Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Talazoparib (as tosilate)

Proprietary Product Name: Talzenna

Sponsor: Pfizer Australia Pty Ltd

February 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BCRP	Breast cancer resistance protein
BID	Twice daily, Latin: *bis in die*
BRCA	Breast cancer susceptibility gene
BSEP	Bile salt export pump
CDK	Cyclin-dependent protein kinase
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CLIA	Clinical laboratory improvement amendments
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCO	Data cut-off
DLP	Data lock point

Abbreviation	Meaning
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency (EU)
ER	Oestrogen receptor
ESRD	End-stage renal disease
EU	European Union
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration (USA)
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practice(s)
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hormone receptor
IC_{50}	Half maximal inhibitory concentration
IRF	Independent radiology facility
ITT	Intent-to-treat
IV	Intravenous(ly)
MATE	Multidrug and toxin extrusion
MBC	Metastatic breast cancer
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide

Abbreviation	Meaning
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PADER	Periodic adverse drug experience report
PARP	Poly adenosine diphosphate ribose polymerase
PCT	Physicians' choice treatment
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PO	By mouth, Latin: *per os*
pop-PK	Population pharmacokinetic(s)
PR	Progesterone receptor
PR	Partial response
PRO	Patient-reported outcomes
PSUR	Periodic safety update report
PT	Preferred Term
QoL	Quality of life
QSR	Quality system regulations
RCT	Randomised controlled trial
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment emergent adverse event
TNBC	Triple negative breast cancer
UGT	Uridine diphosphate-glucuronyltransferase

Abbreviation	Meaning
ULN	Upper limit of normal
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	15 November 2019
Date of entry onto ARTG:	18 November 2019
ARTG numbers:	310749, 310750, 310751, 310752
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Talazoparib (as tosilate)
Product name:	Talzenna
Sponsor's name and address:	Pfizer Australia Pty Ltd 151 Clarence Street Sydney NSW 2000
Dose form:	Hard capsule
Strengths:	0.25 mg and 1 mg
Containers:	Bottle, blister pack
Pack sizes:	Bottle: 30 capsules. Blister pack: 30, 60 or 90 capsules (0.25 mg strength), 30 capsules (1 mg strength).
Approved therapeutic use:	*Talzenna is indicated for the treatment of patients with a deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) mutation according to a validated diagnostic test, who have human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer.*
Route of administration:	Oral
Dosage:	The recommended dose of Talzenna is 1 mg taken orally once daily, with or without food. The capsules should be swallowed whole and must not be opened or dissolved. The 0.25 mg strength capsule is available for dose reduction. Patients should be treated until disease progression or

unacceptable toxicity occurs.

For further information refer to the Product Information.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Talzenna (talazoparib as tosilate) hard capsules for the following proposed indication:

> *[...] for the treatment of patients with germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.*

Metastatic breast cancer is incurable; the aims of treatment are to alleviate symptoms, maintain or improve quality of life (QoL) and increase overall survival (OS) time through sequential use of therapies. The median OS is currently around 3 years.[1] The choice of systemic treatment for locally advanced or metastatic breast cancer is broadly directed by tumour status for genetic driver mutations in the genes encoding human epidermal growth factor receptor 2 (HER2) and/or hormone receptors (HR).[2] Hormone receptor gene mutations may affect the oestrogen receptor (ER) and/or progesterone receptor (PR). The absence of mutations in any of HER2, ER and PR is described as 'triple negative' breast cancer (TNBC).

The incidence of HER2 and HR mutations in breast cancer are approximately as follows:

- HR-positive and HER2-negative: 73%
- TNBC: 13%
- HER2-positive: 15%
  - And HR-positive: 10%
  - And HR-negative: 5%

In addition to HER2 and HR mutations, 5 to 10% of all breast cancers are found to harbour mutations in breast cancer susceptibility gene 1 (BRCA1; 70% of these patients have TNBC) or in breast cancer susceptibility gene 2 (BRCA2; 20% of these patients have TNBC).[3] BRCA testing should be considered for all women with TNBC.[4] The prevalence of patients with BRCA mutation who have HER2-positive breast cancer is low (around 3%).[5]

Talazoparib is a new therapeutic entity, which was proposed for registration for the treatment of patients who have a germline breast cancer susceptibility (BRCA) gene mutation and have locally advanced or metastatic breast cancer that is HER2-negative. Talazoparib is an inhibitor of poly adenosine diphosphate ribose polymerase (PARP) enzymes, which have a role in DNA repair. Use of PARP inhibitors in patients with germline BRCA mutation (also implicated in DNA repair) may further destabilise tumour DNA repair ability. Olaparib, another PARP inhibitor, is on the Australian Register of

[1] Mayer, I.A. Systemic treatment for metastatic breast cancer: General principles. Last updated 2 October 2019. Accessed from the UpToDate website.
[2] Cardoso, F. et al. (2018). 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol (2018); 29: 1634–1657
[3] Balmaña, J. et al. (2011), On behalf of the ESMO Guidelines Working Group, BRCA in breast cancer: ESMO Clinical Practice Guidelines, Annals of Oncology, 2011; 22, vi31–vi34.
[4] Anders CK and Carey LA. ER/PR negative, HER2-negative (triple-negative) breast cancer. Last updated 24 Sep 2018. Accessed from UpToDate.
[5] Evans, D.G. et al. (2016). Low prevalence of HER2 positivity amongst BRCA1 and BRCA2 mutation carriers and in primary BRCA screens. Breast Cancer Res Treat. 2016; 155: 597-601.

Therapeutic Goods (ARTG) with a similar indication to the one proposed for talazoparib, but restricted to use after prior chemotherapy.

The pivotal study for this submission is the EMBRACA trial; a Phase III, open label, multi centre randomised controlled trial (RCT) of talazoparib versus single-agent chemotherapy (physicians' choice treatment (PCT) of capecitabine, eribulin, gemcitabine or vinorelbine) in patients with a deleterious or suspected deleterious germline BRCA mutation, who have HER2-negative locally advanced or metastatic breast cancer.

Regulatory status

Talzenna (talazoparib as tosilate) is a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in Europe, the United States of America (USA) and Canada, and was under consideration in Switzerland (see Table 1).

Table 1: International regulatory status of Talzenna as of September 2019

Region	Status	Indications
Europe	Approved 20 June 2019	*Talzenna is indicated as monotherapy for the treatment of adult patients with germline breast cancer susceptibility gene (gBRCA1/2 mutations, who have human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.*
USA	Approved 16 October 2018	*Talzenna is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for Talzenna.*
Canada	Approved 6 September 2019	*Talzenna (talazoparib) is indicated as a monotherapy for the treatment of adult patients with a deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) negative locally advanced (not amenable to curative radiation or surgery) or metastatic breast cancer, who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting, unless patients were inappropriate for these treatments.*

Region	Status	Indications
Switzerland	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-04458-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2018
First round evaluation completed	31 May 2019
Sponsor provides responses on questions raised in first round evaluation	30 July 2019
Second round evaluation completed	27 September 2019
Delegate's Overall benefit-risk assessment	25 October 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	15 November 2019
Completion of administrative activities and registration on ARTG	18 November 2019
Number of working days from submission dossier acceptance to registration decision*	199

*Statutory timeframe for standard applications is 255 working days

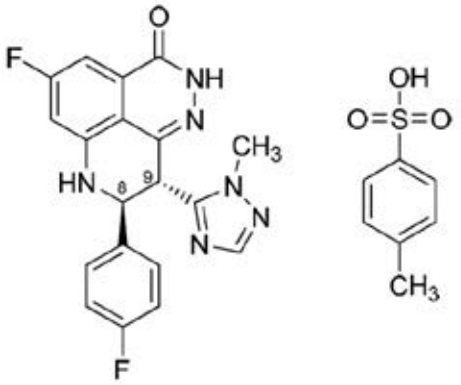
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

The structure of talazoparib tosilate is shown in Figure 1.

