Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Pertuzumab

Proprietary Product Name: Perjeta

Sponsor: Roche Products Pty Limited

June 2016

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 used in this AusPAR

Abbreviation	Meaning
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AEGT	Adverse event grouped term
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibodies
BCS	Breast-conserving surgery
bpCR	Pathological complete response in the breast
CBE	Clinical breast examination
CHF	Congestive heart failure
CISH	Chromogenic in situ hybridisation
CL	Clearance
CMI	Consumer medicine information
CrCl	Creatinine clearance
CSR	Clinical study report
D	Docetaxel
DFS	Disease-free survival
EBC	Early breast cancer
ECD	Extracellular domain
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic case report form
EEA	European economic area
EGFR	Epidermal growth factor receptor 1

Abbreviation	Meaning
ER	Oestrogen receptor
EU	European union
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescence in situ hybridisation
FU	Follow-up
GBG pCR	GBG definition of pCR (ypt0 ypn0).
GCP	Good clinical practice
HER	Human epidermal growth factor receptor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IBC	Inflammatory breast cancer
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
ITT	Intention –to-treat
IV	Intravenous
KM	Kaplan-Meier
LABC	Locally advanced breast cancer
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall survival
pCR	Pathological complete response
PFS	Progression-free survival
Ptz	Pertuzumab
PD	Pharmacodynamics
PgR	Progesterone receptor
PI	Product information
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PP	Per protocol
q3w	Every third week
SAE	Serious adverse event
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SOP	Standard operating procedure
$T_{1/2}$	Half-life
TCH	Docetaxel, carboplatin and trastuzumab
TGA	Therapeutic goods administration
TNM	Tumour Nodes Metastases classification
tpCR	Pathological complete response in the breast and axillary nodes
T	Trastuzumab
ULN	Upper limit of normal

Abbreviation	Meaning
USA	United States of America
Vc	Volume of distribution (central)
Vp	Volume of distribution (peripheral)
ypT0/Tis	The absence of invasive cancer in the breast
ypT0/Tis ypN0	The absence of invasive cancer in the breast and axillary nodes
ypT0 ypN0	The absence of invasive and in situ cancer in the breast and axillary nodes

I. Introduction to product submission

Submission details

Type of submission:	Extension of indication
Decision:	Approved
Date of decision:	13 May 2016
Date of entry onto ARTG	20 May 2016
Active ingredient(s):	Pertuzumab
Product name(s):	Perjeta
Sponsor's name and address:	Roche Products Pty Limited 4-10 Inman Road, Dee Why NSW 2099
Dose form(s):	Concentrate for injection
Strength(s):	420 mg/14 mL
Container(s):	Single use Vial
Pack size(s):	1s
Approved therapeutic use:	*Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2 positive breast cancer as part of a complete treatment regimen.* *Note to the Indication: this approval is based on improvement in pathological complete response rate. No improvement in disease-free, progression-free or overall survival has been shown.*
Route(s) of administration:	Intravenous (IV)
Dosage:	The recommended initial dose of Perjeta is 840 mg, administered as a 60 min IV infusion, followed by, every 3 weeks, a 420 mg dose administered over 30-60 min. When trastuzumab is administered with Perjeta, the recommendation is to follow a 3- weekly schedule, administered as an IV infusion, with an initial trastuzumab dose of 8 mg/kg followed by every 3 weeks, a dose of 6 mg/kg. For further details see the Product Information (Attachment 1)
ARTG number (s):	196218

Product background

This AusPAR describes the application by the sponsor, Roche Products Pty Limited, to extend the indications for Perjeta (pertuzumab).

The sponsor initially proposed on submission of application the following indications:

> *Perjeta is indicated in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin containing treatment regimen.*

In the sponsor's response to first round of clinical evaluation the following indications were proposed:

> *Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence as part of a complete treatment regimen for early breast cancer*

Perjeta is currently indicated for:

> *In combination with trastuzumab and docetaxel for patients with HER2 + metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease*.

Pertuzumab is a recombinant, humanised (rch), immunoglobulin (Ig) G1 kappa (κ) chain monoclonal antibody (MAb) that targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2). The HER2 receptor is a transmembrane glycoprotein with intrinsic tyrosine kinase activity that has been implicated in the development of some breast cancers. Pertuzumab is the first in a new class of targeted cancer treatments called HER2 dimerisation inhibitors. By binding to the subdomain 2 epitope of the extracellular domain of HER2, pertuzumab prevents heterodimerisation of HER2 with other members of the HER family (HER1, HER3 and HER4) and blocks ligand activated downstream signalling.

HER2 positive breast cancer is associated with a relatively high rate of relapse, even after currently registered treatments given in the neoadjuvant or adjuvant setting. An unmet need is recognised.

This is the first application to seek registration for an extension of indications without prior registration based on large trials conducted in the adjuvant setting.

A loading dose of 840 mg intravenously in Cycle 1, and thereafter 420 mg, 3 weekly during neoadjuvant treatment has been proposed by the sponsor for the proposed indications.

Regulatory status

Pertuzumab was granted TGA approval for the existing indication on 6 May 2013 (date of first inclusion in the Australian Register of Therapeutic Goods (ARTG).

The sponsor was granted orphan designation for the existing registered indication on 19 January 2012 but the proposed indication has not received orphan designation.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) and in the USA (see Table 1 below). An application is under consideration in New Zealand.

Table 1: International regulatory status

Country	Approval date	Indications
European Union	28 July 2015	*Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.*
USA	20 September 2013	*Perjeta is a HER2 Neu receptor antagonist indicated for use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival.* *Limitations of usage:* The safety of Perjeta as part of a doxorubicin-containing regimen has not been established. The safety of Perjeta administered for greater than 6 cycles for early breast cancer has not been established.' The following is taken from the FDA website accessed 21 January 2016. 'This accelerated approval is based on demonstration of an improvement in pCR rate. No data are available demonstrating improvement in event-free survival or overall survival. Continued approval for this indication is contingent upon demonstration of improvement in disease-free survival in the confirmatory trial.'
New Zealand	Ongoing	Not applicable

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared 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. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

HER2 positive breast cancer remains a significant health problem, estimated to account for around 60,000 to 90,000 deaths per year globally. A significant proportion of these deaths occur patients previously treated for non-metastatic disease, with clinical trials of neoadjuvant or adjuvant trastuzumab plus chemotherapy reporting 5 year relapse rates ranging from about 17% to 40% depending on stage of disease and tumour characteristics of the patients enrolled. Thus there remains a need to improve outcomes for women with HER2 positive breast cancer treated in the adjuvant and neoadjuvant settings. Historically, decisions relating to which therapies warrant testing (and approval) in the adjuvant and neoadjuvant settings have relied on the demonstration of efficacy in the metastatic setting.

In the CLEOPATRA (WO20698) study, the addition of pertuzumab to trastuzumab plus docetaxel (Ptz + T+D) treatment resulted in a substantial prolongation of both progression free and overall survival (PFS and OS) in patients with metastatic HER2 positive breast cancer (MBC) in comparison to trastuzumab plus docetaxel (Pla + T + D). The median survival estimates were 56.5 months with Ptz+T+D versus 40.8 months with Pla+T+D (HR = 0.68; 95% CI, 0.56 − 0.84; p = 0.0002). The median PFS (investigator assessed) was 18.7 months in the pertuzumab-containing arm and 12.4 months in the placebo arm (hazard ration (HR) = 0.68; 95% CI, 0.58 − 0.80; p < 0.0001).[1]

Two neoadjuvant studies, NEOSPHERE (WO20697) and TRYPHAENA (BO22280) have addressed the role of pertuzumab in the neoadjuvant setting using pathological complete response (pCR) as a surrogate end point. There is a further ongoing neoadjuvant study BERENICE (WO29217), which is a non-randomised, open-label, Phase II study evaluating pertuzumab in combination with trastuzumab and two different neoadjuvant anthracycline based chemotherapy regimens in patients with HER2 +, locally advanced, inflammatory or early stage breast cancer. Data from this study are expected at around the end of 2017. Importantly, there is an adjuvant APHINITY (BO25126) study expected to be analysed in 2016 with reporting in 2017. This study is a randomised Phase III study of adjuvant trastuzumab +/- pertuzumab after adjuvant chemotherapy (either anthracycline or non-anthracycline based as per investigator). Some 4805 patients are enrolled onto this study, which is expected to provide important data relating to Disease-free survival (DFS), OS, long term cardiac safety, quality of life and pharmacokinetic parameters.

Pathological complete response (pCR)

There are several definitions of pCR in use with varying degrees of stringency.

[1] Update Clinical Study Report – WO20698/TOC4129g - A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer – Report No. 1053649, December 2012.

1. ypT0/Tis: Breast pathological complete response (bpCR) = the absence of invasive cancer in the breast
2. ypT0/Tis ypN0: Total pathological complete response (tpCR) = the absence of invasive cancer in the breast and axillary nodes
3. ypT0 ypN0: German Breast Group pathologic complete response (GBG pCR) = the absence of invasive and in situ cancer in the breast and axillary nodes

In the Cortazar analysis of 2012[2],[3] in which data from nearly 13,000 patients was analysed, nodal involvement following neoadjuvant therapy was associated with an increased risk of recurrence and death, but residual ductal carcinoma in situ was not prognostic. Therefore the FDA recognises both ypT0/Tis ypN0 and ypT0 ypN0 as reasonable definitions. In contrast, the smaller (n=6377) German Breast Group/Arbeitsgemeinschaft Gynakologische Onkologie- Breast Group (GBG) meta-analysis determined that there was an improved DFS in patients with ypT0 ypN0 responses in comparison to those with residual in situ disease (ypTis ypN0) with a trend to better OS. Hence the GBG definition of a true pCR is ypT0 ypN0.[4] However, for regulatory purposes the following definition is recommended by the European medicines Agency (EMA): *absence of any residual invasive cancer on haematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of the neoadjuvant systemic therapy (ypT0/is ypN0)*.[5],[6]

In should be noted that in the pivotal NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies, pathological complete response (for the purposes of the main analyses) was confined to the assessment of the response in the breast (bpCR; ypT0/is), that is, a less stringent end point than that recommended for use by regulators elsewhere. However, data were collected in both studies to enable pCR assessment by tpCR and GBG pCR for the purposes of exploratory analyses.

The sponsor has provided data pertaining to the use of pCR as a surrogate endpoint for DFS through analyses of the NOAH and GeparQUATTRO studies as presented below.

Guidance

- EMA/CHMP/703715/2012 Appendix to the guidance on the guideline on the evaluation of anticancer medicinal products in man Condition Specific Guidance Supersedes EMA/CHMP/EWP/520088/2008, Appendix 2 (Adopted by TGA 17 December 2010) Effective: 1 April 2014.
- EMA/CHMP/151853/2014 Committee for Medicinal Products for Human Use (CHMP) Draft guideline on the role of the pathological Complete Response as an endpoint in neoadjuvant breast cancer studies, First published 28/04/2014, Last updated 28/04/2014

[2] Cortazar P, et al. Meta-analysis Results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [abstract]. Cancer Res 2012; 72 (24 Suppl.) 93s, S1-11.
[3]Cortazar P, al. Pathological complete response and long- term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Feb 13. pii: S0140-6736(13)62422-8. doi: 10.1016/S0140-6736(13)62422-8. [Epub ahead of print]
[4]von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30:1796-1804.
[5]EMA/CHMP/151853/2014 Committee for Medicinal Products for Human Use (CHMP) Draft guideline on the role of the pathological Complete Response as an endpoint in neoadjuvant breast cancer studies, First published 28/04/2014, Last updated 28/04/2014
[6]Guidance for Industry - Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), October 2014 , Clinical/Medical)

- Guidance for Industry - Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), October 2014 , Clinical/Medical)

Contents of the clinical dossier

Scope of the clinical dossier

The clinical dossier initially provided, documented pivotal and other clinical trials related to the proposed extension of indications, and included updated clinical trial information from the clinical trial underpinning the existing indication for metastatic breast cancer.

The submission contained the following clinical information:

- 1 clinical pharmacology study, including 1 that provided pharmacokinetic data and 1 that provided pharmacodynamic data
- 2 population pharmacokinetic analyses
- 1 human pharmacodynamics data report
- 1 pivotal efficacy/safety study
- 0 dose-finding studies
- 2 other efficacy/safety studies.
- 1 other report of pCR analyses from more than 1 study.

Additional data provided later:

- Final Clinical Study Report – WO20697 Research Report 1062325/February 2015
- CHMP Assessment Report 25 June 2015
- CHMP Opinion
- EMA Request for Supplemental Information (RSI)
- Response to First RSI
- EMA Second RSI
- Response to Second RSI
- SAG-O Meeting Minutes
- SAG-O Roche Written Response
- Primary CSR from Study WO20697; CSR for an updated analysis from Study WO20697
- Primary and Addendum CSRs from 20698.

Paediatric data

The submission did not include paediatric data. The evaluator does not believe that pertuzumab is likely to be of any clinical relevance for this indication in a paediatric population.

Good clinical practice

The studies reviewed for this submission were conducted in full conformance with the principles of the 'Declaration of Helsinki' (and its subsequent amendments) or with the local laws and regulations of the country in which the research was conducted; whichever provided greater protection to the individual. In countries in which good clinical practice

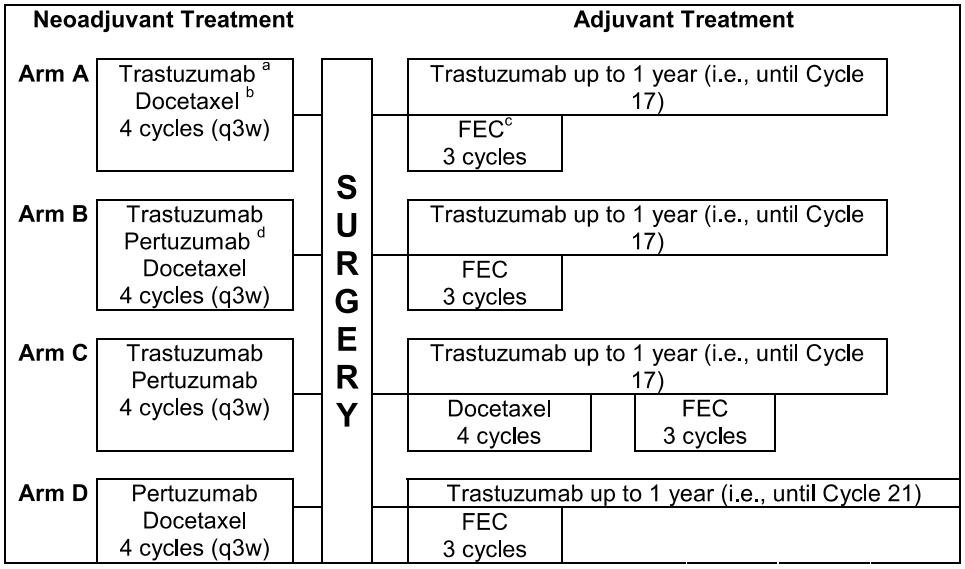
(GCP) guidelines exist, the sponsor and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the Investigator's signature on the protocol agreeing to carry out all of its terms in accordance with applicable regulations and law and to follow International Conference on Harmonization (ICH) guidelines for GCP. All investigators were trained according to company standard operating procedures (SOPs).

Pharmacokinetics

Studies providing pharmacokinetic data

There is one new study examining pharmacokinetic parameters of pertuzumab for consideration, that pertaining to the NEOSPHERE (WO20697 study) (Table 2). The study design is detailed in Figure 1.

Figure 1: NEOSPHERE (WO20697) study schema



FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; q3w = every 3 weeks.

[a] 8 mg/kg loading dose, then 6 mg/kg

[b] 75 mg/m^2 at Cycle 1, then increased to 100 mg/m^2 if there is not limiting toxicity

[c] 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), cyclophosphamide (600 mg/m^2)

[d] 840 mg loading dose, then 420 mg.

The pertuzumab PK results in NEOSPHERE (W020697) were consistent with the previous popPK model predictions, suggesting similarity in pertuzumab PK between the EBC population in NEOSPHERE (W020697) and other historical patient types including the first-line MBC population and others included in the popPK model. The majority of patients (130 out of 133) in the pertuzumab-containing arms of NEOSPHERE (W020697) had an observed pertuzumab trough serum concentration > 20 µg/mL (the target efficacious exposure based on nonclinical efficacy models) at Cycle 2. This target serum concentration is achieved in >90% of neoadjuvant breast cancer patients receiving a 840 mg loading dose of pertuzumab followed by a 420 mg maintenance dose every 3 weeks (q3w).[7] The trastuzumab PK results were similar across the three arms in NEOSPHERE (W020697).

[7]Pharmacokinetic analysis and exposure-response of pertuzumab in combination with trastuzumab and docetaxel in the neoadjuvant setting (2013 07 03 NEOSPHERE PKPD v2 Final).

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in special populations	Target population §- Single dose	NEOSPHERE (WO20697)
PK interactions	Trastuzumab	NEOSPHERE (WO20697)
	Docetaxel	NEOSPHERE (WO20697)
	Other	HANNAH (BO22227)†^

† Bioequivalence of different formulations.
^ Included as a comparator for trastuzumab pharmacokinetics

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

After correcting for baseline differences in body weight and serum albumin concentration between the prior population Pharmacokinetics (popPK) modelling and the data from the NEOPSHERE study, the pertuzumab pharmacokinetics are similar between the neoadjuvant population and those observed in the metastatic setting. In addition, the lack of variation in pertuzumab PK between the arms of the NEOSPHERE (WO20697) study indicates that it is not influenced by co-administered trastuzumab or docetaxel. Drug-drug interactions have not been observed with several other chemotherapeutic agents however this needs to be formally evaluated for co-administered carboplatin.

The measured trastuzumab level was lower in the NEOSPHERE (WO20697) study, with around a third of patients analysed having suboptimal serum trough levels of trastuzumab. *The sponsor is requested to provide updated data as to the explanation for this, and analyses as to the efficacy of trastuzumab at these lower doses.*

Pharmacodynamics

Studies providing pharmacodynamic data

New pharmacodynamic data are submitted to supplement this application from the NEOSPHERE (WO20697) study only.

Evaluator's conclusions on pharmacodynamics

At the proposed dosing schedule, it is likely that clinically relevant drug concentrations will be achieved in the majority of patients. Tumour responses are unlikely to be significantly influenced by the degree of variability in drug levels achieved using this dosing strategy. There are no robust biomarkers of response identified from the NEOSPHERE (WO20697) study.

Although the addition of pertuzumab to trastuzumab and docetaxel was associated with a higher rate of pCR in the breast, this end point is not the standard for registration proposed by international regulators.

Dosage selection for the pivotal studies

NEOSPHERE (WO20697)

Rationale for the dosage selection of trastuzumab and pertuzumab:

- Based on pharmacokinetic data and positive clinical data, fixed, non-weight-based dosing with a dosing interval of three weeks is recommended. In Phase II studies, a loading dose of 840 mg pertuzumab (followed by 420 mg, every 3 weeks (q3w)) was capable of attaining steady-state trough and peak concentrations by the second cycle.
- A three weekly schedule of trastuzumab was also used. Although the registered schedule for trastuzumab administration at the time of protocol preparation was a weekly dose of 2 mg/kg after a loading dose of 4 mg/kg, it is known now that the half-life of trastuzumab using this schedule is approximately 4 weeks. PK and clinical studies support the 3 weekly administration of trastuzumab (8 mg/kg IV loading dose and 6 mg/kg given IV q3w) as a suitable alternative schedule.

