Non-Interventional Study Protocol
Study Number C3441055

Treatment Patterns and Clinical Outcomes Among Talazoparib-Treated Adults with HER2-Negative Metastatic Breast Cancer and Germline BRCA1/2 Mutations: An Observational Study Using Flatiron Electronic Health Record (EHR) Database.

Statistical Analysis Plan
(SAP)

Version: 1

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

This Statistical Analysis Plan (SAP) for study C3441055 is based on the protocol version 1.0 dated 16 November 2021.

Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1/17 Dec2021	16 November 2021	N/A	N/A

2 INTRODUCTION

Breast cancer (BC) represents a major public health problem, with 284,200 new cases and 44,130 deaths estimated in the United States (US) during 2021.[1] Prognosis with metastatic BC (mBC) is poor, with an estimated 5-year survival rate of approximately 28.1%.[2] Although the advent of novel therapeutic interventions such as immunotherapy and targeted agents have brought major strides in the treatment of advanced breast cancer (ABC, including locally advanced or metastatic breast cancer), patients may continue to experience minimal or short-lived responses to these agents.[2] As such, the development and characterization of effective interventions are greatly needed in order to ensure patient-specific, appropriate, and tolerable treatment that achieves meaningful improvement in survival and quality of life. By increasing understanding of the true efficacy, safety, effectiveness, and treatment patterns of ABC-focused regimens in a broad, real-world (RW) patient population, RW studies can add tremendous value to this process.[3]

BC is classified into 4 main disease subtypes based on hormone receptor (HR) status (i.e., estrogen receptor (ER) and progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) expression, including HR-positive/HER2-negative (luminal A), HR-negative/HER2-negative (triple-negative breast cancer [TNBC]), HR-positive/HER2-positive (luminal B), and HR-negative/HER2-positive (HER2-enriched).[4] Each subtype is associated with distinct disease features as well as treatment recommendations.[4,5] Treatment strategy may also be driven by mutation status of certain genes, including the BC susceptibility gene 1 or 2 (BRCA1 or BRCA2), in which mutations may render cells deficient in the repair of DNA double-strand breaks, thereby increasing reliance on poly(adenosine diphosphate–ribose) polymerase (PARP)-dependent, single-strand break repair mechanisms.[5-8] Germline BRCA1 or BRCA2 (gBRCA1/2) mutations account for approximately 5% of all BC cases, with prevalence of these mutations higher among those with HER2-negative disease.[9-11]

Talazoparib (TALZENNA®), which was approved by the US Food and Drug Administration (FDA) on October 16, 2018, is an orally available PARP inhibitor

indicated for treatment of adult patients with HER2-negative ABC (including locally advanced or metastatic breast cancer) and germline breast cancer susceptibility gBRCA1/2 mutations.[12]

To date, the only information available about the real-world experience with talazoparib, including patient characteristics, treatment patterns, and clinical outcomes comes from compassionate use programs in Turkey, and Russia, and the French temporary authorization for use (ATU) program. Since the approval of talazoparib in the United States (US) in 2018, there is no published data about the real-world (RW) experience of talazoparib-treated patients with HER2-negative ABC with gBRCA1/2 mutations in the US.

This approval was based on the Phase 3 EMBRACA trial (NCT01945775), which demonstrated that, in comparison to single-agent chemotherapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine), talazoparib improved median progression-free survival (PFS) by approximately 3 months in adult patients diagnosed with HER2-negative ABC with gBRCA1/2 mutations (8.6 months vs 5.6 months [hazard ratio for disease progression or death, 0.54]; 95% confidence interval (CI), 0.41 to 0.71; P<0.001).[13,14] *Additionally, the objective response rate (ORR) was 62.6% in the talazoparib arm versus 27.2% in the chemotherapy arm (odds ratio (OR), 5.0; 95% CI, 2.9 to 8.8; P<0.001).*[13,14] *Grade 3-4 hematologic adverse events (AEs) occurred in 55% of talazoparib-treated patients (primarily anemia) versus in 38% of chemotherapy-treated patients, whereas nonhematologic Grade 3 adverse events (AEs) occurred in 32% and 38% of patients, respectively.*[13]

2.1 STUDY DESIGN

This is an observational study using de-identified structured EHR data from Flatiron Health Analytic Database.

Study population

The study population includes adult patients with HER2-negative mBC with gBRCA1/2 mutations who initiated talazoparib treatment in first-line or later identified from Flatiron Health Analytic Database.