Figure 1: Structure of talazoparib tosilate



The proposed drug product is an opaque capsule as dosage form in two strengths of 0.25 mg of which the body is printed with 'TLZ 0.25' and the cap printed with 'Pfizer' in black and 1 mg of which the body is printed with 'TLZ 1' and the cap printed with 'Pfizer' in black ink.

The capsules will be packaged in Australia in bottles or blisters with aluminium peel off foil lidding. The proposed pack sizes are 30, 60 and 90 capsules for the 0.25 mg strength and 30 capsules for the 1 mg strength.

The quality evaluator recommended approval for registration of the proposed product from a pharmaceutical chemistry perspective.

Nonclinical

The non-clinical evaluator concluded:

- The pharmacology studies support the use of talazoparib to treat tumours with a mutated BRCA background.
- The combined animal safety studies revealed the following findings of potential clinical relevance:
  - myelosuppression and lymphoid depletion toxicity (including pancytopaenia);
  - diminished immune reactions and opportunistic infections as a result of haematolymphopoietic toxicity;
  - gastrointestinal (GI) toxicity, and to a lesser extent, liver toxicity;
  - the development of additional malignancies as a result of the genotoxic properties of the compound;
  - embryofetal toxicity and lethality;
  - effects in fertility, especially in males and possibly in females;
  - phototoxicity (positive phototoxicity assay, no phototoxicity in a rat study but at subclinical exposure).
- There are no objections on nonclinical grounds to the proposed registration of Talzenna for the treatment of advanced cancer provided that the potential toxicity noted above is outweighed by clinical benefits.

The non-clinical findings are mostly congruent with the clinical data, with the exception of hepatotoxicity and phototoxicity, which do not appear to have been borne out in the clinical setting.

Clinical

The clinical dossier contained eleven clinical studies, summarised in Table 3. All studies were reviewed by the US Food and Drug Administration (FDA) as part of their assessment of talazoparib as a new therapeutic entity, with the exception of p-glycoprotein (P-gp) Study C3441004. The publicly available multidisciplinary report for FDA's assessment of talazoparib was used as a reference for the TGA review.[6]

Table 3: Overview of the clinical studies submitted

Study ID	Design	Subjects (N =)	Status
673-103 (C3441023)	A Phase I, open label, crossover study of 18 healthy volunteers to evaluate the effect of food on bioavailability of talazoparib	18	Complete
MDV3800-03 (C3441003)	Phase I, ^{14}C- labelled excretion study in 6 patients with advanced solid tumours	6	Complete
MDV3800-01 (C3441001)	Phase I pharmacokinetic (PK) study (renal impairment) in patients with advanced solid tumours	24	Ongoing
MDV3800-02 (C3441002)	Phase I PK study (hepatic impairment) in patients with advanced solid tumours	24	Ongoing
MDV3800-04 (C3441004)	Phase I PK study in 36 patients with advanced solid tumours assessing the impact of a P-gp inhibitor (itraconazole) and a P-gp inducer (rifampin) on the single-dose PK of talazoparib	36	Complete
MDV3800-14 (C3441005)	Phase I study in 38 patients with advanced solid tumours to evaluate the effect of talazoparib on cardiac repolarisation, including assessing the QTc	38	Complete
673-301 'EMBRACA' (C3441009) (NCT01945775)	Pivotal Phase III, 2-arm, open-label study of talazoparib versus physicians choice chemotherapy in patients with germline BRCA positive breast cancer who have received prior chemotherapy for metastatic disease	431	Complete

[6] Food and Drug Administration Multi-Discipline Review/Summary, Clinical, Non-Clinical for talazoparib. Review completion date 10 October 2018.

Study ID	Design	Subjects (N =)	Status
673-201 'ABRAZO' (C3441008)	Phase II, 2-cohort study in patients with germline BRCA positive breast cancer to determine the objective response rate (ORR) for each cohort	84	Complete
PRP-001 (C3441007)	Phase I, first-in-humans, dose escalation (39 patients) and dose expansion (74 patients) study in patients with advanced solid tumours	74	Complete
MDV3800-13 (C3441010)	Phase II extended treatment safety study to obtain additional safety data about long term talazoparib	150	Ongoing
PRP-002 (C3441022)	Phase I two-arm tolerability study in patients with haematological malignancies	33	Complete

Pharmacology

Study PRP-001 (C3441007)

This was a first-in-human, single-arm, three-part, dose finding study of talazoparib in patients with locally advanced or metastatic solid tumours without acceptable standard treatment options.

In Part 1 (dose escalation), escalating doses of talazoparib from 0.025 to 1.1 mg daily were evaluated. At a daily dose of 1.1 mg, 2 of 6 patients experienced a dose-limiting toxicity (Grade 4 thrombocytopaenia and Grade 3 thrombocytopaenia that resulted in study drug discontinuation for 5 or more days in a cycle). The maximum tolerated dose was therefore considered to be 1 mg daily and this was selected as the recommended Phase II dose.

In Part 2 (dose expansion), enrolment continued of a larger cohort of patients with BRCA-associated solid tumours (including breast, ovarian, prostate and pancreatic), Ewing sarcoma or small cell lung cancer were treated with talazoparib at 1 mg daily. Treatment was continued until disease progression or unacceptable toxicity (or discontinuation criteria were met). Safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy (tumour responses by RECIST 1.1) were assessed.[7]

Part 3 was a long-term extension study, allowing patients from parts one and two to continue treatment if receiving clinical benefit.

Pharmacokinetics

- The PK of talazoparib is linear from 0.025 mg to 2 mg.
- Median time to maximum plasma concentration (C_{max}) following oral administration: 1 to 2 hours.
- Steady state plasma talazoparib is reached within 2 to 3 weeks.
- Geometric mean area under the concentration time curve (AUC) and C_{max} of talazoparib at steady-state was 208 ng.hr/mL and 16.4 ng/mL, respectively.
- Absolute bioavailability (estimated by mass balance) was at least 55%.

[7] RECIST = Response Evaluation Criteria in Solid Tumors (2016)

- Food effect: food intake decreased rate but not extent of absorption after oral administration of talazoparib to healthy volunteers.
- Clinical comparability of the clinical trial and marketed formulations was demonstrated based on PK, population pharmacokinetics (pop-PK) and clinical data from the ABRAZO and EMBRACA trials.
- Mean apparent volume of distribution: 420 L.
- Plasma protein binding: 74%, independent of plasma talazoparib concentration.
- Metabolism: includes mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib, glucuronide conjugation. Less than 10% was hepatic.
- Mean terminal plasma half-life (± standard deviation (SD)): 90 (± 58) hours.
- Excretion: 19.7% faecal (13.6% unchanged talazoparib), 68.7% urine (54.6% unchanged talazoparib)

Primary pharmacology

In vitro results demonstrated talazoparib inhibits PARP1, PARP2 and PARP 5b with half maximal inhibitory concentration (IC_{50}) values under 5 nM (0.7 nM, 0.3 nM, and 4.7 nM, respectively), and PARP3 and PARP 5a with IC_{50} values of < 25 nM. This level of PARP1 and PARP2 inhibition is similar to that seen for other PARP inhibitors registered in Australia (olaparib and niraparib).

Pharmacodynamics

Pharmacodynamic findings in Study PRP-001 are summarised in the clinical study report (CSR) for that study as follows:

> 'The pharmacodynamic analysis demonstrated consistent on-target effect of talazoparib from 0.20 mg through 1.1 mg. Successful assays were performed on samples from 36 of 39 patients (23 ovarian, 8 breast, 3 pancreatic, 2 colorectal, 2 Ewing, 1 prostate) treated with 0.025 to 1.1 mg talazoparib in part 1. PARP activity was consistently shown to be greater than 2 fold lower than baseline both after the first dose and after daily dosing in patients treated with ³ 0.20 mg/day.'

