRO-2 trial data of mCRPC patients allocated to the talazoparib + enzalutamide treatment arm and included in the safety analysis.

Study size: TALAPRO-2 included two cohorts: Cohort 1, ie, “all-comers” regardless of homologous recombination repair (HRR) gene alteration status, and Cohort 2, ie, “HRR deficient” patients who were enrolled for Cohort 2 plus patients already enrolled in Cohort 1 who were HRR deficient. Data from the non-overlapping set of patients among the two cohorts will be used for this study, including approximately 398 patients from Cohort 1 and 115 patients from Cohort 2.

Data analysis: For Primary Objective 1, descriptive statistics will be used to summarize baseline patient characteristics (demographic, clinical, treatment history, lab values) overall and stratified by subsequent anemia status; to summarize early dose patterns with respect to initial post-index anemia status and dose modification; to summarize baseline patient characteristics and subsequent anemia status by early dose pattern strata; to summarize the proportion of patients who improved, remained the same, or worsened in anemia severity following dose modification; and to summarize the rate of hemoglobin change prior to and after dose modification. Time to dose modification, time to anemia, and time to anemia improvement will be assessed using Kaplan-Meier survival analyses. For Objectives 2 and 3, a variety of machine learning models including LASSO Cox regression, extreme gradient boosting, survival support vector machine, and deep cox proportional hazards model will be applied to identify the best performing model for predicting anemia risk and recovery based on performance metrics such as concordance index (test c-index) and dynamic area under the curves (AUCs). Exploratory objective 1 will be assessed similarly as Objective 1, with descriptive statistics to be used to summarize baseline patient characteristics (demographic, clinical, treatment history, lab values) overall and stratified by subsequent anemia status; and to summarize the rate of hemoglobin change after study initiation. Time to anemia will be assessed using Kaplan-Meier survival analyses. No dose modification-related concepts will be assessed for exploratory objective 1 since dosing is not applicable for the control arm.

Milestones: Start of data collection: 11 November 2024; End of data collection: 31 July 2025; Final study report: 30 June 2026

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.0	12 June 2025	Substantial	6. Milestones	1. End of data collection changed from 14 March 2025 to 31 July 2025 2. Final study report changed from 14 February 2026 to 30 June 2026	Later end of data collection date than originally anticipated due to contracting finalization, data analysis, and quality control requirements for the PASS study

6. MILESTONES

Milestone	Planned Date
Registration in the EU PAS Register	08 November 2024
Start of data collection	11 November 2024
End of data collection	31 July 2025
Final study report	30 June 2026

7. RATIONALE AND BACKGROUND

TALZENNA (talazoparib), a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with enzalutamide, was approved by the US Food and Drug Administration (FDA) in June 2023 for the treatment of homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), and by the European Medicines Agency (EMA) in January 2024 for the treatment of any mCRPC regardless of HRR mutation status. Along with clinically meaningful and statistically significant improvement in radiographic progression-free survival, anemia, a hematologic disorder characterized by insufficient hemoglobin (Hgb) in the blood, was reported as a common adverse event (AE) in the talazoparib group. Grade 3-4 anemia (Hgb < 8.0 g/dL) was observed in 46% of treated patients, with median time to anemia onset of 3.3 months(1). Although many patients resumed talazoparib after treatment-emergent anemia, ultimately 8% of patients permanently discontinued talazoparib. Given the potential barrier in talazoparib utilization and/or premature treatment discontinuation due to anemia risk, successful prediction of this adverse event via an individualized patient-centered approach may be a potential strategy for early detection and prevention measures among at-risk patients.

Based on a review of prespecified target safety events and pharmacokinetics data, a starting dose of 0.5 mg/day talazoparib (in combination with 160 mg daily enzalutamide) was specified for the study, with a reduced 0.35 mg/day given to patients with moderate renal impairment (estimated glomerular filtration rate 30–59 ml/min/1.73 m^2) to account for lower clearance in this subpopulation(2). Per protocol mandate, patients experiencing grade 3-4 anemia underwent dose interruption, followed by dose reduction of talazoparib upon hemoglobin recovery, while patients experiencing grade 1-2 anemia were managed by the investigator as warranted on an individual basis (interruption and/or reduction). Patients at baseline were allowed to have up to grade 2 baseline anemia and still be included in the study. Therefore, a variety of patient characteristics and treatment strategies are represented in the existing data from the clinical trial before and after treatment initiation and modification which allows for the opportunity to characterize and model the dose patterns and trajectories of anemia risk among patients treated with talazoparib.

