BMJ Open

Use and outcomes of targeted therapies in early and metastatic HER2–positive breast cancer in Australia: Observations in a whole of population cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014439
Article Type:	Protocol
Date Submitted by the Author:	27-Sep-2016
Complete List of Authors:	Daniels, Benjamin; University of New South Wales, Medicine Lord, Sarah; University of Notre Dame Australia - Darlinghurst Campus; NHMRC Clinical Trials Centre Kiely, Belinda; University of Sydney, NHMRC Clinical Trials Centre Houssami, Nehmat; Sydney School of Public Health, Sydney Medical School, University of Sydney Haywood, Philip; Centre for Health Economics Research and Evaluation (CHERE) Lu, Christine; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Ward, Robyn; University of Queensland Person, Sallie-Anne; University of New South Wales, Medicines Policy Research Unit
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Epidemiology, Health policy
Keywords:	HER2, breast cancer, trastuzumab, observational study, pharmacoepidemiology

Title: **Use and outcomes of targeted therapies in early and metastatic HER2–positive breast cancer in Australia: Observations in a whole of population cohort**

Authors:

Benjamin Daniels, Medicines Policy Research Unit, Centre for Big Data Research in Health, UNSW. Sydney, Australia.

Sarah J. Lord, School of Medicine, University of Notre Dame Australia; NHMRC Clinical Trials Centre, University of Sydney. Sydney, Australia.

Belinda E Kiely, NHMRC Clinical Trials Centre, University of Sydney. Sydney, Australia.

Nehmat Houssami, Sydney School of Public Health, Sydney Medical School, University of Sydney. Sydney, Australia.

Philip Haywood, Centre for Health Economics Research and Evaluation, University of Technology Sydney, Sydney, Australia.

Christine Lu, Department of Population Medicine, Harvard Medical School, Harvard University. Boston, USA.

Robyn L Ward, University of Queensland. Brisbane, Australia.

*Sallie-Anne Pearson, Medicines Policy Research Unit, Centre for Big Data Research in Health, UNSW. Sydney, Australia.

On behalf of the HER2 therapy observational study (HER2-OBS) investigators.

*Correspondence to: Professor Sallie-Anne Pearson. sallie.pearson@unsw.edu.au +61 2 9385 8895. Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales (UNSW), AGSM, Level 1, Kensington, NSW 2052. Australia.

Keywords: HER2, breast cancer, trastuzumab, observational study, pharmacoepidemiology

Word count: 3,980

Number of tables: 5

Number of figures: 0

Number of references: 56

Number of supplementary files: 0

ABSTRACT

Background: The management of human epidermal growth factor receptor 2 (HER2) positive breast cancer (BC) has changed dramatically with the introduction and widespread use of HER2 targeted therapies. However, there is relatively limited real world information on patterns of use, effectiveness and safety in whole of population cohorts. The research programme detailed in this protocol will generate evidence on the prescribing patterns, safety monitoring and outcomes of BC patients treated with HER2-targeted therapies in Australia.

Methods/Design: Our ongoing research programme will involve a series of retrospective cohort studies that include every patient accessing Commonwealth-funded HER2-targeted therapies for the treatment of early- and advanced BC in Australia. At the time of writing, our cohorts consist of 11,406 early and 5,631 advanced BC patients who accessed trastuzumab and lapatinib between 2001 and 2014. Pertuzumab and trastuzumab emtansine were publically funded for metastatic breast cancer in 2015 and future data updates will include patients accessing these medicines. We will use dispensing claims for cancer and other medicines, medical service claims and demographics data for each patient accessing HER2 therapies to undertake this research.

Ethics and dissemination: Ethics approval has been granted by the Population Health Service Research Ethics Committee and data access approval by the Australian Department of Human Services (DHS) External Review Evaluation Committee.

Results: Our findings will be reported in peer-reviewed publications, conference presentations, and policy forums. By providing detailed information on the use and outcomes associated with HER2-targeted therapies in a national cohort treated in routine clinical care, our research programme will better inform clinicians and patients about the real-world use of these treatments and will assist third party payers to better understand the use and economic costs of these treatments.

Strenths

- One of the largest and only whole-of-country HER2-positive cohorts, internationally
- Currently up to 13 years of data observation, to be extended with future data updates
- Linked medical services and medicines dispensing data for some patients

Limitations

- Lack of clinical measures such as ECOG status and TNM staging
- Lack of clinical diagnoses of comorbidities, adverse events, and cancer progression events
- Medicines that cost less than the Pharmaceutical Benefits Scheme's co-payment threshold will not be captured prior to 2012

INTRODUCTION

Amplification of the human epidermal growth factor receptor 2 (HER2) oncogene is present in approximately 20-30% of breast cancers.[1] The discovery of new and effective HER2-targeted therapies over the past twenty years has significantly improved the outcomes of patients with this aggressive breast cancer subtype. Compared to cytotoxic chemotherapy alone, the addition of HER2-targeted therapies significantly improves response rates, disease-free-survival (DFS)/progression-free-survival (PFS), and overall survival (OS) in patients with HER2-positive breast cancer treated in the neo-adjuvant, adjuvant or metastatic settings.[2-8]

While randomised clinical trials remain the gold standard for demonstrating treatment efficacy, they have some limitations as an evidence-base. The selected population enrolled in a clinical trial is not always representative of the population of "all comers" in routine practice where patients are often older, have more extensive disease, poorer clinical status, and more comorbidities. The sample size and duration of follow-up in clinical trials are often insufficient to detect infrequent events and to determine long-term outcomes. [9-11] As a consequence, medicines can be released to market before their risk benefit profile is fully evaluated, especially when there is increasing demand for early access to potentially life-saving medicines. Observational studies of unselected cohorts of patients are a valuable means of assessing the long-term impact of medicines and their patterns of use in routine practice.[12 13]

In the last decade several observational studies have examined outcomes associated with HER2-targeted therapies in routine clinical practice, utilising data from prospective registries, hospital records, and routinely collected, population-based

administrative data. Registry- and hospital-based data typically contain detailed clinico-pathological measures allowing for studies of the associations between these clinical factors and outcomes such as OS and DFS/PFS.[14-19] Population-based data are often maintained for purposes of reimbursement/payment and tend to have fewer clinical details, but offer much larger sample sizes across health care settings providing evidence more representative of general populations and allowing for better detection of rare events.

To date, studies using population-based administrative data to examine the use of HER2-targeted agents in routine care have focused primarily on trastuzumab, and to a lesser extent lapatinib, examining safety and limited data on long-term outcomes (Table 1, columns 1 and 2). Most of these studies have been conducted in North America, over a period of 5-10 observation years, in populations of up to 4,000 patients. The majority of studies have focused on cardiotoxicity[20-27] and reported an increased risk of cardiotoxicity associated with trastuzumab treatment. A limited number of studies examined cardiac monitoring before and during trastuzumab therapy for metastatic breast cancer (MBC), each reporting less than half of patients underwent an assessment of cardiac function prior to initiation of therapy (range: 11% - 38%).[28-30]

Population-based study estimates of survival outcomes for women receiving HER2-targeted therapies are within the range of pivotal clinical trial estimates. Several studies reported four-year survival rates in early breast cancer (EBC) patients at around 90%,[31 32] and in MBC patients at 41%[24] The four-year relapse-free survival (RFS) rate in MBC was 76%.[31] An Australian study of HER2-positive MBC patients estimated a median OS of 29.9 months.[33]

Issues such as adherence to guideline-specified treatment patterns, off-label use, and overall resource use have also been examined in a number of studies. The only two studies examining lapatinib use did so in the context of quantifying resource use associated with treatment and the factors related to adherence to therapy. They found that costs did not differ between trastuzumab and lapatinib therapy, but the resource use driving costs did;[34] and that prior therapy with a taxane was associated with greater discontinuation of lapatinib.[35] An Australian study found that 22% of patients received trastuzumab in MBC with non-recommended concomitant treatment partners and approximately 20% (or AUD$21 million) of trastuzumab was discarded due to regulations around unused vial portions and weekly treatment schedules.[28]

Table 1. Characteristics of published studies that utilise population-based administrative data and comparison with current programme

	Published studies*				Current programme	
	EBC	Reference #	**MBC**	Reference #	**EBC**	**MBC**
Country						
Australia	0	-	4	28-30 33	**X**	**X**
Canada	1	27	0	-		
Italy	2	25 32	1	24		
United States of America	7	20-23 26 31 36	4	21 22 34 35		
Observation start year						
1998 – 2000	3	21 22 26	3	21 22 35		
2001 – 2005	5	20 23 27 31 36	4	28-30 33		**X**
2006 – 2007	2	25 32	2	24 34	**X**	
Number of observation years						
< 5	2	25 32	1	24		
5 - 10	8	20-23 26 27 31 36	7	21 22 28-30 33 34	**X**	
> 10	0	-	1	35		**X**
Medicine focus						
Trastuzumab	10	20-23 25-27 31 32 36	7	21 22 24 28-30 33-35	**X**	
Lapatinib	0	-	1	35		
Trastuzumab & lapatinib	0	-	1	34		**X**
HER2-positive sample size						
< 1,000 patients	2	21 26	4	21 24 34 35		
1,000 - 2,000 patients	0	-	1	28		
2,000 - 3,000 patients	6	20 22 23 25 32 36	1	22		
3,000 - 4,000 patients	2	27 31	3	29 30 33		
5,000 - 12,000 patients	-	-	-	-	**X**	**X**

Age						
Patients >65 only	4	20-23	2	21 22		
Patients of all ages	6	25-27 31 32 36	7	24 28-30 33-35	X	X
Sex						
Women	9	21-23 25-27 31 32 36	9	21 22 24 28-30 33-35		X
Women & men	1	20	0	-	X	
Study Focus						
Treatment patterns						
Duration of therapy	3	23 25 32	6	28 30 33-35	X	X
Schedules / dosing	2	20 23	2	28 33	X	X
Concomitant cancer therapies	10	20-23 25-27 31 32 36	8	21 22 24 28 30 33-35	X	X
Cancer therapies prior to / following HER2 therapy	1	36	2	34 35	X	X
Non-cancer treatments	2	25 32	1		X	X
Guideline-recommended care	2	21 23	3	21 28 30	X	X
Monitoring						
Cardiac	0	-	3	28-30		X
Other medical services	0	-	2	34 35		X
Outcomes						
Progression-free / Disease-Free Survival, associated factors	3	31 32 36	1	33		
Overall survival (OS), associated factors	4	21 31 32 36	3	21 24 33	X	X
Cardiovascular events, associated factors	6	20 22 23 25-27	2	22 24		

* Shih et al and Tsai et al include both EBC and MBC patients and each study is included in both columns.

Our research programme aims to contribute additional knowledge to the current evidence base on the real world use of HER2 therapies, specifically patterns of prescribing, side-effect monitoring, and outcomes (see Table 1, column 3) using one of the largest whole-of-population cohorts of HER2-positive patients and one of the longest follow-up periods, internationally. We will:

1. Compare the real-world use and outcomes with clinical trials and guideline-recommendations.
2. Determine the duration of HER2-targeted therapies and the long-term benefits and toxicities of treatment.
3. Determine the outcomes of patients receiving HER2-targeted therapies for MBC who also received HER2-targeted therapies for early breast cancer.
4. Estimate total resources— both medicines and health services —used by patients treated with HER2-targeted therapies, and factors associated with resource utilisation.
5. Explore the patient and treatment characteristics associated with survival.
6. Assess the impacts of policy interventions on treatment patterns and outcomes.

METHODS

Study Setting

In this section we discuss the healthcare funding arrangements in Australia as they pertain to HER2-targeted therapies and the administrative datasets generated from these arrangements.

Australia maintains a publically funded universal healthcare system entitling all citizens and permanent residents to a range of subsidised health services. This includes free treatment in public hospitals (funded jointly by the Commonwealth and State/Territory governments) and subsidised treatment in private hospitals (funded jointly by the Commonwealth and private health insurance). Outpatient services, including consultations with medical and selected health care professionals, are funded by the Commonwealth's Medicare Benefits Schedule (MBS). Medicines prescribed in the community and some hospitals are funded by the Commonwealth's Pharmaceutical Benefits Scheme (PBS). The Australian Department of Human Services (DHS) maintains records of medicines dispensed (PBS) and medical services provided (MBS) to patients for the purpose of reimbursement.

Medicines of interest, funding, and access restrictions

There are currently four publically subsidised HER2-targeted therapies available in Australia. Medicines subsidised on the PBS are approved by the Pharmaceutical Benefits Advisory Committee (PBAC) on the basis of efficacy and cost-effectiveness.[37 38] Trastuzumab (Herceptin, Genentech, South San Francisco, CA; Hoffmann-La Roche Ltd., Basel, Switzerland) for metastatic disease was submitted for listing on the PBS in September 2000, December 2000, March 2001, and September 2001 and rejected on each occasion by the PBAC on the grounds that its cost was too high relative to the benefit it provided.[39] Subsidising trastuzumab became an issue in the Australian federal election of October 2001, and the re-instated government created an entirely new funding programme for trastuzumab—one that was distinct from the PBS. By doing so, the requirement of PBAC approval was

bypassed and from December 2001 the *Herceptin Programme* began providing subsidised trastuzumab to women with HER2-positive, MBC in Australia.[40-42] The *Herceptin Programme* is also administered by DHS. Trastuzumab for adjuvant and neoadjuvant treatment was listed on the PBS in October 2006 and December 2012, respectively.

Lapatinib (Tykerb, GlaxoSmithKline, Research Triangle Park, NC) was listed on the PBS as a second line treatment for HER2-positive MBC in May 2008. Pertuzumab (Perjeta, Genentech, South San Francisco, Ca; Hoffmann-La Roche Ltd., Basel, Switzerland) and trastuzumab emastine (T-DM1) [Kadcyla, Genentech, South San Francisco, Ca; Hoffmann-La Roche Ltd., Basel, Switzerland] were listed for first-line and second-line MBC therapy, respectively, in July 2015. At the same time pertuzumab and T-DM1 were considered for subsidy, trastuzumab for MBC was once again submitted for listing on the PBS. A reduced price offered by the manufacturer lead the PBAC to deem the medicine cost-effective and recommend its public subsidy via the PBS.[43] From 1 July 2015 patients initiating trastuzumab for MBC have had their treatment funded by the PBS while patients already receiving trastuzumab through the *Herceptin Programme* began transitioning to receiving the medicine via the PBS.[44] By the end of the 2015 the *Herceptin Programme* was closed.

To ensure that HER2-targeted agents are administered according to clinical trial evidence, the PBS places restrictions on their use. These restrictions have changed with emerging evidence and are summarised in Table 2.