Rationale of dosage selection for docetaxel:

- Docetaxel is an established agent in the therapy of breast cancer and is registered for use in this indication. Docetaxel at a dose of 100 mg/m^2 in combination with trastuzumab has been associated with positive risk and benefit in patients with HER2 overexpressing metastatic breast cancer compared to docetaxel alone (100 mg/m^2 given q3w) and is registered for use with trastuzumab at this dose. The risks and benefits associated with different docetaxel doses (single agent) have been established in a randomised study. Based on the Phase Ib study (BO17021), the maximum tolerated dose of docetaxel in combination with pertuzumab is 75 mg/m^2. The starting dose of docetaxel used in this study was therefore 75 mg/m^2, with escalation according to individual tolerability.

Rationale for post-surgery adjuvant therapy:

- Following surgery, patients received the standard combination 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) as adjuvant chemotherapy. There is evidence that in patients selected for having good cardiac function, the combination of cardio-toxic anthracyclines (such as epirubicin) with trastuzumab may be associated with acceptable cardiac tolerability. Due to uncertainty in relation to the effect of additional pertuzumab on cardiac parameters, the dosing of FEC was separated from the dosing of pertuzumab by a minimum of 5 weeks.

TRYPHAENA (BO22280)

Based on pharmacokinetic and clinical data, an IV dosing interval of three weeks was determined for pertuzumab (half-life of approximately 17 days). A loading dose of 840 mg (followed by 420 mg q3w) was capable of attaining steady-state trough and peak concentrations by the second cycle.

The half-life of trastuzumab is approximately 28.5 days, which supports a dosing of every three weeks.

The intravenous chemotherapy regimens used for docetaxel. FEC, and carboplatin, are based on published data and routine clinical usage. Intravenous docetaxel was used at the starting dose of 75 mg/m^2 and was escalated up to 100 mg/m^2 according to individual tolerability. Higher doses of epirubicin were shown to be superior to lower doses of epirubicin (60 mg/m^2) in the treatment of breast cancer, and so the dose of epirubicin used in this study was 100 mg/m^2. The use of 5- fluorouracil (500 mg/m^2 IV) in combination with an anthracycline (epirubicin in this protocol) and cyclophosphamide is

considered a standard regimen. Data supporting the use of six cycles of therapy, both as neoadjuvant therapy and as adjuvant therapy are available.

Comment: The dosing schedules described are appropriate for current Australian practice, including the separation between HER2 directed therapy and anthracyclines, and the dosing schedule for docetaxel. The choice of FEC and docetaxel regimen is consistent with Australian practice.

Efficacy

Studies providing efficacy data

The sponsor has provided data from two open-label randomised Phase II studies NEOSPHERE (WO20697) and TRYPHAENA (BO22280) with supporting data from the previously reviewed CLEOPATRA (WO20698) study.

Evaluator's conclusions on efficacy

for neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory or early stage breast cancer (either greater than 2 cm in diameter or node positive)

The sponsor has provided data from two open-label randomised Phase II studies NEOSPHERE (WO20697) and TRYPHAENA (BO22280) with supporting data from the previously reviewed CLEOPATRA (WO20698) study.

In the two neoadjuvant studies, the target population were female patients with HER2 + non-metastatic breast cancer where the primary tumour is > 2 cm in size. The choice of study population was appropriate as HER2 + breast cancer is a molecular breast cancer subtype that is highly responsive to neoadjuvant therapy. It is noted that in both studies, approximately half of the patients were endocrine-receptor positive, a subgroup for which neoadjuvant therapy may be less effective.[8,9]

The sponsor is applying to add pertuzumab to a neoadjuvant chemotherapy backbone that involves a taxane (docetaxel) and trastuzumab. Concurrent treatment with anthracycline is not intended in the application although was a component of the adjuvant component of the 4 arms of the NEOSPHERE (WO20697) and the neoadjuvant Arm A (Ptz+T+FEC/Ptz+T+D) of TRYPHAENA (BO22280). The current standard of care in Australia is to avoid concurrent administration of trastuzumab due to the risks of cardiotoxicity and it is critical that the sponsor provides some guidance in the PI as to the appropriate adjuvant regimen to use post-surgery, as a recapitulation of the regimens described in the NEOSPHERE (WO20697) study is not congruent with current Australian practice. As discussed in the review of safety, there were 2.8% and 5.9% rates of significant left ventricular ejection fraction (LVEF) impairment in the Ptz+T+D arm of the NEOSPHERE (WO20697) study during the neoadjuvant and adjuvant phases of the study, higher than the comparator arms. This is of potential concern as this carry over to the adjuvant setting is likely to lead to reduced exposure to adjuvant trastuzumab which does have a proven impact on survival outcomes. Nevertheless, with the concurrent anthracycline component of the regimens omitted, the schedules are reflective of current

[8] Cortazar P, et al. Meta-analysis Results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [abstract]. Cancer Res 2012; 72 (24 Suppl.) 93s, S1-11.
[9]Cortazar P, al. Pathological complete response and long- term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Feb 13. pii: S0140-6736(13)62422-8. doi: 10.1016/S0140-6736(13)62422-8. [Epub ahead of print]

clinical practice in the neoadjuvant setting. As noted, a recent study by Del Mastro et al[10] in an adjuvant breast cancer population showed that the addition of 5-fluorouracil to epirubicin/cyclophosphamide (followed by paclitaxel) was not associated with improved DFS. Therefore it is possible that in some patients, for example those with comorbidities, and older patients, oncologists will use a different chemotherapy in the adjuvant setting (such as epirubicin and cyclophosphamide (EC) or doxorubicin (Adriamycin) and cyclophosphamide (AC)).

The evaluator notes that there was slight variability in the FEC regimens used in the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies. In the former the schedule was 5-fluorouracil administered at 600 mg/m^2 , epirubicin 90 mg/m^2 , and cyclophosphamide 600 mg/m^2 , while in the latter the schedule was 5-fluorouracil administered at 500 mg/m^2 , epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2 . In the pivotal efficacy study, NEOPSHERE (WO20697) the FEC was given in the adjuvant setting and of less relevance to the pCR endpoint of the study. As stated in the detailed review of NEOSPHERE (WO20697), the study was not powered to assess DFS and OS, end points for which the subtleties of the adjuvant therapy dosing may/may not have influence. In contrast the TRYPAHENA (BO22280) study administered the FEC up front, however there was no control arm in this study and it was primarily designed to look at cardiac toxicity. Again this study was not powered to address DFS and OS. The precise FEC schedule may or may not influence long term outcomes however it does not influence decision making in relation to the use of the surrogate end point of pCR (in the case of the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies as measured using bpCR). Likewise, the use of adjuvant endocrine therapy was as per local guidelines, with the potential to influence long-term outcome but not pCR.

The pCR rates were higher in the TRYPHAENA (BO22280) study, likely as a result of combining poly chemotherapy with the anti-HER2 therapies in the neoadjuvant setting. However the influence of these treatments as a neoadjuvant rather than adjuvant therapy with respect to long-term outcome remains unknown.

The reviewer notes that the NEOPSHERE (WO20697) and TRYPHAENA (BO22280) studies were Phase II, open-label studies and therefore potentially subject to bias (especially in relation to the clinical assessment of response). However, given that the primary endpoint of the NEOSPHERE (WO20697) study was pCR, assessed by pathologists who were in large part oblivious to the treatment allocation, the risk of bias in this application, which is based on the use of pCR as a surrogate end point should be low.

From the CLEOPATRA (WO20698) study, pertuzumab added to trastuzumab and docetaxel has high efficacy in the setting of metastatic setting with a response rate of approximately 80% and a meaningful prolongation in both PFS and OS. This provides a strong argument to study this triplet combination in an early breast cancer population. To this end, the APHINITY (BO25126) study has been conducted with results awaited in 2016. Certainly the data from CLEOPATRA (WO20698) are compelling however the duration of treatment with pertuzumab is significantly longer than that used in the NEOSPHERE (WO20697) and TRYPAHENA (BO22280) studies, as it the duration of cytotoxic chemotherapy. It is therefore unclear whether a short course of neoadjuvant treatment will translate into meaningful long-term outcomes as has been so dramatically demonstrated in the metastatic setting.

While the adjuvant pertuzumab study (APHINITY BO25126) has yet to report, both NEOPSHERE (WO20697) and TRYPHAENA (BO22280) show, in very similar populations of patients that the addition of pertuzumab to a combination of trastuzumab and a taxane results in pCR rates by the least stringent definition of ypT0/is of between 46% to over 66%. This least stringent definition is not that which is recommended by the FDA and EMA

[10]Del Mastro et al Lancet. 2015;385(9980):1863-72.

for registration purposes. The sponsor provides data as to the taper and GBGpCR rates, however, in the absence of standardised pre-treatment nodal assessment it is difficult to assess the rates of nodal control by the neoadjuvant strategies used in the various treatment arms of the two neoadjuvant studies. Furthermore the NEOSPHERE (WO20697) study was designed with an alpha level of 0.2, which is not particularly statistically stringent.

From a clinical surgical decision-making perspective, these aggregate data suggest that a neoadjuvant pertuzumab + trastuzumab + taxane triplet results in clinical response rates (that is, that assessed by standard clinical assessment by clinical examination and imaging with mammography and/or ultrasound of around 90%). Nevertheless, breast conservation rates remain low, and relatively uninfluenced by the addition of pertuzumab, with around a quarter to one third of patients study undergoing Breast-conserving surgery (BCS). The reviewer notes that the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies were not designed to show a difference in BCS, and as the numerous factors influencing surgical decision making were not controlled for, it is difficult to draw definitive conclusions.

The current application is predicated on the assumption that pCR after a limited course of pertuzumab + trastuzumab + taxane will result in long-term benefits in DFS and OS. The data for this assumption remain controversial. In particular, current data do not allow for the prediction of the magnitude of the DFS/OS effect from a certain pCR effect. In the absence of the awaited APHINITY (BO25126) data it is unclear if patients with operable HER2 + breast cancer may in fact be better served by a prolonged adjuvant treatment course. The reviewer notes that the striking benefits seen in the metastatic setting occurred with a substantially greater exposure to both chemotherapy and pertuzumab.

The endocrine receptor status of the tumours in these studies did predict pCR, with lower rates observed in the hormone-receptor positive subgroup compared to the hormone receptor negative subgroup. This is in line with data from the Cortazar meta-analysis.[11],[12] This meta-analysis also showed that patients who achieve pCR have better long-term outcomes regardless of endocrine receptor status and indeed in the CLEOPATRA (WO20698) study there was still a clinically meaningful benefit from pertuzumab in the endocrine receptor positive group. Nevertheless, in the neoadjuvant setting, the likelihood of pCR is lower in this group comprising about 50% of patients in the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies. Thus guidelines that suggest a 'large' change in pCR is required to assume that there might be a clinically meaningful change in DFS/OS down the track become increasingly difficult to interpret. Certainly, for a significant proportion of HER2 + patients a pCR benefit (by whatever definition is used) is likely to be 'less large'.

In summary, the addition of pertuzumab to trastuzumab and docetaxel leads to a higher rate of bpCR (in the breast) in patients with HER2 + early breast cancer. This pCR end point is not that which is recommended for registration purposes, and the statistical test used in the NEOPSHERE (WO20697) study used an alpha of 0.2. While the sponsor provides data as to the tpCR and GBGpCR rates, the assessment of the axilla at baseline is not robust and uniform (that is, the true state of nodal involvement pre-treatment is difficult to assess) and therefore these tpCR and GBGpCR data are viewed with some caution. The DFS/OS data have been provided by the sponsor to supplement the pCR data; these end points are likely to be influenced by numerous other factors in the adjuvant

[11] Cortazar P, et al. Meta-analysis Results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [abstract]. Cancer Res 2012; 72 (24 Suppl.) 93s, S1-11.
[12] Cortazar P, al. Pathological complete response and long- term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Feb 13. pii: S0140-6736(13)62422-8. doi: 10.1016/S0140-6736(13)62422-8. [Epub ahead of print]

setting such as variability in chemotherapy schedules and endocrine therapies, and while interesting, are underpowered and exploratory only.

Thus, while the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies show promising results from the perspective of pCR, it is unclear whether this will translate into meaningful long-term benefit. It is the evaluator's view that adding pertuzumab increases the likelihood of a pCR in the breast (and is associated with tumour shrinkage in about 90% of patients); the main benefit of a short course of pertuzumab may in fact be to render patients of borderline operability, surgically amenable. The CLEOPATRA data provide a compelling rationale for the adjuvant APHINITY (BO25126) study that will provide further data as to the benefit of pertuzumab in the early setting. The evaluator notes that both the American and European approvals for neoadjuvant pertuzumab are conditional upon the provision of further data such as that anticipated in the APHINITY (BO25126) study. Such conditional registration does not exist in Australia at present.

Safety

Studies providing safety data

The pivotal efficacy study NEOSPHERE (WO20697), and the two other studies, TRYPHAENA (BO22280) and CLEOPATRA (WO20698) contributed to this safety assessment and provided evaluable safety data .

For ease of comparison and discussion, all 3 studies are grouped together.

- All three studies required adverse events (AEs) (regardless of grade or causality) and serious adverse events (SAEs) to be reported.
- All three studies required regular collection of data on:
  - physical examination
  - vital signs
  - Eastern Cooperative Oncology Group performance status (ECOG PS)
  - full blood count with platelets and differential counts,
  - serum chemistries and electrolytes
  - 12-Lead electrocardiograms (ECGs) and assessment of left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multi gated acquisition (MUGA) scan.
- In the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies, liver function/coagulation parameters (International Normalized Ratio, activated partial thromboplastin time) were collected during the study for all patients; in the CLEOPATRA (WO20698) study these were only required for patients receiving anticoagulants.

Anti-therapeutic antibodies (ATA) were not collected in either of the two neoadjuvant studies. However, pertuzumab immunogenicity was extensively characterised in the CLEOPATRA (WO20698) study in which 6.7% of patients in the Pla + T + D arm developed ATAs versus 3.3% in the Ptz + T + D arm. In the CLEOPATRA (WO20698) study, in those patients where a post baseline ATA titre was detected, this often occurred at the C3 assessment (Day 61 to 65). There was no clear association with anti-therapeutic antibodies to pertuzumab and hypersensitivity/anaphylactic reactions. Most hypersensitivity/anaphylactic reactions occurring on the day of a placebo/pertuzumab infusion were reported in the first two cycles of therapy, although events were reported as late as Cycle 30. Most reactions occurring on the day of a placebo/pertuzumab infusion,

especially in the Pla+T+D arm were Grade 1 to 2 in severity. More patients in the Ptz+T+D arm experienced Grade 3 hypersensitivity/anaphylactic reactions. Overall the proportion of patients experiencing anaphylaxis/hypersensitivity was balanced between the two treatment arms (9.1% of patients in the Pla+T+D arm versus 11.0% of patients in the Ptz+T+D arm with one additional event of hypersensitivity was reported in the Ptz+T+D arm (versus none in the Pla+T+D arm) after the primary clinical cut off.[13,14]

- All patients who received at least one dose of treatment and underwent at least one post baseline safety assessment were included in the safety evaluation for the three studies. The treatment arms for the safety analyses were defined according to the study treatment actually received.
- General AEs were collected as per standard protocols and severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 on a five-point scale (Grade 1 to 5) 15 and reported in detail on the Electronic case report form (eCRF).
- The causality relationship of study drug to the AE was assessed by the Investigator as either 'yes' or 'no'. For non-serious AEs, the Investigator could only specify relationship to 'study medication'; for SAEs, the Investigator could specify a relationship to one component of study medication
- Cardiac events were monitored as Adverse Events to Monitor (Table 3).

Table 3: Cardiac safety data for the NEOSPHERE (WO20697), TRYPHAENA (BO22280) and CLEOPATRA (WO20698) studies - (30 – components reconciled against Clinical study report (CSRs) for the 3 studies)

Parameter	NEOSPHERE (WO2067)	TRYPHAENA (BO22280)	CLEOPATRA (WO20698)
Asymptomatic LVEF decline	Reportable as AEs if they met the following criteria: Asymptomatic decline in LVEF of ≥ 10 % points from baseline to a value of <50% (reportable as an AE) Asymptomatic decline in LVEF requiring	As for NEOSPHERE.	As for NEOSPHERE. I addition, all cardiac AEs occurring during the study and up to 12 months after the last medication of study medications were reportable regardless of causality and seriousness.

[13]Clinical Study Report –WO20698C/TOC4129g - A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer – Report No. 1046288, October 2011. (Module 5)

[14] Update Clinical Study Report – WO20698/TOC4129g - A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer – Report No. 1053649, December 2012. (Module 5)

[15] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Parameter	NEOSPHERE (WO2067)	TRYPHAENA (BO22280)	CLEOPATRA (WO20698)
	treatment or leading to discontinuation of study treatment These had to reported as Non-Serious Adverse Events of Special Interest on both SAE and AE forms These events were to be reported as 'left ventricular systolic dysfunction' (LVSD) and graded according to NCI-CTCAE.		
Symptomatic LVSD (that is, Grade 3 or greater LVD)	Reportable as a SAE, using the term congestive heart failure (CHF).	Reportable as a SAE using the term 'left ventricular systolic dysfunction' (LVSD)	As for TRYPHAENA
	Reportable as a single diagnosis rather than symptoms or signs and graded according to NCI-CTCAE and NYHA classification	As for NEOSPHERE	As for NEOSPHERE
	CHF occurring during the study and up to 24 months after the last dose of study medications was to be reported regardless of causality graded according to NCI-CTCAE and NYHA	As for NEOSPHERE (except using the term symptomatic LVSD rather than CHF)	Symptomatic LVSD occurring during study and up to 36 months after last dose of study medications was to be reported, regardless of causality and graded according

Parameter	NEOSPHERE (WO2067)	TRYPHAENA (BO22280)	CLEOPATRA (WO20698)
	classification		to NCI-CTCAE and NYHA classification
	Specific signs and symptoms of LVSD were entered into the comments section of the AE eForm	A cardiac questionnaire was completed by investigators prior to each treatment cycle. Cardiac symptom and physical findings of symptomatic LVSD were entered into the cardiac questionnaire eForm	Cardiac symptoms and signs were reported on a 'Symptomatic LVSD' eCRF page for patients with LVSD
LVEF schedule of assessments	Between Days 15 and 21 of Cycles 2, 4, 8, 11 and 15, and after surgery, and ≤ 7 days prior to Cycle 5, and after Cycle 17 and 21 (Ptz + D arm only) (that is, every 6 weeks during neoadjuvant and adjuvant therapy). Subsequent LVEF assessments every 6 months for 2 years	Between Days 15 and 21 of Cycles 2, 4 and 6, after surgery and ≤ 7 days prior to Cycle 7, and between Days 15 and 21 of Cycles 10, 12 and 15 and 18 (FEC/Ptz + T + D arm only) (that is, every 6 weeks during the neoadjuvant period and every 6 to 9 weeks during the adjuvant period), at the post-treatment visit, then every 6 months for 2 years, then annually for 2 years	Every 9 weeks during study treatment, at the treatment discontinuation visit, then every 6 months for the first year, then annually for up to 3 years after the treatment discontinuation visit
Central review of cardiac data	Safety data (in general) reviewed by	Copies of MUGA and ECHO recordings were	An independent Cardiac Review Committee (CRC)

Parameter	NEOSPHERE (WO2067)	TRYPHAENA (BO22280)	CLEOPATRA (WO20698)
	steering committee	sent to a central laboratory for independent assessment	reviewed data for all potential cardiac events
CHF= congestive heart failure; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NCI-CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association			

Comment: There was some variability in the terminology used to describe significant cardiac dysfunction, with symptomatic left ventricular systolic dysfunction (Grade 3 and above) being used in the TRYPHAENA (BO22280) and CLEOPATRA (WO20698) studies and symptomatic LVSD being classified as congestive heart failure in the NEOSPHERE (WO20697) study. This is considered in reviewing the aggregate data across the studies.