Anemia risk has previously been described more generally among men with prostate cancer, including due to the cancer itself (replacement of normal marrow with cancer cells); due to treatments including bilateral orchiectomy, androgen deprivation therapy, radiation therapy, chemotherapy, and targeted therapy; as well as being associated with patient characteristics such as advanced age, bone metastasis, low baseline hemoglobin levels(3-13). Prior findings from the EMBRACA trial of talazoparib in patients with germline BRCA-mutated advanced breast cancer also showed that higher talazoparib exposure (calculated using average daily dose intensity divided by the product of talazoparib oral clearance) is associated with higher risk of anemia(14), although

this value is typically only measured in the trial setting during pharmacokinetic analyses and not readily available during routine clinical practice. Given the large number of potential predictors of anemia risk for prostate cancer in general and additional less well-understood risk factors among talazoparib-treated mCRPC patients, an integrated prediction approach may improve the ability to anticipate treatment-related toxicity and in the future, aid early dose management to prevent severe anemia-related discontinuation of talazoparib in the clinical setting.

Machine learning (ML) modeling is increasingly being used to predict outcomes in oncology (15), and drug-related adverse events(16-18), proposed because of its ability to integrate complex, multifaceted data in a customizable and scalable manner, often without assumptions about underlying data distributions. Therefore, ML is a promising tool for prediction, prevention, and ultimately, clinical decision support in the effort to reduce treatment-related toxicity. This study serves as an exploratory effort to assess the ability of machine learning models to predict anemia risk and recovery, with future directions to validate the models in the real-world setting, and eventually, to develop diagnostic tools for predicting and preventing anemia in real time in the clinical setting.

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

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

How well can machine learning models predict anemia events before and after talazoparib dose modification?

Primary objectives:

1. Describe patient characteristics, dosing patterns and hemoglobin trajectories with respect to anemia events in talazoparib-treated metastatic castrate-resistant prostate cancer (mCRPC) patients from the TALAPRO-2 trial data.
2. Develop and evaluate machine learning prediction models of anemia risk after treatment initiation and preceding dose modification.
3. Develop and evaluate machine learning prediction models of anemia recovery after dose modification.

Exploratory objective:

1. Describe patient characteristics and hemoglobin trajectories with respect to anemia events in control-arm mCRPC patients from the TALAPRO-2 trial data

9. RESEARCH METHODS

9.1. Study Design

This is a NI, observational, retrospective cohort study of mCRPC patients who received talazoparib in the treatment arm, utilizing descriptive statistics and machine learning prediction modeling with secondary data analysis of existing trial data from TALAPRO-2. The primary endpoint in this study is anemia, categorized as overall (all grades), mild-to-moderate (grades 1 and 2), and severe (grades 3, 4 and 5), defined based on hemoglobin levels according to Common Terminology Criteria for Adverse Events (CTCAE) classification(19). Patient characteristics will be described with respect to talazoparib dose patterns and subsequent anemia. Machine learning models will be

generated to predict anemia risk/recovery and assessed with respect to prediction performance. While the eventual application of this work includes enabling diagnostic and predictive tools for preventing anemia at the point of care, this initial exploratory study aims to assess the performance of a machine learning model in a controlled setting, ie, in the clinical trial setting. Trial data is less prone to issues of missing data and loss to follow-up that real-world data is susceptible to and serves as an ideal data source for developing model parameters as a preliminary step before assessing real-world data directly. Furthermore, given the recent approval of talazoparib, real-world cohorts are still limited in sample size for talazoparib-treated patients, which may result in the study being underpowered for performing machine learning predictive modeling. The machine learning model approach is selected because of its ability to integrate complex, multifaceted data in a customizable and scalable manner, often without assumptions about underlying data distributions.