Table 2. Access restrictions to HER2-targeted therapies in Australia

Table 2a: **Subsidy restrictions: trastuzumab for HER2+ metastatic breast cancer**		
2001 – 2005	**2006 – 2015**	**2015 – present***
Treatment Qualification: Patients must have HER2 over-expression by		
IHC† 3+ or ISH‡	ISH	No change
Trastuzumab treatment		
• in combination with taxanes in patients not previously receiving chemotherapy for MBC • as monotherapy in patients previously receiving chemotherapy for MBC • Weekly dosing regimen	As per 2001-2005 plus • weekly or 3-weekly dosing regimen	As per 2001-2015 plus • in combination with any chemotherapy except nab-paclitaxel
Cardiac Monitoring		
None required	None required	• ECHO§ or MUGA‖ at baseline then at 3 monthly intervals

Table 2b: **Subsidy restrictions: trastuzumab for HER2+ early breast cancer**	
2006 – 2015	**2015 – present**
Treatment Qualification: Patients must have…	
• HER2 over expression demonstrated by ISH • undergone surgery for breast cancer	No change
Trastuzumab treatment	
• started in combination with chemotherapy • patients are eligible for 52 weeks of treatment	No change
Cardiac Monitoring	
• ECHO or MUGA at baseline then at 3 monthly intervals • LVEF > 45% • no symptomatic heart failure	No change

Table 2c: Subsidy restrictions: lapatinib for HER2+ metastatic breast cancer

2008 – 2010	2010 – 2015	2015 – present
Treatment Qualification: Patients must have…		
• HER2 over expression demonstrated by ISH • prior taxane for ≥3 cycles; or intolerance to taxane • disease progression while receiving trastuzumab for MBC	No change	No change
Lapatinib treatment		
• as sole PBS-subsidised anti-HER2 treatment • in combination with capecitabine • patients **CANNOT** receive trastuzumab subsequent to receiving lapatinib	• as sole PBS-subsidised anti-HER2 treatment • in combination with capecitabine • patients **CAN** receive trastuzumab subsequent to receiving lapatinib	No change
Cardiac Monitoring		
ECHO or MUGA at baseline then at discretion of clinician	No change	• ECHO or MUGA at baseline then at 3 monthly intervals

Table 2d: Subsidy restrictions: trastuzumab for HER2+ neoadjuvant therapy

2012 – present
Treatment Qualification: Patients must have…
• HER2 over expression demonstrated by ISH • NOT undergone surgery for breast cancer
Trastuzumab treatment
• in combination with chemotherapy • patients are eligible for 52 weeks of treatment
Cardiac Monitoring
• ECHO or MUGA at baseline then at 3 monthly intervals • LVEF > 45% • no symptomatic heart failure

Table 2e: Subsidy restrictions: pertuzumab for HER2+ metastatic breast cancer 2015 – present
Treatment Qualification: Patients must have…
• HER2 over expression demonstrated by ISH • WHO performance status of 0 or 1 • no prior HER2 therapy for MBC
Pertuzumab treatment
• in combination with trastuzumab and a taxane (not nab-paclitaxel)
Cardiac Monitoring
• ECHO or MUGA at baseline then at 3 monthly intervals

Table 2f: Subsidy restrictions: T-DM1 for HER2+ metastatic breast cancer

2015 – 2016	2016 – present
Treatment Qualification: Patients must have	
• HER2 over expression demonstrated by ISH • WHO performance status of 0 or 1 • progressed while receiving pertuzumab and trastuzumab for MBC OR while receiving or within 6 months of completing adjuvant trastuzumab • not received prior treatment with lapatinib or developed an intolerance to lapatinib	As per 2015 – 2016 but • patients may have received prior treatment with lapatinib or developed an intolerance to lapatinib
T-DM1 treatment	
• treatment as monotherapy	No change
Cardiac Monitoring	
• ECHO or MUGA at baseline then at 3 monthly intervals	No change

[*] *Herceptin Programme* ceased and trastuzumab for MBC was listed on the PBS
[†] immunohistochemistry
[‡] in situ hybridisation
[§] echocardiography
[‖] multiple gated acquisition scan

Data sources

Our current holdings include unit-record data on patient demographics, PBS dispensing records (all PBS-funded medicines, not just cancer medicines), and all MBS medical services records for persons treated with trastuzumab and lapatinib between January 2001 and April 2014. We will receive annual data updates. T-DM1 and pertuzumab were funded in Australia in July 2015 and patients treated with these medicines will form part of our subsequent data updates.

Australian law prevents the DHS from linking PBS to MBS records without the explicit consent of patients.[45] As a result, our data holding for patients receiving PBS-funded trastuzumab (in the adjuvant or neoadjuvant settings) is currently limited to patient information and PBS dispensing history only. However, due to the *Herceptin Programme* arrangements (active until 2015), DHS can link PBS records and MBS records to *Herceptin Programme* records, separately, and supply the data so that we can undertake the final merging of the entire data holdings. Therefore, our holdings for patients accessing trastuzumab for metastatic disease consist of patient information, PBS history (where we ascertain all other cancer therapies and other prescribed medicines), MBS history, and *Herceptin Programme* data. We have similar data for patients who received lapatinib because access to lapatinib under the PBS required that patients progressed while receiving trastuzumab for metastatic disease, which had been only been possible through the *Herceptin Programme*.

Table 3. Data holdings approved for the research programme.

Dataset	Description	Metastatic				Early Stage	Neoadjuvant
		Trastuzumab	Lapatinib	T-DM1	Pertuzumab	Trastuzumab	Trastuzumab
First available date in Australia		2001	2008	2015	2015	2006	2012
Patient demographics	Year of birth; sex; mm/yy of death; state of residence; and postcode of residence mapped to SLA*	**X**	**X**	**X**	**X**	**X**	**X**
Patient weight	Patient weight (kg) at the time of *Herceptin Programme* enrolment	**X**	**X**				
Treatment qualification	Patient HER2 overexpression levels and the test used to ascertain levels (IHC or ISH †). Initial intended treatment - monotherapy or concomitant treatment with taxanes	**X**	**X**				
Pharmaceutical Benefits Scheme (PBS)	All prescribed medicines reimbursed by the PBS. Variables include medicine name and strength, date of prescribing, date of supply, quantity supplied/pack size, the number of repeats allowed with the prescription, patient co-payment contribution and the cost to government.	**X**	**X**	**X**	**X**	**X**	**X**
Trastuzumab supply	Dates and vials of trastuzumab dispensed to *Herceptin Programme* participants	**X**					
Medicare Benefits Schedule (MBS)	All medical and allied health services. Variables includes the type of service rendered—from outpatient doctor visits to surgeries—the cost and benefit paid for the service, and the date of service	**X**	**X**				

*SLA = Statistical local area. SLA classifies geographic areas of Australia by socioeconomic profile and remoteness[46 47]

† IHC = Immunohistochemistry, ISH = In-situ hybridisation

Data Access

Data extraction was performed by DHS who assigned a unique scrambled ID and extracted all patient information and all dispensing records (not just HER2-targeted medicines) associated with that ID. For *Herceptin Programme* participants, DHS also extracted medical services records from MBS data. Those records, with the unique ID and requested variables, were then sent to the researchers stripped of identifying information such as name and address. The researchers joined the datasets using the unique ID.

Study Design

This ongoing research programme will comprise a series of retrospective cohort studies of all Australian, HER2-positive breast cancer patients accessing publically subsidised treatment with HER2-targeted agents from 2001 to 2020.

Study Population

As this is an ongoing study, the characteristics of the population will change over time. Characteristics of the study population at the date of first dispensing of HER2-targeted therapy, stratified by treatment setting, are summarised below (Table 3).

Table 4. Cohort demographic and clinical characteristics at first HER2-targeted therapy dispensing

	Metastatic		Early Stage
	Trastuzumab	**Lapatinib**	**Trastuzumab**
Patients with at least one dispensing (n)	5,631	1,099	11,406
Age, median (IQR)	56 (48 - 65)	56 (48 - 63)	54 (47 - 63)
Weight in kilograms at first dispensing, median (IQR)	70 (60 - 80)	70 (60 - 81)	-
HER2-positive by IHC* 3+, n (%)	3,542 (62.9)	585 (53.2)	
HER2-positive by ISH†, n (%)	2,193 (38.9)	496 (45.1)	
Fact of death, n (%)	3,777 (67.1)	892 (81.2)	898 (7.9)
Hormone receptor positive, n (%)§	3,113 (55.3)	617 (56.1)	6,439 (56.4)
Comorbidities‡, n (%)			
0-2	492 (8.7)	44 (4.0)	1,928 (16.9)
3-4	921 (16.4)	149 (13.6)	3,054 (26.8)
5-6	1,137 (20.2)	244 (22.2)	2,689 (23.6)
7+	3,081 (54.7)	662 (60.2)	3,735 (32.7)

* Immunohistochemistry
† In-situ hybridisation
‡ comorbidities assessed from dispensing claims using RxRisk algorithm
§ dispensing of a hormonal agent indicated hormone receptor positivity

In our current data holdings there are 5,631 patients who received trastuzumab and 1,100 patients who received lapatinib for MBC; 11,406 patients received trastuzumab in the early stage and neoadjuvant settings. Overall, there are 1.1 million dispensing records associated with *Herceptin Programme* participants and 1.7 million records associated with EBC and neoadjuvant patients (Table 5). *Herceptin Programme* participants generated 2.2 million medical services claims. In total, there are 25,437 total person years in the *Herceptin Programme* dispensing records; 59,154 person years in EBC/neoadjuvant dispensing records; and 27,763 person years in the *Herceptin Programme* medical services claims (Table 5).

Table 5. Characteristics of data holding

	Metastatic		Early Stage
	Trastuzumab	**Lapatinib**	**Trastuzumab**
Dispensing records, total (N)	1,100,594	261,496	1,763,268
Dispensing records, HER2-targeted therapy (N)	145,907	8,000	171,605
Medical services records (N)	2,221,760	536,370	-
Type of medical service, overall, claims N (%)			
Pathology	897,597 (40.4)	225,210 (42.0)	-
Attendances/consults/visits	599,277 (27.0)	135,521 (25.3)	-
Specialist	329,077 (14.8)	79,266 (14.8)	-
General practitioner	236,649 (10.7)	48,614 (9.1)	-
Enhanced primary care	13,045 (0.6)	3,095 (0.6)	-
Practice Nurse	8,264 (0.4)	2,100 (0.4)	-
Other	12,242 (0.6)	2,446 (0.5)	-
Diagnostic imaging	199,411 (9.0)	48,081 (9.0)	-
Radiotherapy / Nuclear Medicine	136,490 (6.1)	36,276 (6.8)	-
Miscellaneous (eg, medical supplies)	388,985 (17.5)	91,282 (17.0)	-

3,113 of the MBC patients (55%) and 6,439 of the EBC patients (56%) received at least one dispensing of a hormonal therapy. There were 125,257 taxane dispensings and 35,664 anthracycline dispensings. With a median observation time of 49.8 months (IQR: 39.5 – 94.8) from first medicine dispensing or medical service until death or censor date (31 March 2014), 3,777 of the patients treated for MBC (67%) have died and 898 of the patients treated for EBC (8%) have died. Reflecting the population distribution of Australia, more than half of patients in all treatment settings resided in New South Wales and Victoria and more than two-thirds of all patients lived in major cities (not shown in Table 4). Among MBC patients, at least 81% of received at least one dispensing of a pain medication; 48% received medication for the treatment of hypertension or angina; 40% received an antidepressant; and 23% received an anti-anxiety medication. Among EBC patients, 64% received at least one

dispensing of a pain medication; 40% received medication for hypertension or angina; 35% received an antidepressant; and 17% received an anti-anxiety medication.

MBC patients accessing trastuzumab had a median of 54 medical service claims per person, per year (IQR: 23 – 106). The majority of claims relate to pathology services (40.4%) and consultations and visits with healthcare professionals (27%). Patients who also received lapatinib for MBC had 536,370 medical service claims, with a median of 68 (27 – 121) per person, per year. These services followed a similar pattern to those for all trastuzumab patients.

Outcomes of interest and statistical analyses

We will use a range of pharmacoepidemiological and statistical analyses to address our aims.

Patterns of use: We will summarise the prescribing patterns of HER2-targeted therapies including: agent used, line of therapy, partnering therapy (chemotherapy, other HER2-targeted therapy, endocrine therapy) and duration of therapy.

We will report the characteristics of patients dispensed HER2-targeted therapies including age, sex, geographical remoteness, socioeconomic status, HR status, presence of comorbidities at dispensing of HER2-targeted therapy and over time. Age, sex, geographical remoteness and socieconomic status will be ascertained from the patient information datasets. We will define HR status using a validated proxy and define the number and nature of comorbidity from dispensing claims using the

validated RxRisk index.[48-50]

Comparison of real-world use with clinical trials and prescribing guidelines: We will compare duration of therapy (based on dispensing records) and survival outcomes associated with HER2-targeted therapies to those from published clinical trials; we will not undertake comparative efficacy analyses as it is prone to confounding by indication bias. We will estimate overall survival (OS) through Kaplan-Meier methods. We will use descriptive statistics to compare characteristics of patients treated with these medicines in the real-world setting to those treated in clinical trials. Finally, we will compare the real-world treatments to published treatment guidelines.

Outcomes in patients who received HER2-targeted therapies for EBC and MBC: We will identify a sub-set of patients who initiate trastuzumab for EBC who are subsequently trastuzumab-treated for MBC; this patient group is underrepresented in clinical trials. We will compare patient characteristics for this patient group with trastuzumab-naïve MBC patients, as well as EBC patients who do not go on to receive trastuzumab for MBC. We will describe patterns of treatment for each of these three patient groups; and use Cox Proportional Hazard Regression to estimate differences in overall survival between these patient groups.

Estimating total resources: We will use multiple metrics to examine the nature and extent of resource use associated with HER2-targeted therapy. We will report on PBS, MBS and Herceptin Programme resource use overall and by service type and stratify resource use by age, treatment setting, patterns of care, socioeconomic status, and remoteness. We will examine the proportion of total resource use accounted for by

each service (e.g. the proportion of total services accounted for by medications, imaging procedures, surgery, specialist consultations, etc…). We will identify predictors of the rate of health service utilisation using Poisson regression or negative binomial regression, as appropriate. In all models we will consider age at initiation of first HER2-targeted therapy, geographical remoteness, socioeconomic status, HR status and comorbidities.

Examining variations in patient response: We will examine predictors of time-to-discontinuation and time-to-death using Kaplan-Meier curves and Cox proportional hazards models. We will ascertain date of death using the patient information dataset. We will use sub-group analysis to interrogate data on patients who die during early stage treatment or soon after its completion and those who survive for many years following initiation of HER2 therapy to determine the characteristics and patterns of treatment associated with short- and long-term survival.

Impact of policy interventions on treatment patterns and outcomes: We will examine specific prescribing policies in Australia to determine the impact they have on treatment patterns and outcomes. For instance, during the first two years of its availability, prescribing lapatinib to a patient prohibited a return to trastuzumab for that same patient. We will explore the impact of policy changes using interrupted time series methodology. [29]

Analyses will be performed using SAS Version 9.4, Stata Version 13 and R Version 3.2.2.

Limitations

As in any epidemiological study we must consider the potential biases in our research. Some of the issues raised in relation to administrative database research and the conduct of pharmacoepidemiological research in Australia are described below.

Medicine exposure

Australia maintains comprehensive pharmaceutical claims data collections for prescribed medicines dispensed in community and private hospitals, but not for public hospital inpatients. The vast majority of oncology protocols are administered in the outpatient setting or to private hospital inpatients (both of which are captured in the PBS data) and we believe the lack of public hospital inpatient dispensing data is unlikely to impact significantly on the outcomes of our analyses.

In addition, the creation of PBS records is tied to those medicines that are subsidised (in part or in full) by the government. Subsidised medicines in Australia require a patient co-payment; AUD$38.30 at the time of writing. Medicines whose cost is below this amount are not subsidised by the PBS and are not recorded in the PBS data. Therefore, the record of patients' PBS medicine use may be incomplete, limiting the scope of some analyses.[51] We do, however, have information on all PBS medicines including their total costs over time as well as the capacity to identify patients for whom we may not have all PBS dispensings (using their entitlement category). We will restrict some of our analyses to persons with complete PBS-medicines ascertainment. Importantly, the vast majority of cancer medicines are above the co-payment threshold.[52] Furthermore, from July 2012 under co-payment

medicines were recorded in PBS data and these records will be a part of future data updates.

Diagnosis, outcome and covariate misclassification

Health administrative data sets lack detailed clinical information and we need to assess the impact of misclassifying diagnoses and outcomes of interest. Due to the structure of the datasets, we know that all MBC patients appear in *Herceptin Programme* datasets. For early BC patients, between 1 October 2006 and 30 November 2012 all dispensings of trastuzumab represent adjuvant therapy, as this was the only PBS-funded indication during this time. As noted earlier, the *Herceptin Programme* was phased out in 2015 and trastuzumab for MBC listed on the PBS, meaning that from late 2015 trastuzumab dispensings across all treatment settings form part of the PBS data; based on our existing current data holdings we will not be able to distinguish between trastuzumab supplied for metastatic and early stage disease from late 2015. Similarly, among early BC patients from 1 December 2012 we are unable determine which dispensings represent adjuvant or neoadjuvant therapy.

To address this issue we will obtain dispensing authority codes. Authority codes are generated when the prescribing doctor gains approval to administer an authority-required medicine (such as all HER2-targeted therapies) for a particular indication and they will allow us to delineate between medicines dispensed across the different settings.

The data also lack certain important covariates, including comorbidities, ECOG status and TNM staging. Identifying adverse events, such as cardiotoxic events, is difficult without detailed clinical information or hospital admissions codes. Additional, external datasets may be used to examine these issues, but we will not attempt these analyses with our current data holdings.

We previously attempted to validate a proxy for disease progression using dispensing claims but demonstrated a sensitivity of 74%, specificity of 88%, and positive predictive value of 61%. [53] As such, we do not currently have the capacity to accurately estimate time to progression or progression free survival using dispensing claims alone.

ETHICS

Ethics approval has been granted by the Population Health Service Research Ethics Committee (Approval Number: 2010/02/213) and data access approval by the Australian Department of Human Services (DHS) External Review Evaluation Committee (Approval Numbers: MI1474, MI1475, MI1477). At the time of writing we have ethical approval for annual data updates until 2020.

The data for the research programme are released without individual consent. The use and disclosure of Commonwealth data are governed under the Privacy Act 1988. Information Privacy Principle (IPP) 2 under the Privacy Act 1988 (Commonwealth) provides that personal information should not be used or disclosed for any purpose other than the primary purpose of the collection.

We sought approval to use the data for a secondary purpose, that of research involving data linkage.