Several other parameters were specifically followed as per Table 4.

Table 4: Other events to monitor in the NEOSPHERE (WO20697), TRYPHAENA (BO22280) and CLEOPATRA (WO20698) studies (17, 22 and 23)

Adverse events to monitor	Safety analysis strategy
Diarrhoea	PT 'Diarrhoea'
Rash	Roche standard AEGT 'EGFR-associated rash'
Leucopoenia, neutropenia	SMQ (narrow) 'Haematopoietic leucopoenia'
Febrile neutropenia	PT 'Febrile neutropenia' – 'subgroup of the search for 'leucopoenia'
Leucopenic infection Febrile neutropenic infection	Events from the 'Infections and infestations' SOC with a start date of a Grade > 3event of SMQ (narrow) 'Haematopoietic leucopenia' and for infections following PT 'Febrile neutropenia'; subgroup of the search for 'Leucopenic infection'
Interstitial lung disease	SMQ (narrow) 'Interstitial lung disease'
Hypersensitivity/anaphylaxis	Roche standard AEGT 'Anaphylaxis and hypersensitivity', containing the MedDRA SMQ (narrow) 'Anaphylactic reaction' plus all MedDRA PTs containing 'Hypersensitivity'
Mucositis	Roche Standard AEGT 'Mucositis of gastrointestinal tract'
Cardiac dysfunction/SAEs suggestive of CHF	Serious events from the SMQ (wide) 'Cardiac failure' (see also preceding table)
QT prolongation	SMQ (wide) 'Torsade de pointes/QT

Adverse events to monitor	Safety analysis strategy
	prolongation'
Venous thromboembolic events	Roche standard AEGT 'Thromboembolic events-venous'
Hepatic related AEs (for TRYPHAENA and CLEOPATRA)	SMQ (wide) 'Drug Related Hepatic Disorders; comprehensive search'
AEGT=adverse events group terms; CHF =congestive heart failure; EGFR=epidermal growth factor receptor; PT=preferred term; SMQ=standard MedDRA queries; SOC=system organ class	

Patient exposure

The number of patients exposed to pertuzumab in the three studies evaluated is as follows:

NEOSPHERE (WO20697): 309

- 107 patients exposed to the combination of pertuzumab, trastuzumab and docetaxel
- 108 patients exposed to the combination of pertuzumab and trastuzumab
- 94 patients exposed to pertuzumab and docetaxel

TRYPHAENA (BO22280): 223

- 72 patients exposed to pertuzumab in combination with trastuzumab, docetaxel and FEC
- 75 patients exposed to pertuzumab in combination with trastuzumab and docetaxel subsequent to FEC
- 76 patients exposed to pertuzumab in combination with trastuzumab, docetaxel and carboplatin

CLEOPATRA (WO20698): 408

- 408 patients on this study received pertuzumab in combination with trastuzumab and docetaxel.

A further 696 patients have been exposed to pertuzumab in earlier studies submitted previously for regulatory review (BO17931, BO17929, BO16934, TOC2689g, TOC2572g, BO17004, TOC2682g, TOC2297g, BO17003, BO17021, WO20024, TOC3258g), and have not been reviewed again here.

Importantly, the patients on the CLEOPATRA study did receive substantially more pertuzumab than those treated in the neoadjuvant studies, receiving a median of 8 cycles of pertuzumab + trastuzumab + docetaxel, and a median of 24 cycles of pertuzumab + trastuzumab, with sufficient follow-up (of greater than 2 years) to allow for the identification of delayed toxicity.

Safety issues with the potential for major regulatory impact

No additional issues identified.

Postmarketing data

Cumulative exposure to pertuzumab is shown in Table 5 below.

Table 5: Cumulative pertuzumab exposure from marketing experience

Indication	Sex			Age (years)				Region			
	M	F	Unk	2 to ≤ 16	> 16 to ≤ 65	> 65	Unk	Europe	USA	RoW	Japan
MBC	50	6,187	4,588	0	3,680	2,557	4,588	2,392	6,237	676	1,520
EBC	4	517	0	0	391	130	0	0	521	0	0
Total	54	6,704	4,588	0	4,071	2,687	4,588	2,392	6,758	676	1,520
Grand Total	11,346			11,346				11,346			

EBC = early breast cancer; F = female; M = male; MBC = metastatic breast cancer; RoW = rest of world; Unk = unknown

In the interval between 11 September 2001 and 7 December 2013, an estimated total of 11,346 patients have received commercial pertuzumab. A cumulative summary of serious adverse events from post-marketing sources between 08 June 2012 and 07 December 2013 is presented below in Table 6.

Table 6: Cumulative Summary Tabulations of Serious Adverse Reactions from Post-Marketing Sources*

System Organ Class	Spontaneous, including regulatory authority and literature	Non-interventional post-marketing study
	Serious Cumulative	Serious Cumulative
Infections and infestations	13	15
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15	29
Blood and lymphatic system disorders	23	33
Immune system disorders	11	4
Endocrine disorders	0	0
Metabolism and nutrition disorders	5	11
Psychiatric disorders	2	0
Nervous system disorders	15	18
Eye disorders	3	1
Ear and labyrinth disorders	0	0
Cardiac disorders	19	23
Vascular disorders	9	1
Respiratory, thoracic and mediastinal disorders	45	19
Gastrointestinal disorders	67	28
Hepatobiliary disorders	5	8
Skin and subcutaneous tissue disorders	22	4
Musculoskeletal and connective tissue disorders	4	6
Renal and urinary disorders	3	5
Pregnancy, puerperium and perinatal conditions	0	0
Reproductive system and breast disorders	0	0
General disorders and administration site conditions	59	78
Investigations	19	10
Injury, poisoning and procedural complications	13	8
Surgical and medical procedures	0	3
Social circumstances	1	0
TOTAL	**353**	**304**

Table is derived from Appendix 3 of PBRER No. 1053870 (08 June 2013 to 07 December 2013).

* Non-interventional studies and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, regulatory authorities, and scientific literature).

Cumulative data covering the period from 08 June 2012 (IBD) to 07 December 2013.

Comment: No new concerns above those raised in the studies are noted.

Evaluator's conclusions on safety

The safety profile for pertuzumab, as shown in the NEOSPHERE (WO20697), TRYPHAENA (BO22280) and CLEOPATRA (WO20698) studies, is consistent with other monoclonal antibodies and agents targeting the HER1 and HER2 receptors and with previous data for pertuzumab in patients with advanced malignancies.

- Administration of pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting did not reveal any new or unexpected safety findings, with the exception of the following:

  - Slightly higher rates of cardiac toxicity with the combination of pertuzumab + trastuzumab + docetaxel. However, the rates of symptomatic LVSD were low. In all treatment groups, LVSD tended to be asymptomatic reversible declines in LVEF.
  - Rates of both neutropenia and diarrhoea are reasonably high – these two toxicities in combination are concerning due to the risk of Gram negative (-ve) neutropenic sepsis, and will possibly lead to a requirement to co-administer Granulocyte-colony stimulating factor (G-CSF). This concern was not reflected in study outcomes.

- Overall, the addition of pertuzumab to a docetaxel/trastuzumab backbone does not appear to increase toxicity markedly and was consistent with the data from the CLEOPATRA (WO20698) study in patients with MBC. In both studies, the addition of pertuzumab to trastuzumab and docetaxel did not result in a major increase in toxicity compared with trastuzumab and docetaxel (T+D).
- Across the studies, the addition of pertuzumab to the regimen appeared to be well tolerated with few discontinuations.
- Across the three studies, the most frequently reported AEs were those typically associated with chemotherapy: alopecia, neutropenia, diarrhea, nausea, vomiting, fatigue and rash. The incidence of diarrhea, rash, hypersensitivity/anaphylaxis and mucositis was higher in the Ptz+T+D arm compared with the T+D arm of the NEOSPHERE (WO20697) study, although few events were Grade ≥ 3. These findings are consistent with those seen in the CLEOPATRA (WO20698) study, apart from hypersensitivity/anaphylaxis that was not more frequent in the Ptz+T+D arm of the CLEOPATRA (WO20698) study.
- Pertuzumab infusions were generally well tolerated and most infusion associated events were Grade 1 or 2 in severity. No fatal events were reported.
- Toxicities appeared to be generally worse in Asian patients, an important caveat for the Australian patient group, and should be addressed in the Product information.

First round benefit-risk assessment

First round assessment of benefits

The NEOSPHERE (WO20697) study demonstrated a statistically significant improvement in pCR in the breast through the addition of pertuzumab to a neoadjuvant schedule of trastuzumab and docetaxel (45.8% vs 29% in the comparator). This is a surrogate end point using a definition of pCR that is not the optimal measure recommended by international regulators in the US and Europe. The high rate of pCR with the addition of pertuzumab was reinforced by the high pCR rates observed in all arms of the TRYPHAENA (BO22280) study. pCR remains a controversial surrogate end point for long term outcome from breast cancer, however the impressive results from the CLEOPATRA (WO20698) study in metastatic breast cancer provide significant optimism that the pCR changes observed in the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies will translate into improved survival.

Nevertheless, in Australia, neoadjuvant therapy for breast cancer is utilised in a small fraction of cases (<3%), a fraction on which will be HER2 +. Of those approximately 50% will be endocrine receptor positive and less likely to achieve pCR using a neoadjuvant strategy. Importantly, the results of the APHINITY (BO25126) study are anticipated to show a benefit for a more substantial period of 1 year of pertuzumab/trastuzumab therapy in the adjuvant setting. If this is the case, then the benefit of 3 to 6 doses of neoadjuvant pertuzumab may be debatable. The possible exception to this are patients for

whom a high likelihood of tumour response will determine the difference between operability and inoperability, as surgical management of breast cancer remains a pillar of breast cancer management especially with regard to local control.

First round assessment of risks

In general, there are slightly higher rates of toxicity with the addition of pertuzumab to a neoadjuvant trastuzumab/chemotherapy backbone, and are comparable to those observed in the CLEOPATRA (WO20697) study. In particular, although there are slight increases in cardiac toxicity observed in the pertuzumab-containing arms, episodes of LV dysfunction were often asymptomatic, and frequently reversible. In particular the rates of $\geq$ Grade 3 toxicity are <5% across the three studies reviewed.

There does however appear to be a high rate of both diarrhoea and neutropenia, a combination of particular concern for medical oncologists due to the risk of Gram negative sepsis, and consequently co-administration of G-CSF is advisable. Asian patients appear to be more susceptible to toxicity.

First round assessment of benefit-risk balance

The benefit-risk balance of the proposed extension of indications, acknowledging that Conditional Registration is not available in Australia, is *unfavourable* given the proposed usage. At the present time, the use of neoadjuvant pertuzumab can be said to increase pCR, but survival end points are essentially speculative. This may change in the light of forthcoming adjuvant data.

First round recommendation regarding authorisation

Increasingly, neoadjuvant chemotherapy has become a reasonable choice of initial treatment of breast cancer, aimed at improving the resectability of disease that is locally advanced, of large tumour size and of inflammatory subtype. The theoretical benefits of a neoadjuvant strategy also include increasing breast conservation as opposed to mastectomy (that is, a cosmetic outcome) and the opportunity to discontinue ineffective systemic therapy in those patients whose cancers fail to respond to treatment. The meta-analysis of Mauri et al[16] reassured clinicians that neoadjuvant chemotherapy did not lead to inferior systemic outcome outcomes, and there are now meta-analyses that show a consistent association between the development of a pathological complete response (pCR) following neoadjuvant therapy and disease-free (DFS) and overall survival (OS).[17],[18]

Although Australian regulators do not yet supply guidance in relation to the use of pCR as a surrogate end point, the FDA in conjunction with the American Society of Clinical Oncology has developed a guidance document that concluded that '*a large improvement in pCR rate based upon analysis of a full intent-to-treat population was reasonably likely to predict clinical benefit, and that the potential advantages of granting accelerated approval based upon pCR from a neoadjuvant randomised controlled trial generally outweighed concerns*'. However the precise magnitude of the pCR improvement remains unknown.

[16]Mauri D, et al. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005; 97:188-194.
[17]Cortazar P, al. Pathological complete response and long- term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Feb 13. pii: S0140-6736(13)62422-8. doi: 10.1016/S0140-6736(13)62422-8. [Epub ahead of print]
[18] von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30:1796-1804.

It is not known is whether an increase in a certain pCR rate, will translate into an increased event free survival (EFS), DFS or OS. The NEOSPHERE (WO20697) study showed that the addition of pertuzumab to docetaxel + trastuzumab increased the bpCR rate (in the breast) about 1.5 fold, the tpCR rate 1.8 fold and the GBG pCR rate 2.7 fold. It is unclear whether this magnitude of change in pCR rate is sufficient to translate into meaningful long term benefit, and no statistically significant changes in long term outcome were presented although the rates of disease recurrence/progression and death were numerically lower in the arm receiving triple therapy. The evaluator notes the document m53531 v000092 '*Pathologic Complete Response Analyses in Early Breast Cancer'* in which meta-analysis regression and simulation approaches on clinical trial data from 656 HER2+ patients in NOAH and GeparQuattro were conducted. These analyses suggested that a difference in pCR of 15 to 20% may lead to a meaningful difference in EFS, at least for a HER2 targeted therapy, although concluded that '*the findings from these exploratory analyses need to be confirmed by data from further studies'*. It should be noted that the Prentice criteria were not met and statistical simulations were used to justify the argument that pCR is a surrogate for long-term outcome.

In addition, there is clear heterogeneity in the utility of pCR as an indicator of outcome in patients with breast cancer, even within the HER2+ group. The findings of the German Breast Group meta-analysis, the NeoALTTO study and the CTNeo BC meta-analysis show that pCR does not predict DFS/OS in HER2+ER/PR+ tumours.[17,18,19] In addition, both the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies showed lower pCR rates in the hormone receptor positive group, questioning the utility of a neoadjuvant strategy in such patients (particularly those who are be clearly operable at baseline).

Finally, although proponents of neoadjuvant therapy for breast cancer cite increased breast conservation rate as a potential benefit, this was not observed in the pivotal NEOSPHERE (WO20697) study.

Thus, the conclusion of the reviewer is that there are insufficient data to recommend the extension of indications in their entirety. The evaluator considers that a consideration should be given to extending the indications to those patients in whom tumour response is critical to allow definitive surgery with a view to optimising local control, with the wording as follows:

Additional indication: for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2 positive, borderline-operable locally advanced breast cancer as part of an anthracycline- or carboplatin-containing treatment regimen. The term 'borderline-operable' pertains to tumours that are inoperable on surgical assessment, in which tumour shrinkage would facilitate definitive surgery with curative intent.

Further extension of indications will require assessment of data from the ongoing adjuvant pertuzumab studies.

Clinical questions

Pharmacokinetics

1. Further explanation for the effect on trastuzumab serum levels should be sought from the sponsor. The measured trastuzumab level was lower in the NEOSPHERE (WO20697) study, with around a third of patients analysed having suboptimal serum trough levels of trastuzumab. The sponsor is requested to provide updated data as to

[19]Piccart-Gebhart MJ, et al. The association between event-free survival and pathological complete response to neoadjuvant lapatanib, trastuzumab or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTTO Study (BIG 1-06). Cancer Res 2013: Abstract S1-01.

the explanation for this, and analyses as to the efficacy of trastuzumab at these lower doses.

Efficacy

2. Further analysis of the implications for ATAs on efficacy should be sought from ongoing studies. The sponsor is requested to provide further data in relation to this question.
3. For the DFS end point the idea of censoring the patients with a non-pCR outcome after neoadjuvant therapy is noted and the reviewer has concerns regarding this as it suggests those who respond less well to the neoadjuvant therapy will not be analysed further after that surgery (as they are censored from the analysis, despite being rendered 'disease free' by surgery). Given this statistical decision it is important to reiterate that the survival end points in this study are descriptive only. The sponsor is requested to provide revised DFS estimates without this censoring.
4. Prior to treatment, lymph nodes were assessed by institutional practice which is potentially quite variable, and did not include lymph node sampling. Thus it is unclear how comparable the baseline nodal status was between the groups. The sponsor is requested to clarify if they have any data in relation to baseline nodal assessment.

Safety

5. Some clarification would assist as to the rates of clinically significant haematological toxicity (e.g. febrile neutropenia) in the different treatment phases of the study.
6. The VTE rate was low at around 2% in most treatment arms studied across all 3 studies. The only exception was that 3.7% of patients in the Ptz+T+D arm had VTEs, of which just under half were pulmonary emboli. Although it is likely that the hypercoagulable state associated with the metastatic setting contributed to this, data from the adjuvant APHINITY (BO25126) study would be helpful to examine the issue of VTE risk in a curative (non-metastatic) setting. The Sponsor is requested to provide any further data relating to this question if available.
7. The sponsor's Summary appears to have a typographical error in the Ptz + D column that reads 7.4%, where is actually should read 6.4%. The sponsor is requested to clarify.

Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to the Clinical questions listed above and the evaluator's comments on the sponsor's responses can be found in Attachment 2 to this AusPAR.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of pertuzumab in the proposed usage are unchanged from those identified in the first round evaluation. The evaluator notes the comprehensive review of the data pertaining to pCR rate across breast cancers of differing disease extent (operable, locally advanced, and inflammatory) provided by the sponsor in addition to the responses to the clinical questions. These data

do indicate higher pCR rates, regardless of pCR definition used, with pertuzumab-containing neoadjuvant regimens. These data do not and cannot address the issues related to the use of pCR as a surrogate end point as detailed in the Clinical rationale section of the report. Nevertheless, the survival data for pertuzumab in metastatic disease are compelling and thus it is very likely that use of neoadjuvant pertuzumab in will ultimately result in survival benefit in this setting also. This expectation is congruent with the tenor of discussions around this area among Australian thought leaders. Furthermore, the evaluator recognises that pertuzumab has been approved for the neoadjuvant indication by regulators in Europe and in the United States.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of pertuzumab in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of pertuzumab, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

After consideration of the clinical data submitted and the responses to the Clinical questions, the evaluator recommends the following indication statement:

Additional indication: Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2+, locally advanced, inflammatory or early stage breast cancer (> 2 cm in diameter) as part of a complete treatment regimen for early breast cancer.