9.2. Setting

This study will use the existing TALAPRO-2 trial data of metastatic castrate-resistant prostate cancer (mCRPC) patients allocated to the talazoparib + enzalutamide treatment arm and included in the safety analysis. Details of the clinical trial are published elsewhere(2). Patients with mCRPC were enrolled between 07 January 2019, and 17 September 2020 from hospitals, cancer centers and medical centers from 26 countries in North America, Europe, Israel, South America, South Africa, and the Asia-Pacific region and received talazoparib plus enzalutamide versus placebo plus enzalutamide as a first-line treatment. The trial included two cohorts: Cohort 1, ie, “all-comers” regardless of homologous recombination repair (HRR) gene alteration status, and Cohort 2, ie, “HRR deficient” patients who were enrolled for Cohort 2 plus patients already enrolled in Cohort 1 who were HRR deficient. Non-overlapping patient data from both cohorts will be included in this study. Data cutoff was 16 August 2022 for Cohort 1 and 03 October 2022 for Cohort 2.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria as specified in the TALAPRO-2 protocol and included in the safety analysis to be eligible for inclusion in the study. Key inclusion criteria are listed below with the full list reported previously(2):

1. Male
2. Aged ≥18 years (≥20 years in Japan)
3. Histologically/cytologically confirmed adenocarcinoma of the prostate
4. Asymptomatic or mildly symptomatic mCRPC
5. Underwent bilateral orchiectomy or receiving ongoing ADT with a gonadotropin-releasing hormone agonist/antagonist, with serum testosterone ≤50 ng/dl (≤1.73 nmol/l) at screening
6. Progressive disease at study entry defined by at least one of the following: PSA progression, defined as ≥2 rising PSA values from three consecutive assessments with ≥7 days between assessments; and/or soft tissue disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; and/or bone disease progression per Prostate Cancer Working Group 3 (PCWG3) guidelines, with ≥2 new metastatic bone lesions on whole body radionuclide bone scan.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Receipt of any prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state, with the exception of prior treatment with ADT and first-generation antiandrogens. Docetaxel and abiraterone received in the castrate sensitive prostate cancer setting are not exclusionary.
2. Has known or suspected brain metastases, or active leptomeningeal disease; any history of myelodysplastic syndrome, acute myeloid leukemia, or prior malignancy (except for carcinoma *in situ* or nonmelanoma skin cancer, any prior malignancies ≥3 years before randomization with no subsequent evidence of recurrence or progression regardless of the stage, or American Joint Committee on Cancer Stage 0/1 cancer <3 years before randomization that has a remote probability of recurrence or progression as per investigator opinion); clinically significant cardiovascular disease; or significant renal, hepatic or bone marrow organ dysfunction

Note that only key exclusion criteria are listed above, with the full list reported previously(2):

9.3. Variables

Exposure variables in this study are defined as potential predictors for anemia risk, including demographic characteristics, clinical characteristics, treatment history, talazoparib and enzalutamide starting dosages, medical comorbidities, baseline anemia, and baseline and longitudinal laboratory values. Baseline characteristics are captured up to the index date, which is defined as the time of talazoparib treatment initiation, while longitudinal lab values are captured any time after treatment initiation throughout the study. The outcome is anemia, categorized as overall (all grades), mild-to-moderate (grades 1 and 2), and severe (grades 3, 4 and 5), defined based on hemoglobin levels according to Common Terminology Criteria for Adverse Events (CTCAE) classification. While Objective 1 aims to characterize anemia events both before and after (or in the absence of) a dose modification event, Objective 2 aims to model only anemia events preceding dose modification, and Objective 3 aims to model only anemia events after dose modification. This is to allow optimal parameterization of the machine learning model without potential unmeasured confounding associated with patient receiving non-randomized dose modification during the trial. Covariates are defined as potential predictors of anemia risk that are considered interventions intended to manage anemia such as dose modification (ie, interruption or reduction) and standard supportive care (e.g. transfusions, erythropoiesis-stimulating agents, iron supplementation) received either at baseline or due to anemia events, which may be received in a non-random way during the trial, such that it is associated with both patient baseline characteristics (whether measured or unmeasured), as well as anemia events. However, these treatment-related intervention variables may also be considered as exposure or outcome variables depending on the objective.

The main study variables of interest, including demographics, diagnostic, therapeutic and laboratory/examinations and outcomes, along with associated roles, and operational definitions are listed in Table 1: Study variables. Further details on operational definitions and any additional variables will be provided in the SAP.