Population pharmacokinetics

The conclusions of the sponsor's pop-PK analysis included:

- Regarding renal impairment:
  - Mild renal impairment decreased apparent clearance by 14.4%.
  - Moderate renal impairment decreased apparent clearance by 37.1%, and dose reduction is recommended in these patients.
  - Insufficient data were available in patients with severe renal impairment and end-stage renal disease (ESRD).
- Regarding hepatic impairment:
  - Mild hepatic impairment did not affect talazoparib PK.
  - Moderate and severe hepatic impairment were not represented in the analysis
- Dosing with food decreased rate but not extent of talazoparib absorption
- Co-administration of strong P-gp inhibitors increased talazoparib exposure by an average of 45%, and dose reduction is recommended in patients requiring co-administration of P-gp inhibitors.

The FDA pop-PK reviewer agreed that 'moderate renal impairment and concomitant use with a strong P-gp inhibitor are the only significant covariate that have clinically relevant impact on talazoparib exposure, based on pop-PK analysis.'

Potential for interactions

Based on the minimal reliance on metabolic pathways, inhibition or induction of metabolism is considered unlikely to affect talazoparib exposure.

- Talazoparib is not an inhibitor of:
  - Cytochrome P450 (CYP) enzymes; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.
  - Uridine diphosphate-glucuronyltransferase (UGT) enzymes; UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15.
  - P-gp, breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, organic anion transporter (OAT)1, OAT3, bile salt export pump (BSEP), multidrug and toxin extrusion (MATE)1, or MATE2-K.
- Talazoparib is not an inducer of:
  - CYP1A2, CYP2B6, or CYP3A4.

Efficacy

EMBRACA trial (Study 673-301/C3441009)

A Phase III, randomised, open-label, 2-arm, multicentre study of talazoparib versus chemotherapy (physicians' choice capecitabine, eribulin, gemcitabine or vinorelbine) in patients with germline BRCA mutation positive, HER2 negative locally advanced or metastatic breast cancer.

Study size, inclusion/exclusion criteria, dates and locations

Population size: 431 subjects

Inclusion criteria (abridged):

- Consenting, willing and able adults with incurable locally advanced or metastatic HER2-negative breast cancer.
- Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation according to a Myriad Genetics test or by special agreement.
- Maximum 3 prior cytotoxic chemotherapy-containing regimens.
- Must have had a prior taxane or anthracycline in the neoadjuvant, adjuvant, locally advanced or metastatic setting unless medically contraindicated.
- Evaluable disease (RECIST 1.1).
- Adequate bone marrow and organ function.

Exclusion criteria (abridged):

- Prior treatment with a PARP inhibitor other than iniparib.
- Active inflammatory breast cancer.
- Patient wouldn't be a candidate for any of the comparator regimens.
- Progression on prior platinum in the metastatic setting, unless low dose in combination with radiation therapy.

- Prior platinum in the neoadjuvant or adjuvant setting, unless relapse occurred later than 6 months after last dose of platinum.
- Recent (14 days) anticancer therapy (radiation, endocrine, targeted or cytotoxic), investigational therapy, major surgery.
- Unresolved, important toxicity of prior treatments including radiotherapy.
- Prior malignancy with reasonable possibility of recurrence (specific criteria for same).
- Central nervous system (CNS) disease except stable metastases not requiring significant corticosteroid management.
- Known human immunodeficiency virus (HIV), active Hepatitis B or Hepatitis C.
- Significant cardiac disease (specific criteria for same).
- Concurrent conditions that may interfere (active infection, coagulopathies, non-healing wound or ulcer).
- Pregnancy, lactating, or lack of sufficient contraception.

Locations: 145 sites, across 16 countries (USA, Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK, Russia, Ukraine, Israel, Australia, Brazil, South Korea, and Taiwan).

Dates: recruitment commenced October 2013. Data cut-off (DCO) for primary analysis 15 September 2017. Survival follow-up ongoing.

In vitro diagnostic testing for BRCA:

- 408 out of 431 (94.7%) were prospectively and centrally tested using a clinical trial assay for BRCA:
  - 354 (82%) were tested or retested with the Quality System Regulations (QSR) version, that is, BRACAnalysis, which was registered as the companion diagnostic in the USA.
  - 54 patients were centrally tested only with the Clinical Laboratory Improvement Amendments (CLIA) version of the clinical trial assay.
- 23 out of 431 (5.3%) were intended for the same central analysis but this was not possible due to process problems (sample storage);
  - 16 had retrospective BRACAnalysis results available.
  - 7 (1.6% of the total enrolled population) had a positive BRCA result per non-BRACAnalysis local testing:
    - 5 hospital lab-developed tests.
    - 1 Foundation Medicine.
    - 1 Ambry Genetics.

Of the 431 patients randomised in the EMBRACA trial, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious germline BRCA mutation using a clinical trial assay; out of which 354 (82%) were confirmed using the BRACAnalysis CDx.

Study treatments

Intervention (n = 287):

- Talazoparib 1 mg by mouth (PO) daily.
- Dose reductions permitted: by 0.25 mg daily per reduction level.

Comparator (n = 144)

PCT;[8] consisting of one of:

- Capecitabine 1250 mg/m^2 PO twice daily (BID) for 14 days, repeated every 21 days.
- Eribulin mesylate 1.4 mg/m^2 intravenously (IV) on Day 1 and Day 8, repeated every 21 days.
- Gemcitabine 1250 mg/m^2 IV on Day 1 and Day 8, repeated every 21 days.
- Vinorelbine 30 mg/m^2 IV on Day 1, 8 and 15, repeated every 21 days.

Dose modifications permitted per product information.

Crossover was not permitted.

Concomitant therapies permitted in both arms:

- Supportive medications (prophylactically or therapeutically) were allowed at the investigator's discretion, with the exception of granulocyte-colony stimulating factor (G-CSF; rescue only).
- Bisphosphonates or denosumab for treatment or prophylaxis of bone metastases was permitted, per local standards of care.
- Investigators were instructed to avoid use of strong (and use caution for other) P-gp inhibitors, P-gp inducers, or BCRP inhibitors.
- External beam radiotherapy was allowed, following consultation with the medical monitor.
- Surgery for metastatic lesions was permitted, with study drug continuation if clinical benefit was maintained. But if the target lesions were removed, subject was excluded from the measurable disease population.

Study outcomes

Endpoints: tumour response assessments were made according to modified RECIST 1.1;[9]

- Primary:
  - Progression-free survival (PFS) per blinded central review by independent radiology facility (IRF).
- Secondary:
  - OS.
  - ORR per investigator.
- Exploratory:
  - Patient-reported outcomes (PRO). European Organisation for Research and Treatment of Cancer (EORTC) questionnaires; EORTC QLQ-C30 and EORTC QLQ-BR23.
  - Duration of response (DOR).

Analysis populations

- Intent-to-treat (ITT) – all randomised patients.

[8] PCT options were agreed with FDA input in 2013.
[9] Modifications to the criteria were, in brief: requirement for progression to be confirmed by imaging (digital photography or physical examination disallowed for superficial lesions) and requirements for more careful confirmation of bone scan-based progression (with confirmatory computed tomography (CT)/ magnetic resonance imaging (MRI) if possible), and bone metastasis-based progression (due to possible flare phenomenon).

- Safety population – all randomised patients who received any study drug (and per actual treatment received; not ITT).
- PRO evaluable population – questionnaire completed at baseline and at least one post baseline.