- Under IPP2.1(d) use or disclosure for another purpose is permitted if (1) it is necessary for research and it is impracticable to gain consent and (2) the use is in accordance with the section 95A guidelines (which provide a process to resolve the conflict that may arise between the public interest in privacy and the public interest in medical research).

We applied for these exemptions to the current research programme. Individual consent for the release of data has been waived because:

- It is not possible or practical to obtain consent because of the large study population (more than 15,000 patients) and a large proportion of patients were likely to be deceased.
- Obtaining consent would prejudice the scientific value of the research due to the high participation rates required for unbiased samples (at least 90%)[54] and the Australian evidence about the sociodemographic differences between participants who consent to data linkage research and those that do not[55]
- The public interest in the research outweighs the public interest in privacy protection, as we know little about the way in which HER2-blockade medicines are used in the real-world marketplace.

DISSEMINATION PLAN

We will consult clinicians, policy makers and consumers where appropriate for guidance in interpreting and disseminating our results. The outcomes of this research will be submitted to international peer-reviewed journals; in particular oncology, general medical, and pharmacoepidemiology journals. We will also present our findings at national and international oncology and pharmacoepidemiology conferences. We will communicate study outcomes to relevant professional cancer/oncology societies such as the Clinical Oncology Society of Australia and the Medical Oncology Group of Australia; and policy groups such as the Pharmaceutical Benefits Advisory Committee and NPSMedicinewise. We will also develop lay summaries of research findings as needed.

In accordance with our DHS data agreement, we will submit all data that will be communicated in the public domain to the DHS for review and approval. Authorship will be based on the International Committee of Medical Journal Editors guidelines.[56] Outcomes will also be posted on the University of New South Wales web page of the lead investigator and the Centre for Big Data Research in Health website. Direct access to the data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

DISCUSSION

The programme of research outlined in this protocol will provide valuable evidence of the real-world, clinical use and outcomes of HER2-targeted therapies. The unique funding structure of these medicines in Australia has created one of the largest and only whole-of-country, HER2-targeted therapies datasets in the world. Observational studies of the kind described in this protocol are particularly important given many of the patients treated in routine practice would not meet typical clinical trial inclusion criteria. The existing observational research has highlighted the use of trastuzumab in populations significantly different from those in the clinical trials and at present there is limited information on the real-world use of lapatinib and no studies addressing T-DM1 or pertuzumab.

The strengths of this programme lie in the use of best practice methods to examine patterns of use and long-term outcomes associated with HER2-targeted therapy, this is particularly important for patients with survival times longer than the typical clinical trial follow-up period. Given these data come from a single payer and are national in scope, loss to follow-up is likely to be much lower than observational studies conducted in countries where health service provision and insurance is more fragmented. Due to the whole-of-population nature of the data, our findings are likely to be highly generalisable, and provide opportunities to extend knowledge on the population impact of HER2-targeted therapy.

ACKNOWLEDGEMENTS

This research is supported, in part, by a Cancer Australia Priority Driven Collaborative Support Scheme (ID: 1050648) and funding from the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA) (ID: 1060407). Benjamin Daniels is supported by an NHMRC Postgraduate Research Scholarship (ID: 1094325), the Sydney Catalyst Translational Cancer Research Centre, and a CREMA PhD scholarship top-up. We thank the Department of Human Services for providing the data for this research.

Contributorship Statement

BD, SJL, BEK, NH, and SAP conceived of the study protocol. BD, RLW, and SAP contributed to the acquisition of the data. BD conducted the literature search and performed the data analyses. BD, SJL, BEK, NH, PH, CL, RLW, and SAP contributed to the design of the work and interpretation of the data. All authors contributed to drafting and critical revisions of the manuscript and have agreed to the final content.

Competing Interests

The authors declare no competing interests.

Funding

This research is supported, in part, by a Cancer Australia Priority Driven Collaborative Support Scheme (ID: 1050648) and funding from the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA) (ID: 1060407). Benjamin Daniels is supported by an NHMRC Postgraduate Research Scholarship (ID: 1094325), the Sydney Catalyst Translational Cancer Research Centre, and a CREMA PhD scholarship top-up.

Data Sharing Statement

Direct access to the data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

REFERENCES

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;**235**(4785):177-82.
2. Harris CA, Ward RL, Dobbins TA, et al. The efficacy of HER2-targeted agents in metastatic breast cancer: a meta-analysis. Ann Oncol 2011;**22**(6):1308-17.
3. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev 2012;**4**:CD006243.
4. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2014;**6**:CD006242.
5. Valachis A, Nearchou A, Lind P, et al. Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence. Breast Cancer Res Treat 2012;**135**(3):655-62.
6. Hicks M, Macrae ER, Abdel-Rasoul M, et al. Neoadjuvant dual HER2-targeted therapy with lapatinib and trastuzumab improves pathologic complete response in patients with early stage HER2-positive breast cancer: a meta-analysis of randomized prospective clinical trials. Oncologist 2015;**20**(4):337-43.
7. Sun J, Chen C, Yao X, et al. Lapatinib combined with neoadjuvant paclitaxel-trastuzumab-based chemotherapy in patients with human epidermal growth factor receptor 2-positive breast cancer: A meta-analysis of randomized controlled trials. Oncol Lett 2015;**9**(3):1351-58.
8. Kawalec P, Lopuch S, Mikrut A. Effectiveness of targeted therapy in patients with previously untreated metastatic breast cancer: a systematic review and meta-analysis. Clin Breast Cancer 2015;**15**(2):90-100 e1.
9. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;**341**(27):2061-7.
10. Avorn J. In defense of pharmacoepidemiology--embracing the yin and yang of drug research. N Engl J Med 2007;**357**(22):2219-21.
11. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet 2008;**372**(9656):2152-61.
12. Banks E, Pearson SA. A life-cycle approach to monitoring benefits and harms of medicines. Med J Aust 2012;**197**(6):313-4.
13. Kelman CW, Pearson SA, Day RO, et al. Evaluating medicines: let's use all the evidence. Med J Aust 2007;**186**(5):249-52.
14. Kaufman PA, Brufsky AM, Mayer M, et al. Treatment patterns and clinical outcomes in elderly patients with HER2-positive metastatic breast cancer from the registHER observational study. Breast Cancer Res Treat 2012;**135**(3):875-83.
15. Tripathy D, Kaufman PA, Brufsky AM, et al. First-line treatment patterns and clinical outcomes in patients with HER2-positive and hormone receptor-positive metastatic breast cancer from registHER. Oncologist 2013;**18**(5):501-10.

16. Yardley DA, Kaufman PA, Brufsky A, et al. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. Breast Cancer Res Treat 2014;**145**(3):725-34.
17. Yardley DA, Tripathy D, Brufsky AM, et al. Long-term survivor characteristics in HER2-positive metastatic breast cancer from registHER. Br J Cancer 2014;**110**(11):2756-64.
18. Jackisch C, Schoenegg W, Reichert D, et al. Trastuzumab in advanced breast cancer--a decade of experience in Germany. BMC Cancer 2014;**14**:924.
19. Jackisch C, Welslau M, Schoenegg W, et al. Impact of trastuzumab treatment beyond disease progression for advanced/metastatic breast cancer on survival - results from a prospective, observational study in Germany. Breast 2014;**23**(5):603-8.
20. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol 2013;**31**(33):4222-8.
21. Shih YC, Xu Y, Dong W, et al. First do no harm: population-based study shows non-evidence-based trastuzumab prescription may harm elderly women with breast cancer. Breast Cancer Res Treat 2014;**144**(2):417-25.
22. Tsai HT, Isaacs C, Fu AZ, et al. Risk of cardiovascular adverse events from trastuzumab (Herceptin((R))) in elderly persons with breast cancer: a population-based study. Breast Cancer Res Treat 2014;**144**(1):163-70.
23. Vaz-Luis I, Keating NL, Lin NU, et al. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol 2014;**32**(9):927-34.
24. Rossi M, Carioli G, Bonifazi M, et al. Trastuzumab for HER2+ metastatic breast cancer in clinical practice: Cardiotoxicity and overall survival. Eur J Cancer 2016;**52**:41-9.
25. Bonifazi M, Franchi M, Rossi M, et al. Trastuzumab-related cardiotoxicity in early breast cancer: a cohort study. Oncologist 2013;**18**(7):795-801.
26. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012;**104**(17):1293-305.
27. Goldhar HA, Yan AT, Ko DT, et al. The Temporal Risk of Heart Failure Associated With Adjuvant Trastuzumab in Breast Cancer Patients: A Population Study. J Natl Cancer Inst 2016;**108**(1).
28. Pearson SA, Ringland CL, Ward RL. Trastuzumab and metastatic breast cancer: trastuzumab use in Australia--monitoring the effect of an expensive medicine access program. J Clin Oncol 2007;**25**(24):3688-93.
29. Lu CY, Srasuebkul P, Drew AK, et al. Positive spillover effects of prescribing requirements: increased cardiac testing in patients treated with trastuzumab for HER2+ metastatic breast cancer. Intern Med J 2012;**42**(11):1229-35.
30. Lu CY, Srasuebkul P, Drew AK, et al. Trastuzumab therapy in Australia: which patients with HER2+ metastatic breast cancer are assessed for cardiac function? Breast 2013;**22**(4):482-7.
31. Gallagher CM, More K, Masaquel A, et al. Survival in patients with non-metastatic breast cancer treated with adjuvant trastuzumab in clinical practice. Springerplus 2016;**5**:395.

32. Bonifazi M, Franchi M, Rossi M, et al. Long term survival of HER2-positive early breast cancer treated with trastuzumab-based adjuvant regimen: a large cohort study from clinical practice. Breast 2014;**23**(5):573-8.
33. Parkinson B, Viney R, Haas M, et al. Real-World Evidence: A Comparison of the Australian Herceptin Program and Clinical Trials of Trastuzumab for HER2-Positive Metastatic Breast Cancer. Pharmacoeconomics 2016.
34. Guerin A, Lalla D, Gauthier G, et al. Comparison of treatment patterns and economic outcomes in metastatic breast cancer patients initiated on trastuzumab versus lapatinib: a retrospective analysis. Springerplus 2014;**3**:236.
35. Delea TE, Kartashov A, Sharma PP. Retrospective Study of the Prevalence, Predictors, and Consequences of Nonadherence With Lapatinib in Women With Metastatic Breast Cancer Who Were Previously Treated With Trastuzumab. Journal of Pharmacy Technology 2013:8755122513513428.
36. Gallagher CM, More K, Kamath T, et al. Delay in initiation of adjuvant trastuzumab therapy leads to decreased overall survival and relapse-free survival in patients with HER2-positive non-metastatic breast cancer. Breast Cancer Res Treat 2016;**157**(1):145-56.
37. Pharmaceutical Benefits Advisory Committee. Secondary Pharmaceutical Benefits Advisory Committee October 22, 2015 2015. http://www.pbs.gov.au/info/industry/listing/participants/pbac.
38. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC research notes 2015;**8**(1):634.
39. Public Summary Document for Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Nov 2008. Secondary Public Summary Document for Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Nov 2008 March 25, 2009 2009. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-trastuzumab-nov08.
40. Budget briefs. *Sunday Tasmanian* 2002 May 19, 2002.
41. Cooke G. Govt to make breast cancer treatment drug free of charge. *Canberra Times* 2001 October 13, 2001;19.
42. Metherell M. Free drug for women with breast cancer. *Sydney Morning Herald* 2001 October 12, 2001;3.
43. Public Summary Document -- November 2014 PBAC Meeting. In: Committee PBA, ed. Australia, 2014.
44. Transitioning of Herceptin Subsidy to the Pharmaceutical Benefits Scheme (PBS). In: Health Do, ed. http://www.pbs.gov.au/info/news/2015/07/transitioning-of-herceptin-subsidy-to-pbs: Department of Health, 2015.
45. Kearny B, Smith M. Response to the Senate Select Committee on Health. In: Australia Po, ed. http://www.aph.gov.au/DocumentStore.ashx?id=f263db77-ba89-466e-8edb-ae95b880ce72, 2014.
46. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC). Statistical Local Area (SLA). Secondary Australian Standard Geographical Classification (ASGC). Statistical Local Area (SLA).

http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/2901.0Chapter2300 2011.
47. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC). Secondary Australian Standard Geographical Classification (ASGC). http://www.abs.gov.au/websitedbs/D3310114.nsf/home/Australian+Standard+Geographical+Classification+%28ASGC%29.
48. Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. Med Care 2003;**41**(6):761-74.
49. Srasuebkul P, Dobbins TA, Elements of Cancer Care I, et al. Validation of a proxy for estrogen receptor status in breast cancer patients using dispensing data. Asia Pac J Clin Oncol 2014;**10**(2):e63-8.
50. Lu CY, Barratt J, Vitry A, et al. Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting. J Clin Epidemiol 2011;**64**(2):223-8.
51. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC Res Notes 2015;**8**:634.
52. Do pharmaceutical claims accurately reflect oncology prescribing practice? Evidence from an Australian HER2+ early breast cancer cohort (HER2EBC). ASCO Annual Meeting Proceedings; 2013.
53. A Proxy of Cancer Progression in Dispensing Claims: Validation and Performance. Pharmacoepidemiology and Drug Safety; 2013. John Wiley & Sons.
54. Holman CD. The impracticable nature of consent for research use of linked administrative health records. Aust N Z J Public Health 2001;**25**(5):421-2.
55. Young AF, Dobson AJ, Byles JE. Health services research using linked records: who consents and what is the gain? Aust N Z J Public Health 2001;**25**(5):417-20.
56. Internation Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. December 2015 ed, 2015.

BMJ Open

Use and outcomes of targeted therapies in early and metastatic HER2–positive breast cancer in Australia: Observations in a whole of population cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014439.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2016
Complete List of Authors:	Daniels, Benjamin; University of New South Wales, Medicine Lord, Sarah; University of Notre Dame Australia - Darlinghurst Campus; NHMRC Clinical Trials Centre Kiely, Belinda; University of Sydney, NHMRC Clinical Trials Centre Houssami, Nehmat; Sydney School of Public Health, Sydney Medical School, University of Sydney Haywood, Philip; Centre for Health Economics Research and Evaluation (CHERE) Lu, Christine; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Ward, Robyn; University of Queensland Person, Sallie-Anne; University of New South Wales, Medicines Policy Research Unit
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Epidemiology, Health policy
Keywords:	HER2, breast cancer, trastuzumab, observational study, pharmacoepidemiology

Title: **Use and outcomes of targeted therapies in early and metastatic HER2–positive breast cancer in Australia: Observations in a whole of population cohort**

Authors:

Benjamin Daniels, Medicines Policy Research Unit, Centre for Big Data Research in Health, UNSW. Sydney, Australia.

Sarah J. Lord, School of Medicine, University of Notre Dame Australia; NHMRC Clinical Trials Centre, University of Sydney. Sydney, Australia.

Belinda E Kiely, NHMRC Clinical Trials Centre, University of Sydney. Sydney, Australia.

Nehmat Houssami, Sydney School of Public Health, Sydney Medical School, University of Sydney. Sydney, Australia.

Philip Haywood, Centre for Health Economics Research and Evaluation, University of Technology Sydney, Sydney, Australia.

Christine Y. Lu, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute. Boston, USA.

Robyn L Ward, University of Queensland. Brisbane, Australia.

*Sallie-Anne Pearson, Medicines Policy Research Unit, Centre for Big Data Research in Health, UNSW. Sydney, Australia.

On behalf of the HER2 therapy observational study (HER2-OBS) investigators.

*Correspondence to: Professor Sallie-Anne Pearson. sallie.pearson@unsw.edu.au +61 2 9385 8895. Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales (UNSW), AGSM, Level 1, Kensington, NSW 2052. Australia.

Keywords: HER2, breast cancer, trastuzumab, observational study, pharmacoepidemiology

Word count: 3,984

Number of tables: 5

Number of figures: 0

Number of references: 75

Number of supplementary files: 0

ABSTRACT

Background: The management of human epidermal growth factor receptor 2 (HER2) positive breast cancer (BC) has changed dramatically with the introduction and widespread use of HER2-targeted therapies. However, there is relatively limited real world information on patterns of use, effectiveness and safety in whole of population cohorts. The research programme detailed in this protocol will generate evidence on the prescribing patterns, safety monitoring and outcomes of BC patients treated with HER2-targeted therapies in Australia.

Methods/Design: Our ongoing research programme will involve a series of retrospective cohort studies that include every patient accessing Commonwealth-funded HER2-targeted therapies for the treatment of early- and advanced BC in Australia. At the time of writing, our cohorts consist of 11,406 early and 5,631 advanced BC patients who accessed trastuzumab and lapatinib between 2001 and 2014. Pertuzumab and trastuzumab emtansine were publicly funded for metastatic breast cancer in 2015 and future data updates will include patients accessing these medicines. We will use dispensing claims for cancer and other medicines, medical service claims and demographics data for each patient accessing HER2-targeted therapies to undertake this research.