Inclusion criteria:

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

1. *Diagnosed with breast cancer (ICD-9 174.x or 175.x or ICD-10 C50x)*
2. *At least two visits in the Flatiron database on or after 01 January 2011*
3. *Pathology consistent with breast cancer*
4. *Has evidence of stage IV or recurrent metastatic breast cancer with a metastatic diagnosis date on or after 01 January 2011. This includes patients who were diagnosed with stage IV at diagnosis or were diagnosed with earlier stage disease, then developed a distant metastasis later on, or had recurrence of the disease via a distant metastasis*
5. *Confirmed receipt of talazoparib as treatment for mBC via abstraction initiated on or after 01 January 2018*
6. *HER2 negative test result on or before the start of patient's first talazoparib-containing line of therapy, as defined by Flatiron's line of therapy rules*
7. *BRCA1, BRCA2, BRCA1 and BRCA2 germline mutation, or BRCA germline mutation not otherwise specified, identified on or before the start date of patient's first talazoparib-containing line of therapy, as defined by Flatiron's line of therapy business rules*
8. *Age 18 or older at the time of first talazoparib-containing line of therapy*

Exclusion criteria:

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

1. *Lacking relevant unstructured documents in the Flatiron database for review by the abstraction team*
2. *Receipt of drug as part of a clinical trial (captured in the database as "clinical study drug" without additional information about active ingredient or whether the patient received placebo), defined as any non-cancelled order, administration, or oral episode for a drug used in a clinical trial, on or prior to start of first talazoparib line of therapy, as defined by Flatiron's line of therapy business rules*

Data source

This retrospective observational study will utilize Flatiron Health's longitudinal, demographically, and geographically diverse database derived from EHR data from over 265 cancer clinics (~800 sites of care) including more than 2.5 million active US cancer patients available for analysis. The Flatiron EHRs include the entire patient chart of all patients treated in the Flatiron network.

Across the clinics in the Flatiron Health Network, data become available in near real time after each clinical encounter and contribute to Flatiron's continuously aggregating centralized data set. Flatiron accesses both structured data (i.e., data points that are organized in a predefined manner, such as dropdown fields that reside in an EHR to capture a patient's gender or date of birth or laboratory data) as well as unstructured data (i.e., information that is not organized in a preexisting data model, such as free text from a physician note or a portable document format (PDF) laboratory report). The data used in this analysis already exist as structured data in an electronic database.

Treatment/cohort labels

Single cohort study of talazoparib-treated patients.

Treatment group	Treatment label
Talazoparib	Talazoparib

2.2 STUDY OBJECTIVES

The following objectives will be assessed descriptively among adult patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (mBC) with germline breast cancer susceptibility gene 1 or 2 (gBRCA1/2) mutations treated with talazoparib in first-line or later line of therapy in the real-world (RW) practice setting in the United States (US):

Primary objective

- *Describe time to treatment failure (TTF) with talazoparib for talazoparib-treated patients*

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3 HYPOTHESES AND DECISION RULES

N/A

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Includes adult patients with HER2-negative mBC with gBRCA1/2 mutations who initiated talazoparib treatment in first-line or later identified from Flatiron Health Analytic Database

4.2 SAFETY ANALYSIS SET

Not Applicable.

4.3 OTHER ANALYSIS SET

Not Applicable.

4.4 SUBGROUPS

If sample size allows, clinical outcomes will also be reported for post-hoc analytic subgroups of interest.
Subgroups may include the following, to be determined once sample sizes for subgroups are assessed:

- *HR-positive/HER2-negative mBC*
- *Metastatic TNBC*
- *With or without prior platinum therapy in mBC*
- *With or without prior CDK4/6 inhibitor in mBC*
- *Subgroups by line of therapy of talazoparib initiation*

5 ENDPOINTS AND COVARIATES

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Clinical outcomes

Variable	***Operational definition***
Time to treatment failure (TTF)	*Continuous.* *Time(in months) from initiation of talazoparib to treatment discontinuation for any reason, including disease progression, treatment toxicity, and death.*
	Patients still on therapy at the end of follow-up (earliest of last patient-level structured or abstracted

	activity (i.e., the last record of patient vitals, medication administrations, or reported laboratory tests/results, or abstracted end date of oral medications) or date of data cut-off (30 September 2020)) will be censored.

5.2 SAFETY ENDPOINTS

Not Applicable.