Statistical plan

- The minimal clinically important difference for hazard ratio (PFS) was 0.67.
- Sample size: up to 429 patients, calculated for 90% power with 2-sided alpha of 5% to detect a PFS hazard ratio of 0.67 and 80% power with 2-sided alpha of 5% to detect a hazard ratio of 0.72. Primary analysis planned at approximately 288 PFS events, with descriptive interim analysis for OS. Final OS analysis at approximately 321 deaths.
- OS was the only endpoint other than PFS for which multiplicity adjustment was planned.

Randomisation: 2:1.

Stratification by:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 versus 1, 2, or 3).
- TNBC based on most recent biopsy (yes versus no).
- History of CNS metastases (yes versus no).

Same stratification applied to log-rank test of PFS and Cox proportional hazards model used to derive hazard ratios.

Commentary on trial design from the FDA reviewer included:

> 'The selected doses appear appropriate. The talazoparib dosage is the dose selected from the Phase I study. The doses for capecitabine and eribulin are the FDA-approved doses for advanced/metastatic breast cancer. Gemcitabine is FDA approved at the selected dose in combination with paclitaxel for metastatic breast cancer (MBC); however, single agent gemcitabine at the selected dose is listed as a treatment option in the NCCN Breast Cancer guidelines. Vinorelbine is not FDA-approved for use in breast cancer; however, single agent vinorelbine at the dose selected is often used in clinical practice and is listed as a treatment option in the NCCN Breast Cancer guidelines. During an End of Phase 2 (EOP2) Meeting (April 12, 2013), the choice of control arm agents for this Phase III study was discussed and agreed by the agency.
>
> […]
>
> Prior therapy with hormonal therapy was not required for patients with HR-positive disease.'

Protocol amendments

A major protocol amendment (Amendment 1) was finalised in December 2015, after 184 patients had been randomised (43% of the planned total of 429). The amendment included the following changes:

- Change of sponsor.
- Allowed 3 prior cytotoxic regimens (previously 2).
- Allowed enrolment despite prior neoadjuvant or adjuvant platinum, as long as progression had not occurred within 6 months of last dose of platinum (previously 12 months).

- Allowed patients with no prior anthracycline/taxane, as long as use was medically contraindicated.
- Allowed *de novo* metastatic disease if the treatment plan involves a protocol-specified PCT.
- Allowed an Eastern Cooperative Oncology Group (ECOG) performance status score of 2.

Enrolled population

The distribution of baseline demographics (Table 4) and baseline disease characteristics (Table 5) was broadly consistent with successful randomisation. Imbalances in age, geographic region and PR status are noted between arms, but based on magnitude and clinical judgement these are unlikely to have significantly affected results.

PCT was most commonly capecitabine (55 patients (44%)), followed by eribulin (50 patients (40%)), gemcitabine (12 patients (10%)), and vinorelbine (9 patients (7%)).

Regarding potential for enrolment site-based bias, the FDA reviewer's comments were:

> 'Sites that had significant disclosable interests enrolled approximately 10.7% (N = 46) of the total number of patients in the EMBARCA study. Each individual site enrolled between 0.2 to 1.9% of the population which is small and unlikely to affect the results of the study.'

Previous anti-neoplastic therapy for metastatic disease included a cyclin-dependent protein kinase (CDK) 4/6 inhibitor for 4.5% of the talazoparib and 3.5% of the PCT arm. A small number of men were enrolled in the study.

As a result of Protocol Amendment 1**,** a small number of patients were included in the study who had not been previously treated with a taxane or anthracycline (7 patients [2%] in the talazoparib arm and 5 patients (3%) in the PCT arm). Based on the exclusion criteria, such therapy must have been medically contraindicated in these patients. There were also a small number of patients who had not received previous endocrine therapy despite having HR-positive disease (15 patients (5%) in the talazoparib arm and 14 patients (10%) in the PCT arm). Data on the clinical rationale for an individual patient being considered appropriate for PCT treatment was not collected.

Table 4: Baseline demographics of the EMBRACA trial study population

	Talazoparib N = 287	**PCT N = 144**
Sex		
Female	283 (99%)	141 (98%)
Male	4 (1%)	3 (2%)
Age		
Mean (SD)	47.5 (11.6)	49.4 (12.1)
Median (Min - Max)	45 (27 - 84)	50 (24 - 88)
< 50 years	182 (63%)	67 (47%)
50 to < 65 years	78 (27%)	67 (47%)

	Talazoparib N = 287	PCT N = 144
> = 65 years	27 (9%)	10 (7%)
Race		
White	192 (67%)	108 (75%)
Black or African American	12 (4%)	1 (1%)
Asian	31 (11%)	16 (11%)
Other	5 (2%)	1 (1%)
Not reported	47 (16%)	18 (13%)
Ethnic group		
Hispanic or Latino	31 (11%)	15 (10%)
Not Hispanic or Latino	210 (73%)	111 (77%)
Not reported	46 (16%)	18 (13%)
ECOG		
0	153 (53%)	84 (58%)
1	127 (44%)	57 (40%)
2	6 (2%)	2 (1%)
Unknown	1 (< 1%)	1 (1%)
Geographic region		
Europe	134 (47%)	56 (39%)
North America	99 (35%)	57 (40%)
Rest of the world	54 (19%)	31 (22%)

Table 5: Baseline disease characteristics of the EMBRACA trial study population

	Talazoparib N = 287 (%)	PCT N = 144 (%)
BRCA status		
BRCA1 positive	133 (47)	63 (44)
BRCA2 positive	154 (54)	81 (56)

	Talazoparib N = 287 (%)	PCT N = 144 (%)
HER2 status		
Negative	287 (100)	144 (100)
ER status		
Positive	151 (53)	80 (56)
Negative	136 (47)	64 (44)
PR status		
Positive	104 (36)	66 (46)
Negative	181 (63)	77 (53)
Unknown	2 (< 1)	1 (< 1)
ER and PR status		
ER+ and PR+	98 (34)	62 (43)
ER- and PR+	6 (2)	4 (3)
ER+ and PR-	51 (18)	17 (12)
ER- and PR-	130 (45)	60 (42)
ER unknown or PR unknown	2 (< 1)	1 (< 1)
Primary tumour location at Baseline		
Bone only metastatic disease	25 (9)	16 (11)
Other	262 (91)	128 (89)
History of CNS metastasis[10]		
Yes	43 (15)	20 (14)
No	244 (85)	124 (86)
Prior hormonal therapy		
Yes	161 (56)	77 (53)
No	126 (44)	67 (47)

[10] Per electronic case reporting form (eCRF)

	Talazoparib N = 287 (%)	PCT N = 144 (%)
Prior neo/adjuvant therapy		
Yes	238 (83)	121 (84)
No	49 (17)	23 (16)
Prior anthracycline treatment		
Yes	243 (85)	115 (80)
No	44 (15)	29 (20)
Prior taxane treatment		
Yes	262 (91)	130 (90)
No	25 (9)	14 (10)
Prior taxane or anthracycline treatment		
Yes	280 (98)	139 (97)
No	7 (2)	5 (3)
Prior platinum for advanced disease		
Yes	24 (8)	16 (11)
No	263 (92)	128 (89)
Received prior platinum as neo/adjuvant treatment		
Yes	24 (8)	15 (10)
No	263 (92)	129 (90)
Prior cytotoxic chemo for advanced disease (eCRF)		
Yes	176 (61)	90 (63)
No	111 (39)	54 (38)
Prior radiotherapy		
Yes	223 (78)	107 (74)
No	64 (22)	37 (26)

Results

Results for the primary and secondary efficacy outcomes are summarised in Table 6. No multiplicity adjustments were planned for secondary endpoints other than OS, so the ORR analysis is considered exploratory. Independent review was only undertaken for progression events, so IRF-adjudicated ORR is not available.