Ethics and dissemination: Ethics approval has been granted by the Population Health Service Research Ethics Committee and data access approval by the Australian Department of Human Services (DHS) External Review Evaluation Committee.

Results: Our findings will be reported in peer-reviewed publications, conference presentations, and policy forums. By providing detailed information on the use and outcomes associated with HER2-targeted therapies in a national cohort treated in routine clinical care, our research programme will better inform clinicians and patients about the real-world use of these treatments and will assist third party payers to better understand the use and economic costs of these treatments.

Strengths

- One of the largest and only whole-of-country HER2-positive cohorts, internationally
- Currently up to 13 years of data observation, to be extended with future data updates
- Linked medical services and medicines dispensing data for some patients

Limitations

- Lack of clinical measures such as ECOG status and TNM staging
- Lack of clinical diagnoses of comorbidities, adverse events, and cancer progression events
- Medicines that cost less than the Pharmaceutical Benefits Scheme's co-payment threshold will not be captured prior to 2012

INTRODUCTION

Amplification of the human epidermal growth factor receptor 2 (HER2) oncogene is present in approximately 20-30% of breast cancers.[1] The discovery of new and effective HER2-targeted therapies over the past twenty years has significantly improved the outcomes of patients with this aggressive breast cancer subtype. Compared to cytotoxic chemotherapy alone, the addition of HER2-targeted therapies significantly improves response rates, disease-free-survival (DFS)/progression-free-survival (PFS), and overall survival (OS) in patients with HER2-positive breast cancer treated in the neo-adjuvant, adjuvant or metastatic settings.[2-12]

While randomised clinical trials remain the gold standard for demonstrating treatment efficacy, they have some limitations as an evidence-base. The selected population enrolled in a clinical trial is not always representative of the population of "all comers" in routine practice where patients are often older, have more extensive disease, poorer clinical status, and more comorbidities. The sample size and duration of follow-up in clinical trials are often insufficient to detect infrequent events and to determine long-term outcomes.[13-15] As a consequence, medicines can be released to market before their risk benefit profile is fully evaluated, especially when there is increasing demand for early access to potentially life-saving medicines. Observational studies of unselected cohorts of patients are a valuable means of assessing the long-term impact of medicines and their patterns of use in routine practice.[16 17]

In the last decade a number of observational studies have examined outcomes associated with HER2-targeted therapies in routine clinical practice, utilising data from prospective registries, hospital records, and routinely collected, population-

based administrative data. The heterogeneity in the available data used by these studies has driven their focus. Registry- and hospital-based data typically include records for relatively smaller numbers of patients observed for short periods of time, but contain detailed clinico-pathological measures allowing for studies of the associations between these clinical factors and outcomes such as patterns of care following relapse, adverse events, OS, and DFS/PFS.[18-34]

Population-based data are often maintained for purposes of reimbursement/payment and tend to have fewer clinical details, but offer much larger sample sizes across health care settings providing evidence more representative of general populations and allowing for better detection of rare events. To date, studies using population-based administrative data to examine the use of HER2-targeted agents in routine care have focused primarily on trastuzumab, and to a lesser extent lapatinib, examining safety and long-term outcomes (Table 1, columns 1 and 2). Most of these studies have been conducted in North America, over a period of 5-10 observation years, in populations of up to 4,000 patients. The majority of studies have focused on cardiotoxicity[35-43] and reported an increased risk of cardiotoxicity associated with trastuzumab treatment. A limited number of studies examined cardiac monitoring before and during trastuzumab therapy for metastatic breast cancer (MBC), each reporting less than half of patients underwent an assessment of cardiac function prior to initiation of therapy (range: 11% - 38%).[44-46]

Population-based study estimates of survival outcomes for women receiving HER2-targeted therapies are within the range of pivotal clinical trial estimates. Several studies reported four-year survival rates in early breast cancer (EBC) patients at around 90%,[47 48] and in MBC patients at 41%[39] The four-year relapse-free survival

(RFS) rate in MBC was 76%.[47] An Italian study found no difference in OS (hazard ratio 0.79 [95%CI 0.50 – 1.26]) between metastatic patients previously treated with trastuzumab for EBC who are subsequently treated with trastuzumab for MBC and patients first diagnosed with MBC receiving trastuzumab for MBC.[49] An Australian study of HER2-positive MBC patients estimated a median OS of 29.9 months.[50]

Issues such as factors associated with use of trastuzumab, adherence to guideline-specified treatment patterns, off-label use, and overall resource use have also been examined in a number of studies. A US study found that tumour grade, ethnicity, and area of residence were associated with use of trastuzumab for EBC.[51] The only two studies examining lapatinib use did so in the context of quantifying resource use associated with treatment and the factors related to adherence to therapy. They found that costs did not differ between trastuzumab and lapatinib therapy, but the resource use driving costs did;[52] and that prior therapy with a taxane was associated with greater discontinuation of lapatinib.[53] An Australian study found that 22% of patients received trastuzumab in MBC with non-recommended concomitant treatment partners and approximately 20% (or AUD$21 million) of trastuzumab was discarded due to regulations around unused vial portions and weekly treatment schedules.[44]

Table 1. Characteristics of published studies that utilise population-based administrative data and comparison with current programme

	Published studies*				Current programme	
	EBC	Reference #	**MBC**	Reference #	**EBC**	**MBC**
Country						
Australia	0	-	4	44-46 50	**X**	**X**
Canada	1	42	0	-		
Italy	3	40 48 49	2	39 49		
United States of America	10	35-38 41 43 47 51 54 55	4	36 37 52 53		
Observation start year						
1998 – 2000	4	36 37 41 43	3	36 37 53		
2001 – 2005	5	35 38 42 47 54	4	44-46 50		**X**
2006 – 2010	5	40 48 49 51 55	3	39 49 52	**X**	
Number of observation years						
< 5	4	40 48 49 51	2	39 49		
5 - 10	10	35-38 41-43 47 54 55	7	36 37 44-46 50 52	**X**	
> 10	0	-	1	53		**X**
Medicine focus						
Trastuzumab	14	35-38 40-43 47-49 51 54 55	8	36 37 39 44-46 49 50 52 53	**X**	
Lapatinib	0	-	1	53		
Trastuzumab & lapatinib	0	-	1	52		**X**
HER2-positive sample size						
< 1,000 patients	6	36 41 43 49 51 55	5	36 39 49 52 53		
1,000 - 2,000 patients	0	-	1	44		
2,000 - 3,000 patients	6	35 37 38 40 48 54	1	37		
3,000 - 4,000 patients	2	42 47	3	45 46 50		

5,000 - 12,000 patients	-	-	-	-	X	X
Age						
Patients >65 only	6	35-38 43 51	2	36 37		
Patients of all ages	9	40-42 47-49 54 55	8	39 44-46 49 50 52 53	X	X
Sex						
Women	13	36-38 40-43 47-49 51 54	10	36 37 39 44-46 49 50 52 53		X
Women & men	2	35 55	0	-	X	
Study Focus						
Treatment patterns						
Duration of therapy	4	38 40 48 55	6	44 46 50 52 53	X	X
Schedules / dosing	2	35 38	2	44 50	X	X
Concomitant cancer therapies	13	35-38 40-43 47 48 51 54 55	8	36 37 39 44 46 50 52 53	X	X
Cancer therapies prior to / following HER2 therapy	2	49 54	3	49 52 53	X	X
Non-cancer treatments	2	40 48	1		X	X
Guideline-recommended care	2	36 38	3	36 44 46	X	X
Monitoring						
Cardiac	0	-	3	44-46		X
Other medical services	0	-	2	52 53		X
Outcomes						
Progression-free / Disease-Free Survival, associated factors	3	47 48 54	1	50		
Overall survival (OS), associated factors	5	36 47-49 54	4	36 39 49 50	X	X
Cardiovascular events, associated factors	7	35 37 38 40-43	2	37 39		

* Shih et al, Tsai et al, and Negri et al include both EBC and MBC patients and each study is included in both columns.

Our research programme aims to provide insights into issues that clinical trials are not designed to address and contribute additional knowledge to the current evidence base on the real world use of HER2 therapies. Specifically, we will examine real-world patterns of prescribing, side-effect monitoring, and outcomes (see Table 1, column 3) using one of the largest whole-of-population cohorts of HER2-positive patients and one of the longest follow-up periods, internationally. We will:

1. Compare the real-world use and outcomes with clinical trials and guideline-recommendations.
2. Determine the duration of HER2-targeted therapies and the long-term benefits and toxicities of treatment.
3. Determine the outcomes of patients receiving HER2-targeted therapies for MBC who also received HER2-targeted therapies for early breast cancer.
4. Estimate total resources— both medicines and health services —used by patients treated with HER2-targeted therapies, and factors associated with resource utilisation.
5. Explore the patient and treatment characteristics associated with survival.
6. Assess the impacts of policy interventions on treatment patterns and outcomes.

METHODS

Study Setting

In this section we discuss the healthcare funding arrangements in Australia as they pertain to HER2-targeted therapies and the administrative datasets generated from these arrangements.

Australia maintains a publicly funded universal healthcare system entitling all citizens and permanent residents to a range of subsidised health services. This includes free treatment in public hospitals (funded jointly by the Commonwealth and State/Territory governments) and subsidised treatment in private hospitals (funded jointly by the Commonwealth and private health insurance). Outpatient services, including consultations with medical and selected health care professionals, are funded by the Commonwealth's Medicare Benefits Schedule (MBS). Medicines prescribed in the community and some hospitals are funded by the Commonwealth's Pharmaceutical Benefits Scheme (PBS). The Australian Department of Human Services (DHS) maintains records of medicines dispensed (PBS) and medical services provided (MBS) to patients for the purpose of reimbursement.

Medicines of interest, funding, and access restrictions

There are currently four publicly subsidised HER2-targeted therapies available in Australia. Medicines subsidised on the PBS are approved by the Pharmaceutical Benefits Advisory Committee (PBAC) on the basis of efficacy and cost-effectiveness.[56 57] Trastuzumab (Herceptin, Genentech, South San Francisco, CA; Hoffmann-La Roche Ltd., Basel, Switzerland) for metastatic disease was not considered to be cost-effective by PBAC but was subsidised through a separate programme.[58] From December 2001 until June 2015 the *Herceptin Programme* provided free access to trastuzumab for MBC. The *Herceptin Programme* was also administered by the DHS until its close in June 2015; since July 2015 trastuzumab for MBC has been PBS subsidised.[59-63] Trastuzumab for adjuvant and neoadjuvant treatment was listed on the PBS in October 2006 and December 2012, respectively.

Lapatinib (Tykerb, GlaxoSmithKline, Research Triangle Park, NC) was listed on the PBS as a second line treatment for HER2-positive MBC in May 2008. Pertuzumab (Perjeta, Genentech, South San Francisco, Ca; Hoffmann-La Roche Ltd., Basel, Switzerland) and trastuzumab emtansine (T-DM1) [Kadcyla, Genentech, South San Francisco, Ca; Hoffmann-La Roche Ltd., Basel, Switzerland] were listed for first-line and second-line MBC therapy, respectively, in July 2015.

To ensure that HER2-targeted agents are administered according to clinical trial evidence, the PBS places restrictions on their use. These restrictions have changed with emerging evidence and are summarised in Table 2.

Table 2. Access restrictions to HER2-targeted therapies in Australia

Table 2a: **Subsidy restrictions: trastuzumab for HER2+ metastatic breast cancer**		
2001 – 2005	**2006 – 2015**	**2015 – present***
Treatment Qualification: Patients must have HER2 over-expression by		
IHC† 3+ or ISH‡	ISH	No change
Trastuzumab treatment		
• in combination with taxanes in patients not previously receiving chemotherapy for MBC • as monotherapy in patients previously receiving chemotherapy for MBC • Weekly dosing regimen	As per 2001-2005 plus • weekly or 3-weekly dosing regimen	As per 2001-2015 plus • in combination with any chemotherapy except nab-paclitaxel
Cardiac Monitoring		
None required	None required	• ECHO§ or MUGA‖ at

		baseline then at 3 monthly intervals

Table 2b: **Subsidy restrictions: trastuzumab for HER2+ early breast cancer**

2006 – 2015	2015 – present
Treatment Qualification: Patients must have…	
• HER2 over expression demonstrated by ISH • undergone surgery for breast cancer	No change
Trastuzumab treatment	
• started in combination with chemotherapy • patients are eligible for 52 weeks of treatment	No change
Cardiac Monitoring	
• ECHO or MUGA at baseline then at 3 monthly intervals • LVEF > 45% • no symptomatic heart failure	No change

Table 2c: Subsidy restrictions: lapatinib for HER2+ metastatic breast cancer

2008 – 2010	2010 – 2015	2015 – present
Treatment Qualification: Patients must have…		
• HER2 over expression demonstrated by ISH • prior taxane for ≥3 cycles; or intolerance to taxane • disease progression while receiving trastuzumab for MBC	No change	No change
Lapatinib treatment		
• as sole PBS-subsidised anti-HER2 treatment • in combination with capecitabine • patients **CANNOT** receive trastuzumab subsequent to receiving lapatinib	• as sole PBS-subsidised anti-HER2 treatment • in combination with capecitabine • patients **CAN** receive trastuzumab subsequent to receiving lapatinib	No change
Cardiac Monitoring		
ECHO or MUGA at baseline then	No change	• ECHO or MUGA

at discretion of clinician		at baseline then at 3 monthly intervals

Table 2d: Subsidy restrictions: trastuzumab for HER2+ neoadjuvant therapy

2012 – present

Treatment Qualification: Patients must have…
• HER2 over expression demonstrated by ISH • NOT undergone surgery for breast cancer
Trastuzumab treatment
• in combination with chemotherapy • patients are eligible for 52 weeks of treatment
Cardiac Monitoring
• ECHO or MUGA at baseline then at 3 monthly intervals • LVEF > 45% • no symptomatic heart failure

Table 2e: Subsidy restrictions: pertuzumab for HER2+ metastatic breast cancer

2015 – present

Treatment Qualification: Patients must have…
• HER2 over expression demonstrated by ISH • WHO performance status of 0 or 1 • no prior HER2 therapy for MBC
Pertuzumab treatment
• in combination with trastuzumab and a taxane (not nab-paclitaxel)
Cardiac Monitoring
• ECHO or MUGA at baseline then at 3 monthly intervals

Table 2f: Subsidy restrictions: T-DM1 for HER2+ metastatic breast cancer

2015 – 2016	**2016 – present**
Treatment Qualification: Patients must have	
• HER2 over expression demonstrated by ISH	As per 2015 – 2016 but

• WHO performance status of 0 or 1 • progressed while receiving pertuzumab and trastuzumab for MBC OR while receiving or within 6 months of completing adjuvant trastuzumab • not received prior treatment with lapatinib or developed an intolerance to lapatinib	• patients may have received prior treatment with lapatinib or developed an intolerance to lapatinib
T-DM1 treatment	
• treatment as monotherapy	No change
Cardiac Monitoring	
• ECHO or MUGA at baseline then at 3 monthly intervals	No change

* *Herceptin Programme* ceased and trastuzumab for MBC was listed on the PBS
† immunohistochemistry
‡ in situ hybridisation
§ echocardiography
‖ multiple gated acquisition scan

Data sources

Our current holdings include unit-record data on patient demographics, PBS dispensing records (all PBS-funded medicines, not just cancer medicines), and all MBS medical services records for persons treated with trastuzumab and lapatinib between January 2001 and April 2014. We will receive annual data updates. T-DM1 and pertuzumab were funded in Australia in July 2015 and patients treated with these medicines will form part of our subsequent data updates.

Australian law prevents the DHS from linking PBS to MBS records without the explicit consent of patients.[64] As a result, our data holding for patients receiving PBS-funded trastuzumab (in the adjuvant or neoadjuvant settings) is currently limited to patient information and PBS dispensing history only. However, due to the *Herceptin Programme* arrangements (active until 2015), DHS can link PBS records and MBS

records to *Herceptin Programme* records, separately, and supply the data so that we can undertake the final merging of the entire data holdings. Therefore, our holdings for patients accessing trastuzumab for metastatic disease consist of patient information, PBS history (where we ascertain all other cancer therapies and other prescribed medicines), MBS history, and *Herceptin Programme* data. We have similar data for patients who received lapatinib because access to lapatinib under the PBS required that patients progressed while receiving trastuzumab for metastatic disease, which had been only been possible through the *Herceptin Programme*.

Table 3. Data holdings approved for the research programme.