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Demographic characteristics

Variable	***Operational definition***
Age	*Continuous:* *Age (years) at index date (date of first talazoparib-containing line of therapy in mBC)*
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Gender	*Categorical:* *Male, female, unknown*
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Hispanic/Latino ethnicity	*Categorical:* *Yes, No/unknown*
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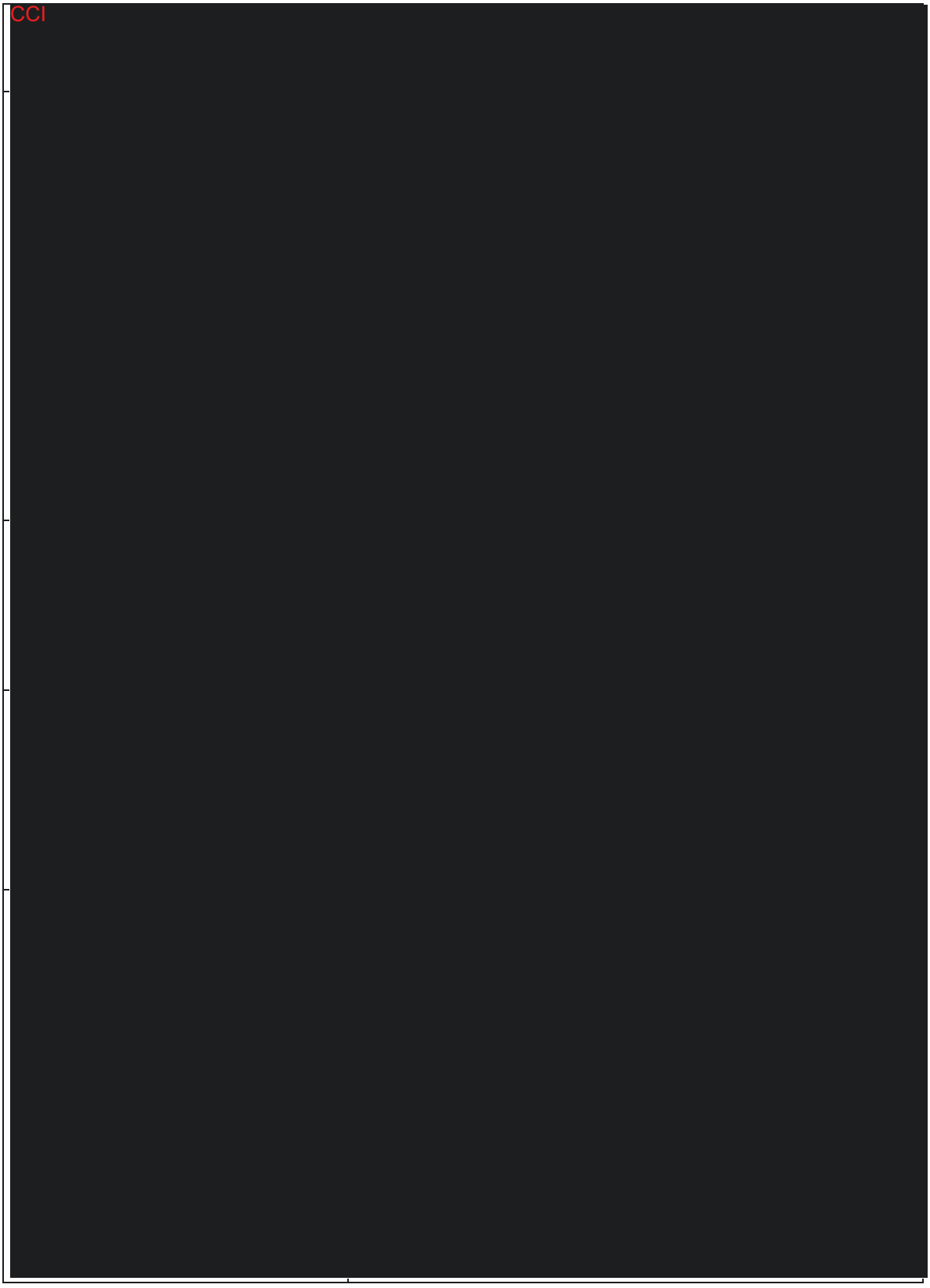
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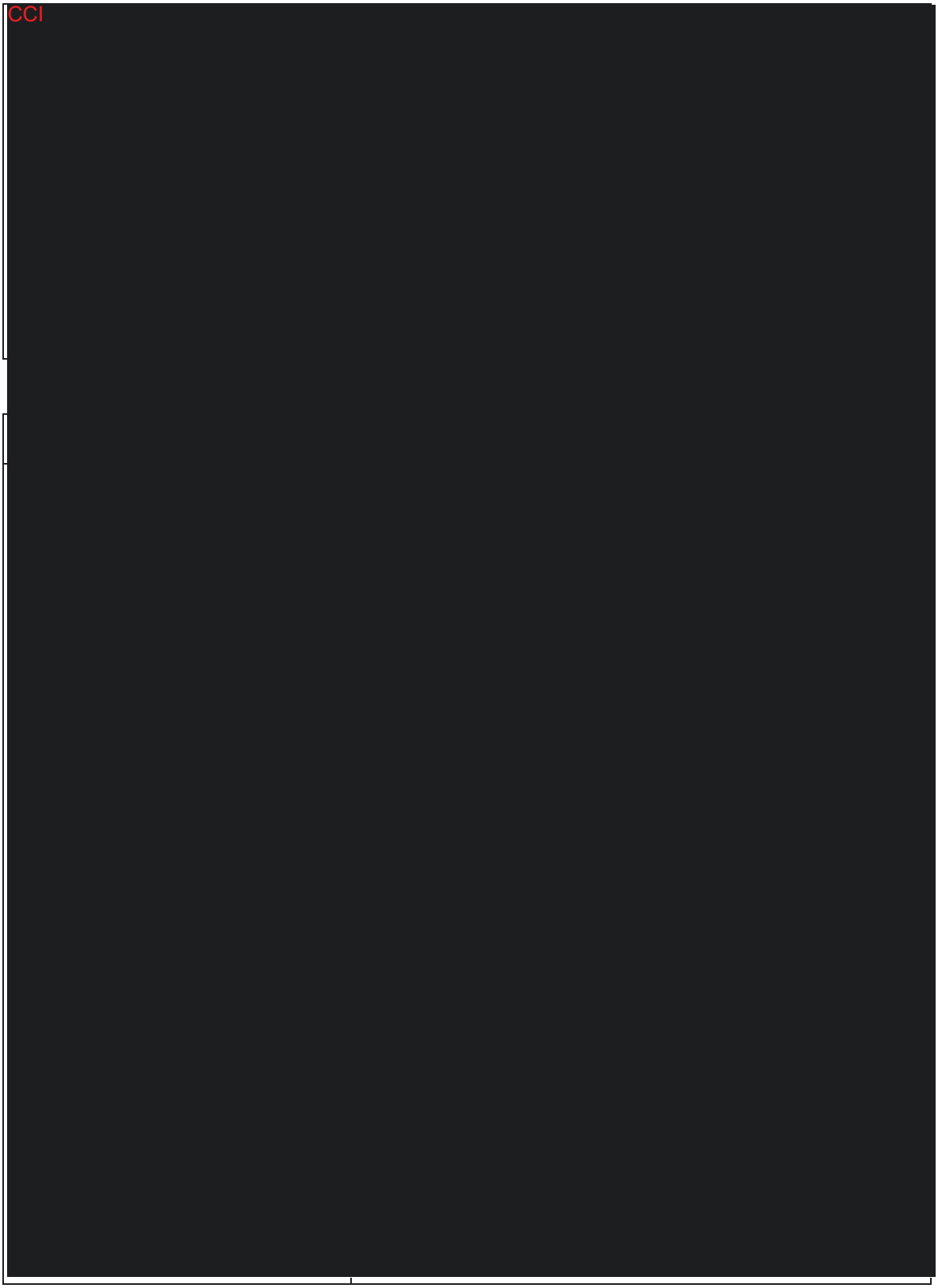