Table 6: Efficacy results (primary and secondary) in the EMBRACA trial

	Talazoparib (n = 287)	PCT (n = 144)
PFS per IRF		
Events	186 (65%)	83 (58%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
p-value (stratified log-rank test)	<0.0001	
HR (95% CI) stratified, Cox-PH model	0.54 (0.41, 0.71)	
***OS** (interim analysis [DCO 15 Sep 2017])*		
Events	108 (37.6%)	55 (38.2%)
Median (95% CI), months	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
p-value (stratified log-rank test)	0.1053	
HR (95% CI) stratified, Cox-PH model	0.76 (0.55, 1.06)	
ORR per investigator		
Patients with measurable disease	n=219	n=114
Complete response, n(%) Partial response, n(%) Stable disease, n(%) Progressed, n(%) Non-evaluable, n(%)	12 (5.48) 98 (44.75) 69 (31.51) 36 (16.44) 4 (1.83)	0 (0) 21 (18.42) 45 (39.47) 29 (25.44) 19 (16.67)
Events, n (ORR)	110 (50.23)	21 (18.42)
95% CI (%)	(43.41, 57.04)	(11.78, 26.77)

DCO = data cut-off

Predefined sensitivity analyses for the primary efficacy outcome indicated IRF-assessed PFS was consistent with PFS by investigator assessment, and with PFS across patient subgroups defined by study stratification factors (line of therapy, TNBC status, and history of CNS metastases).

Higher rates of censoring in the primary efficacy analysis were observed in the PCT arm than the talazoparib arm, both at randomisation and at last assessment prior to beginning new antineoplastic therapy. Based on the open-label trial design, this may be attributable to patients being more likely to withdraw from the trial if randomised to PCT (rather than talazoparib), and investigators being more likely to define clinical progression and recommend trial discontinuation prior to radiographic progression for patients on PCT (compared to talazoparib), respectively. FDA-conducted sensitivity analyses to evaluate the impact of these possible biases did not indicate a significant effect on results.

The difference in OS between arms was not statistically significant at the interim analysis (carried out when 163 events had occurred, that is, 37.8% of patients). Final OS analysis is planned at 321 events. Subsequent therapies may confound the final OS analysis: the most common subsequent therapy at the DCO date for this analysis in both arms was carboplatin (25 to 30% of both arms), but 18% of the PCT arm and 1% of the talazoparib arm subsequently received a PARP inhibitor (mostly olaparib).

DOR (95% confidence interval (CI)) was an exploratory outcome, and was 6.4 (5.4, 9.5) months in the talazoparib arm versus 3.9 (3.0, 7.6) months in the PCT arm. The results of exploratory analyses of PRO data were also provided, however in an open-label setting against a heterogeneous control arm, interpretation of such analyses is limited. The PRO

analyses did not contribute significantly to the benefit-risk assessment for the purposes of this submission so are not discussed further in this overview.

ABRAZO trial (Study 673-201/C3441008)

This Phase II, open-label study enrolled 84 patients with unresectable breast cancer with a germline BRCA mutation whose metastatic disease had previously responded to their most recently received platinum-containing regimen without disease progression for > 8 weeks following the last dose (Cohort 1) or who had at least 3 prior non-platinum cytotoxic regimens for metastatic disease (Cohort 2). Patients were treated with talazoparib at the proposed dosage (1 mg daily, orally) with dose reductions allowed for toxicity. The primary outcome was ORR but the study was ceased early to prioritise enrolment in the EMBRACA trial, when a protocol amendment to the EMBRACA trial created significant overlap between its enrolment criteria and those of the ABRAZO trial.

As stated in the CSR:

> 'Both cohorts met the criteria for continuation to the second stage (≥ 5 objective responses in the first 35 patients in each cohort); however, enrollment was stopped by the sponsor before 70 additional patients were enrolled in the study (35 additional patients were planned for each cohort). The study did not meet the primary endpoint of talazoparib effectiveness based on ≥ 16 objective responses out of 70 patients by central radiology assessment in either cohort. Although enrollment was not completed, an analysis of the efficacy data was conducted to determine the effectiveness of talazoparib in those patients who were enrolled.
>
> The ORR by IRF assessment was 20.8% (95% CI: 10.47, 34.99) in Cohort 1 and 37.1% (95% CI: 21.47, 55.08) in Cohort 2.'

Study PRP-001/C3441007

For 14 evaluable patients with advanced breast cancer and a BRCA mutation receiving talazoparib 1.0 mg/day in this Phase I study, the ORR was 50% (1 complete response (CR) and 6 partial responses (PR)). Responses were seen in two of 5 patients with a deleterious germline BRCA1 mutation and 5 of 9 patients with a deleterious germline BRCA2 mutation.

Efficacy-related conclusions

The findings of the EMBRACA study indicate that, compared to standard-of-care chemotherapy, talazoparib has efficacy in patients who have advanced HER-2 negative breast cancer and a positive result for deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation using a Myriad Genetics diagnostic test.

Responses in earlier phase trials provide supportive evidence that talazoparib is active in patients with advanced breast cancer and deleterious germline BRCA mutations.

Safety

Safety overview

Sponsor-initiated studies of talazoparib are summarised in Table 7. The clinical evaluation primarily focuses on safety from the pivotal EMBRACA trial, in 286 patients with advanced breast cancer. Safety data from three earlier phase studies in which patients with solid tumours were treated at the proposed dosage of 1 mg daily is considered supportive, and was consistent with the safety profile seen with talazoparib in the EMBRACA trial.

Table 7: Talazoparib exposure in sponsor-initiated studies

Study	Description	Number exposed to 1 mg/day	Number of patients or subjects treated overall	Mean (SD) duration of exposure	Study status
Studies in patients with solid tumours					
EMBRACA trial (Study 673-301)	Phase III, germline BRCA (gBRCA) mutated locally advanced or metastatic breast cancer	286	412 (126 treated with PCT)	Talazoparib arm: 8.4 (7.01) months PCT arm: 4.5 (3.54) months	Ongoing
ABRAZO trial / Study 673-201	Phase II, gBRCA mutated locally advanced or metastatic breast cancer	83	83	5.7 (3.4) months	Ongoing
Study PRP-001 *(C3441007)*	Phase I, first in human dose escalation study in advanced solid tumours	77	110 (33 at other doses)	187.9 (210.68) days	Completed
MDV3800-14 (C3441005)	Phase I, cardiac repolarisation study in patients with advanced solid tumours	37	37	19.7 (5.26) days	Completed
MDV3800-13 (C3441010)	Single arm, open label extension study	46*	80 (37 at other doses)	NA	Ongoing
MDV3800-01 *(C3441001)*	Phase I, PK study in patients with advanced solid tumours with renal impairment	0	NA		Ongoing
MDV3800-02 (C3441002)	Phase I, PK study in patients with advanced solid tumours with hepatic impairment	0	NA		Ongoing
MDV3800-03 (C3441003)	Phase I, ^{14}C-labeled talazoparib in patients with advanced solid tumours	6	6		Completed
MDV3800-04 *(C3441004)*	Phase I, PK study with rifampin and itraconazole in	0	NA		Ongoing

Study	Description	Number exposed to 1 mg/day	Number of patients or subjects treated overall	Mean (SD) duration of exposure	Study status
	advanced solid tumours				
Studies in patients with haematological malignancies or healthy volunteers					
Study 673-103 (C3441023)	Food effect study in healthy male volunteers	0	18		Completed
Study PRP-002 *(C3441022)*	Phase I, patients with advanced haematological malignancies	0	33		Completed

PCT = physician's choice therapy; NA = not available for these ongoing studies. *Six (6) patients who started Study PRP-001 and 29 patients who started Study MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (Study MDV3800-13) were counted only once.