Dataset	Description	Metastatic				Early Stage	Neoadjuvant
		Trastuzumab	Lapatinib	T-DM1	Pertuzumab	Trastuzumab	Trastuzumab
First available date in Australia		2001	2008	2015	2015	2006	2012
Patient demographics	Year of birth; sex; mm/yy of death; state of residence; and postcode of residence mapped to SLA*	**X**	**X**	**X**	**X**	**X**	**X**
Patient weight	Patient weight (kg) at the time of *Herceptin Programme* enrolment	**X**	**X**				
Treatment qualification	Patient HER2 overexpression levels and the test used to ascertain levels (IHC or ISH †). Initial intended treatment - monotherapy or concomitant treatment with taxanes	**X**	**X**				
Pharmaceutical Benefits Scheme (PBS)	All prescribed medicines reimbursed by the PBS. Variables include medicine name and strength, date of prescribing, date of supply, quantity supplied/pack size, the number of repeats allowed with the prescription, patient co-payment contribution and the cost to government.	**X**	**X**	**X**	**X**	**X**	**X**
Trastuzumab supply	Dates and vials of trastuzumab dispensed to *Herceptin Programme* participants	**X**					
Medicare Benefits Schedule (MBS)	All medical and allied health services. Variables includes the type of service rendered—from outpatient doctor visits to surgeries—the cost and benefit paid for the service, and the date of service	**X**	**X**				

*SLA = Statistical local area. SLA classifies geographic areas of Australia by socioeconomic profile and remoteness[65 66]

† IHC = Immunohistochemistry, ISH = In-situ hybridisation

Data Access

Data extraction was performed by DHS who assigned a unique scrambled ID and extracted all patient information and all dispensing records (not just HER2-targeted medicines) associated with that ID. For *Herceptin Programme* participants, DHS also extracted medical services records from MBS data. Those records, with the unique ID and requested variables, were then sent to the researchers stripped of identifying information such as name and address. The researchers joined the datasets using the unique ID.

Study Design

This ongoing research programme will comprise a series of retrospective cohort studies of all Australian, HER2-positive breast cancer patients accessing publically subsidised treatment with HER2-targeted agents from 2001 to 2020.

Study Population

As this is an ongoing study, the characteristics of the population will change over time. Characteristics of the study population at the date of first dispensing of HER2-targeted therapy, stratified by treatment setting, are summarised below (Table 4).

Table 4. Cohort demographic and clinical characteristics at first HER2-targeted therapy dispensing

	Metastatic		Early Stage
	Trastuzumab	**Lapatinib**	**Trastuzumab**
Patients with at least one dispensing (n)	5,631	1,099	11,406
Age, median (IQR)	56 (48 - 65)	56 (48 - 63)	54 (47 - 63)
Weight in kilograms at first dispensing, median (IQR)	70 (60 - 80)	70 (60 - 81)	-
HER2-positive by IHC* 3+, n (%)	3,542 (62.9)	585 (53.2)	
HER2-positive by ISH†, n (%)	2,193 (38.9)	496 (45.1)	
Fact of death, n (%)	3,777 (67.1)	892 (81.2)	898 (7.9)
Hormone receptor positive, n (%)§	3,113 (55.3)	617 (56.1)	6,439 (56.4)
Comorbidities‡, n (%)			
0-2	492 (8.7)	44 (4.0)	1,928 (16.9)
3-4	921 (16.4)	149 (13.6)	3,054 (26.8)
5-6	1,137 (20.2)	244 (22.2)	2,689 (23.6)
7+	3,081 (54.7)	662 (60.2)	3,735 (32.7)

* Immunohistochemistry
† In-situ hybridisation
‡ comorbidities assessed from dispensing claims using RxRisk algorithm
§ dispensing of a hormonal agent indicated hormone receptor positivity

In our current data holdings there are 5,631 patients who received trastuzumab and 1,100 patients who received lapatinib for MBC; 11,406 patients received trastuzumab in the early stage and neoadjuvant settings. Overall, there are 1.1 million dispensing records associated with *Herceptin Programme* participants and 1.7 million records associated with EBC and neoadjuvant patients (Table 5). *Herceptin Programme* participants generated 2.2 million medical services claims. In total, there are 25,437 total person years in the *Herceptin Programme* dispensing records; 59,154 person years in EBC/neoadjuvant dispensing records; and 27,763 person years in the *Herceptin Programme* medical services claims (Table 5).

Table 5. Characteristics of data holding

	Metastatic		Early Stage
	Trastuzumab	**Lapatinib**	**Trastuzumab**
Dispensing records, total (N)	1,100,594	261,496	1,763,268
Dispensing records, HER2-targeted therapy (N)	145,907	8,000	171,605
Medical services records (N)	2,221,760	536,370	-
Type of medical service, overall, claims N (%)			
Pathology	897,597 (40.4)	225,210 (42.0)	-
Attendances/consults/visits	599,277 (27.0)	135,521 (25.3)	-
Specialist	329,077 (14.8)	79,266 (14.8)	-
General practitioner	236,649 (10.7)	48,614 (9.1)	-
Enhanced primary care	13,045 (0.6)	3,095 (0.6)	-
Practice Nurse	8,264 (0.4)	2,100 (0.4)	-
Other	12,242 (0.6)	2,446 (0.5)	-
Diagnostic imaging	199,411 (9.0)	48,081 (9.0)	-
Radiotherapy / Nuclear Medicine	136,490 (6.1)	36,276 (6.8)	-
Miscellaneous (eg, medical supplies)	388,985 (17.5)	91,282 (17.0)	-

3,113 of the MBC patients (55%) and 6,439 of the EBC patients (56%) received at least one dispensing of a hormonal therapy. There were 125,257 taxane dispensings and 35,664 anthracycline dispensings. With a median observation time of 49.8 months (IQR: 39.5 – 94.8) from first medicine dispensing or medical service until death or censor date (31 March 2014), 3,777 of the patients treated for MBC (67%) have died and 898 of the patients treated for EBC (8%) have died. Reflecting the population distribution of Australia, more than half of patients in all treatment settings resided in New South Wales and Victoria and more than two-thirds of all patients lived in major cities (not shown in Table 4). Among MBC patients, at least 81% of received at least one dispensing of a pain medication; 48% received medication for the treatment of hypertension or angina; 40% received an antidepressant; and 23%

received an anti-anxiety medication. Among EBC patients, 64% received at least one dispensing of a pain medication; 40% received medication for hypertension or angina; 35% received an antidepressant; and 17% received an anti-anxiety medication.

MBC patients accessing trastuzumab had a median of 54 medical service claims per person, per year (IQR: 23 – 106). The majority of claims relate to pathology services (40.4%) and consultations and visits with healthcare professionals (27%). Patients who also received lapatinib for MBC had 536,370 medical service claims, with a median of 68 (27 – 121) per person, per year. These services followed a similar pattern to those for all trastuzumab patients.

Outcomes of interest and statistical analyses

We will use a range of pharmacoepidemiological and statistical analyses to address our aims.

Patterns of use: We will summarise the prescribing patterns of HER2-targeted therapies including: agent used, line of therapy, partnering therapy (chemotherapy, other HER2-targeted therapy, endocrine therapy) and duration of therapy.

We will report the characteristics of patients dispensed HER2-targeted therapies including age, sex, geographical remoteness, socioeconomic status, HR status, presence of comorbidities at dispensing of HER2-targeted therapy and over time. Age, sex, geographical remoteness and socieconomic status will be ascertained from the patient information datasets. We will define HR status using a validated proxy and

define the number and nature of comorbidity from dispensing claims using the validated RxRisk index.[67-69]

Comparison of real-world use with clinical trials and prescribing guidelines: We will compare duration of therapy (based on dispensing records) and survival outcomes associated with HER2-targeted therapies to those from published clinical trials; we will not undertake comparative efficacy analyses as it is prone to confounding by indication bias. We will estimate overall survival (OS) through Kaplan-Meier methods. We will use descriptive statistics to compare characteristics of patients treated with these medicines in the real-world setting to those treated in clinical trials. Finally, we will compare the real-world treatments to published treatment guidelines.

Outcomes in patients who received HER2-targeted therapies for EBC and MBC: We will identify a sub-set of patients who initiate trastuzumab for EBC who are subsequently trastuzumab-treated for MBC; this patient group is underrepresented in clinical trials. We will compare patient characteristics for this patient group with trastuzumab-naïve MBC patients, trastuzumab-naïve MBC patients whose first cancer medicine was trastuzumab (as a proxy for patients first diagnosed with MBC), and EBC patients who do not go on to receive trastuzumab for MBC. We will describe patterns of treatment for each of these three patient groups; and use Cox Proportional Hazard Regression to estimate differences in overall survival between these patient groups.

Estimating total resources: We will use multiple metrics to examine the nature and extent of resource use associated with HER2-targeted therapy. We will report on PBS,

MBS and Herceptin Programme resource use overall and by service type and stratify resource use by age, treatment setting, patterns of care, socioeconomic status, and remoteness. We will examine the proportion of total resource use accounted for by each service (e.g. the proportion of total services accounted for by medications, imaging procedures, surgery, specialist consultations, etc…). We will identify predictors of the rate of health service utilisation using Poisson regression or negative binomial regression, as appropriate. In all models we will consider age at initiation of first HER2-targeted therapy, geographical remoteness, socioeconomic status, HR status and comorbidities.

Examining variations in patient response: We will examine predictors of time-to-discontinuation and time-to-death using Kaplan-Meier curves and Cox proportional hazards models. We will ascertain date of death using the patient information dataset. We will use sub-group analysis to interrogate data on patients who die during early stage treatment or soon after its completion and those who survive for many years following initiation of HER2 therapy to determine the characteristics and patterns of treatment associated with short- and long-term survival.

Impact of policy interventions on treatment patterns and outcomes: We will examine specific prescribing policies in Australia to determine the impact they have on treatment patterns and outcomes. For instance, during the first two years of its availability, prescribing lapatinib to a patient prohibited a return to trastuzumab for that same patient. We will explore the impact of policy changes using interrupted time series methodology. [45]

Analyses will be performed using SAS Version 9.4, Stata Version 13 and R Version 3.2.2.

Limitations

As in any epidemiological study we must consider the potential biases in our research. Some of the issues raised in relation to administrative database research and the conduct of pharmacoepidemiological research in Australia are described below.

Medicine exposure

Australia maintains comprehensive pharmaceutical claims data collections for prescribed medicines dispensed in community and private hospitals, but not for public hospital inpatients. The vast majority of oncology protocols are administered in the outpatient setting or to private hospital inpatients (both of which are captured in the PBS data) and we believe the lack of public hospital inpatient dispensing data is unlikely to impact significantly on the outcomes of our analyses.

In addition, the creation of PBS records is tied to those medicines that are subsidised (in part or in full) by the government. Subsidised medicines in Australia require a patient co-payment; AUD$38.30 at the time of writing. Medicines whose cost is below this amount are not subsidised by the PBS and are not recorded in the PBS data. Therefore, the record of patients' PBS medicine use may be incomplete, limiting the scope of some analyses.[70] We do, however, have information on all PBS medicines including their total costs over time as well as the capacity to identify patients for whom we may not have all PBS dispensings (using their entitlement

category). We will restrict some of our analyses to persons with complete PBS-medicines ascertainment. Importantly, the vast majority of cancer medicines are above the co-payment threshold.[71] Furthermore, from July 2012 under co-payment medicines were recorded in PBS data and these records will be a part of future data updates.

Diagnosis, outcome and covariate misclassification

Health administrative data sets lack detailed clinical information and we need to assess the impact of misclassifying diagnoses and outcomes of interest. Due to the structure of the datasets, we know that all MBC patients appear in *Herceptin Programme* datasets. For early BC patients, between 1 October 2006 and 30 November 2012 all dispensings of trastuzumab represent adjuvant therapy, as this was the only PBS-funded indication during this time. As noted earlier, the *Herceptin Programme* was phased out in 2015 and trastuzumab for MBC listed on the PBS, meaning that from late 2015 trastuzumab dispensings across all treatment settings form part of the PBS data; based on our existing current data holdings we will not be able to distinguish between trastuzumab supplied for metastatic and early stage disease from late 2015. Similarly, among early BC patients from 1 December 2012 we are unable determine which dispensings represent adjuvant or neoadjuvant therapy.

To address this issue we will obtain dispensing authority codes. Authority codes are generated when the prescribing doctor gains approval to administer an authority-required medicine (such as all HER2-targeted therapies) for a particular indication

and they will allow us to delineate between medicines dispensed across the different settings.

The data also lack certain important covariates, including comorbidities, ECOG status and TNM staging. Identifying adverse events, such as cardiotoxic events, is difficult without detailed clinical information or hospital admissions codes. Additional, external datasets may be used to examine these issues, but we will not attempt these analyses with our current data holdings.

We previously attempted to validate a proxy for disease progression using dispensing claims but demonstrated a sensitivity of 74%, specificity of 88%, and positive predictive value of 61%.[72] As such, we do not currently have the capacity to accurately estimate time to progression or progression free survival using dispensing claims alone. This will limit the scope of outcomes research in the patients with early stage disease; at present, the main contributions based on our available data are likely to lie in the metastatic setting.

ETHICS

Ethics approval has been granted by the Population Health Service Research Ethics Committee (Approval Number: 2010/02/213) and data access approval by the Australian Department of Human Services (DHS) External Review Evaluation Committee (Approval Numbers: MI1474, MI1475, MI1477). At the time of writing we have ethical approval for annual data updates until 2020.

The data for the research programme are released without individual consent. The use and disclosure of Commonwealth data are governed under the Privacy Act 1988. Information Privacy Principle (IPP) 2 under the Privacy Act 1988 (Commonwealth) provides that personal information should not be used or disclosed for any purpose other than the primary purpose of the collection.

We sought approval to use the data for a secondary purpose, that of research involving data linkage.

- Under IPP2.1(d) use or disclosure for another purpose is permitted if (1) it is necessary for research and it is impracticable to gain consent and (2) the use is in accordance with the section 95A guidelines (which provide a process to resolve the conflict that may arise between the public interest in privacy and the public interest in medical research).

We applied for these exemptions to the current research programme. Individual consent for the release of data has been waived because:

- It is not possible or practical to obtain consent because of the large study population (more than 15,000 patients) and a large proportion of patients were likely to be deceased.
- Obtaining consent would prejudice the scientific value of the research due to the high participation rates required for unbiased samples (at least 90%) and the Australian evidence about the sociodemographic differences between participants who consent to data linkage research and those that do not.[73 74]

- The public interest in the research outweighs the public interest in privacy protection, as we know little about the way in which HER2-blockade medicines are used in the real-world marketplace.

DISSEMINATION PLAN

We will consult clinicians, policy makers and consumers where appropriate for guidance in interpreting and disseminating our results. The outcomes of this research will be submitted to international peer-reviewed journals; in particular oncology, general medical, and pharmacoepidemiology journals. We will also present our findings at national and international oncology and pharmacoepidemiology conferences. We will communicate study outcomes to relevant professional cancer/oncology societies such as the Clinical Oncology Society of Australia and the Medical Oncology Group of Australia; and policy groups such as the Pharmaceutical Benefits Advisory Committee and NPSMedicinewise. We will also develop lay summaries of research findings as needed.

In accordance with our DHS data agreement, we will submit all data that will be communicated in the public domain to the DHS for review and approval. Authorship will be based on the International Committee of Medical Journal Editors guidelines.[75] Outcomes will also be posted on the University of New South Wales web page of the lead investigator and the Centre for Big Data Research in Health website. Direct access to the data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

DISCUSSION

The programme of research outlined in this protocol will provide valuable evidence of the real-world, clinical use and outcomes of HER2-targeted therapies. The unique funding structure of these medicines in Australia has created one of the largest and only whole-of-country, HER2-targeted therapies datasets in the world. Observational studies of the kind described in this protocol are particularly important given many of the patients treated in routine practice would not meet typical clinical trial inclusion criteria. The existing observational research has highlighted the use of trastuzumab in populations significantly different from those in the clinical trials and at present there is limited information on the real-world use of lapatinib and no studies addressing T-DM1 or pertuzumab.

The strengths of this programme lie in the use of best practice methods to examine patterns of use and long-term outcomes associated with HER2-targeted therapy, this is particularly important for patients with survival times longer than the typical clinical trial follow-up period. Given these data come from a single payer and are national in scope, loss to follow-up is likely to be much lower than observational studies conducted in countries where health service provision and insurance is more fragmented. Due to the whole-of-population nature of the data, our findings are likely to be highly generalisable, and provide opportunities to extend knowledge on the population impact of HER2-targeted therapy.

ACKNOWLEDGEMENTS

This research is supported, in part, by a Cancer Australia Priority Driven Collaborative Support Scheme (ID: 1050648) and funding from the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA) (ID: 1060407). Benjamin Daniels is supported by an NHMRC Postgraduate Research Scholarship (ID: 1094325), the Sydney Catalyst Translational Cancer Research Centre, and a CREMA PhD scholarship top-up. We thank the Department of Human Services for providing the data for this research.