Table 1. Study Variables

Variable	Role	Operational Definition
Demographics		
Age at treatment initiation	Baseline, Exposure	Continuous (years)

Table 1. Study Variables

Variable	Role	Operational Definition
Race	Baseline, Exposure	White; Black or African American; Asian; Other; Unknown/missing
Ethnicity	Baseline, Exposure	Hispanic; Non-Hispanic; Unknown/missing
Geographic region	Baseline, Exposure	North America; Europe; Israel; South America; South Africa; Asia-Pacific; Unknown/Missing
Study cohort	Baseline, Exposure	Cohort 1; Cohort 2
Trial site	Baseline, Exposure	Trial site 1; Trial site 2; …, Trial site n
Clinical characteristics		
Body weight	Baseline, Exposure	Continuous (kg)
BMI	Baseline, Exposure	Continuous (kg/m^3)
Charlson Comorbidity Index (CCI)	Baseline, Exposure	Continuous
Baseline anemia	Baseline, Exposure	No anemia; Grade 1; Grade 2; Unknown/missing
Prior medical history of anemia	Baseline, Exposure	Yes; No; Unknown/missing
Prior medical history of kidney disease	Baseline, Exposure	Yes; No; Unknown/missing
Date of prostate cancer diagnosis	Baseline, Exposure	Year/Month/Day
AJCC Stage at prostate cancer diagnosis	Baseline, Exposure	I, II, III, IV, Unknown/missing
Gleason score	Baseline, Exposure	<8; ≥ 8; Unknown/missing
Date of mCRPC diagnosis	Baseline, Exposure	Year/Month/Day
Bone Metastases at Baseline	Baseline, Exposure	Yes; No
Number of bone metastases at screening	Baseline, Exposure	Continuous
Somatic HRR mutation status	Baseline, Exposure	Deficient; Non-deficient; Unknown/missing
Germline HRR mutation status	Baseline, Exposure	Deficient; Non-deficient; Unknown/missing
BRCA1.2 alteration status	Baseline, Exposure	Altered; Unaltered; Unknown/missing
ECOG	Baseline, Exposure	0; 1; Other; Unknown/missing
Pre-index treatments		
Androgen deprivation therapy at baseline type	Baseline, Exposure	Chemical castration; Bilateral orchiectomy; Unknown/missing
Prior radiotherapy	Baseline, Exposure	Yes; No; Unknown/missing
Prior radiotherapy dose (Gy)	Baseline, Exposure	Continuous
Prior radiotherapy start date	Baseline, Exposure	Year/Month/Day
Prior radiotherapy end date	Baseline, Exposure	Year/Month/Day
Prior ADT	Baseline, Exposure	Yes; No; Unknown/missing

Table 1. Study Variables

Variable	Role	Operational Definition
Prior ADT start date	Baseline, Exposure	Year/Month/Day
Prior ADT stop date	Baseline, Exposure	Year/Month/Day
Prior second generation ARPI	Baseline, Exposure	Yes; No; Unknown/missing
Prior second generation ARPI start date	Baseline, Exposure	Year/Month/Day
Prior second generation ARPI end date	Baseline, Exposure	Year/Month/Day
Prior chemotherapy	Baseline, Exposure	Yes; No; Unknown/missing
Prior chemotherapy Start date	Baseline, Exposure	Year/Month/Day
Prior chemotherapy Stop date	Baseline, Exposure	Year/Month/Day
Index treatments		
Talazoparib dose 1	Baseline, Exposure	0.5 mg; 0.35 mg; Other
Talazoparib dose 1 initiation date	Baseline, Exposure	Year/Month/Day
Time between initial prostate diagnosis and talazoparib initiation	Baseline, Exposure	Continuous (days)
Concomitant antineoplastic treatment received	Baseline, Exposure	<drug name>
Concomitant antineoplastic treatment start date	Baseline, Exposure	Year/Month/Day
Concomitant treatment stop date	Baseline, Exposure	Year/Month/Day
Post-index treatments		
Talazoparib dose 2 quantitative	Exposure, Covariate, Outcome	0.35 mg; 0.25mg; 0.1 mg; 0 mg; Other
Talazoparib dose 2 descriptive narrow	Exposure, Covariate, Outcome	Interruption; Reduction; No change
Talazoparib dose 2 descriptive broad	Exposure, Covariate, Outcome	Dose modification; No change
Talazoparib dose 2 initiation date	Exposure, Covariate, Outcome	Year/Month/Day
Talazoparib dose 2 modification reason	Exposure, Covariate, Outcome	Toxicity; Not toxicity; Unknown/missing
Anemia management		
Oral iron supplementation start date	Baseline, Exposure, Covariate	Year/Month/Day
Oral iron supplementation stop date	Baseline, Exposure, Covariate	Year/Month/Day
Intravenous iron supplementation date	Baseline, Exposure, Covariate	Year/Month/Day
RBC transfusion date	Baseline, Exposure, Covariate	Year/Month/Day