This indication must have appended to it, the following 'Note to the Indication': the approval is based upon a surrogate endpoint and improvement in disease free, progression free or overall survival have not been demonstrated.

This '*Note to the Indication'* must be included in any marketing material as a condition of registration. Once confirmatory data are available demonstrating survival benefit, the '*Note to the Indication'* can be removed.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 5.1 (dated 20 May 2015, Data Lock Point (DLP) 28 February 2015) and Australian Specific Annex Version 3.0 (dated July 2015)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7: Summary of ongoing concerns

Summary of Safety Concerns	
Important Identified Risks	Exacerbation of chemotherapy/docetaxel associated neutropenia
	Infusion-related reactions, Hypersensitivity reactions/anaphylaxis
	Congestive heart failure
	Mucositis
	Grade ≥3 diarrhoea
	Interstitial lung disease
Important Potential Risk	Oligohydramnios*
Missing Information	Risk in patients aged 75 years or older
	Risk in pregnant women
	Risk in lactating women
	Risk in fertility in humans
	Risk in male breast cancer patients
	Risk in patients with cardiovascular impairment
	Risk in patients with hepatic impairment
	Risk in patients with severe renal impairment
	Risk of lack of efficacy due to immunogenicity

*From the sponsor: Oligohydramnios has not been reported in patients treated with pertuzumab but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities. No additional risk minimisation activities are proposed.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the clinical evaluators through the TGA's consolidated request for further information and Clinical Evaluation Report. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor deferred their response pending receipt of the Delegate's Overview.	The sponsor's response is noted.
The proposed PI indicates a degree of risk regarding cardiotoxicity in patients with prior anthracycline use, and notes that '*There is insufficient evidence to recommend concomitant administration of an anthracycline with Perjeta.'* The Delegate may wish to consider contraindicating coadministration of Perjeta with anthracyclines based on the limited data and potential increased risk of cardiac toxicity.	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.
There are additional adverse effects specified under the 'Undesirable Effects' for the Metastatic Breast Cancer indication in the EU Summary of Product Characteristics (SmPC): this includes 'pain in extremity (13.4%), back pain (12.1%) and cough (12.1%).' Cough also appears as 'Very Common' in the table of 'Undesirable Effects' in the SmPC. The Delegate may wish to	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
include these adverse effects in the PI.		
The SmPC notes that '*The safety of Perjeta administered for more than 6 cycles in the neoadjuvant setting has not been established.'* The Delegate may wish to include this advice in the PI.	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.
There is a typographical error in the proposed PI (under 'Left Ventricular Dysfunction'): the word 'LVD' is missing in the last paragraph following the term 'symptomatic'. This should be corrected.	The sponsor deferred their response pending receipt of the Delegate's Overview.	The recommendation remains that this typographical error be corrected.
There is additional Clinical Trial information included in the SmPC under 'Undesirable Effects' for febrile neutropenia. Febrile neutropenia is included in the Precautions of the PI, however the advice is different. The Delegate may wish to consider aligning the advice in the Adverse Effects section of the PI.	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.
The potential severity of diarrhoea is not communicated as strongly in the PI as in the SmPC. The Delegate may wish to consider aligning the advice to include text similar to the SmPC, and particularly that diarrhoeal events were responsive to proactive management with anti-diarrhoeal agents. Further, Clinical Trial advice is included in the SmPC and may be considered for inclusion in the PI.	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.
'Rash' is noted under 'Undesirable Effects' in the SmPC but is not included in the PI. The Delegate may wish to consider aligning the advice.	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.
There is additional Clinical Trial	The sponsor deferred	This issue is

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
information included under 'Laboratory abnormalities' in the SmPC that is not included in the proposed PI. The Delegate may wish to consider aligning the advice.	their response pending receipt of the Delegate's Overview.	deferred for final determination by the Delegate.
The sponsor notes that Interstitial Lung Disease is listed in the SmPC as an uncommon adverse event but is not included as an adverse event in the Australian PI (or company core data sheet [CCDS]). The Delegate may wish to include advice relating to interstitial lung disease in the PI given it has been categorised by the sponsor as an important identified risk (that is, advice included in Precautions and Adverse Effects).	The sponsor deferred their response pending receipt of the Delegate's Overview.	This issue is deferred for final determination by the Delegate.
Any changes made to the PI as a result of the evaluation process should be reflected in the Consumer Medicine Information.	The sponsor deferred their response pending receipt of the Delegate's Overview.	The recommendation remains that any changes made to the PI as a result of the evaluation process should be reflected in the Consumer Medicine Information.

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has not addressed all of the issues identified in the RMP evaluation report. Outstanding issues are summarised below.

Outstanding issues

Issues in relation to the RMP

The sponsor notes the following in their response of 3 December 2015:

> *As per the email communication with [the TGA] on 26 November 2015, comments on the suggestions for revisions to the PI that were raised by the RMP evaluator for consideration by the Delegate have not been included in this response, given the timeframe between receipt of the report on 26 November and the due date for the consolidated S31 responses. The updates will be addressed when the Delegates Overview is received.*

The issues raised in the first round RMP evaluation report relate to PI changes that are deferred to the Delegate for final approval. If these recommendations are accepted by the Delegate, any changes to the PI must ultimately be reflected in an updated ASA to the RMP.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

No updated RMP was submitted in response to the request.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU RMP Version 5.1 (dated 20 May 2015, data lock point 28 February 2015) with Australian Specific Annex Version 3.0 (dated July 2015) and any future updates as a condition of registration.*

VI. Overall conclusion and risk/benefit assessment

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

Neoadjuvant treatment (systemic treatment given prior to definitive breast surgery) is used in Australia to downstage locally advanced and/or inoperable breast cancers to improve surgical outcomes, and is the primary treatment modality for inflammatory breast cancer. It is also used for less advanced breast cancers to facilitate breast-conserving surgery in those where surgical options would otherwise be mastectomy or partial mastectomy, or to improved cosmesis in those already candidates for breast-conserving surgery. Consistent with other systemic treatments, the goal is also to reduce the risk of distant recurrence.

Neoadjuvant treatment also allows an assessment of the efficacy of a treatment, with clinical, radiological, pathological complete response and biomarker assessments possible means for determining a treatment response. A change in treatment and/or modality can be made for those not responding. Neoadjuvant treatment strategies are also used to assess novel therapies in the clinical research setting and have been accepted by international regulatory agencies as a means of accelerating the approval process for the development of therapies usually supported by data from trials in the metastatic setting, using pathological complete response rate as a surrogate endpoint for long term benefit. Such approvals are designed to encourage development of new therapies, and to provide access to populations at high risk of relapse for whom access would otherwise delayed while awaiting the results from clinical trials conducted in the adjuvant setting.

In October 2014, the FDA released a Guidance document for Industry document '*Pathological Complete Response in Neoadjuvant Treatment of High-risk early-stage breast cancer: use as an endpoint to support accelerated approval*'. In such approvals, confirmation of the clinical benefit is required for conversion to a full approval, usually from a large randomised Phase III trial in the adjuvant setting. Similarly, in July 2015, the EMA released guidance on '*the role of the pathological complete response as an endpoint in neoadjuvant breast cancer studies'* in Appendix 4 to the guideline on '*The evaluation of*

anticancer products in man'. Of note, conditional marketing authorisation can only be granted at the time of initial registration by the EMA (not for extensions of indications), and therefore there may be agreed conditions of registration for clinical trials confirming the clinical benefit to be submitted. The TGA has decided not to adopt the EMA guideline incorporating the guidance on pCR. However, the advice provided in both guidelines has been considered in the evaluation of this application, and preparation of this overview.

In the pooled analysis conducted by Cortazar et al (2014)[20] in which data from nearly 12,000 patients was analysed, 'eradication' of tumour from both the breast and lymph nodes following neoadjuvant therapy had a stronger association with improved event-free survival (EFS) and overall survival (OS), but residual ductal carcinoma in situ was not prognostic. The strongest correlation was seen in triple negative or HER2 positive, hormone receptor negative subtypes; for ER-positive breast cancer a lower pCR did not necessarily predict a poorer long term outcome. pCR response rates with the addition of targeted therapy (for example, 20% improvement with the addition of trastuzumab to neoadjuvant chemotherapy in the NOAH trial) in patients selected by their tumour target expression (HER 2 status), were greater than in trials of chemotherapy combinations in heterogeneous populations.

For regulatory purposes, both the FDA and EMA define pathological complete response (pCR) as the absence of residual invasive cancer on haematoxylin and eosin evaluation of the complete resected specimen and all sampled ipsilateral nodes following completion of the neoadjuvant systemic therapy (ypT0/is ypN0); the FDA also accepts clinical trial designs incorporating the more stringent definition of the absence of invasive and in situ cancer in the breast specimen and all sampled regional nodes (ypT0/ypN0) (see Attachment 2) In this application, the former is accepted, that is, ypT0/is ypN0.

HER positive breast cancer

HER2 is involved in regulating cell growth, survival and differentiation.[21]. Amplification and/or overexpression of HER2 occurs in 15 to 20% of breast cancers and is associated with an aggressive tumour phenotype, higher rates of recurrence, and increased mortality A significant proportion of these deaths occur patients previously treated for non-metastatic disease, with clinical trials of neoadjuvant or adjuvant trastuzumab plus chemotherapy (the current standard of care) reporting 5 year relapse rates ranging from 17% to 40% depending on stage of disease and tumour characteristics of the patients enrolled. Thus there remains significant unmet need for a more effective treatment of early HER2 positive breast cancer.

Neoadjuvant trastuzumab (a HER2 targeting monoclonal antibody) is approved in Australia for the treatment of HER2 positive locally advanced breast cancer in combination with chemotherapy followed by adjuvant trastuzumab (NOAH trial; see Attachment 2). Approval for neoadjuvant use was based on an improvement in pCR rates in a trial conducted after demonstration of an improvement in both disease free and overall survival in the metastatic and adjuvant settings.

In 2015, results from the large adjuvant ALTTO trial did not demonstrate a statistically significant increase in disease free or overall survival with the addition of lapatinib (a small molecule HER1 and HER2 tyrosine kinase inhibitor) to trastuzumab in the adjuvant setting); an earlier neoadjuvant study, NeoALTTO, had demonstrated a statistically significant 21% improvement in pCR rates of that combination added to chemotherapy compared with chemotherapy with trastuzumab.[22] This created some uncertainties as to

[20]Cortazar et al, Lancet 2014; 384:164-72

[21] Sundaresan, S et al, Current Oncology Reports 1999 1:16-22.

[22] Baselga et al, Lancet. 2012 Feb 18;379(9816):633-40

whether pCR could be used as a surrogate measure of longer term benefit in this HER2 positive subtype. The authors in reporting the study outcomes emphasised the lessons to be learned in planning adjuvant trials: the importance of tolerability of any added treatment, of understanding efficacy data from both clinical and preclinical data when designing a trial (that is, the totality of the data), as well as the challenges of demonstrating improvement in DFS and OS in the adjuvant trial setting where improved outcomes make demonstration of an additional, incremental benefit more difficult.[23] Recruitment of a relatively high proportion of lower risk patients (for example, those with node negative disease) may make demonstration of a statistically significant improvement in EFS, DFS or OS even more difficult. Both the FDA and EMA guidelines emphasise the importance of the magnitude of the pCR and totality of the existing data drawn from other trial settings required to support pCR.

Pertuzumab

Pertuzumab (Perjeta) is a recombinant, humanised, immunoglobulin (Ig) subtype G1κ monoclonal antibody, which targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity.

By binding to the subdomain 2 epitope of the extracellular domain of HER2, Pertuzumab prevents hetero-dimerization of HER2 with other members of the HER family (HER1, HER3 and HER4). As a result, ligand activated downstream signalling is blocked by pertuzumab. Pertuzumab is also capable of activating antibody dependent cell mediated cytotoxicity (ADCC). When combined with trastuzumab, pertuzumab provides a more complete blockade of the HER pathway resulting in augmented anti-cancer activity in patients with HER2 positive breast cancer.

Pertuzumab was approved by the TGA on 6 May 2013 for the first line treatment of metastatic HER2 positive breast cancer based on the CLEOPATRA (WO20698) study findings of improved median progression free survival when added to docetaxel and trastuzumab compared with placebo and docetaxel and trastuzumab: 18.7 months in the pertuzumab-containing arm versus 12.4 months in the placebo arm (HR = 0.68; 95% CI, 0.58 – 0.80; $p < 0.0001$). Updated median OS estimates provided in this application show a 16 month improvement in the pertuzumab arm: 56.5 months with pertuzumab/trastuzumab/docetaxel versus 40.8 months with placebo/trastuzumab/docetaxel (HR = 0.68; 95% CI, 0.56, 0.84; $p = 0.0002$).

Supported by this marked improvement in both PFS and OS in the metastatic setting, this application seeks registration of pertuzumab in combination with trastuzumab and chemotherapy based on pCR rates; confirmation of whether there is a benefit (EFS) in earlier stage disease with adjuvant usage and information regarding the duration of treatment required, will be determined in the Phase III randomised, controlled adjuvant clinical trial, APHINITY, scheduled to report at the end of 2016/early 2017 with a clinical study report likely to be available in 2017. It is the first such application for registration for neoadjuvant use using pCR without supportive data from the adjuvant setting.

TGA approach to this application

The sponsor did not seek a pre submission meeting with the TGA to discuss the application with the TGA prior to lodgement. After completion of the evaluation phase, an Oncology Working Group (OWG) was set up to obtain expert advice from Australian medical oncologists specialising in breast cancer to inform on key matters relevant to

[23] Piccart-Gebhart et al Journal of Clinical Oncology 2015 November accessed Feb 8, 2016 at http://jco.ascopubs.org/content/early/2015/11/23/JCO.2015.62.1797.full.pdf+html

inform the decision. The following information was provided to the OWG: a Delegate Report including the questions to be addressed, the final (Round 2) clinical evaluation report following completion of both rounds of evaluation, and the EMA guidelines and FDA guidance, (noting that neither of these guidelines has been adopted by the TGA).

The sponsor made the following documents available to the TGA for reference:

- Final Clinical Study Report – WO20697 Research Report 1062325/February 2015
- CHMP Assessment Report 25 June 2015
- CHMP Opinion
- EMA Request for Supplemental Information (RSI)
- Response to first RSI
- EMA second RSI
- Response to second RSI
- SAG-O (Specialist Advisory Group – Oncology) Meeting Minutes
- SAG-O Roche Written Response
- Primary CSR from Study WO20697; CSR for an updated analysis from Study WO20697
- Primary and Addendum CSRs from 20698

The FDA clinical review and label were used for reference and accessed at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

The FDA Guidance for Industry document 'Pathological Complete Response in Neoadjuvant Treatment of High-risk early-stage breast cancer: use as an endpoint to support accelerated approval'

The EMA Guideline 'The evaluation of anticancer products in man. Appendix 4' point 6: 'the role of the pathological complete response as an endpoint in neoadjuvant breast cancer studies'

Overseas regulatory history

In September 30 2013, the FDA granted accelerated approval for the following indication:

> *Perjeta is a Her2 Neu receptor antagonist indicated for use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival.*
>
> *Limitations of usage:*
>
> *The safety of Perjeta as part of a doxorubicin-containing regimen has not been established. The safety of Perjeta administered for greater than 6 cycles for early breast cancer has not been established.*

The following is taken from the FDA website accessed 21 January 2016. '*This accelerated approval is based on demonstration of an improvement in pCR rate. No data are available demonstrating improvement in event-free survival or overall survival. Continued approval for this indication is contingent upon demonstration of improvement in disease-free survival in the confirmatory trial*.'

The EMA granted marketing authorisation on 31 July 2015 for the following indication:

> *Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.*

Delegate comment: Submission of the CSR for the APHINITY trial (see Conditions of Registration) was made a condition of registration by the EMA and is the confirmatory trial defined in the FDA indication. The advice of the Oncology Working Group as to whether the APHINITY Trial design is likely to address this question is sought (see Advice sought and also Background section on HER2 positive breast cancer).

No application has been lodged in Canada.

Oncology working group responses to delegate's request for advice

The Delegate's questions are in italics.

1. *Whether the observed 17.8% (95% CI: 5.4, 29.4) increase in pathological complete response (pCR) with adding pertuzumab to trastuzumab and docetaxel preoperatively is considered sufficiently large to translate into a significant improvement in longer term outcomes such as disease-free survival or overall survival.*

While the increase in pathological complete response rate in NEOSPHERE is noted, it cannot be determined from the data presented whether the increase in pCR will result in an improvement in longer-term outcomes such as disease-free or overall survival. Concern was also raised, particularly given what is known about the optimal duration of HER2 blockade with trastuzumab, that the optimal duration of therapy with pertuzumab has not yet been identified and that it cannot be certain that 4 to 6 cycles of pertuzumab given preoperatively are sufficient to see the benefit observed in the pCR rate translated into an improvement in longer term outcomes such as disease-free or overall survival. This is particularly so for those in the study with a lower risk of relapse, who might already be sufficiently and adequately treated with currently approved therapies. The sponsor has proposed that this be used in those with a 'high risk of relapse' and this issue is further addressed in the response to Question 4.

2. *Whether the observed 10% improvement in pCR rates in those with hormone-receptor positive tumours is considered sufficiently large to translate into a significant improvement in longer term outcomes such as disease-free survival or overall survival.*

It is recognised that there is hetereogeneity within HER2 positive ER-positive tumours, with variable response rates to anti-HER2 therapies. This is likely to explain the lower pCR rate observed compared with the overall study population in the NEOPSHERE study. The wide confidence intervals around the sample mean estimate of 10% pCR rate was noted. It was also noted from the Cortazar meta-analysis that pCR is a poor endpoint for predicting long term disease-free and overall survival outcomes in patients with this tumour subtype. For this population, the pCR is a measure taken when such patients have not received complete therapy, and in particular endocrine therapy. In the pivotal efficacy study (NEOSPHERE), these patients had neither received the full chemotherapy regimen (FEC given post-operatively) nor endocrine therapy.

Direct supportive evidence for a benefit of pertuzumab in this subgroup is provided by the improved PFS and OS observed in the metastatic setting in the CLEOPATRA study; indirect supportive evidence can be drawn for a benefit from anti-Her2 directed therapy by the improved PFS and OS observed in both adjuvant and metastatic trials with trastuzumab.

Therefore, acknowledging the limitations of pCR as an endpoint in this population, the lower rate should not be taken to mean these patients will not benefit and there is insufficient evidence to exclude them from any approved indication.

As stated above, it is not possible to determine from the data presented whether this pCR rate will translate into a longer term benefit, and it cannot be ascertained that 4 to 6 cycles of pertuzumab given preoperatively are sufficient to see the benefit observed the pCR rate translated into an improvement in longer term outcomes such as disease-free or overall survival, particularly for those with early stage breast cancer.