Contributorship Statement

BD, SJL, BEK, NH, PH, CYL, RLW, and SAP conceived of the study protocol. BD, RLW, and SAP contributed to the acquisition of the data. BD conducted the literature search and performed the data analyses. BD, SJL, BEK, NH, PH, CYL, RLW, and SAP contributed to the design of the work and interpretation of the data. All authors contributed to drafting and critical revisions of the manuscript and have agreed to the final content.

Competing Interests

The authors declare no competing interests.

Funding

This research is supported, in part, by a Cancer Australia Priority Driven Collaborative Support Scheme (ID: 1050648) and funding from the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA) (ID: 1060407). Benjamin Daniels is supported by an NHMRC Postgraduate Research Scholarship (ID: 1094325), the Sydney Catalyst Translational Cancer Research Centre, and a CREMA PhD scholarship top-up.

Data Sharing Statement

Direct access to the data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

REFERENCES

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235(4785):177-82.
2. Harris CA, Ward RL, Dobbins TA, et al. The efficacy of HER2-targeted agents in metastatic breast cancer: a meta-analysis. *Ann Oncol* 2011;22(6):1308-17. doi: 10.1093/annonc/mdq593
3. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;4:CD006243. doi: 10.1002/14651858.CD006243.pub2
4. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2014;6:CD006242. doi: 10.1002/14651858.CD006242.pub2
5. Valachis A, Nearchou A, Lind P, et al. Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence. *Breast Cancer Res Treat* 2012;135(3):655-62. doi: 10.1007/s10549-012-2189-z
6. Hicks M, Macrae ER, Abdel-Rasoul M, et al. Neoadjuvant dual HER2-targeted therapy with lapatinib and trastuzumab improves pathologic complete response in patients with early stage HER2-positive breast cancer: a meta-analysis of randomized prospective clinical trials. *Oncologist* 2015;20(4):337-43. doi: 10.1634/theoncologist.2014-0334
7. Sun J, Chen C, Yao X, et al. Lapatinib combined with neoadjuvant paclitaxel-trastuzumab-based chemotherapy in patients with human epidermal growth factor receptor 2-positive breast cancer: A meta-analysis of randomized controlled trials. *Oncol Lett* 2015;9(3):1351-58. doi: 10.3892/ol.2015.2848
8. Kawalec P, Lopuch S, Mikrut A. Effectiveness of targeted therapy in patients with previously untreated metastatic breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer* 2015;15(2):90-100 e1. doi: 10.1016/j.clbc.2014.10.006
9. Broglio KR, Quintana M, Foster M, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. *JAMA Oncol* 2016;2(6):751-60. doi: 10.1001/jamaoncol.2015.6113
10. Kumler I, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2-positive breast cancer. *Cancer Treat Rev* 2014;40(2):259-70. doi: 10.1016/j.ctrv.2013.09.002
11. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366(2):109-19. doi: 10.1056/NEJMoa1113216
12. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367(19):1783-91. doi: 10.1056/NEJMoa1209124
13. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341(27):2061-7. doi: 10.1056/NEJM199912303412706

14. Avorn J. In defense of pharmacoepidemiology--embracing the yin and yang of drug research. *N Engl J Med* 2007;357(22):2219-21. doi: 10.1056/NEJMp0706892
15. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. *Lancet* 2008;372(9656):2152-61. doi: 10.1016/s0140-6736(08)61930-3 [published Online First: 2008/12/23]
16. Banks E, Pearson SA. A life-cycle approach to monitoring benefits and harms of medicines. *Med J Aust* 2012;197(6):313-4.
17. Kelman CW, Pearson SA, Day RO, et al. Evaluating medicines: let's use all the evidence. *Med J Aust* 2007;186(5):249-52.
18. Kaufman PA, Brufsky AM, Mayer M, et al. Treatment patterns and clinical outcomes in elderly patients with HER2-positive metastatic breast cancer from the registHER observational study. *Breast Cancer Res Treat* 2012;135(3):875-83. doi: 10.1007/s10549-012-2209-z
19. Tripathy D, Kaufman PA, Brufsky AM, et al. First-line treatment patterns and clinical outcomes in patients with HER2-positive and hormone receptor-positive metastatic breast cancer from registHER. *Oncologist* 2013;18(5):501-10. doi: 10.1634/theoncologist.2012-0414
20. Yardley DA, Kaufman PA, Brufsky A, et al. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2014;145(3):725-34. doi: 10.1007/s10549-014-2916-8
21. Yardley DA, Tripathy D, Brufsky AM, et al. Long-term survivor characteristics in HER2-positive metastatic breast cancer from registHER. *Br J Cancer* 2014;110(11):2756-64. doi: 10.1038/bjc.2014.174
22. Jackisch C, Schoenegg W, Reichert D, et al. Trastuzumab in advanced breast cancer--a decade of experience in Germany. *BMC Cancer* 2014;14:924. doi: 10.1186/1471-2407-14-924
23. Jackisch C, Welslau M, Schoenegg W, et al. Impact of trastuzumab treatment beyond disease progression for advanced/metastatic breast cancer on survival - results from a prospective, observational study in Germany. *Breast* 2014;23(5):603-8. doi: 10.1016/j.breast.2014.06.003
24. Hamy-Petit AS, Belin L, Bonsang-Kitzis H, et al. Pathological complete response and prognosis after neoadjuvant chemotherapy for HER2-positive breast cancers before and after trastuzumab era: results from a real-life cohort. *Br J Cancer* 2016;114(1):44-52. doi: 10.1038/bjc.2015.426
25. Seferina SC, Lobbezoo DJ, de Boer M, et al. Real-Life Use and Effectiveness of Adjuvant Trastuzumab in Early Breast Cancer Patients: A Study of the Southeast Netherlands Breast Cancer Consortium. *Oncologist* 2015;20(8):856-63. doi: 10.1634/theoncologist.2015-0006
26. Mustacchi G, Puglisi F, Molino AM, et al. Observational study on adjuvant trastuzumab in HER2-positive early breast cancer patients. *Future Oncol* 2015;11(10):1493-500. doi: 10.2217/fon.15.34
27. Menard S, Balsari A, Tagliabue E, et al. Biology, prognosis and response to therapy of breast carcinomas according to HER2 score. *Ann Oncol* 2008;19(10):1706-12. doi: 10.1093/annonc/mdn369

28. Dall P, Lenzen G, Gohler T, et al. Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany. *J Geriatr Oncol* 2015;6(6):462-9. doi: 10.1016/j.jgo.2015.06.003
29. Outcome of HER2-positive breast cancer patients following metastatic relapse after adjuvant trastuzumab treatment since EMA regulatory approval. ASCO Annual Meeting Proceedings; 2012.
30. Krell J, James CR, Shah D, et al. Human epidermal growth factor receptor 2-positive breast cancer relapsing post-adjuvant trastuzumab: pattern of recurrence, treatment and outcome. *Clin Breast Cancer* 2011;11(3):153-60. doi: 10.1016/j.clbc.2011.03.012
31. First-line patterns of care and outcomes of HER2-positive breast cancer patients who progressed after receiving adjuvant trastuzumab in the outpatient community setting. ASCO Annual Meeting Proceedings; 2010.
32. Vaz-Luis I, Seah D, Olson EM, et al. Clinicopathological features among patients with advanced human epidermal growth factor-2-positive breast cancer with prolonged clinical benefit to first-line trastuzumab-based therapy: a retrospective cohort study. *Clin Breast Cancer* 2013;13(4):254-63. doi: 10.1016/j.clbc.2013.02.010
33. Marla S, Cardale J, Dodwell DJ, et al. HER2-positive early breast cancers: What proportion are receiving adjuvant trastuzumab therapy? A multicenter audit. *Journal of Clinical Oncology* 2010;28(15_suppl):668-68. doi: doi:10.1200/jco.2010.28.15_suppl.668
34. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Impact of hormone receptor status on patterns of recurrence and clinical outcomes among patients with human epidermal growth factor-2-positive breast cancer in the National Comprehensive Cancer Network: a prospective cohort study. *Breast Cancer Res* 2012;14(5):R129. doi: 10.1186/bcr3324
35. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol* 2013;31(33):4222-8. doi: 10.1200/JCO.2013.48.7884
36. Shih YC, Xu Y, Dong W, et al. First do no harm: population-based study shows non-evidence-based trastuzumab prescription may harm elderly women with breast cancer. *Breast Cancer Res Treat* 2014;144(2):417-25. doi: 10.1007/s10549-014-2874-1
37. Tsai HT, Isaacs C, Fu AZ, et al. Risk of cardiovascular adverse events from trastuzumab (Herceptin((R))) in elderly persons with breast cancer: a population-based study. *Breast Cancer Res Treat* 2014;144(1):163-70. doi: 10.1007/s10549-014-2836-7
38. Vaz-Luis I, Keating NL, Lin NU, et al. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. *J Clin Oncol* 2014;32(9):927-34. doi: 10.1200/JCO.2013.51.1261
39. Rossi M, Carioli G, Bonifazi M, et al. Trastuzumab for HER2+ metastatic breast cancer in clinical practice: Cardiotoxicity and overall survival. *Eur J Cancer* 2016;52:41-9. doi: 10.1016/j.ejca.2015.09.012
40. Bonifazi M, Franchi M, Rossi M, et al. Trastuzumab-related cardiotoxicity in early breast cancer: a cohort study. *Oncologist* 2013;18(7):795-801. doi: 10.1634/theoncologist.2013-0065

41. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst* 2012;104(17):1293-305. doi: 10.1093/jnci/djs317
42. Goldhar HA, Yan AT, Ko DT, et al. The Temporal Risk of Heart Failure Associated With Adjuvant Trastuzumab in Breast Cancer Patients: A Population Study. *J Natl Cancer Inst* 2016;108(1) doi: 10.1093/jnci/djv301
43. Chen J, Long JB, Hurria A, et al. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol* 2012;60(24):2504-12. doi: 10.1016/j.jacc.2012.07.068
44. Pearson SA, Ringland CL, Ward RL. Trastuzumab and metastatic breast cancer: trastuzumab use in Australia--monitoring the effect of an expensive medicine access program. *J Clin Oncol* 2007;25(24):3688-93. doi: 10.1200/jco.2007.11.2516 [published Online First: 2007/08/21]
45. Lu CY, Srasuebkul P, Drew AK, et al. Positive spillover effects of prescribing requirements: increased cardiac testing in patients treated with trastuzumab for HER2+ metastatic breast cancer. *Intern Med J* 2012;42(11):1229-35. doi: 10.1111/j.1445-5994.2011.02604.x
46. Lu CY, Srasuebkul P, Drew AK, et al. Trastuzumab therapy in Australia: which patients with HER2+ metastatic breast cancer are assessed for cardiac function? *Breast* 2013;22(4):482-7. doi: 10.1016/j.breast.2013.04.011
47. Gallagher CM, More K, Masaquel A, et al. Survival in patients with non-metastatic breast cancer treated with adjuvant trastuzumab in clinical practice. *Springerplus* 2016;5:395. doi: 10.1186/s40064-016-2008-9
48. Bonifazi M, Franchi M, Rossi M, et al. Long term survival of HER2-positive early breast cancer treated with trastuzumab-based adjuvant regimen: a large cohort study from clinical practice. *Breast* 2014;23(5):573-8. doi: 10.1016/j.breast.2014.05.022
49. Negri E, Zambelli A, Franchi M, et al. Effectiveness of trastuzumab in first-line HER2+ metastatic breast cancer after failure in adjuvant setting: a controlled cohort study. *Oncologist* 2014;19(12):1209-15. doi: 10.1634/theoncologist.2014-0227
50. Parkinson B, Viney R, Haas M, et al. Real-World Evidence: A Comparison of the Australian Herceptin Program and Clinical Trials of Trastuzumab for HER2-Positive Metastatic Breast Cancer. *Pharmacoeconomics* 2016 doi: 10.1007/s40273-016-0411-2
51. Vaz-Luis I, Lin NU, Keating NL, et al. Treatment of early-stage human epidermal growth factor 2-positive cancers among medicare enrollees: age and race strongly associated with non-use of trastuzumab. *Breast Cancer Res Treat* 2016;159(1):151-62. doi: 10.1007/s10549-016-3927-4
52. Guerin A, Lalla D, Gauthier G, et al. Comparison of treatment patterns and economic outcomes in metastatic breast cancer patients initiated on trastuzumab versus lapatinib: a retrospective analysis. *Springerplus* 2014;3:236. doi: 10.1186/2193-1801-3-236
53. Delea TE, Kartashov A, Sharma PP. Retrospective Study of the Prevalence, Predictors, and Consequences of Nonadherence With Lapatinib in Women With Metastatic Breast Cancer Who Were Previously Treated With Trastuzumab. *Journal of Pharmacy Technology* 2013:8755122513513428.

54. Gallagher CM, More K, Kamath T, et al. Delay in initiation of adjuvant trastuzumab therapy leads to decreased overall survival and relapse-free survival in patients with HER2-positive non-metastatic breast cancer. *Breast Cancer Res Treat* 2016;157(1):145-56. doi: 10.1007/s10549-016-3790-3
55. DaCosta Byfield S, Buck PO, Blauer-Peterson C, et al. ReCAP: Treatment Patterns and Cost of Care Associated With Initial Therapy Among Patients Diagnosed With Operable Early-Stage Human Epidermal Growth Factor Receptor 2-Overexpressed Breast Cancer in the United States: A Real-World Retrospective Study. *J Oncol Pract* 2016;12(2):159-67. doi: 10.1200/JOP.2015.004747
56. Pharmaceutical Benefits Advisory Committee 2015 [updated October 22, 2015. Available from: http://www.pbs.gov.au/info/industry/listing/participants/pbac accessed April 05 2016.
57. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC research notes* 2015;8(1):634.
58. Public Summary Document for Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Nov 2008 2009 [updated March 25, 2009. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-trastuzumab-nov08 accessed April 5 2016.
59. Budget briefs. *Sunday Tasmanian* 2002 May 19, 2002.
60. Cooke G. Govt to make breast cancer treatment drug free of charge. *Canberra Times* 2001 October 13, 2001;19.
61. Metherell M. Free drug for women with breast cancer. *Sydney Morning Herald* 2001 October 12, 2001;3.
62. Public Summary Document -- November 2014 PBAC Meeting. In: Committee PBA, ed. Australia, 2014.
63. Transitioning of Herceptin Subsidy to the Pharmaceutical Benefits Scheme (PBS). In: Health Do, ed. http://www.pbs.gov.au/info/news/2015/07/transitioning-of-herceptin-subsidy-to-pbs: Department of Health, 2015.
64. Kearny B, Smith M. Response to the Senate Select Committee on Health. In: Australia Po, ed. http://www.aph.gov.au/DocumentStore.ashx?id=f263db77-ba89-466e-8edb-ae95b880ce72, 2014.
65. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC). Statistical Local Area (SLA). [Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/2901.0Chapter23002011 accessed April 5 2016.
66. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC) [Available from: http://www.abs.gov.au/websitedbs/D3310114.nsf/home/Australian+Standard+Geographical+Classification+%28ASGC%29 accessed April 5 2016.

67. Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care* 2003;41(6):761-74. doi: 10.1097/01.MLR.0000064641.84967.B7
68. Srasuebkul P, Dobbins TA, Elements of Cancer Care I, et al. Validation of a proxy for estrogen receptor status in breast cancer patients using dispensing data. *Asia Pac J Clin Oncol* 2014;10(2):e63-8. doi: 10.1111/ajco.12015
69. Lu CY, Barratt J, Vitry A, et al. Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting. *J Clin Epidemiol* 2011;64(2):223-8. doi: 10.1016/j.jclinepi.2010.02.015
70. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes* 2015;8:634. doi: 10.1186/s13104-015-1616-8
71. Do pharmaceutical claims accurately reflect oncology prescribing practice? Evidence from an Australian HER2+ early breast cancer cohort (HER2EBC). ASCO Annual Meeting Proceedings; 2013.
72. A Proxy of Cancer Progression in Dispensing Claims: Validation and Performance. Pharmacoepidemiology and Drug Safety; 2013. John Wiley & Sons.
73. Young AF, Dobson AJ, Byles JE. Health services research using linked records: who consents and what is the gain? *Aust N Z J Public Health* 2001;25(5):417-20.
74. Holman CD. The impracticable nature of consent for research use of linked administrative health records. *Aust N Z J Public Health* 2001;25(5):421-2.
75. Internation Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. December 2015 ed, 2015.