Table 1. Study Variables

Variable	Role	Operational Definition
Erythropoiesis-stimulating agent administration date	Baseline, Exposure, Covariate	Year/Month/Day
Lab values (at visit 0, 1, 2, …n)		
eGFR	Baseline, Exposure	Continuous
eGFR date	Baseline, Exposure	Year/Month/Day
ALT	Baseline, Exposure	Continuous
ALT date	Baseline, Exposure	Year/Month/Day
Albumin	Baseline, Exposure	Continuous
Albumin date	Baseline, Exposure	Year/Month/Day
ALP	Baseline, Exposure	Continuous
ALP date	Baseline, Exposure	Year/Month/Day
AST	Baseline, Exposure	Continuous
AST date	Baseline, Exposure	Year/Month/Day
HCO3	Baseline, Exposure	Continuous
HCO3 date	Baseline, Exposure	Year/Month/Day
Total bilirubin	Baseline, Exposure	Continuous
Total bilirubin date	Baseline, Exposure	Year/Month/Day
BUN	Baseline, Exposure	Continuous
BUN date	Baseline, Exposure	Year/Month/Day
Ca	Baseline, Exposure	Continuous
Ca date	Baseline, Exposure	Year/Month/Day
Cl	Baseline, Exposure	Continuous
Cl date	Baseline, Exposure	Year/Month/Day
CK	Baseline, Exposure	Continuous
CK date	Baseline, Exposure	Year/Month/Day
Random glucose	Baseline, Exposure	Continuous
Random glucose date	Baseline, Exposure	Year/Month/Day
LDH	Baseline, Exposure	Continuous
LDH date	Baseline, Exposure	Year/Month/Day
Mg	Baseline, Exposure	Continuous
Mg date	Baseline, Exposure	Year/Month/Day
K	Baseline, Exposure	Continuous
K date	Baseline, Exposure	Year/Month/Day
Total protein	Baseline, Exposure	Continuous
Total protein date	Baseline, Exposure	Year/Month/Day
Na	Baseline, Exposure	Continuous
Na date	Baseline, Exposure	Year/Month/Day
Creatinine	Baseline, Exposure	Continuous
Creatinine date	Baseline, Exposure	Year/Month/Day
Phosphate	Baseline, Exposure	Continuous
Phosphate date	Baseline, Exposure	Year/Month/Day
Testosterone	Baseline, Exposure	Continuous
Testosterone date	Baseline, Exposure	Year/Month/Day
Folic acid	Baseline, Exposure	Continuous
Folic acid date	Baseline, Exposure	Year/Month/Day
Vitamin B12	Baseline, Exposure	Continuous