3. *Whether the Aphinity clinical trial design is likely to address adequately the question of whether there is a long term benefit from combining pertuzumab with chemotherapy and trastuzumab in the adjuvant setting.*

   Protocol amendments made to address this specifically (Sept 2012)

   Increase sample size (3806 to 4800)

   No more node negative patients

   At 3 yr assessment, expecting 2.6% difference. 'The smallest estimated difference detectable at a 5%, 2 sided significance level is HR = 0.818, under which the magnitude of treatment effect will be 1.9%.'

The Working Group's view is that the APHINITY trial is designed to address the different question of whether one year of treatment with pertuzumab in addition to chemotherapy and trastuzumab confers statistically significant benefit in improving invasive disease-free survival. No data are presented or available, so it is not possible to make any further comment. The Working Group did not feel this study could inform the present decision, which considers the effect of 4 to 6 cycles of pertuzumab administered solely in the neoadjuvant setting.

4. *Whether the sponsor's currently proposed indication adequately defines the target population.Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence as part of a complete treatment regimen for early breast cancer.*

The Working Group felt the current indication was too broad, and the subjective interpretation of 'at high risk of recurrence' could be extrapolated beyond what was supportable by the currently limited evidence available from the two Phase II studies. An improvement in pathological complete response rate supports an increased potential for immediate clinical benefit at the completion of neoadjuvant treatment where there is the greatest risk of relapse, that is, for those with locally advanced or inflammatory breast cancer. In this population, an improved pCR rate would translate into an improved surgical outcome where surgery may otherwise have been difficult or perhaps not possible. This potential clinical benefit balanced the concerns about the lack of data to support longer term outcomes, leading to an overall positive benefit-risk assessment for these patients.

In the absence of any data demonstrating a longer-term benefit from adding pertuzumab to pre-operative trastuzumab and chemotherapy, it could not be stated that pCR rates indicate a clinical benefit for those with early breast cancer. Evidence to support usage in this lower risk population will be informed by the results of the APHINITY trial, and this is required before a benefit-risk assessment can be made.

It was also noted that although the toxicities might be reported as 'manageable', the addition of pertuzumab increased adverse event rates with a significant potential to impact quality of life negatively, such as diarrhoea, which often requires daily anti-diarrhoeals to control. The negative impact on quality of life should not be overlooked and informed the Working Group's view that use should be restricted to those where a benefit can be established on currently available evidence.

Thus, the Working Group considered that the indication should be modified to restrict usage in those with inflammatory or locally advanced HER2 positive breast cancer and that there was insufficient evidence demonstrating a clinical benefit in those with early stage breast cancer.

5. *Is the improvement in pCR rate in NEOSPHERE, supported by the findings in Tryphaena and Cleopatra, sufficient as an endpoint in its own right that is,. is neoadjuvant usage supportable without reference to longer term clinical benefit which requires extrapolation?*

Large studies and meta-analyses have demonstrated that pCR is associated with improved longer term outcomes, particularly in certain HER2 positive subgroups (oestrogen receptor-negative), but it is difficult from the limited data presented here to state with any certainty that this will be the case because:

a. It is uncertain whether 4 to 6 cycles of pertuzumab are sufficient treatment to have an impact upon longer term outcomes, such as event-free, disease-free or overall survival. Current evidence from trastuzumab studies suggests that more effective blockade of HER2 pathways occurs with a longer duration of exposure than proposed here. Any potential long term gain with the addition of pertuzumab is particularly uncertain in the lower risk groups; the DFS and OS gains made from the addition of trastuzumab, which is the standard of care in Australia, may make it difficult to demonstrate a statistically significant incremental improvement in outcome with the addition of a short (or perhaps even a longer) course of pertuzumab. The results of the APHINITY trial are awaited to inform regarding this.

b. The optimal duration of pertuzumab therapy has not been determined in HER2 positive breast cancer treatment. Concern was expressed that this is an important question, in order to avoid over or under-treatment of patients with different baseline risks of recurrence. This is not addressed here.

c. It was considered important that, rather than try to determine benefits for which there is currently no direct evidence, the benefit of pathological response rate as an endpoint in its own right could be used to identify a population who might benefit from neoadjuvant usage of pertuzumab.

d. The need for more effective therapies is recognised, particularly for those with advanced or inoperable disease; here an increase in the pathological complete response rate is a relevant outcome in its own right and supports a higher likelihood of achieving a better surgical outcome for this group. Whether additional benefit beyond this in controlling local or distant recurrence is also conferred by this short course of pertuzumab added to existing therapies remains uncertain. This view informs the response to the advice regarding the indication (see Response to Question 4)

It was realistic to view pCR as an immediate potential clinical benefit in patients with locally advanced or inflammatory breast cancer and therefore to support the use of pertuzumab for these patients.

The longer term improvement in disease free, event free or overall survival remain unknown.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

During the evaluation, a mutual 5 month stop clock was required to allow evaluation of the CSR for the pivotal study, NEOSPHERE, which had not been included in the dossier.

Two pivotal Phase II studies NEOSPHERE (WO20697) and TRYPHAENA (BO22280) addressed the role of pertuzumab in the neoadjuvant setting using pathological complete response (pCR) as a surrogate end-point.

For the details of the clinical data and information submitted please *Scope of the clinical dossie*r, above.

Clinical evaluator's recommendation

The following in italics, reflects the clinical evaluator's recommendation and requirements for the application to be approved:

> *'Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory or early stage breast cancer (>2cm in diameter) as part of a complete treatment regimen for early breast cancer'.*
>
> **This indication must have appended to it, the following *'Note to the Indication':*** *the approval is based upon a surrogate endpoint and improvement in disease free, progression free or overall survival have not been demonstrated.*
>
> *This 'Note to the Indication' must be included in any marketing material as a condition of registration. Once confirmatory data are available demonstrating survival benefit, the 'Note to the Indication' can be removed.'*

The Delegate is in agreement with the clinical evaluator that any decision should clearly state the basis on which the decision was made, but considers that the *Note to the Indication* should specify that the endpoint is a demonstrated improvement in pathological complete response rate. The context of the Delegate's proposed modified indication is that pathological complete response is not being used as a surrogate marker of future clinical benefit.

Efficacy

NEOSPHERE (WO20697) was a multicentre, randomised trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2+ breast cancer (T2-4d). HER2 overexpression was defined as a score of 3+ Immunohistochemistry (IHC) or Fluorescence in situ hybridisation (FISH) amplification ratio of >2.0 as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery (see Figure 1 above) Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and oestrogen receptor (ER) or progesterone receptor (PgR) positivity.

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks for a total of 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles; the dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m^2),

epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After surgery, patients in the Perjeta plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC.

Primary endpoint

The primary endpoint of the study was pCR rate in the breast (ypT0/is). To enable cross trial comparisons, data on pCR rates as defined by the more stringent definitions requiring no residual invasive disease in the nodes, ypT0/ypN0 and ypT0/is ypN0, were also collected as exploratory endpoints.

Nodal involvement at baseline was predominantly determined clinically; assessment by ultrasound, magnetic resonance imaging (MRI) or computerised tomography (CT) was reported in 5.7%, 2.6% and 0.5%, respectively. Pathological assessment of the lymph nodes was not required by the NEOSPHERE and TRYPHAENA protocols and was reported in <2% of patients. Response rates in the breast and nodes were based on clinical examination after each cycle of treatment, up until surgery.

Delegate comment: The sensitivity of physical examination in determining lymph node involvement has been reported to be as low as 56.5%, increasing to 86% if that is accompanied by MRI imaging[24],[25]. Thus, although the sponsor indicates clinical examination alone was the clinical practice standard, the baseline nodal involvement is uncertain, was not a stratification factor (even distribution across the arms cannot be assumed) and in the absence of baseline histological or cytological data, it is not possible to attribute the absence of invasive cancer to a neoadjuvant treatment effect.

Pathologists were not blinded to treatment allocation (although most were unlikely to be aware of the treatment allocation) and there was no centralised review of the pathology from the surgical specimen.

Demographics were well balanced (median age was 49 to 50 years old, the majority were 572 Caucasian (71%) and all were female. 7% of patients had inflammatory cancer, 32% had locally advanced cancer, and 61% had operable cancer. Approximately half the patients in each treatment group had hormone receptor positive disease (defined as ER positive and/or PgR positive).

The efficacy results are summarized in Table 9. Statistically significant improvements in pCR rates by both the study (16.8%) and the more stringent and preferred definition of ypT0/is ypN0 (17.8%) were observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared with patients receiving trastuzumab plus docetaxel. In these two arms, the pCR rates were improved but to a lesser extent (10%) in the hormone receptor positive subgroups in favour of the pertuzumab arm. In the study overall, absolute pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor positive tumours compared with patients with hormone receptor negative tumours.

[24] Valente, S et al Annals of Surgical Oncology 2012 19:1825-30

[25] Dialani et al, Annals of Surgical Oncology 2015:22; 1416-24

Table 9: Summary of Efficacy for NEOSPHERE trial using ypT0/is ypN0 (absence of invasive cancer in the breast and lymph nodes)

	T+D	Ptz+T+D	Ptz+T	Ptz+D
Overall ITT	N=107	N=107	N=107	N=96
pCR, n (%) [95% CI]1	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes correction for CMH test)[2]	0.0063 (vs. T+D)	0.0223 (versus. T+D)	0.0018 (versus Ptz+T+D)	
Hormone receptor-positive subgroup	N=50	N=50	N=51[3]	N=46
pCR, n (%) [95% CI][1]	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormone receptor-negative subgroup	N=57	N=57	N=55[4]	N=50
pCR, n (%) [95% CI][1]	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13 (26.0%) [14.6, 40.3]

T=trastuzumab, D=docetaxel, Ptz=Perjeta, CI=Confidence Interval; 195% CI for one sample binomial using Pearson-Clopper method; 2p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment; 3One patient had unknown hormone receptor status. The patient did not achieve a pCR.

The sponsor provided a breakdown of the improvement in pCR, demonstrating a consistent effect across all groups including those with operable disease, the long term risk of relapse is lower in such patients and the longer term benefit of this improved pCR is uncertain. Interpretation of the small improvement in pCR rates with those with inflammatory breast cancer is difficult with the small numbers recruited due to this being a less common, but nonetheless very high-risk presentation of HER2 positive disease.

Table 10: Efficacy in Arm B (Ptz+T+D) versus Arm A (T+D) for the operable and ITT populations in NEOSPHERE

Efficacy of Ptz+T+D (Arm B) versus T+D (Arm A)	ITT	Operable (>2cm)
tpCR rate	Δ=17.8%	Δ=21.2%
PFS Hazard Ratio	0.69	0.67

Efficacy of Ptz+T+D (Arm B) versus T+D (Arm A)	ITT	Operable (>2cm)
DFS Hazard Ratio	0.60	0.61

Delegate comment: the study was designed as a proof of concept study:

i. With an overall alpha level of 0.2, to have an 80% power to detect an absolute percentage increase of 15% in pCR rates between each of the three primary comparisons; it is not known if this 15% predicts a longer term benefit.

ii. To isolate the effect of adding pertuzumab which may overestimate the effect of pertuzumab. In particular, the clinical benefit from FEC and endocrine therapy in those with oestrogen receptor positive tumours has not been captured and these would also be expected to affect DFS and OS.

iii. The study is not powered to demonstrate longer term efficacy endpoints so all such data are descriptive.

iv. The improvement in breast pCR rates was consistent at 16.8% (45.8% compared with 29%) and statistically significant with the addition of pertuzumab to docetaxel and trastuzumab. This statistical significance was maintained if the more stringent requirement of an alpha level of 0.05 was stipulated.

Secondary objectives (these are descriptive only and are discussed in detail in Attachment 2)

Notably, the increased rates of pCR seen in the pertuzumab/trastuzumab/docetaxel arm did not result in a higher conversion from planned mastectomy to breast conserving surgery in this treatment arm; however, the trial was not designed to answer this question and this outcome is likely to be influenced by factors including patient preference and these findings cannot be interpreted.

At the 2015 American Society of Clinical Oncology meeting, the 3 year survival rates, hazard ratios (HRs), and 95% confidence intervals (CIs) across all four treatment arms pooled, for all patients who achieved tpCR versus all patients who did not achieve tpCR, the HR for DFS was 0.68 (95% CI, 0.36 to 1.26) and the HR for PFS was 0.54 (95% CI, 0.29–1.00). These data are taken from the presentation and have not been evaluated by the TGA.

Table 11: 3 year survival estimates for patients in the NEOSPHERE trial (Gianni et al, 2015)[26]

		T+D (n = 107)	P+T+D (n = 107)
DFS	3 year Kaplan–Meier survival estimate, %	85	92
	HR*	–	0.60
	(95% CI)	–	(0.28,1.27)
PFS	3 year Kaplan–Meier survival estimate, %	86	90

[26] Gianni et al, J Clin Oncol 33, 2015 (suppl; abstr 505)

		T+D (n = 107)	P+T+D (n = 107)
	HR*	–	0.69
	(95% CI)	–	(0.34,1.40)

* Compared with trastuzumab and docetaxel; T=trastuzumab, D=docetaxel, P= pertuzumab

Delegate comment: The numeric improvement in 3 year survival with the addition of pertuzumab is not statistically significant and the wide confidence intervals limit any conclusions that can be drawn about long term benefit. The study was not powered to demonstrate longer term outcomes but it is somewhat reassuring that these figures remain aligned with the improvement in the pCR noted at the time of surgery.

TRYPHAENA (BO22280)

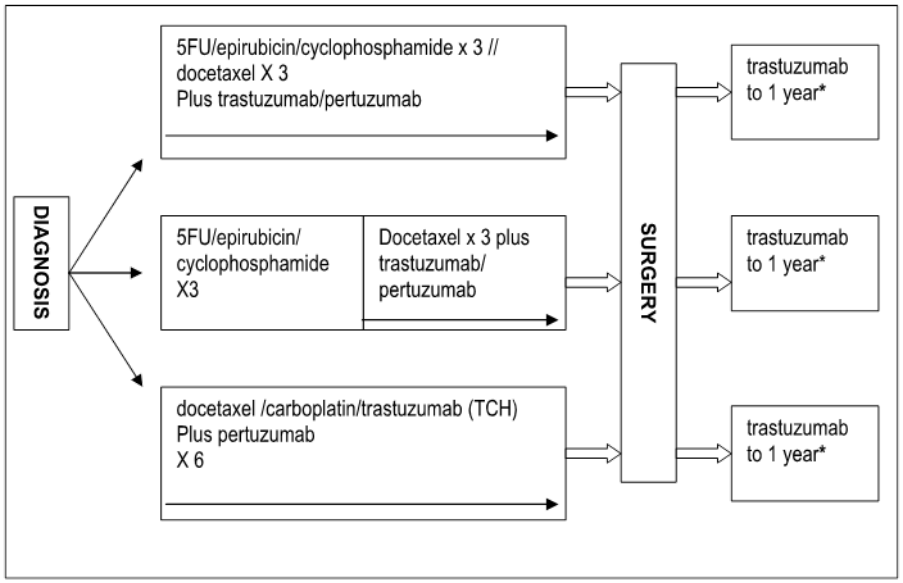
This Phase II neoadjuvant open-label, randomised, multinational, multi-centre trial was conducted in 225 patients with HER2+ locally advanced, operable or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included Perjeta. HER2 overexpression was defined as a score of IHC 3+ or FISH amplification ratio of ≥2.0 as determined by a central laboratory. Patients were randomly allocated to receive one of three neoadjuvant chemotherapy regimens, all in combination with pertuzumab and trastuzumab (See Figure 2). Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and/or PgR positivity.

Delegate comment: Concomitantly administering anti-Her2 therapy with anthracyclines (FEC) is not standard practice in Australia and this regimen is not included in the PI.

Pertuzumab was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks; trastuzumab at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 3 cycles. In the pertuzumab plus trastuzumab, docetaxel and FEC arms, docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100 mg/m^2 at the investigator's discretion. In the pertuzumab plus Docetaxel, carboplatin and trastuzumab (TCH) arm, docetaxel was given intravenously at 75 mg/m^2 (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles. Following surgery all patients received trastuzumab to complete 1 year of therapy.

Demographics were well balanced (median age was 49 to 50 years old, the majority were Caucasian (76%)) and all were female. Overall 6% of patients had inflammatory cancer, 25% had locally advanced cancer and 69% had operable cancer, with approximately half the patients in each treatment group having ER-positive and/or PgR-positive disease.

Figure 2: TRYPHAENA (BO22280) study schema. The ITT population consisted of 73 patients receiving the first regimen, 75 the second and 77 the third regimen.



* Additional radiotherapy, hormonal therapy and chemotherapy post-surgery and during adjuvant trastuzumab treatment is allowed if considered necessary by the investigator. Post-surgery chemotherapy was to be recommended as follows: the combination of cyclophosphamide, methotrexate and fluorouracil for patients who received anthracycline-based neoadjuvant treatment (ie, Arms A and B), and FEC for patients who received carboplatin-based neoadjuvant treatment (ie, Arm C).

Efficacy endpoints

These were secondary endpoints and reported as breast pCR in the study but are presented below (Table 12) as defined by the accepted regulatory standard of absence of invasive disease in the breast and axillary nodes.

Table 12: pCR rates in the TRYPHAENA study

Regimen	pCR rates (ypT0/is ypN0)	Hormone receptor +ve	Hormone receptor -ve
Pertuzumab/trastuzumab/FEC followed by pertuzumab/ trastuzumab/docetaxel	56.2% (95% CI: 44.1%, 67.8%)	41.0% (95% CI: 25.6%, 57.9%),	73.5% (95% CI: 55.6%, 87.1%)
FEC alone followed by pertuzumab/trastuzumab/ docetaxel	54.7% (95% CI: 42.7%, 66.2%)	45.7% (95% CI: 28.8%, 63.4%)	62.5% (95% CI: 45.8%, 77.3%)
Pertuzumab/TCH	63.6% (95% CI: 51.9%, 74.3%)	47.5% (95% CI: 31.5%, 63.9%)	81.1% (95% CI: 64.8%, 92.0%)

Delegate comments:

1. The increased pCR rates in all 3 TRYPHAENA study arms compared with the pertuzumab/trastuzumab/docetaxel arm in the NEOSPHERE study most likely to reflect the additional chemotherapy received preoperatively, although differences in the FEC dose schedules between the two studies add to the difficulties inherent in making cross-study comparisons.
2. The pCR results were consistent across all three arms although most marked in the pertuzumab/TCH arm.

3. The higher pCR rates where 6 doses of pertuzumab were administered raise questions about the optimal duration of dual mAb treatment. This will not be addressed by the current confirmatory studies planned and this will need to be addressed, if the APHINITY trial confirms the clinical benefit observed above.
4. Again, there was no standardised manner for assessing baseline nodal status making attribution to treatment of the improved breast and axillary node clearance rates uncertain.