EMBRACA trial safety findings

Overview

The safety population included all randomised patients who received at least one dose of treatment. One patient randomised to talazoparib and 18 patients randomised to PCT did not receive any treatment. DCO dates for the safety data summarised in this section refer to an original safety dataset submitted to FDA (15 September 2017) and a safety update (31 January 2018). Adverse event (AE) data were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0, and severity grading of AEs and laboratory parameters used the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Dose modification (reduction or interruption) occurred at a similar rate between study arms, and was associated with an AE in 66.4% of patients in the talazoparib arm. AEs of anaemia, neutropaenia, and thrombocytopaenia were associated with dose modification at a ≥ 5% higher incidence in talazoparib-treated patients, while decreased neutrophil count, nausea, diarrhoea, and palmar-plantar erythrodysaesthesia syndrome were reported at least 5% more commonly in patients in the PCT arm.

Table 8: Exposure and overview of safety in EMBRACA

	Talazoparib N = 286	PCT N = 126
Mean (SD) duration of treatment (months)	8.4 (7.01)	4.5 (3.54)
Mean (SD) relative dose intensity (%)	91.7 (173.73)	
capecitabine (n = 55)		83.3 (17.96)
eribulin (n = 50)		90.5 (12.73)

	Talazoparib N = 286	PCT N = 126
gemcitabine (n = 12)		86.3 (11.70)
vinorelbine (n = 9)		68.5 (20.77)
Grade 1 to 4 TEAEs, n (%)	282 (99)	123 (98)
Grade 3 to 4 TEAEs, n (%)	193 (68)	80 (64)
Serious TEAEs (SAEs), n (%)	91 (32)	37 (29)
Deaths due to TEAEs within 30 days, n (%)	6 (2)	4 (3)
Treatment discontinuation due to TEAEs, n (%)	13 (5)	7 (6)
Dose reduction due to TEAEs, n (%)	51 (18)	29 (23)
Dose modification* (reduction and/or interruption) due to TEAEs	190 (66)	75 (60)

Source: FDA safety analysis based on EMBRACA adae.xpt and adsl.xpt datasets, and CSR for EMBRACA submitted to TGA, dated 15 March 2018. * Dose modifications are defined as a dose reduction or dosing interruption. Dose reductions are defined as any reduction of planned dosage. Dosing interruptions for talazoparib are defined as doses skipped due to AE but resumed per investigator judgement. SAE = serious adverse event. TEAE = treatment emergent adverse event.

Deaths

Deaths in the EMBRACA trial are shown in Table 9.

Table 9: Deaths in the EMBRACA trial (data cut-off 31 January 2018)

	Talazoparib (n = 286) n (%)	PCT (n = 126) n (%)
Total deaths, n (%)	143 (50)	61 (48)
Deaths < 30 days after last treatment dose, n (%)	10 (4)	5 (4)
Disease progression, n (%)	7 (2)	4 (3)
Cerebral haemorrhage , n (%)	1 (< 1)	0
Veno-occlusive liver disease (VOD), n (%)	1 (< 1)*	0
Worsening neurological symptoms, n (%)	1 (< 1)	0
Sepsis, n (%)	0	1 (1)**
Deaths (> 30 days after last treatment dose)	133 (47)	56 (44)

Source: FDA safety analysis based on EMBRACA adae.xpt and adsl.xpt datasets. *This case was considered more likely to be due to disease progression than VOD by the clinical reviewer. **Considered likely treatment-related by the clinical reviewer

Serious adverse events

Rates of SAEs were similar between arms (Table 10), and the types of SAEs in the talazoparib arm were consistent with events that might be expected given the known safety profile of other PARP inhibitors and the studied indication.

Table 10: Serious adverse events that occurred in at least 2 patients in either arm in the EMBRACA trial (data cut-off 15 September 2017)

	Talazoparib (n = 286) n (%)	PCT (n = 126) n (%)
Total patients with at least one SAE	91 (32)	37 (29)
Anaemia	17 (6)	0
Pyrexia	7 (2)	2 (2)
Vomiting	5 (2)	2 (2)
Back pain	5 (2)	1 (1)
Pleural effusion	4 (1)	7 (6)
Dyspnoea	4 (1)	0
Headache	4 (1)	0
Platelet count decreased	4 (1)	0
Neutropaenia	3 (1)	4 (3)
Abdominal pain	3 (1)	2 (2)
Pneumonia	3 (1)	2 (2)
Metastases to central nervous system	3 (1)	0
Pulmonary embolism	3 (1)	0
General physical health deterioration	2 (1)	2 (2)
Nausea	2 (1)	1 (1)
Bone pain	2 (1)	0
Cytomegalovirus infection	2 (1)	0
Diplopia	2 (1)	0
Non-cardiac chest pain	2 (1)	0
Pain in extremity	2 (1)	0

	Talazoparib (n = 286) n (%)	PCT (n = 126) n (%)
Pericardial effusion	2 (1)	0
Respiratory tract infection	2 (1)	0
Seizure	2 (1)	0
Thrombocytopaenia	2 (1)	0
Deep vein thrombosis	1 (< 1)	2 (2)
Neutrophil count decreased	1 (< 1)	2 (2)
Diarrhoea	0	3 (2)
Abdominal pain upper	0	2 (2)
Dehydration	0	2 (2)

Common adverse events and laboratory abnormalities

Adverse events that were reported more frequently (> 5% difference) in the talazoparib arm were anaemia, thrombocytopenia, fatigue, dizziness, headache, arthralgia, asthenia and back pain. Pyrexia, palmar-plantar erythrodysaesthesia syndrome, paraesthesia, increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT) were reported more with PCT. Laboratory abnormalities that were reported more frequently (> 5% difference) in the talazoparib arm were decrease in haemoglobin, decrease in platelets, decrease in lymphocytes, decrease in leukocytes, and decrease in calcium. A laboratory abnormality reported more frequently (> 5% difference) in the PCT arm was increased AST.

Review did not identify significant differences in adverse event profiles between groups based on age, but noted that data was limited (n = 29) for patients over 64 years of age.

Table 11: Treatment-emergent adverse events that occurred in at least 10% in either arm of the EMBRACA trial

Preferred Terms (PTs)	Talazoparib (n=286) n (%)			PCT (n=126) n (%)		
	Grade 1-4	Grade 3	Grade 4	Grade 1-4	Grade 3	Grade 4
Blood and lymphatic system disorders						
Anaemia	150 (52)	109 (38)	2 (1)	23 (18)	5 (4)	1 (1)
Leukopenia	23 (8)	8 (3)	1 (<1)	12 (10)	5 (4)	2 (2)
Neutropenia	76 (27)	43 (15)	8 (3)	37 (29)	17 (14)	14 (11)
Thrombocytopenia	46 (16)	18 (6)	5 (2)	7 (6)	2 (2)	0
Gastrointestinal disorders						
Abdominal pain	32 (11)	2 (1)	0	20 (16)	2 (2)	0
Constipation	63 (22)	1 (<1)	0	27 (21)	0	0
Diarrhoea	63 (22)	2 (1)	0	33 (26)	7 (6)	0
Dyspepsia	28 (10)	0	0	9 (7)	0	0
Nausea	139 (49)	1 (<1)	0	59 (47)	2 (2)	0
Vomiting	71 (25)	7 (2)	0	29 (23)	2 (2)	0
General disorders and administration site conditions						
Asthenia	42 (15)	5 (2)	0	12 (10)	2 (2)	0
Fatigue	144 (50)	5 (2)	0	54 (43)	4 (3)	0
Pyrexia	30 (11)	1 (<1)	0	21 (17)	0	0
Infections and infestations						
Upper respiratory tract infection	37 (13)	0	0	13 (10)	0	0
Urinary tract infection	28 (10)	1	0	3 (2)	0	0
Viral upper respiratory tract infection	30 (11)	2 (1)	0	8 (6)	0	0
Investigations						
Neutrophil count decreased	28 (10)	11 (4)	1 (<1)	18 (14)	8 (6)	5 (4)
Platelet count decreased	35 (12)	14 (5)	5 (2)	3 (2)	0	0
Weight decreased	22 (8)	0	0	15 (12)	1 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	61 (21)	1 (<1)	0	28 (22)	1 (1)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	49 (17)	1 (<1)	0	15 (12)	0	0
Back pain	60 (21)	7 (2)	0	20 (16)	2 (2)	0
Myalgia	21 (7)	0	0	13 (10)	0	0
Pain in extremity	40 (14)	2 (1)	0	14 (11)	0	0
Nervous system disorders						
Dizziness	48 (17)	1 (<1)	0	13 (10)	2 (2)	0
Dysgeusia	29 (10)	0	0	11 (9)	0	0
Headache	93 (33)	5 (2)	0	28 (22)	1 (1)	0
Paraesthesia	12 (4)	1 (<1)	0 (0)	15 (12)	0 (0)	0 (0)
Psychiatric disorders						
Insomnia	35 (12)	0	0	10 (8)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	56 (20)	2 (1)	0	20 (16)	0	0
Dyspnoea	50 (18)	7 (2)	0	19 (15)	3 (2)	0
Skin and subcutaneous tissue disorders						
Alopecia	72 (25)	0	0	35 (28)	0	0
Palmar-plantar erythrodysaesthesia syndrome	4 (1)	1 (<1)	0 (0)	28 (22)	3 (2)	0 (0)