BMJ Open

Use and outcomes of targeted therapies in early and metastatic HER2–positive breast cancer in Australia: Protocol detailing observations in a whole of population cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014439.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Dec-2016
Complete List of Authors:	Daniels, Benjamin; University of New South Wales, Medicine Lord, Sarah; University of Notre Dame Australia - Darlinghurst Campus; NHMRC Clinical Trials Centre Kiely, Belinda; University of Sydney, NHMRC Clinical Trials Centre Houssami, Nehmat; Sydney School of Public Health, Sydney Medical School, University of Sydney Haywood, Philip; Centre for Health Economics Research and Evaluation (CHERE) Lu, Christine; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Ward, Robyn; University of Queensland Person, Sallie-Anne; University of New South Wales, Medicines Policy Research Unit
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Epidemiology, Health policy
Keywords:	HER2, breast cancer, trastuzumab, observational study, pharmacoepidemiology

Title: **Use and outcomes of targeted therapies in early and metastatic HER2–positive breast cancer in Australia: Protocol detailing observations in a whole of population cohort**

Authors:

Benjamin Daniels, Medicines Policy Research Unit, Centre for Big Data Research in Health, UNSW. Sydney, Australia.

Sarah J. Lord, School of Medicine, University of Notre Dame Australia; NHMRC Clinical Trials Centre, University of Sydney. Sydney, Australia.

Belinda E Kiely, NHMRC Clinical Trials Centre, University of Sydney. Sydney, Australia.

Nehmat Houssami, Sydney School of Public Health, Sydney Medical School, University of Sydney. Sydney, Australia.

Philip Haywood, Centre for Health Economics Research and Evaluation, University of Technology Sydney, Sydney, Australia.

Christine Y. Lu, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute. Boston, USA.

Robyn L Ward, University of Queensland. Brisbane, Australia.

*Sallie-Anne Pearson, Medicines Policy Research Unit, Centre for Big Data Research in Health, UNSW. Sydney, Australia.

On behalf of the HER2 therapy observational study (HER2-OBS) investigators.

*Correspondence to: Professor Sallie-Anne Pearson. sallie.pearson@unsw.edu.au

+61 2 9385 8895. Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales (UNSW), AGSM, Level 1, Kensington, NSW 2052. Australia.

Keywords: HER2, breast cancer, trastuzumab, observational study, pharmacoepidemiology

Word count: 3,984

Number of tables: 5

Number of figures: 0

Number of references: 75

Number of supplementary files: 0

ABSTRACT

Background: The management of human epidermal growth factor receptor 2 (HER2) positive breast cancer (BC) has changed dramatically with the introduction and widespread use of HER2-targeted therapies. However, there is relatively limited real world information on patterns of use, effectiveness and safety in whole of population cohorts. The research programme detailed in this protocol will generate evidence on the prescribing patterns, safety monitoring and outcomes of BC patients treated with HER2-targeted therapies in Australia.

Methods/Design: Our ongoing research programme will involve a series of retrospective cohort studies that include every patient accessing Commonwealth-funded HER2-targeted therapies for the treatment of early- and advanced BC in Australia. At the time of writing, our cohorts consist of 11,406 early and 5,631 advanced BC patients who accessed trastuzumab and lapatinib between 2001 and 2014. Pertuzumab and trastuzumab emtansine were publicly funded for metastatic breast cancer in 2015 and future data updates will include patients accessing these medicines. We will use dispensing claims for cancer and other medicines, medical service claims and demographics data for each patient accessing HER2-targeted therapies to undertake this research.

Ethics and dissemination: Ethics approval has been granted by the Population Health Service Research Ethics Committee and data access approval by the Australian Department of Human Services (DHS) External Review Evaluation Committee.

Our findings will be reported in peer-reviewed publications, conference presentations, and policy forums. By providing detailed information on the use and outcomes associated with HER2-targeted therapies in a national cohort treated in routine clinical care, our research programme will better inform clinicians and patients about the real-world use of these treatments and will assist third party payers to better understand the use and economic costs of these treatments.

Strengths

- One of the largest and only whole-of-country HER2-positive cohorts, internationally
- Currently up to 13 years of data observation, to be extended with future data updates
- Linked medical services and medicines dispensing data for some patients

Limitations

- Lack of clinical measures such as ECOG status and TNM staging
- Lack of clinical diagnoses of comorbidities, adverse events, and cancer progression events
- Medicines that cost less than the Pharmaceutical Benefits Scheme's co-payment threshold will not be captured prior to 2012

INTRODUCTION

Amplification of the human epidermal growth factor receptor 2 (HER2) oncogene is present in approximately 20-30% of breast cancers.[1] The discovery of new and effective HER2-targeted therapies over the past twenty years has significantly improved the outcomes of patients with this aggressive breast cancer subtype. Compared to cytotoxic chemotherapy alone, the addition of HER2-targeted therapies significantly improves response rates, disease-free-survival (DFS)/progression-free-survival (PFS), and overall survival (OS) in patients with HER2-positive breast cancer treated in the neo-adjuvant, adjuvant or metastatic settings.[2-12]

While randomised clinical trials remain the gold standard for demonstrating treatment efficacy, they have some limitations as an evidence-base. The selected population enrolled in a clinical trial is not always representative of the population of "all comers" in routine practice where patients are often older, have more extensive disease, poorer clinical status, and more comorbidities. The sample size and duration of follow-up in clinical trials are often insufficient to detect infrequent events and to determine long-term outcomes.[13-15] As a consequence, medicines can be released to market before their risk benefit profile is fully evaluated, especially when there is increasing demand for early access to potentially life-saving medicines. Observational studies of unselected cohorts of patients are a valuable means of assessing the long-term impact of medicines and their patterns of use in routine practice.[16 17]

In the last decade a number of observational studies have examined outcomes associated with HER2-targeted therapies in routine clinical practice, utilising data from prospective registries, hospital records, and routinely collected, population-

based administrative data. The heterogeneity in the available data used by these studies has driven their focus. Registry- and hospital-based data typically include records for relatively smaller numbers of patients observed for short periods of time, but contain detailed clinico-pathological measures allowing for studies of the associations between these clinical factors and outcomes such as patterns of care following relapse, adverse events, OS, and DFS/PFS.[18-34]

Population-based data are often maintained for purposes of reimbursement/payment and tend to have fewer clinical details, but offer much larger sample sizes across health care settings providing evidence more representative of general populations and allowing for better detection of rare events. To date, studies using population-based administrative data to examine the use of HER2-targeted agents in routine care have focused primarily on trastuzumab, and to a lesser extent lapatinib, examining safety and long-term outcomes (Table 1, columns 1 and 2). Most of these studies have been conducted in North America, over a period of 5-10 observation years, in populations of up to 4,000 patients. The majority of studies have focused on cardiotoxicity[35-43] and reported an increased risk of cardiotoxicity associated with trastuzumab treatment. A limited number of studies examined cardiac monitoring before and during trastuzumab therapy for metastatic breast cancer (MBC), each reporting less than half of patients underwent an assessment of cardiac function prior to initiation of therapy (range: 11% - 38%).[44-46]

Population-based study estimates of survival outcomes for women receiving HER2-targeted therapies are within the range of pivotal clinical trial estimates. Several studies reported four-year survival rates in early breast cancer (EBC) patients at around 90%,[47 48] and in MBC patients at 41%[39] The four-year relapse-free survival

(RFS) rate in MBC was 76%.[47] An Italian study found no difference in OS (hazard ratio 0.79 [95%CI 0.50 – 1.26]) between metastatic patients previously treated with trastuzumab for EBC who are subsequently treated with trastuzumab for MBC and patients first diagnosed with MBC receiving trastuzumab for MBC.[49] An Australian study of HER2-positive MBC patients estimated a median OS of 29.9 months.[50]

Issues such as factors associated with use of trastuzumab, adherence to guideline-specified treatment patterns, off-label use, and overall resource use have also been examined in a number of studies. A US study found that tumour grade, ethnicity, and area of residence were associated with use of trastuzumab for EBC.[51] The only two studies examining lapatinib use did so in the context of quantifying resource use associated with treatment and the factors related to adherence to therapy. They found that costs did not differ between trastuzumab and lapatinib therapy, but the resource use driving costs did;[52] and that prior therapy with a taxane was associated with greater discontinuation of lapatinib.[53] An Australian study found that 22% of patients received trastuzumab in MBC with non-recommended concomitant treatment partners and approximately 20% (or AUD$21 million) of trastuzumab was discarded due to regulations around unused vial portions and weekly treatment schedules.[44]

Table 1. Characteristics of published studies that utilise population-based administrative data and comparison with current programme

	Published studies*				Current programme	
	EBC	Reference #	**MBC**	Reference #	**EBC**	**MBC**
Country						
Australia	0	-	4	44-46 50	**X**	**X**
Canada	1	42	0	-		
Italy	3	40 48 49	2	39 49		
United States of America	10	35-38 41 43 47 51 54 55	4	36 37 52 53		
Observation start year						
1998 – 2000	4	36 37 41 43	3	36 37 53		
2001 – 2005	5	35 38 42 47 54	4	44-46 50		**X**
2006 – 2010	5	40 48 49 51 55	3	39 49 52	**X**	
Number of observation years						
< 5	4	40 48 49 51	2	39 49		
5 - 10	10	35-38 41-43 47 54 55	7	36 37 44-46 50 52	**X**	
> 10	0	-	1	53		**X**
Medicine focus						
Trastuzumab	14	35-38 40-43 47-49 51 54 55	8	36 37 39 44-46 49 50 52 53	**X**	
Lapatinib	0	-	1	53		
Trastuzumab & lapatinib	0	-	1	52		**X**
HER2-positive sample size						
< 1,000 patients	6	36 41 43 49 51 55	5	36 39 49 52 53		
1,000 - 2,000 patients	0	-	1	44		
2,000 - 3,000 patients	6	35 37 38 40 48 54	1	37		
3,000 - 4,000 patients	2	42 47	3	45 46 50		

5,000 - 12,000 patients	-	-	-	-	X	X
Age						
Patients >65 only	6	35-38 43 51	2	36 37		
Patients of all ages	9	40-42 47-49 54 55	8	39 44-46 49 50 52 53	X	X
Sex						
Women	13	36-38 40-43 47-49 51 54	10	36 37 39 44-46 49 50 52 53		X
Women & men	2	35 55	0	-	X	
Study Focus						
Treatment patterns						
Duration of therapy	4	38 40 48 55	6	44 46 50 52 53	X	X
Schedules / dosing	2	35 38	2	44 50	X	X
Concomitant cancer therapies	13	35-38 40-43 47 48 51 54 55	8	36 37 39 44 46 50 52 53	X	X
Cancer therapies prior to / following HER2 therapy	2	49 54	3	49 52 53	X	X
Non-cancer treatments	2	40 48	1		X	X
Guideline-recommended care	2	36 38	3	36 44 46	X	X
Monitoring						
Cardiac	0	-	3	44-46		X
Other medical services	0	-	2	52 53		X
Outcomes						
Progression-free / Disease-Free Survival, associated factors	3	47 48 54	1	50		
Overall survival (OS), associated factors	5	36 47-49 54	4	36 39 49 50	X	X
Cardiovascular events, associated factors	7	35 37 38 40-43	2	37 39		

* Shih et al, Tsai et al, and Negri et al include both EBC and MBC patients and each study is included in both columns.

Our research programme aims to provide insights into issues that clinical trials are not designed to address and contribute additional knowledge to the current evidence base on the real world use of HER2 therapies. Specifically, we will examine real-world patterns of prescribing, side-effect monitoring, and outcomes (see Table 1, column 3) using one of the largest whole-of-population cohorts of HER2-positive patients and one of the longest follow-up periods, internationally. We will:

1. Compare the real-world use and outcomes with clinical trials and guideline-recommendations.
2. Determine the duration of HER2-targeted therapies and the long-term benefits and toxicities of treatment.
3. Determine the outcomes of patients receiving HER2-targeted therapies for MBC who also received HER2-targeted therapies for early breast cancer.
4. Estimate total resources— both medicines and health services —used by patients treated with HER2-targeted therapies, and factors associated with resource utilisation.
5. Explore the patient and treatment characteristics associated with survival.
6. Assess the impacts of policy interventions on treatment patterns and outcomes.

METHODS

Study Setting

In this section we discuss the healthcare funding arrangements in Australia as they pertain to HER2-targeted therapies and the administrative datasets generated from these arrangements.

Australia maintains a publicly funded universal healthcare system entitling all citizens and permanent residents to a range of subsidised health services. This includes free treatment in public hospitals (funded jointly by the Commonwealth and State/Territory governments) and subsidised treatment in private hospitals (funded jointly by the Commonwealth and private health insurance). Outpatient services, including consultations with medical and selected health care professionals, are funded by the Commonwealth's Medicare Benefits Schedule (MBS). Medicines prescribed in the community and some hospitals are funded by the Commonwealth's Pharmaceutical Benefits Scheme (PBS). The Australian Department of Human Services (DHS) maintains records of medicines dispensed (PBS) and medical services provided (MBS) to patients for the purpose of reimbursement.

Medicines of interest, funding, and access restrictions

There are currently four publicly subsidised HER2-targeted therapies available in Australia. Medicines subsidised on the PBS are approved by the Pharmaceutical Benefits Advisory Committee (PBAC) on the basis of efficacy and cost-effectiveness.[56 57] Trastuzumab (Herceptin, Genentech, South San Francisco, CA; Hoffmann-La Roche Ltd., Basel, Switzerland) for metastatic disease was not considered to be cost-effective by PBAC but was subsidised through a separate programme.[58] From December 2001 until June 2015 the *Herceptin Programme* provided free access to trastuzumab for MBC. The *Herceptin Programme* was also administered by the DHS until its close in June 2015; since July 2015 trastuzumab for MBC has been PBS subsidised.[59-63] Trastuzumab for adjuvant and neoadjuvant treatment was listed on the PBS in October 2006 and December 2012, respectively.

Lapatinib (Tykerb, GlaxoSmithKline, Research Triangle Park, NC) was listed on the PBS as a second line treatment for HER2-positive MBC in May 2008. Pertuzumab (Perjeta, Genentech, South San Francisco, Ca; Hoffmann-La Roche Ltd., Basel, Switzerland) and trastuzumab emtansine (T-DM1) [Kadcyla, Genentech, South San Francisco, Ca; Hoffmann-La Roche Ltd., Basel, Switzerland] were listed for first-line and second-line MBC therapy, respectively, in July 2015.

To ensure that HER2-targeted agents are administered according to clinical trial evidence, the PBS places restrictions on their use. These restrictions have changed with emerging evidence and are summarised in Table 2.

Table 2. Access restrictions to HER2-targeted therapies in Australia

Table 2a: **Subsidy restrictions: trastuzumab for HER2+ metastatic breast cancer**		
2001 – 2005	**2006 – 2015**	**2015 – present***
Treatment Qualification: Patients must have HER2 over-expression by		
IHC† 3+ or ISH‡	ISH	No change
Trastuzumab treatment		
• in combination with taxanes in patients not previously receiving chemotherapy for MBC • as monotherapy in patients previously receiving chemotherapy for MBC • Weekly dosing regimen	As per 2001-2005 plus • weekly or 3-weekly dosing regimen	As per 2001-2015 plus • in combination with any chemotherapy except nab-paclitaxel
Cardiac Monitoring		
None required	None required	• ECHO§ or MUGA‖ at

		baseline then at 3 monthly intervals

Table 2b: **Subsidy restrictions: trastuzumab for HER2+ early breast cancer**

2006 – 2015	2015 – present
Treatment Qualification: Patients must have…	
• HER2 over expression demonstrated by ISH • undergone surgery for breast cancer	No change
Trastuzumab treatment	
• started in combination with chemotherapy • patients are eligible for 52 weeks of treatment	No change
Cardiac Monitoring	
• ECHO or MUGA at baseline then at 3 monthly intervals • LVEF > 45% • no symptomatic heart failure	No change

Table 2c: Subsidy restrictions: lapatinib for HER2+ metastatic breast cancer

2008 – 2010	2010 – 2015	2015 – present
Treatment Qualification: Patients must have…		
• HER2 over expression demonstrated by ISH • prior taxane for ≥3 cycles; or intolerance to taxane • disease progression while receiving trastuzumab for MBC	No change	No change
Lapatinib treatment		
• as sole PBS-subsidised anti-HER2 treatment • in combination with capecitabine • patients **CANNOT** receive trastuzumab subsequent to receiving lapatinib	• as sole PBS-subsidised anti-HER2 treatment • in combination with capecitabine • patients **CAN** receive trastuzumab subsequent to receiving lapatinib	No change
Cardiac Monitoring		
ECHO or MUGA at baseline then	No change	• ECHO or MUGA

at discretion of clinician		at baseline then at 3 monthly intervals

Table 2d: Subsidy restrictions: trastuzumab for HER2+ neoadjuvant therapy

2012 – present

Treatment Qualification: Patients must have…
• HER2 over expression demonstrated by ISH • NOT undergone surgery for breast cancer
Trastuzumab treatment
• in combination with chemotherapy • patients are eligible for 52 weeks of treatment
Cardiac Monitoring
• ECHO or MUGA at baseline then at 3 monthly intervals • LVEF > 45% • no symptomatic heart failure

Table 2e: Subsidy restrictions: pertuzumab for HER2+ metastatic breast cancer

2015 – present

Treatment Qualification: Patients must have…
• HER2 over expression demonstrated by ISH • WHO performance status of 0 or 1 • no prior HER2 therapy for MBC
Pertuzumab treatment
• in combination with trastuzumab and a taxane (not nab-paclitaxel)
Cardiac Monitoring
• ECHO or MUGA at baseline then at 3 monthly intervals

Table 2f: Subsidy restrictions: T-DM1 for HER2+ metastatic breast cancer

2015 – 2016	**2016 – present**
Treatment Qualification: Patients must have	
• HER2 over expression demonstrated by ISH	As per 2015 – 2016 but

• WHO performance status of 0 or 1 • progressed while receiving pertuzumab and trastuzumab for MBC OR while receiving or within 6 months of completing adjuvant trastuzumab • not received prior treatment with lapatinib or developed an intolerance to lapatinib	• patients may have received prior treatment with lapatinib or developed an intolerance to lapatinib
T-DM1 treatment	
• treatment as monotherapy	No change
Cardiac Monitoring	
• ECHO or MUGA at baseline then at 3 monthly intervals	No change

* *Herceptin Programme* ceased and trastuzumab for MBC was listed on the PBS
† immunohistochemistry
‡ in situ hybridisation
§ echocardiography
‖ multiple gated acquisition scan

Data sources

Our current holdings include unit-record data on patient demographics, PBS dispensing records (all PBS-funded medicines, not just cancer medicines), and all MBS medical services records for persons treated with trastuzumab and lapatinib between January 2001 and April 2014. We will receive annual data updates. T-DM1 and pertuzumab were funded in Australia in July 2015 and patients treated with these medicines will form part of our subsequent data updates.