Safety

The following studies provided safety data for patients exposed to pertuzumab: TRYPHAENA (223 patients; primarily a safety study), NEOSPHERE (309 patients), and CLEOPATRA (408 patients). In the CLEOPATRA study in metastatic patients, there was a median exposure of 8 cycles of pertuzumab + trastuzumab + docetaxel, and a median of 24 cycles of pertuzumab + trastuzumab, with sufficient follow-up (of greater than 2 years) to allow for the identification of delayed toxicity.

A further 696 patients have been exposed to pertuzumab in earlier studies submitted previously for regulatory review (BO17931, BO17929, BO16934, TOC2689g, TOC2572g, BO17004, TOC2682g, TOC2297g, BO17003, BO17021, WO20024, TOC3258g), and were reviewed again here.

The majority of patients completed the scheduled doses of pertuzumab in the NEOSPHERE (90 to 93%) and TRYPHAENA studies (88% to 96%).

Delegate comments:

1. The key arms in the NEOSPHERE study are the trastuzumab/docetaxel and pertuzumab/trastuzumab/docetaxel; in TRYPHAENA, all 3 arms are of interest for safety signals but administering anthracyclines concomitantly with Her2 blockade (FEC with pertuzumab/trastuzumab) is not standard practice in Australia.
2. Key signals in addition to the Adverse events of Special Interest identified by the sponsor, are treatment-related discontinuations, as this potentially compromises efficacy, especially if it results in a suboptimal treatment with trastuzumab, an agent known to improve PFS and OS.
3. While NEOSPHERE isolates potential differences in toxicities attributable to pertuzumab (albeit limited by the small numbers and not being designed or powered to demonstrate infrequent events), TRYPHAENA represents a real world assessment of the impact of a full course of neoadjuvant treatment given preoperatively but lacks a control arm with either no pertuzumab or placebo, and has the limitations of small numbers and limited power.

In the NEOSPHERE study, the most common adverse reactions in patients receiving four cycles of pertuzumab, trastuzumab and docetaxel administered were similar to those seen in the CLEOPATRA Study. The most common adverse reactions (> 30%) were alopecia, neutropenia, diarrhoea and nausea. The most common Grade 3 to 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia and diarrhoea. In this group, one patient permanently discontinued neoadjuvant treatment due to an adverse event of fulminant hepatitis. Grade ≥ 3 AEs were more frequent in the trastuzumab/docetaxel than pertuzumab/trastuzumab/docetaxel arms (74.8% and 60.7%, respectively) as were SAEs (16.8% versus 11.2%, respectively). However, the rate of AEs for the triplet combination was higher for diarrhoea, rash and mucositis, and asymptomatic cardiac dysfunction (3 patients versus 1) in comparison with trastuzumab and docetaxel. In the adjuvant phase of the study (FEC followed by trastuzumab), 5 more patients developed asymptomatic LVD (>10% points from baseline to < 50%) in the triplet arm compared with 1 further case in the docetaxel/trastuzumab arm. All improved subsequently to have an LVEF >50%, and

none developed congestive heart failure. In the post-adjuvant phase (final data cut-off October 2014), a further 3 patients in the triplet arm had developed cardiac toxicity compared with 2 in the trastuzumab/docetaxel arm.

Discontinuations during the overall study period due to AEs were higher in the triplet arm than the trastuzumab/docetaxel arm (4.7% versus 0%). Of the two patients discontinuing treatment in the neoadjuvant phase, one was due to fulminant hepatitis (causation for this event is unclear due the lack of investigations reported e.g. no liver biopsy, hepatitis serology or autopsy) and the other was due to docetaxel hypersensitivity. In the adjuvant phase, the 3 patients discontinued due to LVD (2) and a strangulated abdominal hernia.

Delegate comment: The numbers in the study are small and the impact therefore of small imbalances can appear to be large, especially when presented as a percentage. Neither of the discontinuations in the neoadjuvant phase could be attributed to the addition of pertuzumab and the discontinuations due to LVD in the adjuvant phase may reflect the known adverse effects of trastuzumab. The role of pertuzumab remains uncertain, and the randomised, double blind, placebo controlled Phase III trial APHINITY will further inform; until this is available and evaluated, this uncertainty should be included in the PI (see PI Changes).

In the TRYPHAENA study, the most common adverse reactions with 3 cycles of FEC followed by 3 cycles of pertuzumab/trastuzumab/docetaxel (> 30%) were diarrhoea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common Grade 3/4 adverse reactions (> 2%) were neutropenia, leukopenia, febrile neutropenia, diarrhoea, left ventricular dysfunction, anaemia, dyspnoea, nausea and vomiting. Discontinuation rates were 6.7% (5 patients). With TCH plus pertuzumab for 6 cycles, the most common adverse reactions (> 30%) were diarrhoea, alopecia, neutropenia, nausea, fatigue, vomiting, anaemia, and thrombocytopenia. The most common Grade 3/4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, anaemia, leukopenia, diarrhoea, thrombocytopenia, vomiting, fatigue, a rise in ALT, hypokalaemia and hypersensitivity. Discontinuation rates were 7.9% (6 patients). The use of G-CSF may have contributed to the relatively low incidence of febrile neutropenia and this should be Dosage and Administration section of the Product Information.

Cardiac events

Comparisons between the trials are hampered by reporting differences for cardiac AEs. However, a clear cardiac toxicity signal emerged from the two neoadjuvant studies, which is new and needs to be included in the PI, regardless of whether the currently sought indication is approved.

An increase in cardiac toxicity was observed in the NEOSPHERE study, whereas no signal had emerged from the CLEOPATRA study in metastatic breast cancer. During the overall treatment period, the incidence of LVD was higher in the pertuzumab, trastuzumab and docetaxel-treated group (8.4%) compared with the trastuzumab and docetaxel-treated group (1.9%); one patient in the triplet arm had a Grade ≥3 LVD and two patients in the same arm withdrew from the adjuvant phase of the study treatment due to LVD. No symptomatic cardiac events occurred in the treatment arms of interest in this trial (pertuzumab/trastuzumab/docetaxel and trastuzumab/docetaxel arms); however, symptomatic CHF necessitating cessation of all treatment did occur in a patient (who had significant cardiac risk factors) in the pertuzumab and trastuzumab arm indicating the potential for more severe toxicity, particularly for those with cardiac risk factors. In all cases, the cardiac events resolved with treatment suggesting they are manageable.

In the overall treatment period of the TRYPHAENA trial including follow-up, the rates of LVD determined by local and central review in patients treated with:

1. Pertuzumab/ trastuzumab/FEC followed by pertuzumab/trastuzumab/docetaxel, were 6.6% with no reports of symptomatic LVSD
2. FEC followed by pertuzumab/trastuzumab/docetaxel, LVD occurred in 16% with 1.3% developing symptomatic LVSD
3. Pertuzumab with TCH, were 10.5 % and symptomatic LVSD occurred in 1.3%

LVEF recovered to ≥ 50% in all but one patient. No data are available for treatment beyond 6 cycles of pertuzumab.

Table 13: Key Safety Data for the NEOSPHERE (WO20697), TRYPHAENA (BO22280) and CLEOPATRA (WO20698) Studies – data have been reconciled with that found in submission by the clinical evaluator

	Patients experiencing event								
	Neoadjuvant setting							MBC setting	
	NEOSPHERE (WO20697) Neoadjuvant treatment period (%) Arm A Arm D	Arm B	Arm C		TRYPHAENA (BO22280) Neoadjuvant treatment period (%) Arm A Arm C	Arm B		CLEOPATRA (WO20698) Overall treatment period (%)	
	T+D N=107	Ptz + T+D N=107	Ptz + T N=108	Ptz + D N=94	Ptz + T + FEC /Ptz + T+D N=72	FEC/Ptz +T+D N=75	Ptz +TCH N=76	Pla +T + D N=396	Ptz + T + D N=408
Any AE	98.1	97.2	70.4	98.9	100.0	96.0	100	98.7	100.0
Grade ≥ 3	74.8	60.7	11.1	71.3	69.4	60.0	73.7	73.5 %	76.2
Related AE	97.2	95.3%	66.7	97.9	100.0	94.7	100.0	96.2 %	97.3
AE → disc	0	1.9	2.8	2.1	5.6	6.7	7.9	28.8	30.6
AE → i/m	34.6	32.7	14.8	43.6	36.1	29.3	50.0	54.3	61.8
SAE	16.8	11.2	3.7	17.0	27.8	20.0	35.5	29.0	36.3
AE → death	0	0.9	0	0	0	0	0	3.0	2.0
Death,	0	0	0	0	0	0	0	34.3	24.5

	Patients experiencing event								
PD									
Death,other	0	0.9	0	0	0	0	0	4.0	3.2

AE → disc =any AE leading to discontinuation of one or more study drugs; AE →i/m= any AE leading to interruption or modification; SAE=any SAE; AE→death=AE with outcome of death (i.e. Grade 5); Death, PD=death due to progressive disease; Death, other=death due to causes other than progressive disease

Risk management plan

The RMP evaluator identified that there were still outstanding issues:

1. The Delegate does not consider the data currently support a contraindication for concomitant use of pertuzumab with anthracyclines; however, there are insufficient data presented to support its use and it is not currently proposed in the Clinical Trials section. The BERENICE study will provide further data to inform on this matter and submission for evaluation is a condition of registration.
2. The Delegate supports inclusion of the adverse events of pain in extremity, back pain and cough noted in the SmPC in the metastatic usage (see PI Changes).

The Delegate proposes additional pharmacovigilance activities including a patient registry (described above).

Risk-benefit analysis

Delegate's summary and discussion

Summary

The sponsor has provided data from two open-label randomised Phase II studies, NEOSPHERE (WO20697) and TRYPHAENA (BO22280), with supporting data from the previously reviewed CLEOPATRA (WO20698) study.

In the two neoadjuvant studies, the target population were female patients with HER2+ non-metastatic breast cancer where the primary tumour is > 2 cm in size. The majority were considered 'operable' (a stratification factor) but there were sufficient who were deemed inoperable to assess a potential benefit in this group.

In NEOSPHERE, the addition of pertuzumab to docetaxel and trastuzumab showed a consistent, statistically significant and clinically relevant improvement in pCR rates regardless of the different definitions used. Lower rates were observed in the hormone receptor positive (HR+) subgroup. It is noted that the NEOSPHERE study does not provide evidence of the benefit of adding pertuzumab to a *complete* neoadjuvant regimen to clarify whether that benefit differential was maintained. It is thus likely that the benefit of adding pertuzumab is overstated in this trial. TRYPHAENA incorporated pertuzumab at varying stages of a complete 6-cycle course of two different neoadjuvant chemotherapy regimens (three arms: with FEC-docetaxel, after FEC with docetaxel and with all cycles of TCH) with trastuzumab but lacked a control arm to demonstrate any potential incremental effect, and was primarily a study designed to investigate cardiac safety; it was not designed or powered to determine longer term efficacy. The findings of consistently high rates of pCR (54.7 to 63.6%) achieved across the three different regimens supports the addition of pertuzumab to different chemotherapy regimens, although concurrent administration with anthracyclines is not standard practice in Australia. In a small study with no control

arm, it is difficult to determine whether the increased pCR rates with six cycles is due to the greater exposure; but it does raise the question of what is the optimal duration of pertuzumab treatment in this setting.

Results of long term clinical endpoints, EFS and DFS from NEOSPHERE reported at American Society of Clinical Oncology (ASCO) 2015 (not formally evaluated by the TGA) did not contradict the pCR results; the data are not mature for TRYPHAENA but will offer little additional information due to the Phase II study aims and design. BERENICE is a study designed to assess the effect of pertuzumab added concurrently to two neoadjuvant anthracycline based regimens and trastuzumab, with both antibodies continued into the adjuvant setting but does not have a placebo arm.

Comparisons with the pCR rates in other neoadjuvant study outcomes inevitably are complicated and virtually precluded by differences in the disease stage of the population recruited, chemotherapy regimens used (including the agents themselves, dosage differences, number of cycles and so on) and stringency of both baseline assessment (for example, determining baseline nodal status) and endpoint assessments.

The safety analysis demonstrated that in addition to the haematological and gastrointestinal toxicities, a cardiac safety signal has emerged, although it is noted that discontinuations of therapy due to this were low in NEOSPHERE and did not occur in TRYPHAENA. The PI requires updating to present the figures of LVD and CHF to inform prescribers; given discontinuation occurred in a patient with pre-existing cardiac risk factors this information should be clearly stated. The introduction of a boxed warning regarding cardiomyopathy in the US label is noted. The Dosage and Administration section does not include concomitant administration of anthracyclines and the pertuzumab and trastuzumab combination and depending on the outcomes from BERENICE study, when it is available for evaluation, it is recommended that it is stated more overtly that there is insufficient evidence to support concurrent usage. Otherwise, the regimens described are reflective of current Australian clinical practice in the neoadjuvant setting.

Discussion

This is the first marketing application using pCR as the primary efficacy endpoint for neoadjuvant treatment of breast cancer, without supportive data from the adjuvant setting. The magnitude of increase in pCR required to predict a benefit long term, remains to be determined. It is not clear whether the observed 17.8% improvement in pCR after only 4 to 6 cycles of pertuzumab added to neoadjuvant treatment, will be sufficient to translate into long term clinical benefit for all patients described by the sponsor's proposed indication. The now standard use of 12 months of trastuzumab with chemotherapy has improved outcomes substantially for women with early stage HER2 positive breast cancer and one of the key uncertainties affecting this application is whether that will be further improved by the addition of pertuzumab, given only for 4 to 6 neoadjuvant cycles. The Oncology Working Group advised that it is uncertain whether a longer term benefit would be demonstrated, particularly in those with earlier stage disease who may already be adequately treated. This question will not be answered directly by the APHINITY study, rather this will inform as to whether the addition of 12 months of treatment with pertuzumab to standard care improves invasive disease free survival in women with operable HER2 positive breast cancer. As such, the outcomes of this study do not inform the present decision.

The Oncology Working Group considered that pCR as an endpoint in its own right, supports a greater likelihood of response prior to surgery; this could be seen as of immediate clinical benefit for those with inflammatory or locally advanced disease, where surgery might otherwise be difficult or not possible. This benefit is considered sufficient to outweigh the uncertainties as to whether there are accompanying longer term benefits for this group, particularly with such a short duration of therapy. In contrast, the immediate

short term benefits of an increase in pCR are not certain and longer term improvement in disease-free or overall survival remain unknown for those with earlier stage HER2 positive disease. For this reason, registration in those with early stage disease is not supported due to the lack of data to support a clear benefit in this population; this also acknowledges the advice from the Working Group regarding the potential detrimental effect on quality of life understood from clinical experience in using pertuzumab, which has to be considered in the benefit-risk equation. Notably, neither Phase II study submitted in this application collected data on quality of life to inform otherwise.

Longer term outcomes with the current standard of care are influenced by adjuvant continuation of trastuzumab, plus endocrine therapy in those with hormone receptor-positive (HR+) disease. In both studies, approximately half of the patients were endocrine receptor positive, a subgroup for which neoadjuvant therapy may be less effective and pCR a poorer predictor of long term benefit. The lower response in hormone receptor positive disease in the two Phase II studies is consistent with the majority of data reported in the literature. Direct support for the benefit of pertuzumab in HR+ disease was demonstrated in the CLEOPATRA study, with a HR for OS of 0.71 (0.51, 0.96) in patients with HR+ disease, compared with 0.61 (0.47, 0.81) in patients with hormone receptor negative disease. Additional indirect support comes from the use HER2 targeted therapy, in particular trastuzumab, in both HR+ and HR- in the adjuvant and metastatic settings. Thus, the lower pCR rate does not indicate that these women do not benefit from neoadjuvant treatment and the Oncology Working Group endorsed their inclusion in any proposed indication.

The randomised, controlled, double blind Phase III adjuvant study, APHINITY, is designed to provide efficacy and safety data to answer a different question: whether 12 months of pertuzumab added to the standard of care (chemotherapy and 12 months of trastuzumab), all given postoperatively, improves invasive disease free survival for those with operable, HER2 positive early breast cancer. Important long term data about safety in this setting are also expected. Thus this answers the broader question about pertuzumab for the treatment of early breast cancer but there are no data until the CSR is made available to inform directly about the benefit of the usage proposed here. This will help identify whether, in particular for those at a lower risk of relapse, there is a benefit from combination with chemotherapy initially, followed by a much longer course of treatment of dual mAB therapy than proposed here. The Delegate considers having this information is essential to inform about the benefit-risk, and may inform regarding extending usage then to the neoadjuvant setting for those with earlier stage disease; extrapolation 'forward' in anticipation of a positive result is not supported, either by the Delegate or the Oncology Working Group; nor is it supported by the TGA's current legislative framework, which does not allow provisional registration and the opportunity for reconsideration of any decision made now with evidence to be supplied in the future. For the purposes of clarity, the Delegate has removed all reference to 'early stage breast cancer' from the sponsor's proposed indication. The Delegate notes that this is in essence, a similar proposition to the sponsor's currently proposed indication, just more clearly defined.

The Oncology Working Group's concern that the optimal duration of therapy should be determined to avoid both under and over treatment is shared by the Delegate and the sponsor is strongly recommended to consider this in future study designs. This is particularly so as the toxicity profile, although described as 'manageable', has potential for a considerable detrimental impact on quality of life.

Uncertainties, risk management and pharmacovigilance

The longer term clinical benefit and safety outcomes of adding pertuzumab only to the neoadjuvant phase of treatment will not be addressed; there are no further appropriately powered or designed studies underway. Thus postmarketing data are the only potential source of data to inform about the real world usage and the Delegate considers a registry

should be formed to capture the efficacy and safety outcomes for all patients receiving neoadjuvant pertuzumab in Australia; this is a condition of registration. This is particularly important if the APHINITY trial does not confirm a longer term clinical benefit of the addition of pertuzumab to standard treatment for operable HER2 positive breast cancer. In any case, outcomes for this group with more locally advanced disease will not necessarily be captured by the APHINITY trial as many will not be considered operable and thus ineligible for that trial. So a registry data would complement the data from APHINITY trial.

The Delegate's modified indication recommends approval for use in patients where the improvement in pCR reflects can be considered to confer an immediate potential benefit, that is, as an endpoint in its own right. Thus, the population and likely usage will differ from that in the USA and also in Europe (depending upon definition of 'high risk'). Specific information about efficacy endpoints (pCR rates, conversion from inoperable to operable, and longer term outcomes such as disease-free survival and so on) should be included. Safety data are also important, particularly information about cardiac safety, discontinuations. The sponsor is requested to present an appropriate design for such a registry in the pre Advisory committee on Prescription Medicines (ACPM) response for consideration by the ACPM, Delegate and RMP evaluator.

Summary of issues

HER2 positive breast cancer is associated with a relatively high rate of relapse, even after currently registered treatments given in the neoadjuvant or adjuvant setting. Unmet need is recognised.

This is the first application to seek registration for an extension of indications without prior registration based on large trials conducted in the adjuvant setting. The application relies upon an improvement in pathological complete response (pCR) to demonstrate the efficacy of pertuzumab only given during the neoadjuvant phase of treatment in addition to standard chemotherapy and trastuzumab; while trastuzumab continues after surgery, with or without endocrine therapy as required. That is, only 4 to 6 cycles of pertuzumab were administered preoperatively in a treatment period that otherwise lasts 12 months for anti-HER2 therapy (and longer for any endocrine therapy required).