Source: FDA safety analysis based on EMBRACA adae.xpt dataset

Table 12: Laboratory abnormalities that occurred in at least 25% of evaluable patients for each parameter in either arm of the EMBRACA trial

	Talazoparib (% of evaluable patients)			PCT (% of evaluable patients)		
Parameter	Grades 1-4	Grade 3	Grade 4	Grades 1-4	Grade 3	Grade 4
Decrease in haemoglobin	90	39	0	77	6	0
Decrease in platelets	55	11	4	29	2	0
Decrease in neutrophils	68	17	3	70	21	17
Decrease in lymphocytes	76	17	0.7	53	8	0.8
Decrease in leukocytes	84	14	0.3	73	22	2
Increase in glucose (non-fasting)	54	2	0	51	2	0
Increase in aspartate aminotransferase	37	2	0	48	3	0
Increase in alkaline phosphatase	36	2	0	34	2	0
Increase in alanine aminotransferase	33	1	0	37	2	0
Decrease in calcium	28	1	0	16	0	0

Source: FDA safety analysis based on EMBRACA adlb.xpt dataset

Adverse events of special interest

The sponsor identified hepatic disorders and myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) as adverse events of special interest (AESI). The FDA review identified new secondary malignancies and pneumonitis as other AESI based on the known safety profile of other PARP inhibitors.

Hepatotoxicity

Across all patients treated with 1 mg daily talazoparib, no cases consistent with Hy's Law;[11] have been reported.

Rates of hepatotoxicity-related AEs were higher in the PCT arm than the talazoparib arm of the EMBRACA trial (19.8% versus 9.1%, respectively). Hepatotoxicity-related AEs occurred in 12.7% of patients taking capecitabine, 20.0% of patients taking eribulin, 41.7% of patients taking gemcitabine, and 33.3% of patients taking vinorelbine.

Myelodysplastic syndrome/acute myeloid leukaemia

Across all patients treated with 1 mg daily talazoparib, two cases of pancytopenia occurred. Neither case of pancytopenia was considered consistent with MDS.

Across the talazoparib development program, at the time of the FDA approval, two cases of AML had been reported in patients exposed to talazoparib, both confounded by prior chemotherapy known to be associated with second primary malignancies including AML.

One case of AML occurred in a patient with salivary gland cancer in Study C3441010. The total duration of talazoparib treatment was 4 months, initially at 0.5 mg daily then escalated to 0.75 mg daily. A diagnosis of AML originating from MDS was established based on bone marrow biopsy. The patient had previously been treated with chemotherapy including cyclophosphamide.

The other case of AML was reported in a patient treated with talazoparib in the EMBRACA trial, approximately 24 months after starting study drug. The patient had previously been treated with neoadjuvant doxorubicin/docetaxel/cyclophosphamide, bilateral mastectomy, paclitaxel albumin/carboplatin, and surgery and radiotherapy for lung and brain metastases. There was one event of acute promyelocytic leukaemia in the PCT arm of the EMBRACA trial.

[11] Hy's Law: Evidence of hepatocellular injury with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN and no other diagnostic reason to explain rise in aminotransferases/bilirubin.

Other new primary malignancies

Across all patients treated with talazoparib at the proposed dose of 1 mg daily there have been seven reports of a second primary malignancy for 6 patients:

- squamous cell carcinoma of skin and basal cell carcinoma;
- squamous cell carcinoma of skin;
- glioblastoma multiforme;
- intraductal proliferative breast lesion;
- neoplasm skin;
- ovarian neoplasm.

Three of these patients were in the talazoparib arm of the EMBRACA trial. By comparison, one patient in the PCT arm of the EMBRACA trial had second primary malignancy reported ('malignant melanoma' and 'second primary malignancy' both reported as SAEs).

Pneumonitis

Across the clinical development program for talazoparib, one case of pneumonitis has been reported. This case occurred in a patient treated with talazoparib at the proposed dose (1 mg daily PO) in the ABRAZO trial, was of Grade 1 severity and was associated with a Grade 3 event of pneumonia for which talazoparib treatment was interrupted. Talazoparib was recommenced after resolution of pneumonia, and continued for a further 9 months without recurrence of pneumonitis.

Study C3441005/MDV3800-14

In this dedicated Phase I cardiac repolarisation study conducted in the USA, 37 patients with solid tumours were exposed for a median of 22 days to talazoparib at the proposed dose of 1 mg daily PO. There were no patients with absolute post baseline mean QT interval;[12] corrected for heart rate (QTc) > 500 msec or an increase from time-matched Baseline of > 60 msec, either corrected by Fridericia's formula (QTcF) or Bazett's formula (QTcB). Exposure response analyses were conducted using matched PK-electrocardiogram (ECG) data, and did not indicate any dose-dependent effect on heart rate, QTcF, or QTcB at the proposed dose.

Post market data

Two reports incorporating postmarket data and clinical trial data (PADER) since approval in the USA have been provided by the sponsor in the submission:

- PADER dated 7 February 2019 (reporting period: 16 October 2018 to 15 January 2019);
- PADER dated 7 May 2019 (reporting period: 16 January 2019 to 15 April 2019).

In providing these reports, the sponsor stated:

> 'Both PADERs concluded that the type and occurrence of adverse drug experiences contained in these documents are consistent with the known safety profile of the product. No new safety information was identified that altered the benefit-risk profile of Talzenna (talazoparib). The data do not reflect a change in adverse experience occurrence and no change to the product's current FDA-approved labelling is warranted at this time.'

[12] The QT interval is the time taken from the start of the QRS wave complex to the end of the corresponding T wave on an electrocardiogram. The QT interval represents cardiac ventricular depolarisation and repolarisation and roughly corresponds with the start of cardiac ventricular contraction to the end of cardiac ventricular relaxation.

An event of leukaemia was noted in the second of these documents (included above under MDS/AML) and was a follow up of the case of AML in the patient with salivary gland cancer in Study C3441010.

Safety-related conclusions

The safety profile of talazoparib appeared consistent between the EMBRACA trial and the supporting safety data from patients with solid tumours treated with talazoparib at the proposed dosage of 1 mg daily across the clinical development program.