Table 1. Study Variables

Variable	Role	Operational Definition
Vitamin B12 date	Baseline, Exposure	Year/Month/Day
Urea	Baseline, Exposure	Continuous
Urea date	Baseline, Exposure	Year/Month/Day
PSA	Baseline, Exposure	Continuous
PSA date	Baseline, Exposure	Year/Month/Day
MCV	Baseline, Exposure	Continuous
MCV date	Baseline, Exposure	Year/Month/Day
RBC	Baseline, Exposure	Continuous
RBC date	Baseline, Exposure	Year/Month/Day
HCT	Baseline, Exposure	Continuous
HCT date	Baseline, Exposure	Year/Month/Day
WBC	Baseline, Exposure	Continuous
WBC date	Baseline, Exposure	Year/Month/Day
Differential	Baseline, Exposure	Continuous
Differential date	Baseline, Exposure	Year/Month/Day
PLTS	Baseline, Exposure	Continuous
PLTS date	Baseline, Exposure	Year/Month/Day
Retics	Baseline, Exposure	Continuous
Retics date	Baseline, Exposure	Year/Month/Day
EPO	Baseline, Exposure	Continuous
EPO date	Baseline, Exposure	Year/Month/Day
Lab values principal components	Baseline, Exposure	Continuous
Hemoglobin	Baseline, Exposure, Outcome	Continuous
Hemoglobin date	Baseline, Exposure, Outcome	Year/Month/Day
Hemoglobin change from baseline (g/dL)	Baseline, Exposure, Outcome	Continuous
Symptoms (at visit 0, 1, 2, …n)		
Fatigue	Baseline, Exposure	Yes; No; Unknown/missing
Fatigue visit date	Baseline, Exposure	Year/Month/Day
Shortness of breath	Baseline, Exposure	Yes; No; Unknown/missing
Shortness of breath visit date	Baseline, Exposure	Year/Month/Day
Decreased appetite	Baseline, Exposure	Yes; No; Unknown/missing
Decreased appetite visit date	Baseline, Exposure	Year/Month/Day
Asthenia	Baseline, Exposure	Yes; No; Unknown/missing
Asthenia visit date	Baseline, Exposure	Year/Month/Day
Dyspnea	Baseline, Exposure	Yes; No; Unknown/missing
Dyspnea visit date	Baseline, Exposure	Year/Month/Day
Dizziness	Baseline, Exposure	Yes; No; Unknown/missing
Dizziness visit date	Baseline, Exposure	Year/Month/Day
Outcomes		

Table 1. Study Variables

Variable	Role	Operational Definition
Anemia status during visit For visit 1, 2, …n.	Exposure, Outcome	No anemia; Grade 1; Grade 2; Grade 3; Grade 4; Grade 5
Anemia status visit date For visits 1, 2, …n.	Exposure, Outcome	Year/Month/Day
Highest-grade anemia	Outcome	No anemia; Grade 1; Grade 2; Grade 3; Grade 4; Grade 5
Highest-grade anemia date	Outcome	Year/Month/Day
Post-index pre-dose modification anemia shift Shift is defined as moving between the rollup anemia categories: No anemia; Grades 1/2; Grades 3+. If no dose modification observed during study, take 1st shift in anemia status after index. If no shift during study, value is "No worse". If dose modification is observed, take the most recent shift prior to dose modification date. If no shift prior to dose modification date, value is "Not worse"	Outcome	Not worse; Worse by 1 category; Worse by 2 categories
Early dose pattern narrow Derived variable describing initial post-index anemia status up to 1st dose modification (ie, Talazoparib dose 2 initiation date).	Outcome	1; 2a; 2b; 3; 4a; 4b; 5; 6a; 6b See Table 2
Early dose pattern broad Rolled up categories from "early dose pattern narrow"	Outcome	1; 2; 3; 4; 5; 6 See Table 2
Time to minimum hemoglobin (days)	Outcome	Continuous
Pre-dose modification hemoglobin change (Hemoglobin from talazoparib initiation up to dose modification date. g/dL per week)	Outcome	Continuous (NA if no dose modification)

Table 1. Study Variables

Variable	Role	Operational Definition
Post-dose modification hemoglobin change 1 (Hemoglobin from dose modification date to following visit. g/dL per week)	Outcome	Continuous (NA if no dose modification)
Post-dose modification hemoglobin change 2 (Hemoglobin from dose modification date to 2 visits later. g/dL per week)	Outcome	Continuous (NA if no dose modification)
Post-dose modification anemia status 1 Anemia status 1st visit after dose modification	Outcome	Improved; Unchanged; Worsened; NA
Post-dose modification anemia status 2 Anemia status 2nd visit after dose modification	Outcome	Improved; Unchanged; Worsened; NA
Date of death	Outcome	Year/Month/Day
Date of loss to follow-up	Outcome	Year/Month/Day
Time to dose modification	Outcome	Followed from the date of talazoparib initiation until the date of talazoparib treatment modification, or censored at the first of: (1) death; (2) date of last contact; or (3) study end date
Time to grade 3+ anemia	Outcome	Followed from the date of talazoparib initiation until the date of grade 3+ anemia, or censored at the first of: (1) dose modification; (2) death, (3) date of last contact; or (4) study end date
Time to worse-grade anemia	Outcome	Followed from the date of talazoparib initiation until the date of worse-grade anemia compared to baseline, or censored at the first of: (1) dose modification; (2) death, (3) date of last contact; or (4) study end date