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5.4 COVARIATES

Not Applicable

6 HANDLING OF MISSING VALUES

No imputation for missing values will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

For analysis of baseline characteristics

Mean, standard deviation (STD), median, interquartile range (IQR), and minimum/maximum values will be calculated for continuous variables and for categorical data, counts and proportions will be calculated when performing descriptive analysis. The numbers of missing and unknown observations will be described for both categorical and continuous variables.

No data imputation will be conducted. Patients with missing/unknown data will be reported as such.

For analysis of clinical outcomes

Mean, standard deviation (STD), median, interquartile range (IQR), and minimum/maximum values will be calculated for continuous/numeric non–time-to-event variables and for categorical variables, frequencies and percentages will be provided.

*All **time-to-event endpoints** will be estimated using univariate analysis and KM methods, as appropriate. KM survival curves, KM survival proportions at specified intervals, the number of events, and the number of patients censored will be provided. KM-estimated median values, first and third quartiles, and 95% CIs around each point estimate will be reported when estimable.*

If post-hoc subgroup analyses are performed, the log-rank test may be used to assess a difference in median time-to-event data among subgroups.

Additionally, depending on sample size Cox PH models may be used to assess the impact of specific characteristics on time-to-event outcomes during post-hoc analysis.

7.2 STATISTICAL ANALYSES

7.2.1 Safety Analyses

Not applicable

7.2.2 Analyses of demographics characteristics

Descriptive analysis will be performed on variables (Listed in Section 5.3) related to patient demographics.

Listings will also be provided.

7.2.3 Analyses of Clinical characteristics

The following will be described descriptively:

- Time (in months) from the date of initial BC diagnosis to the date of metastatic diagnosis.
- Time (in months) from mBC diagnosis to talazoparib start.

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Listings will also be provided.

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7.2.5 Analyses of Clinical outcomes

The following will be analysed by K-M method:

- Time (in months) from start of talazoparib to discontinuation for any reason, including disease progression, treatment toxicity, and death.
- Time (in months) from start of talazoparib to death from any cause or disease progression.
- Time (in months) from start of talazoparib to death.

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[redacted]

8 REFERENCES

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