The magnitude of benefit in improvement in pCR that is required or deemed likely to result in an improvement in the established, longer term endpoints of disease-free or overall survival has not been defined for a given treatment. Advice received from the Oncology Working Group was that the increase in pCR rate could be used as a clinically meaningful endpoint demonstrating the short term outcome of potentially improving surgical outcome in those where surgery might otherwise be difficult or not possible (that is, those with inflammatory or locally advanced HER2 positive breast cancer). For those with earlier stages of HER2 positive breast cancer, in the absence of data to support clearly an improvement in longer term outcomes, efficacy has not been adequately established. Further data to inform of the efficacy and safety in this population will be provided from the Phase III APHINITY trial of pertuzumab or placebo added to standard treatment in the adjuvant setting.

Neither Phase II study presented in support of this application was powered to demonstrate long term efficacy or safety of neoadjuvant pertuzumab usage. This application is supported by compelling efficacy and acceptable safety in the metastatic setting. The Oncology Working Group noted that there was an increase in toxicities that while 'manageable' have a significant potential for a detrimental effect on quality of life, and needed to be considered when assessing benefit-risk.

No quality of life data were collected or presented. No further trials examining safety, efficacy or quality of life from addition of pertuzumab solely in the neoadjuvant setting are

underway to confirm whether such patients benefit from usage in this setting. The Delegate considers an Australian patient registry is required to inform on the safety, efficacy and quality of life outcomes from this treatment.

Data deficiencies/limitations

- There were very few patients over 65 years in the submitted studies. Limited data are available on the safety and efficacy of pertuzumab in patients that are ≥ 65 years of age.
- Patients with cardiac risk factors were excluded.
- No quality of life data were collected.
- The optimal duration of treatment has not been identified and the current design of future studies does not appear to address this. There exists a high likelihood that some patients with early stage HER2 positive breast cancer will be over-treated.

Proposed action

Registration is supported in those patients where pathological complete response is a clinically relevant endpoint, rather than as a surrogate marker for future benefit which remains uncertain on the data/evidence provided. The following modification (inclusive of the Note to the Indication', clarifying the sponsor's broad definition of 'at high risk of recurrence', is supported by the Delegate:

> *Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2 positive breast cancer as part of a complete treatment regimen.*
>
> *Note to the Indication: this approval is based on improvement in pathological complete response rate. No improvement in disease-free, progression-free or overall survival has been shown.*

Conditions of registration

The following are proposed as conditions of registration:

1. Implementation of the EU RMP Version 5.1 (dated 20 May 2015, data lock point 28 February 2015) with Australian Specific Annex Version 3.0 (dated July 2015) and any future updates as a condition of registration.
2. Any promotional material must include the Indication followed immediately by the Note to the Indication, that is, these must be stated together.
3. The sponsor is required to set up a registry to collect efficacy and safety data for all neoadjuvant pertuzumab usage in Australian patients.
4. Submission of the following clinical trial(s) as Category 1 submissions for evaluation by the TGA within 6 months of completion:
    a. BERENICE (WO29217), a non-randomised, open-label, phase II study evaluating pertuzumab in combination with trastuzumab and two different neoadjuvant anthracycline-based chemotherapy regimens in patients with HER2 positive, locally advanced, inflammatory or early-stage breast cancer.
    b. APHINITY (BO25126), a randomized phase III study of adjuvant trastuzumab +/- pertuzumab after adjuvant chemotherapy (either anthracycline or non-anthracycline based as per investigator). 4805 patients are enrolled onto this study, which is expected to provide important data relating to DFS, OS, long term cardiac safety, quality-of-life and pharmacokinetic parameters.

c. PERUSE (MO28047), a multicentre, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer

Request for Advisory Committee on Prescription Medicines (ACPM) advice

Advice is sought on the following matters:

- The Delegate considers a registry is important given the Phase III trial (APHINITY) will not provide further direct information about the efficacy and safety outcomes with neoadjuvant usage. The committee is requested to provide any additional recommendations regarding additional pharmacovigilance activities required.

Response from sponsor

Comment on the delegate's proposed action

Roche notes the Delegate's proposed indication:

> *Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2 positive breast cancer as part of a complete treatment regimen.*
>
> *Note to indication: this approval is based on improvement in pathological complete response rate; no improvement in disease-free, progression-free or overall survival has been shown.*

Roche also notes the advice sought from the ACPM on the following matter:

The Delegate considers a registry is important given the Phase III trial (APHINITY) will not provide further direct information about the efficacy and safety outcomes with neoadjuvant usage. The Committee is requested to provide any additional recommendations regarding additional pharmacovigilance activities required.

Responses to the Delegate's request for ACPM advice and the proposed indication are included below.

Introduction

HER2 positive breast cancer is an aggressive form of breast cancer with a high risk of recurrence and death.

Neoadjuvant therapy is widely accepted as the treatment of choice for patients with inoperable disease (inflammatory breast cancer (IBC) or locally advanced breast cancer (LABC)). Neoadjuvant therapy has become a treatment option for selected women with larger (> 2 cm) early stage breast cancer[27] due to potential advantages over a surgery-first approach, which include: down staging which could potentially allow breast conserving surgery for some women who would otherwise have required a mastectomy; reducing the volume of surgically resected breast and axillary tissue; and providing

[27]Zdenkowski N, Butow P, et al; A survey of Australian and New Zealand clinical practice with neoadjuvant systemic therapy for breast cancer. Intern Med J. 2016 Mar 1 [Epub ahead of print

prognostic information based on the tumour response to therapy.[28,29,30] The option of neoadjuvant therapy for operable breast cancer is endorsed by international guidelines.[31]

The optimal outcome of neoadjuvant therapy is a pathological complete response (pCR). The rate of pCR has been previously used to assess the efficacy of neoadjuvant breast cancer treatment in clinical trials. pCR is a high therapeutic hurdle, indicating the complete elimination of invasive malignant disease.

There is a strong biological rationale for combining Perjeta with Herceptin in patients with HER2 positive breast cancer. The addition of Perjeta to Herceptin and docetaxel has been shown to produce a statistically significant increase in pCR rates in patients with HER2 positive locally advanced, inflammatory and operable breast cancer in the NEOSPHERE study. This same regimen increased overall response rates, PFS and OS in patients with locally recurrent, inoperable and metastatic breast cancer in the CLEOPATRA study. The improvement in overall survival in CLEOPATRA was unprecedented in patients with advanced breast cancer; an increase in median survival of 15.7 months for patients treated with Perjeta, Herceptin and docetaxel compared to patients treated with placebo, Herceptin and docetaxel, bringing the median survival of these patients to nearly 5 years (56.5 months) (WO20698 Research Report 1059844/July 2014).

The safety profile of Perjeta is now well established with data from almost 10,000 patients in ongoing and completed investigational clinical trials sponsored by the Roche (1,631 patients from completed studies, including NEOSPHERE, TRYPHAENA and CLEOPATRA). To date, an additional 81,644 patients have been exposed to Perjeta in the post-marketing setting, including 31,092 patients treated with neoadjuvant Perjeta. In the neoadjuvant setting, no new or unexpected toxicities have been encountered with Perjeta added to four commonly used neoadjuvant Herceptin containing regimens, other than those that are known for Perjeta in metastatic disease and are generally expected for agents that target the HER family of receptors.

No subgroups of patients have been identified that are more (or less) susceptible to Perjeta related toxicity. The addition of Perjeta to standard regimens of Herceptin and chemotherapy appears to be well tolerated in patients of all ages and races and regardless of baseline tumour characteristics.

Overall, based on the totality of data currently available, the sponsor considers that the benefit-risk balance for Perjeta given as part of a neoadjuvant treatment regimen is strongly positive for patients with HER2 positive locally advanced, inflammatory, or early stage breast cancer (> 2 cm diameter) at high risk of recurrence. Based on current data, the sponsor has not identified any subgroup within this population who should be denied the potential benefits of Perjeta.

Comments on indication statement

The indication proposed by the Delegate excludes patients with early breast cancer, that is, patients with operable disease on the basis that pCR is not a clinically relevant endpoint in this patient population without evidence of the long term benefits.

In the NEOSPHERE and TRYPHAENA studies, 60.9% and 69.3% of patients respectively had operable disease. However, analysis of stage and other baseline factors in the

[28]Van der Hage JH, van de Velde CCJH, Mieog SJSD. Preoperative chemotherapy in women with operable breast cancer. Cochrane Database Syst Review 2012
[29]Symmans WF, Peintinger F, Hatzis C, et al. Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy. J Clin Oncol 2007;25:4414-22.
[30]Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72WO20698 Research Report 1059844/July 2014
[31]Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013; 24:2206-2223.[10809]

NEOSPHERE and TRYPHAENA studies indicates that the great majority of patients (> 80%) were in a high risk category for relapse (> 20% risk of relapse). Furthermore the great majority of patients included in the studies (and in the indication statement proposed by the sponsor) would have been offered neoadjuvant therapy with Herceptin and chemotherapy, according to current guidelines.[32,33,34 35,36,37,38] The addition of Perjeta to neoadjuvant Herceptin plus docetaxel produced a marked increase in pCR rates in the NEOSPHERE study. High pCR rates have also been reported with Perjeta plus Herceptin and chemotherapy in the TRYPHAENA and GEPAR-SEPTO studies and these data are supported by the improvements in efficacy seen in the CLEOPATRA study in patients with metastatic disease (including an improvement in median survival of 15.7 months). The improvements in efficacy seen with the addition of 4 to 6 cycles of Perjeta to neoadjuvant therapy with Herceptin and chemotherapy were just as striking for patients with operable disease (a doubling of pCR rates for treatment with Perjeta+Herceptin+Docetaxel compared with Herceptin+Docetaxel in the NEOSPHERE study) as for patients with inoperable disease at diagnosis. The addition of 4 to 6 doses of Perjeta to neoadjuvant Herceptin and chemotherapy resulted in modest increases in manageable, reversible toxicities.

Excluding patients with operable early breast cancer (> 2 cm) from the indication statement would exclude the majority of patients who participated in the trials and would thereby exclude patients at high risk of recurrence who may currently receive neoadjuvant therapy with Herceptin and chemotherapy in clinical practice.

Efficacy in patients with early breast cancer (operable disease)

Exploratory subgroup analyses of pCR based on disease stage/type (operable, locally advanced [LABC] and inflammatory [IBC]) have been conducted for NEOSPHERE and TRYPHAENA. These were provided in the sponsor's Summary of Clinical Efficacy (SCE) and key tpCR rates by disease stage/type are provided in Table 14.

[32]Amoroso V, Generali D, Buchholz T et al. International expert consensus on primary systemic therapy in the management of early breast cancer: highlights of the fifth symposium on primary systemic therapy in the management of operable breast cancer, Cremona, Italy (2013). J Natl Cancer Inst Monogr. 2015 May;2015(51):90-6.

[33] Senkus E, Kyriakides S, Ohno S et al; ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v8-30. et al, 2015

[34] Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. Ann Oncol. 2009; 20:1319-1329. [10519]

[35] Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013; 24:2206-2223.[10809]

[36] Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011; 22:1736-1747. [10710]

[37]Coates AS, Winer EP, Goldhirsch A, et al Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46

[38] Gradishar WJ, Anderson BO, Balassanian R et al. Breast Cancer Version 2.2015. J Natl Compr Canc Netw. 2015 Apr;13(4):448-75.

Table 14: Summary of pCR Rates by Disease Stage/Type and According to Different Definitions: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Overall							
N	107	107	107	96	73	75	77
N (%) achieving bpCR	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
N (%) achieving tpCR	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
N (%) achieving GBG pCR	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.5%)	37 (50.7%)	34 (45.3%)	40 (51.9%)
Operable breast cancer							
N	64	65	65	60	53	54	49
N (%) achieving bpCR	15 (23.4%)	31 (47.7%)	11 (16.9%)	16 (26.7%)	34 (64.2%)	29 (53.7%)	32 (65.3%)
N (%) achieving tpCR	12 (18.8%)	26 (40.0%)	9 (13.8%)	14 (23.3%)	32 (60.4%)	28 (51.9%)	31 (63.3%)
N (%) achieving GBG pCR	5 (7.8%)	22 (33.8%)	4 (6.2%)	10 (16.7%)	28 (52.8%)	23 (42.6%)	27 (55.1%)
LABC							
N	36	32	35	31	15	17	24
N (%) achieving bpCR	15 (41.7%)	14 (43.8%)	5 (14.3%)	5 (16.1%)	8 (53.3%)	13 (76.5%)	15 (62.5%)
N (%) achieving tpCR	10 (27.8%)	13 (40.6%)	2 (5.7%)	2 (6.5%)	8 (53.3%)	12 (70.6%)	14 (58.3%)
N (%) achieving GBG pCR	7 (19.4%)	12 (37.5%)	1 (2.9%)	2 (6.5%)	8 (53.3%)	10 (58.8%)	11 (45.8%)
IBC							
N	7	10	7	5	5	4	4
N (%) achieving bpCR	1 (14.3%	4 (40.0%)	2 (28.6%)	2 (40.0%)	3 (60.0%)	1 (25.0%)	4 (100%)
N (%) achieving tpCR	1 (14.3%)	3 (30.0%)	1 (14.3%)	1 (20.0%)	1 (20.0%)	1 (25.0%)	4 (100.0%)
N (%) achieving GBG pCR	1 (14.3%)	1 (10.0%)	1 (14.3%)	1 (20.0%)	1 (20.0%)	1 (25.0%)	2 (50.0%)

In both studies, pCR rates in patients with operable breast cancer were consistent with pCR rates in the overall study population, regardless of the pCR definition used (see Table 14). Patients with all stages/sub-types of HER2 positive, early stage breast cancer appeared to have a higher pCR rate with Perjeta-containing therapy than control groups without Perjeta. In particular, tpCR rates for patients with operable disease in the NEOSPHERE study were 40.0% for patients in the Perjeta+Herceptin+Docetaxel arm (Arm B), compared with 18.8% for the Herceptin+Docetaxel arm (Arm A), a difference of 21.2%. This difference was associated with encouraging and consistent PFS/DFS data in the operable subgroup (PFS HR Intention –to-treat (ITT): 0.69; Operable: 0.67 and DFS HR ITT: 0.60; Operable: 0.61 as detailed in Table 15).

Table 15: Efficacy in Arm B (Ptz+T+D) versus Arm A (T+D) for the operable and ITT populations in NEOSPHERE

Efficacy of Ptz+T+D (Arm B) vs T+D (Arm A)	ITT	Operable (>2cm)
tpCR rate	Δ=17.8%	Δ=21.2%
PFS Hazard Ratio	0.69	0.67
DFS Hazard Ratio	0.60	0.61

Further subgroups analyses of pCR rates by tumour stage (T2, T3, T4) and by nodal stage (N0, N1, N2/3) have been conducted using all three pCR definitions. Results are provided in the SCE. In general, the pCR rates by tumour size and nodal stage were consistent with those seen for the overall population of the relevant study.

Safety in patients with operable disease

Overall safety data indicate that Perjeta is well tolerated and can be given in combination with Herceptin and a range of other therapeutic agents with modest additional toxicity. Administration of 4 to 6 cycles of Perjeta in combination with neoadjuvant Herceptin and chemotherapy was well tolerated with manageable increases in Grade 1 to 2 diarrhoea,

rash and mucositis, and no apparent increase in leukopenia or febrile neutropenia and (with the TCH regimen) small increases in febrile neutropenia and possibly anaemia, leukopenia, neutropenia and thrombocytopenia.

The incidence and severity of cardiac toxicity following treatment with neoadjuvant Perjeta, Herceptin and chemotherapy was consistent with that expected for Herceptin-based chemotherapy regimens in the neoadjuvant/adjuvant setting.[39] Importantly no evidence of delayed cardiotoxicity has emerged for neoadjuvant Perjeta-based combination regimens (as is also the case for neoadjuvant/adjuvant Herceptin-based combination regimens).

Diarrhoea was confirmed as one of the most common AE reported in Perjeta containing regimens; however only a minority of episodes were of Grade 3 to 4 severity and none led to treatment discontinuation. Exploratory subgroup analyses of safety for a range of baseline factors (including operability at study entry) have not revealed any patient groups at increased risk of Perjeta toxicity. The safety profile of Perjeta+Herceptin+Docetaxel in the subgroup of patients with operable disease at baseline is consistent with that of the Intention –to-treat (ITT) population. Importantly, cardiac safety data from NEOSPHERE shows that no patients with operable disease experienced symptomatic left ventricular dysfunction during neoadjuvant treatment with Perjeta+Herceptin+Docetaxel (see Table 16).

Table 16: Cardiac safety in patients with operable disease during the neoadjuvant period (NEOSPHERE)

	ITT		Operable	
	T+D (Arm A) n=107	Ptz+T+D (Arm B) n=107	T+D (Arm A) n=64	Ptz+T+D (Arm B) n=65
Symptomatic left ventricular dysfunction (LVD)	0	0	0	0
NYHA Class III/IV	0	0	0	0
LVD, all grades	1 (0.9%)	3 (5.3%)	1 (0.9%)	0

Risk of relapse in patients with early breast cancer (operable disease)

In the NEOSPHERE and TRYPHAENA studies, patients had primary tumours > 2 cm in diameter (that is, T2 disease; Stage II or greater), regardless of nodal (NO) stage (see Table 17). Patients with T1 tumours (that is, primary tumour < 2 cm in diameter) were specifically excluded from these trials and are consistently excluded from the indication statement proposed by the sponsor. It is important to note that 'operable disease' includes patients with large primary tumours (T3 disease that is, > 5 cm in diameter). Such patients, particularly those with T3N1 disease (Stage IIIA) and patients with relatively small breasts may barely meet surgical operability criteria.

[39]Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No. CD006243. DOI: 10.1002/14651858.CD006243.pub2.

Table 17: Neoadjuvant Treatment of Invasive Breast Cancer: Summary by Stage

Common name	Stage Grouping	TNM Stage			Operable at Diagnosis	Pre-Op (Neoadjuvant) Therapy Indicated
		T	N	M		
Operable or EBC	I	1	0	0	Yes	No
	IIA	0	1	0		
		1	1	0		
		2	0	0		For large tumors to enable BCS
	IIB	2	1	0		
		3	0	0		
Inoperable or LABC	IIIA	0	2	0	No	Yes
		1	2	0		
		2	2	0		
Operable or EBC		3	1	0	Yes	For large tumors to enable BCS
Inoperable or LABC		3	2	0	No	Yes
	IIIB	4[a]	0	0		
		4[a]	1	0		
		4[a]	2	0		
	IIIC	Any[a]	3	0		
Metastatic	IV	Any[a]	Any	1		No[b]

Shaded rows indicate patients by TNM staging included in NEOSPHERE and TRYPHAENA studies.

BCS = breast-conserving surgery; EBC = early breast cancer (also sometimes called 'primary breast cancer'); LABC = locally advanced breast cancer; TNM = tumor, nodes, metastasis staging.

[a] Inflammatory breast cancer (IBC) is always considered T4 and therefore may fall into stage IIIB, IIIC or stage IV.