Table 1. Study Variables

Variable	Role	Operational Definition
Time to anemia improvement	Outcome	Followed from the date of 1st dose modification until the date of anemia improvement, or censored at the first of: (1) subsequent dose modification; (2) death; (3) date of last contact; or (4) study end date

Table 2 further defines "early dose pattern narrow" and "early dose pattern broad" as derived variables based on the values of variables "post-index pre-dose modification anemia shift" and "Talazoparib dose 2 descriptive" variables.

Table 2. Early dose patterns for patients initiating talazoparib.

Post-index pre-dose modification anemia shift	Talazoparib dose 2 descriptive narrow	Talazoparib dose 2 descriptive broad	Early dose pattern narrow	Early dose pattern broad
Not worse	No change	No change	1	1
Not worse	Interruption	Dose modification	2a	2
Not worse	Reduction	Dose modification	2b	2
Worse by 1 category	No change	No change	3	3
Worse by 1 category	Interruption	Dose modification	4a	4
Worse by 1 category	Reduction	Dose modification	4b	4
Worse by 2 categories	No change	No change	5	5
Worse by 2 categories	Interruption	Dose modification	6a	6
Worse by 2 categories	Reduction	Dose modification	6b	6

9.4. Data Sources

This study will use the existing TALAPRO-2 trial data of mCRPC patients allocated to the talazoparib + enzalutamide treatment arm and included in the safety analysis. No additional data review or abstraction will be conducted.

9.5. Study Size

This is a NI study with no *a priori* hypotheses specified; therefore, sample size calculations are not applicable. TALAPRO-2 included two cohorts: Cohort 1, ie, “all-comers” regardless of homologous recombination repair (HRR) gene alteration status, and Cohort 2, ie, “HRR deficient” patients who were enrolled for Cohort 2 plus patients already enrolled in Cohort 1 who were HRR deficient. Data from the non-overlapping set of patients among the two cohorts will be used for this study, including approximately 398 patients from Cohort 1 and 115 patients from Cohort 2.

9.6. Data Management

TALAPRO-2 trial data will be shared by the clinical trial team with the GME analytics team through CDARS, a web-based application that manages regulatory reporting components for clinical studies.

An analytic dataset will be created composing the minimum set of data required to perform the statistical analyses for the primary objectives of this study.

All analyses for this study will be conducted in SAS (version 9.4 or higher, SAS Institute, Cary, NC, US) and R (R Foundation for Statistical Computing, https://www.R-project.org, Vienna, Austria)

9.7. Data Analysis

To address Primary Objective 1 description of patient characteristics, baseline patient characteristics (demographic, clinical, treatment history, baseline anemia) will be summarized across the overall study cohort and by strata defined as the highest-grade anemia category (any, grade 1/2, grade 3/4/5) experienced during the study. Total numbers in each stratum will be shown. Variables specified under “Demographics”, “Clinical characteristics”, “Pre-index treatments”, and “Index treatments” sections of Table 1 defined as continuous variables (e.g. age at treatment initiation, body weight, number of bone metastases at screening) will be summarized with mean, standard deviation (SD), median (Q1 – Q3), min and max. Variables defined as categorical variables (e.g. race, ethnicity, geographic region, Gleason score) will be summarized as number (n) and percent (%).

To address Primary Objective 1 description of dosing patterns, patients belonging to each dosing pattern category (Table 2) will be counted, and baseline patient characteristics will be summarized by strata defined as the dosing pattern categories. Variables will be summarized as continuous or categorical variables as described above. In addition, the proportion of patients experiencing anemia during the study (none, any, grade 1/2, grade 3/4/5) will be summarized by dose pattern categories. Finally, time to dose modification will be summarized for the overall study cohort and stratified by initial anemia status and highest-grade anemia status during the study using Kaplan-Meier survival analyses.