AEs seen with talazoparib were in keeping with the safety profile that might be predicted based on the known toxicities of other PARP inhibitors, featuring myelosuppression and sequelae most prominently. Adverse events and dose modifications occurred at similar rates in the talazoparib and PCT arms, although the duration of exposure was longer for talazoparib-treated patients. Long-term safety data is not yet available.

A number of cases of second primary malignancy, including AML, have occurred, and although these are often confounded (for example by previous chemotherapy exposure), pre-clinical data points to a causal role for talazoparib. Along with haematological toxicity, AML and reproductive/fetal toxicity require precautionary labelling.

Hepatotoxicity, phototoxicity and pneumonitis do not appear to be of concern based on the data available to date.

Risk management plan

The sponsor has submitted European Union-Risk Management Plan (EU-RMP) version 0.1 (date 10 April 2018; data lock point (DLP) 15 September 2017) and Australian specific Annex (ASA) version 1.0 (date 18 October 2018) in support of this application. With the response to TGA questions, the sponsor provided an updated EU-RMP version 0.2 (date 27 November 2017; DLP 15 September 2017) and an ASA version 1.1 (27 June 2019).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 13.[13]

Table 13: Summary of safety concerns for talazoparib

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None				
Important potential risks	Myelodysplastic syndrome/Acute myeloid leukaemia	ü	–	ü	–
	Second primary malignancies	ü	–	ü	–

[13] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	(other than MDS/AML)				
	Reproductive and developmental toxicity	ü#	–	ü	–
Missing information	Use in Severe Renal Impairment	ü	ü*	ü	–

*Clinical trial. #Pregnancy follow-up questionnaire.

The RMP evaluator found the proposed pharmacovigilance plan acceptable.

Talazoparib will be included in the Black Triangle scheme, as it is a new chemical entity.

Risk-benefit analysis

Delegate's considerations

Benefits and uncertainties

The primary endpoint was met. Patients in the talazoparib arm had a median PFS 3 months longer than patients in the PCT arm (hazard ratio 0.54 (95% CI 0.41, 0.71, p < 0.0001). The median PFS (95% CI) was 8.6 months (7.2, 9.3) in the talazoparib arm and 5.6 months (4.2, 6.7) in the PCT arm. Subgroup analyses and sensitivity analyses were supportive of the primary endpoint.

OS was not mature at the time of analysis, with hazard ratio (95% CI) 0.761 (95% CI: 0.547, 1.060) (data cut off 15 September 2017). Final OS analysis is planned at approximately 321 events, noting potential confounding by subsequent therapies (which include a PARP inhibitor for 18% of the PCT arm to the data cut-off date).

The ORR (95% CI) was 50% (43, 57) with talazoparib treatment versus 18% (12, 27) with PCT. Due to lack of adjustment for multiplicity, results for ORR (secondary endpoint per protocol) are considered exploratory.

Response data from earlier phase trials (ABRAZO trial, a Phase II study, and Study PRP-001, Phase I) are supportive that talazoparib has activity in BRCA-positive, HER2-negative breast cancer.

Whether talazoparib efficacy would be similar for patients with tumours carrying somatic BRCA mutation, and the optimal place in therapy sequence for talazoparib relative to platinum therapy, remains unclear.

Harms and uncertainties

The overall safety profile of talazoparib appears to be consistent with that described for other PARP inhibitors.

The types of adverse events in the talazoparib arm of the EMBRACA trial were principally consistent with myelosuppression: the most common events (incidence > 20%) were anaemia, fatigue, nausea, neutropaenia, headache, thrombocytopaenia, vomiting, alopecia, diarrhoea and decreased appetite. Of talazoparib-treated patients, Grade 3 anaemia occurred in 38%, life threatening (Grade 4) anaemia occurred in 2 (1%) and serious events of anaemia were reported in 6%.

The duration of exposure to talazoparib was almost double that of the PCT arm, however unadjusted rates of TEAEs, including higher grade and serious events, as well as discontinuations and dose modifications were similar between arms. Dose modification was associated with an AE in 66.4% of patients in the talazoparib arm. Dose modification

for anaemia, neutropaenia, and thrombocytopaenia occurred at least 5% more frequently with talazoparib than PCT, while dose modification for decreased neutrophil count, nausea, diarrhoea, and palmar-plantar erythrodysaesthesia syndrome occurred at least 5% more commonly in patients in the PCT arm.

Two patients treated at the proposed dose across the clinical development program developed MDS/AML: one with 4 months and one with 24 months duration of exposure. Both patients also had prior exposure to chemotherapies known to be associated with second primary malignancy. One case occurred in the EMBRACA trial, compared to one event of acute promyelocytic leukaemia in the PCT arm of the EMBRACA trial. A third case of second primary malignancy (leukaemia) with limited detail was reported in a recent PADER. Based on biological plausibility, pre-clinical data and the observed cases (despite confounding) this event should be included as a Warning/Precaution in the PI.

Talazoparib exposure is increased if co-administered with certain P-gp inhibitors, and in moderate renal impairment, and dose reduction is required in these settings. Based on toxicology data, embryofoetal toxicity or lethality and effects on fertility (particularly male) are predicted.

Talazoparib will be included in the TGA's black triangle scheme automatically, as a new chemical entity. The RMP for Australia also lists AML and other second primary malignancies as important potential risks for monitoring, alongside reproductive and developmental toxicity. Within the Australian health system, it is highly unlikely that talazoparib will be prescribed by anyone other than medical oncologists.

Missing information includes use in severe renal impairment, and investigation is ongoing as part of Study C3441001. Data for use in moderate or severe hepatic impairment is pending (Study C3441002), but based on the minimal hepatic metabolism of talazoparib, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has requested to remove this from the 'missing information' section of the RMP summary of safety concerns.

Benefit-risk balance

The benefit of treatment with talazoparib has been demonstrated in a single, high-quality randomised controlled trial (EMBRACA trial), which showed a statistically significant progression-free survival advantage of approximately 3 months over physician's choice of single-agent chemotherapeutic agents in common use (at the time of trial design), in the treatment of patients with germline BRCA mutation who have advanced HER2-negative breast cancer. The hazard ratio for this comparison is 0.54 (95% CI 0.41, 0.71, $p < 0.0001$). Overall survival data was not mature at the time of data cut off. The point estimate for the hazard ratio for overall survival was not suggestive of a survival detriment, however, at 0.76.

The safety database is sufficient to support registration; however, further data is expected from ongoing extension trials and post-market activities. This should consolidate the safety profile in terms of population size and duration of exposure/follow up, and the likelihood of detection of rare AEs. Toxicities of talazoparib treatment were principally related to myelosuppression or gastrointestinal toxicity, and adverse reactions were generally manageable with dose modifications and supportive care. The safety profile is acceptable in the setting of this serious, life-threatening disease.

The Delegate is seeking impartial advice from independent Australian clinical experts in the treatment of breast cancer regarding specification of prior therapies in the wording of the indication, and will consider any additional matters raised by the clinical experts.

Proposed action

The benefit-risk balance of registration of talazoparib for the proposed usage is considered positive, pending modifications to the proposed Australian PI.

Request for independent expert advice

Australian independent clinical experts provided the TGA with impartial advice on the Australia-specific clinical context. The independent Australian clinical experts did not identify additional specific concerns or areas of uncertainty regarding talazoparib registration in Australia.

Advisory Committee considerations[14]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Talzenna (talazoparib as tosilate) hard capsules, indicated for:

> *Talzenna is indicated for the treatment of patients with a deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) mutation according to a validated diagnostic test, who have human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer.*

Specific conditions of registration applying to these goods

- Talzenna (talazoparib) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Talzenna must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Talzenna EU-RMP (version 0.2, date 27 November 2017; DLP 15 September 2017), with ASA (version 1.1, date 27 June 2019), included with submission PM-2018-04458-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of European Union (EU) reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

[14] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Talzenna approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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