[b] Systemic therapy required but surgery not usually indicated

Based on National Comprehensive Cancer Network (NCCN) Guidelines (Gradishar et al, 2014), European Society for Medical Oncology (ESMO) Clinical Recommendations (Aebi et al, 2011), and St Gallen Consensus Conference Guidelines (Goldhirsch et al, 2009).

Around 70% of patients in the NEOSPHERE and TRYPHAENA studies were node positive at baseline. Of the patients with operable disease, about two thirds had Stage IIB disease or greater in NEOSPHERE (Primary NEOSPHERE WO20697 CSR) and around 70% in TRYPHAENA (Primary TRYPHAENA CSR BO22280).

Hormone receptor (HR) status and tumour grade are also important prognostic factors for patients with breast cancer. Overall, around half the patients in the two studies had disease that was HR negative, and around half the patients had disease that was poorly differentiated (Grade 3) (Primary NEOSPHERE CSR). Very few patients (approximately 4%) had disease that was well-differentiated (Grade 1).

It is known that only 6 patients in NEOSPHERE and 5 patients in TRYPHAENA had tumours that were both low grade *and* HR positive. Of the six patients with HR positive and low grade disease in NEOSPHERE, three had operable disease and these three patients all had T3 tumours and N1 or N2 disease. Baseline tumour size in the overall group of 6 patients ranged from 5 to 10 cm in diameter based on clinical breast examination. Of the 5 patients with HR positive and low grade disease in TRYPHAENA, 2 had operable disease, one of which had stage IIB disease (T3 primary tumour, that is >5 cm in diameter).

Thus, very few patients with operable disease who entered the studies had low risk disease in terms of hormone receptor status and histological grade. Many of the patients with operable disease had large primary tumours (T3 disease) and/or palpable lymph nodes at diagnosis. These findings all support the view that patients with HER2 positive early breast cancer with tumours >2 cm in diameter are a high risk group who tend to have additional adverse prognostic factors.

Around 17% to 40% of patients with HER2 positive early breast cancer develop disease recurrence within 5 years, despite treatment with Herceptin-based neoadjuvant/adjuvant chemotherapy regimens.[40,41,42,43,44,45] The CTNeoBC meta-analysis found relapse rates of >

[40] Perez EA, Suman VJ, Davidson NE, Gralow JR, Kaufman PA, Visscher DW, et al. Sequential versus concurrent Herceptin in adjuvant chemotherapy for breast cancer. JCO 2011; 29:4491-4497. [10821]
[41] Slamon D, Eiermann W, Robert N, et al. Adjuvant Herceptin in HER2-positive breast cancer. N Engl J Med 2011; 365:1273-1283. [10517]
[42] Romond EH, Suman VJ, Jeong J-H, Sledge GW, Geyer CE, Martino S, et al. Herceptin plus adjuvant chemotherapy for HER2-positive breast cancer: Final planned joint analysis of overall survival (OS) from

20% (range 31% to 54%) for all higher grade, Stage II/III HER2 positive tumours, except for Grade 2, Stage II HR-positive tumours, in whom the relapse rate was 19% (FDA-ASCO AACR public workshop, March 2013).

Analysis of stage, tumour grade and hormone receptor status in the NEOSPHERE and TRYPHAENA studies indicates that the great majority of patients (> 80%) fell into one of the CTNeoBC-defined high risk categories (>20% risk of relapse). It is important to note that according to the CTNeoBC analysis, many of the patients with Stage II (that is, operable) disease have a risk of recurrence of > 39% (that is, considerably higher than the 20% risk of recurrence used to define the 'high risk' group).

Benefit/risk balance and sponsor's proposed indication

A consistent, positive balance of benefit and risk is seen in patients with operable HER2 positive breast cancer with large primary tumours (> 2 cm in diameter) and in patients with inoperable disease at diagnosis. Accordingly, the sponsor proposes the following indication statement in line with the patient population included in the trials (HER2 positive, locally advanced, inflammatory, or early stage breast cancer [> 2 cm in diameter] at high risk of recurrence (differences with the Delegate's proposed indication are highlighted in bold)

> *Perjeta is indicated in combination with Herceptin and chemotherapy for the neoadjuvant treatment of patients with HER2 positive, locally advanced, inflammatory,* ***or early stage breast cancer (> 2cm in diameter) at high risk of recurrence*** *as part of a complete treatment regimen for early breast cancer.*
>
> *Note to indication: this approval is based on improvement in pathological complete response rate; no improvement in disease-free, progression-free or overall survival has been shown.*

Roche supports the Delegate's proposal to include the context for the basis of approval as a note to the indication and in marketing materials. To complement the proposed indication statement, the sponsor proposes to include the following text in the Clinical Trial section of the PI in line with identified high risk factors:

'*In the neoadjuvant setting, locally advanced and inflammatory breast cancers are considered as high risk irrespective of hormone receptor status. In early stage breast cancer, tumour size, grade, hormone receptor status and lymph node metastases should be taken into account in the risk assessment*.'

Comments on the registry request

The sponsor agrees that there are areas of uncertainty around the long term outcomes of neoadjuvant Perjeta. However, the sponsor does not feel that an Australian registry would provide useful data in this regard, for the reasons outlined below. An update on recent trial activity of relevance to the use of neoadjuvant Perjeta is also provided.

NSABP B-31 and NCCTG N9831. Cancer Research 2012; Volume 72, Issue 24, Supplement 3 doi: 10.1158/0008-5472.SABCS12-S5-5. [10822]

[43] Gianni L et al. Follow up results of NOAH, a randomized phase III trial evaluating neoadjuvant chemotherapy with Herceptin (CT+H) followed by adjuvant H versus CT alone, in patients with HER2- positive locally advanced breast cancer. ASCO 2013; JCO 31 (suppl; abs 503). [10808]

[44] Goldhirsch A, Piccart-Gebhart MJ, Procter M, de Azambuja E, Weber HA, Untch M, et al. HERA TRIAL: 2 years versus 1 year of Herceptin after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. Cancer Research, 2012; Volume 72, Issue 24, Supplement 3 doi: 10.1158/0008-5472.SABCS12-S5-2. [10820]

[45] Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013; 24:2206-2223.[10809]

Issues with an Australian registry of neoadjuvant perjeta

There are approximately 15,500 new cases of breast cancer per year in Australia.[46] Of these, around 2,000 are estimated to be HER2 positive early breast cancer (including patients with tumours < 2 cm in diameter) or LABC (based on HER2 positive rate of approximately 15%). Robust figures for incidence by stage are not readily available for Australia. However, 0.1% of newly diagnosed cases (15 cases) were IBC in 2008.[47] In Europe, around 79% of breast cancer are stage T1-3N0/+M0, 7% are T4NxM0 (LABC/IBC), and 6% are metastatic (M1) at diagnosis.[48] Figures are similar in the US[49] and likely to be similar in Australia. Based on these figures and Medicare data for neoadjuvant Herceptin use, in Australia around 200 patients per year would be expected to have HER2 positive LABC/IBC and therefore be potentially eligible for Perjeta/Herceptin based neoadjuvant treatment according to the TGA proposed indication. Some of these patients would not be considered eligible for HER2 targeted and taxanes based neoadjuvant therapy due to co-morbidities (such as cardiac disease) or other factors. Assuming around 20% of patients are not eligible for HER2/taxanes based neoadjuvant therapy or decline enrolment in the registry, around 160 patients might potentially enrol in the registry per year.

It is estimated that a registry would not be ready for patient enrolment in Australia before the second half of 2017, allowing for protocol writing, regulatory and ethics approval and so on. With results from the APHINITY study predicted to be available before the end of 2017, around 80 patients might be enrolled in the registry before the APHINITY results are widely known.

If results of the APHINITY study are positive (as anticipated based on current data in the metastatic and neoadjuvant setting), one year of adjuvant Perjeta therapy (in addition to one year of Herceptin, plus adjuvant chemotherapy) will rapidly become the standard of care for patients with HER2 positive early breast cancer (following TGA approval, which is targeted for 2018). Although the APHINITY study does not include patients with LABC/IBC, the positive findings in patients with earlier stage disease (operable breast cancer) will be extrapolated to them, given the known survival advantages of Perjeta when given in the metastatic setting (patients with LABC/IBC have a prognosis between that of patients with operable early breast cancer and patients with metastatic disease). Thus, it is anticipated that 4 to 6 cycles of neoadjuvant Perjeta without subsequent adjuvant Perjeta to complete one year of therapy, will soon become obsolete (and with it, the Australian registry).

Since patients participating in the Australian registry would enrol in the registry several months before surgery, at least some would be offered postoperative/adjuvant Perjeta to complete a year of adjuvant Perjeta along with their planned Herceptin based adjuvant therapy (as in the APHINITY study), after the APHINITY results are known and adjuvant pertuzumab is approved. Only a proportion of the patients in the registry (perhaps two thirds) would not go on to receive adjuvant Perjeta. Even if extensive data were to be collected from these patients, by the time the long term follow-up data were available it would be of limited clinical interest since standard of care would be one year of therapy. Moreover, as uncontrolled data from a relatively small number of patients, the registry

[46] Cancer Council of Australia; Cancer Australia Cancer Australia: http://canceraustralia.gov.au/affected-cancer/cancer-types/breastcancer/breast-cancer-statistics
[47] Australian Institute of Health and Welfare & Cancer Australia 2012. Breast cancer in Australia: an overview: http://www.aihw.gov.au/publication-detail/?id=10737423008
[48] Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer 2003; 106: 416-422.
[49] Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD. Available from: http://seer.cancer.gov/csr/1975_2010/.

data could not establish or refute the safety and efficacy of Perjeta when given only in the neoadjuvant setting.

Should data from the APHINITY study be negative or equivocal, the sponsor concedes that there will be uncertainty as to the short and long-term benefits of 4 to 6 cycles of pre-operative Perjeta for patients with LABC/IBC (+/- patients with operable disease and large tumours who are planning to undergo neoadjuvant therapy). However, accumulating data from the NEOSPHERE, TRYPHAENA, GEPAR- SEPTO (now fully published[50]) and other neoadjuvant studies (to be discussed in the next section) will be available. These data will be more mature than the registry data (no registry patient will have been registered for more than around 6 months when APHINITY results are known; most will not have undergone primary surgery) and therefore more informative for decision-making than the registry data.

Update on neoadjuvant trials

New neoadjuvant data will become available before the end of 2017:

TRYPHAENA: Up-dated safety and efficacy data, based on a clinical cut-off of January 25 2016 (final analysis)

BERENICE: Primary analysis from this non-randomised, open label, Phase II study designed to evaluate Perjeta in combination with Herceptin and two different neoadjuvant anthracycline-based chemotherapy regimens. The study includes a similar (but not identical) patient population to that enrolled in the NEOSPHERE and TRYPHAENA studies (n=400) (in BERENICE patients with tumours < 2 cm in diameter are also allowed if node-positive).

PEONY: In addition, a randomised, double-blind, placebo-controlled Phase III neoadjuvant trial is about to start (first patient expected in March 2016). This study, which is being conducted in Asia, will evaluate treatment with Herceptin+Perjeta+docetaxel versus Herceptin+placebo+docetaxel in chemotherapy-naive patients with early stage (T2-3, NO-I, MO) or locally advanced (T2-3, N2 or N3, MO; T4, any N, MO) HER2 positive breast cancer (see Table 17 for details of stages). As in the BERENICE study, in PEONY patients will receive Perjeta (or placebo) before surgery and in the adjuvant setting for a total of one year. A total of 328 patients are planned and the primary efficacy endpoint is tpCR (with tpCR by local pathologist, bpCR by IRC, bpCR by local pathologist, clinical response, EFS, DFS, and overall survival as secondary efficacy endpoints).

The sponsor accepts that the PEONY study will not provide definitive data on the efficacy of neoadjuvant Perjeta without adjuvant Perjeta. However, as outlined above, the sponsor expects the regimen of neoadjuvant Perjeta without subsequent adjuvant Perjeta to be superseded by one year of Perjeta, assuming the APHINITY data are positive. Nevertheless, the PEONY study will provide robust, placebo-controlled data on the addition of Perjeta to standard neoadjuvant therapy, in a randomised, double-blind, placebo-controlled trial. These data will likely be available before a substantial number of patients are recruited into the Australian registry and (because PEONY is a placebo-controlled study) will be more informative than the registry data can ever be in terms of improvements in tpCR rate with the addition of pertuzumab to standard neoadjuvant therapy.

Quality of life data

Quality of life (QoL) data was collected in the CLEOPATRA study and this showed no detrimental effect of Perjeta on any QoL parameter, despite the administration of many

[50]Untch M, Jackisch C, Schneeweiss A et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016 Feb 8. pii: S1470-2045(15)00542-2. doi: 10.1016/S1470- 2045(15)00542-2. [Epub ahead of print]

cycles of Perjeta (median 18, range 1-56 in the Perjeta arm at the time of the QoL analysis). Exploratory analyses showed evidence of a beneficial effect on QoL. QoL is also being collected in the APHINITY study (in which patients receive one year of Perjeta or placebo). QoL has not been evaluated in the BERENICE study and will not be evaluated in the PEONY study because both studies are evaluating one year of neoadjuvant/adjuvant Perjeta and it is unlikely that findings would differ from those in the APHINITY study.

QoL was not evaluated in the NEOSPHERE or TRYPHAENA studies because QoL was already being evaluated in the placebo controlled CLEOPATRA and APHINITY studies, in which Perjeta/placebo was given for much longer than in the neoadjuvant studies. Moreover, it was felt that the effects of 4 to 6 cycles of neoadjuvant Perjeta on QoL were unlikely to be detectable in the context of the extensive treatment these patients undergo (chemotherapy, surgery +/- radiotherapy +/- hormone therapy). Many of the questions that are asked in QoL questionnaires relate to broad issues (financial worries, fears about the future, appearance and sexuality) that are more likely to be influenced by the diagnosis itself, by surgery for breast cancer and by other therapy administered (for example, alopecia from chemotherapy). For the same reasons and because of the limited number of patients likely to be included and because the data would be uncontrolled, the sponsor does not think that QoL data from an Australian registry of neoadjuvant Perjeta would provide useful information to supplement the data already available or soon to be available for Perjeta.

Conclusion

Overall, the sponsor considers that an Australian registry for patients treated with neoadjuvant Perjeta is unlikely to provide meaningful safety, efficacy or QoL data in view of the likely availability of data from the APHINITY study in the near future, which is expected to significantly change treatment paradigms for these patients. Further data from ongoing neoadjuvant Perjeta trials will become available before end 2017 (TRYPHAENA final analysis and BERENICE primary analysis), as well as placebo controlled data from PEONY later on.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Perjeta concentrated solution for infusion containing 420 mg/14 mL vial of pertuzumab to have an overall positive benefit–risk profile for the Delegate's amended indication;

> *Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2 positive breast cancer as part of a complete treatment regimen.*
>
> *Note to the Indication: this approval is based on improvement in pathological complete response rate. No improvement in disease-free, progression-free or overall survival has been shown.*

In making this recommendation the ACPM

- Noted the two Phase II studies presented were not powered to assess long term safety in the neoadjuvant setting and that results from the Phase III study (APHINITY) will not be available for about 18 months
- Strongly supported the NOTE proposed by the Delegate to be incorporated in the indication to alert prescribers that approval is based on early data from a limited numbers of patients
- Agreed with the Oncology Working Group advice that improvement in pCR rate supported neoadjuvant use of pertuzumab where there is there is a very high risk of

local recurrence that is in patients with locally advanced or inflammatory breast cancer.

- Was of the view that the addition of pertuzumab would be of potential benefit for the treatment of patients with locally advanced breast cancer with its high risk of local and distant recurrence that is closely aligned with large tumour size, where local control was an important quality of life endpoint and treatment with pertuzumab may increase the likelihood of surgical excision
- Was of the view that the data presented at this time did not support neoadjuvant use in early stage breast cancer, as the limited number of cycles of pertuzumab (4 to 6 cycles) being administered with trastuzumab and chemotherapy preoperatively could not be determined to have an effect on long term outcomes, especially as current evidence has resulted in a recommendation that anti-Her2 therapy with trastuzumab be continued postoperatively for a total treatment duration of one year (18 cycles).
- Was of the view that varying definitions for locally advanced cancer exist: T2/N2, T3 (which may be operable) and T4 as well as inflammatory breast cancer are universally accepted. Some patients with T2/N1 disease may be regarded as locally advanced, particularly those with clinically enlarged lymph nodes. It was noted that these patients were eligible for the APHINITY study (and potentially enriched for recruitment following a protocol amendment which restricted eligibility to those with node-positive disease), and the potential benefit of treatment with pertuzumab in this subgroup overall, may best be defined when that adjuvant trial reports.

Proposed conditions of registration

The ACPM agreed with the Delegate on all the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following;

- Statements highlighting the potential for risk of tumour lysis syndrome in patients with bulky disease in the PI, which was identified from the post-marketing safety report.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- *The Delegate considers a registry is important given the Phase III trial (APHINITY) will not provide further direct information about the efficacy and safety outcomes with neoadjuvant usage. The committee is requested to provide any additional recommendations regarding additional pharmacovigilance activities required.*

The ACPM advised that a registry would be useful in providing information in the neoadjuvant setting and will ascertain different information than that in the APHINITY trial, which will not be available for at least 18 months. The ACPM noted that this would enable gathering of safety data in addition to efficacy data. The ACPM also noted that the indication proposed by the Delegate is different from that of overseas jurisdictions and the establishment of a registry would provide information such as surgical outcomes and pCR rate, in addition to safety data.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Perjeta concentrate injection containing pertuzumab *rch* 30 mg/mL for the new indication:

> *Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2 positive breast cancer as part of a complete treatment regimen.*
>
> *Note to the Indication: this approval is based on improvement in pathological complete response rate. No improvement in disease-free, progression-free or overall survival has been shown.*

Specific conditions of registration applying to these goods

1. The Perjeta EU RMP Version 5.1 (dated 20 May 2015, data lock point 28 February 2015) with Australian Specific Annex Version 3.0 (dated July 2015), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. Any promotional material must include the Indication followed immediately by the Note to the Indication that is these must be stated together.
3. The sponsor is required to set up a registry to collect efficacy and safety data for all neoadjuvant pertuzumab usage in Australian patients.
4. Submission of the following clinical trial(s) as Category 1 submissions for evaluation by the TGA within 6 months of completion:
    a. BERENICE (WO29217), a non-randomised, open-label, Phase II study evaluating pertuzumab in combination with trastuzumab and two different neoadjuvant anthracycline-based chemotherapy regimens in patients with HER2 positive, locally advanced, inflammatory or early-stage breast cancer.
    b. APHINITY (BO25126), a randomised Phase III study of adjuvant trastuzumab +/- pertuzumab after adjuvant chemotherapy (either anthracycline or non-anthracycline based as per investigator). 4805 patients are enrolled onto this study, which is expected to provide important data relating to DFS, OS, long-term cardiac safety, quality-of-life and pharmacokinetic parameters.
    c. PERUSE (MO28047), a multicentre, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer.

Attachment 1. Product Information

The PI approved for Perjeta at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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