To address Primary Objective 1 description of hemoglobin trajectories, the proportion of patients who improved, remained the same, or worsened in anemia severity in the following visit among patients who experienced dose modification due to an anemia event will be summarized as number (n) and percent (%). This summary will be performed for the overall study cohort and stratified by initial dose, and dose modification will be defined as dose interruption or reduction after any anemia in general and stratified by grade 1/2 and grade 3/4 anemia-related modification. In addition, the rate of hemoglobin change before and after dose modification will be summarized, with stratification by initial dose for the former and stratification by anemia severity triggering dose modification for the latter. Time to anemia events (time to grade 3+ anemia, time to worse-grade anemia) will be assessed using Kaplan-Meier survival analyses. Finally, time to anemia improvement after dose

modification among patients who experienced dose modification will be summarized using Kaplan-Meier survival analyses.

For Objectives 2 and 3, a variety of machine learning models including LASSO Cox regression, extreme gradient boosting, survival support vector machine, and deep cox proportional hazards model will be applied to identify the best performing model for predicting anemia risk and recovery based on performance metrics such as concordance index (test c-index) and dynamic area under the curves (AUCs). All variables labeled as “Exposure” and “Covariate” in the “Role” column of Table 1 will be considered as features for building the models.

Exploratory objective 1 will be assessed similarly as Objective 1, with descriptive statistics to be used to summarize baseline patient characteristics (demographic, clinical, treatment history, lab values) overall and stratified by subsequent anemia status; and to summarize the rate of hemoglobin change after study initiation. Time to anemia will be assessed using Kaplan-Meier survival analyses. No dose modification-related concepts will be assessed for exploratory objective 1 since dosing is not applicable for the control arm.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

All efforts will be made to ensure quality and safe storing of data and reports. Quality control (QC) checks will be performed on all programming, data tables, and reports generated in the course of this research. QC review and documentation of reports will be conducted by the GME Technical Review Committee to assure that the deliverable meets defined expectations for the six dimensions of quality: Best Practice, Timeliness, Accuracy, Completeness, Clarity and Relevance. QC findings and documentation of remedial action will be maintained. Storage of programming, data, and reports will be carried out per standard procedures, including being uploaded to the Global Document Management System (GDMS).

A second programmer will independently check the SAS program and outputs and make sure that they are consistent with the protocol and tables in the study report. The quality control (QC) form will be signed and documented.

9.9. Limitations of the Research Methods

Some potential limitations exist for this study: despite trial data being less prone to missing data and loss to follow-up, it is still possible for some amount of missingness to occur due to skipped visits or labs. Due to the effort to incorporate longitudinal data from laboratory results as predictor variables for the machine learning model objectives, incomplete data can affect model performance. Missingness will be assessed across all laboratory values used for the machine learning model. While less susceptible to assumptions about underlying data distributions and relationships, the machine learning approach is not immune to all assumptions and biases. Therefore, multiple machine learning methods with differing parameters will be performed and compared. Another potential limitation is potential overfitting of the machine learning model to the training data, resulting in potential lack of generalizability to external datasets. A potential future follow-up study to address this possible limitation is to further evaluate the models from this study using real-world datasets of talazoparib-treated patients. Additionally, while machine learning models can be powerful tools for prediction, any associations identified should not be interpreted as causal. Finally,

while the assessment of a common condition in a sample size of the total study cohort of ~500 patients is “reasonably powered”(20), some subgroup/stratified analyses may be limited in power for precise estimates.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

The clinical trial was originally governed by its respective IRB protocol. The current study is a non-interventional analysis of deidentified, structured, secondary data only and therefore does not require IRB/EC approval.

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 Guidelines for Good Pharmacoepidemiology Practices (GPP)(21) and the European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (22).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes de-identified data that exist as structured data by the time of study start, and it is therefore not possible to link (ie, identify a possible association between) a product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports. Furthermore, individual clinical trials adhered to their respective AE reporting requirements at the time that the trials were conducted, and all AEs would have already been reported before data is used in the current non-interventional study. Therefore, reporting of AEs is not required in the current study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final clinical study report (CSR) describing the study endpoints will be disseminated to the Pfizer Global Development Team. One or more abstracts may be developed and submitted to relevant scientific conference(s) and one or more manuscripts may be developed and submitted to relevant peer-reviewed medical journals. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). 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.

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 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. Study variables

Table 2. Early dose patterns for patients initiating talazoparib.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

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