Australian law prevents the DHS from linking PBS to MBS records without the explicit consent of patients.[64] As a result, our data holding for patients receiving PBS-funded trastuzumab (in the adjuvant or neoadjuvant settings) is currently limited to patient information and PBS dispensing history only. However, due to the *Herceptin Programme* arrangements (active until 2015), DHS can link PBS records and MBS

records to *Herceptin Programme* records, separately, and supply the data so that we can undertake the final merging of the entire data holdings. Therefore, our holdings for patients accessing trastuzumab for metastatic disease consist of patient information, PBS history (where we ascertain all other cancer therapies and other prescribed medicines), MBS history, and *Herceptin Programme* data. We have similar data for patients who received lapatinib because access to lapatinib under the PBS required that patients progressed while receiving trastuzumab for metastatic disease, which had been only been possible through the *Herceptin Programme*.

Table 3. Data holdings approved for the research programme.

Dataset	Description	Metastatic				Early Stage	Neoadjuvant
		Trastuzumab	Lapatinib	T-DM1	Pertuzumab	Trastuzumab	Trastuzumab
First available date in Australia		2001	2008	2015	2015	2006	2012
Patient demographics	Year of birth; sex; mm/yy of death; state of residence; and postcode of residence mapped to SLA*	**X**	**X**	**X**	**X**	**X**	**X**
Patient weight	Patient weight (kg) at the time of *Herceptin Programme* enrolment	**X**	**X**				
Treatment qualification	Patient HER2 overexpression levels and the test used to ascertain levels (IHC or ISH †). Initial intended treatment - monotherapy or concomitant treatment with taxanes	**X**	**X**				
Pharmaceutical Benefits Scheme (PBS)	All prescribed medicines reimbursed by the PBS. Variables include medicine name and strength, date of prescribing, date of supply, quantity supplied/pack size, the number of repeats allowed with the prescription, patient co-payment contribution and the cost to government.	**X**	**X**	**X**	**X**	**X**	**X**
Trastuzumab supply	Dates and vials of trastuzumab dispensed to *Herceptin Programme* participants	**X**					
Medicare Benefits Schedule (MBS)	All medical and allied health services. Variables includes the type of service rendered—from outpatient doctor visits to surgeries—the cost and benefit paid for the service, and the date of service	**X**	**X**				

*SLA = Statistical local area. SLA classifies geographic areas of Australia by socioeconomic profile and remoteness[65 66]

† IHC = Immunohistochemistry, ISH = In-situ hybridisation

Data Access

Data extraction was performed by DHS who assigned a unique scrambled ID and extracted all patient information and all dispensing records (not just HER2-targeted medicines) associated with that ID. For *Herceptin Programme* participants, DHS also extracted medical services records from MBS data. Those records, with the unique ID and requested variables, were then sent to the researchers stripped of identifying information such as name and address. The researchers joined the datasets using the unique ID.

Study Design

This ongoing research programme will comprise a series of retrospective cohort studies of all Australian, HER2-positive breast cancer patients accessing publically subsidised treatment with HER2-targeted agents from 2001 to 2020.

Study Population

As this is an ongoing study, the characteristics of the population will change over time. Characteristics of the study population at the date of first dispensing of HER2-targeted therapy, stratified by treatment setting, are summarised below (Table 4).

Table 4. Cohort demographic and clinical characteristics at first HER2-targeted therapy dispensing

	Metastatic		Early Stage
	Trastuzumab	**Lapatinib**	**Trastuzumab**
Patients with at least one dispensing (n)	5,631	1,099	11,406
Age, median (IQR)	56 (48 - 65)	56 (48 - 63)	54 (47 - 63)
Weight in kilograms at first dispensing, median (IQR)	70 (60 - 80)	70 (60 - 81)	-
HER2-positive by IHC* 3+, n (%)	3,542 (62.9)	585 (53.2)	
HER2-positive by ISH†, n (%)	2,193 (38.9)	496 (45.1)	
Fact of death, n (%)	3,777 (67.1)	892 (81.2)	898 (7.9)
Hormone receptor positive, n (%)§	3,113 (55.3)	617 (56.1)	6,439 (56.4)
Comorbidities‡, n (%)			
0-2	492 (8.7)	44 (4.0)	1,928 (16.9)
3-4	921 (16.4)	149 (13.6)	3,054 (26.8)
5-6	1,137 (20.2)	244 (22.2)	2,689 (23.6)
7+	3,081 (54.7)	662 (60.2)	3,735 (32.7)

* Immunohistochemistry
† In-situ hybridisation
‡ comorbidities assessed from dispensing claims using RxRisk algorithm
§ dispensing of a hormonal agent indicated hormone receptor positivity

In our current data holdings there are 5,631 patients who received trastuzumab and 1,100 patients who received lapatinib for MBC; 11,406 patients received trastuzumab in the early stage and neoadjuvant settings. Overall, there are 1.1 million dispensing records associated with *Herceptin Programme* participants and 1.7 million records associated with EBC and neoadjuvant patients (Table 5). *Herceptin Programme* participants generated 2.2 million medical services claims. In total, there are 25,437 total person years in the *Herceptin Programme* dispensing records; 59,154 person years in EBC/neoadjuvant dispensing records; and 27,763 person years in the *Herceptin Programme* medical services claims (Table 5).

Table 5. Characteristics of data holding

	Metastatic		Early Stage
	Trastuzumab	**Lapatinib**	**Trastuzumab**
Dispensing records, total (N)	1,100,594	261,496	1,763,268
Dispensing records, HER2-targeted therapy (N)	145,907	8,000	171,605
Medical services records (N)	2,221,760	536,370	-
Type of medical service, overall, claims N (%)			
Pathology	897,597 (40.4)	225,210 (42.0)	-
Attendances/consults/visits	599,277 (27.0)	135,521 (25.3)	-
Specialist	329,077 (14.8)	79,266 (14.8)	-
General practitioner	236,649 (10.7)	48,614 (9.1)	-
Enhanced primary care	13,045 (0.6)	3,095 (0.6)	-
Practice Nurse	8,264 (0.4)	2,100 (0.4)	-
Other	12,242 (0.6)	2,446 (0.5)	-
Diagnostic imaging	199,411 (9.0)	48,081 (9.0)	-
Radiotherapy / Nuclear Medicine	136,490 (6.1)	36,276 (6.8)	-
Miscellaneous (eg, medical supplies)	388,985 (17.5)	91,282 (17.0)	-

3,113 of the MBC patients (55%) and 6,439 of the EBC patients (56%) received at least one dispensing of a hormonal therapy. There were 125,257 taxane dispensings and 35,664 anthracycline dispensings. With a median observation time of 49.8 months (IQR: 39.5 – 94.8) from first medicine dispensing or medical service until death or censor date (31 March 2014), 3,777 of the patients treated for MBC (67%) have died and 898 of the patients treated for EBC (8%) have died. Reflecting the population distribution of Australia, more than half of patients in all treatment settings resided in New South Wales and Victoria and more than two-thirds of all patients lived in major cities (not shown in Table 4). Among MBC patients, at least 81% of received at least one dispensing of a pain medication; 48% received medication for the treatment of hypertension or angina; 40% received an antidepressant; and 23%

received an anti-anxiety medication. Among EBC patients, 64% received at least one dispensing of a pain medication; 40% received medication for hypertension or angina; 35% received an antidepressant; and 17% received an anti-anxiety medication.

MBC patients accessing trastuzumab had a median of 54 medical service claims per person, per year (IQR: 23 – 106). The majority of claims relate to pathology services (40.4%) and consultations and visits with healthcare professionals (27%). Patients who also received lapatinib for MBC had 536,370 medical service claims, with a median of 68 (27 – 121) per person, per year. These services followed a similar pattern to those for all trastuzumab patients.

Outcomes of interest and statistical analyses

We will use a range of pharmacoepidemiological and statistical analyses to address our aims.

Patterns of use: We will summarise the prescribing patterns of HER2-targeted therapies including: agent used, line of therapy, partnering therapy (chemotherapy, other HER2-targeted therapy, endocrine therapy) and duration of therapy.

We will report the characteristics of patients dispensed HER2-targeted therapies including age, sex, geographical remoteness, socioeconomic status, HR status, presence of comorbidities at dispensing of HER2-targeted therapy and over time. Age, sex, geographical remoteness and socieconomic status will be ascertained from the patient information datasets. We will define HR status using a validated proxy and

define the number and nature of comorbidity from dispensing claims using the validated RxRisk index.[67-69]

Comparison of real-world use with clinical trials and prescribing guidelines: We will compare duration of therapy (based on dispensing records) and survival outcomes associated with HER2-targeted therapies to those from published clinical trials; we will not undertake comparative efficacy analyses as it is prone to confounding by indication bias. We will estimate overall survival (OS) through Kaplan-Meier methods. We will use descriptive statistics to compare characteristics of patients treated with these medicines in the real-world setting to those treated in clinical trials. Finally, we will compare the real-world treatments to published treatment guidelines.

Outcomes in patients who received HER2-targeted therapies for EBC and MBC: We will identify a sub-set of patients who initiate trastuzumab for EBC who are subsequently trastuzumab-treated for MBC; this patient group is underrepresented in clinical trials. We will compare patient characteristics for this patient group with trastuzumab-naïve MBC patients, trastuzumab-naïve MBC patients whose first cancer medicine was trastuzumab (as a proxy for patients first diagnosed with MBC), and EBC patients who do not go on to receive trastuzumab for MBC. We will describe patterns of treatment for each of these three patient groups; and use Cox Proportional Hazard Regression to estimate differences in overall survival between these patient groups.

Estimating total resources: We will use multiple metrics to examine the nature and extent of resource use associated with HER2-targeted therapy. We will report on PBS,

MBS and Herceptin Programme resource use overall and by service type and stratify resource use by age, treatment setting, patterns of care, socioeconomic status, and remoteness. We will examine the proportion of total resource use accounted for by each service (e.g. the proportion of total services accounted for by medications, imaging procedures, surgery, specialist consultations, etc…). We will identify predictors of the rate of health service utilisation using Poisson regression or negative binomial regression, as appropriate. In all models we will consider age at initiation of first HER2-targeted therapy, geographical remoteness, socioeconomic status, HR status and comorbidities.

Examining variations in patient response: We will examine predictors of time-to-discontinuation and time-to-death using Kaplan-Meier curves and Cox proportional hazards models. We will ascertain date of death using the patient information dataset. We will use sub-group analysis to interrogate data on patients who die during early stage treatment or soon after its completion and those who survive for many years following initiation of HER2 therapy to determine the characteristics and patterns of treatment associated with short- and long-term survival.

Impact of policy interventions on treatment patterns and outcomes: We will examine specific prescribing policies in Australia to determine the impact they have on treatment patterns and outcomes. For instance, during the first two years of its availability, prescribing lapatinib to a patient prohibited a return to trastuzumab for that same patient. We will explore the impact of policy changes using interrupted time series methodology. [45]

Analyses will be performed using SAS Version 9.4, Stata Version 13 and R Version 3.2.2.

Limitations

As in any epidemiological study we must consider the potential biases in our research. Some of the issues raised in relation to administrative database research and the conduct of pharmacoepidemiological research in Australia are described below.

Medicine exposure

Australia maintains comprehensive pharmaceutical claims data collections for prescribed medicines dispensed in community and private hospitals, but not for public hospital inpatients. The vast majority of oncology protocols are administered in the outpatient setting or to private hospital inpatients (both of which are captured in the PBS data) and we believe the lack of public hospital inpatient dispensing data is unlikely to impact significantly on the outcomes of our analyses.

In addition, the creation of PBS records is tied to those medicines that are subsidised (in part or in full) by the government. Subsidised medicines in Australia require a patient co-payment; AUD$38.30 at the time of writing. Medicines whose cost is below this amount are not subsidised by the PBS and are not recorded in the PBS data. Therefore, the record of patients' PBS medicine use may be incomplete, limiting the scope of some analyses.[70] We do, however, have information on all PBS medicines including their total costs over time as well as the capacity to identify patients for whom we may not have all PBS dispensings (using their entitlement

category). We will restrict some of our analyses to persons with complete PBS-medicines ascertainment. Importantly, the vast majority of cancer medicines are above the co-payment threshold.[71] Furthermore, from July 2012 under co-payment medicines were recorded in PBS data and these records will be a part of future data updates.

Diagnosis, outcome and covariate misclassification

Health administrative data sets lack detailed clinical information and we need to assess the impact of misclassifying diagnoses and outcomes of interest. Due to the structure of the datasets, we know that all MBC patients appear in *Herceptin Programme* datasets. For early BC patients, between 1 October 2006 and 30 November 2012 all dispensings of trastuzumab represent adjuvant therapy, as this was the only PBS-funded indication during this time. As noted earlier, the *Herceptin Programme* was phased out in 2015 and trastuzumab for MBC listed on the PBS, meaning that from late 2015 trastuzumab dispensings across all treatment settings form part of the PBS data; based on our existing current data holdings we will not be able to distinguish between trastuzumab supplied for metastatic and early stage disease from late 2015. Similarly, among early BC patients from 1 December 2012 we are unable determine which dispensings represent adjuvant or neoadjuvant therapy.

To address this issue we will obtain dispensing authority codes. Authority codes are generated when the prescribing doctor gains approval to administer an authority-required medicine (such as all HER2-targeted therapies) for a particular indication

and they will allow us to delineate between medicines dispensed across the different settings.

The data also lack certain important covariates, including comorbidities, ECOG status and TNM staging. Identifying adverse events, such as cardiotoxic events, is difficult without detailed clinical information or hospital admissions codes. Additional, external datasets may be used to examine these issues, but we will not attempt these analyses with our current data holdings.

We previously attempted to validate a proxy for disease progression using dispensing claims but demonstrated a sensitivity of 74%, specificity of 88%, and positive predictive value of 61%.[72] As such, we do not currently have the capacity to accurately estimate time to progression or progression free survival using dispensing claims alone. This will limit the scope of outcomes research in the patients with early stage disease; at present, the main contributions based on our available data are likely to lie in the metastatic setting.

ETHICS

Ethics approval has been granted by the Population Health Service Research Ethics Committee (Approval Number: 2010/02/213) and data access approval by the Australian Department of Human Services (DHS) External Review Evaluation Committee (Approval Numbers: MI1474, MI1475, MI1477). At the time of writing we have ethical approval for annual data updates until 2020.

The data for the research programme are released without individual consent. The use and disclosure of Commonwealth data are governed under the Privacy Act 1988. Information Privacy Principle (IPP) 2 under the Privacy Act 1988 (Commonwealth) provides that personal information should not be used or disclosed for any purpose other than the primary purpose of the collection.

We sought approval to use the data for a secondary purpose, that of research involving data linkage.

- Under IPP2.1(d) use or disclosure for another purpose is permitted if (1) it is necessary for research and it is impracticable to gain consent and (2) the use is in accordance with the section 95A guidelines (which provide a process to resolve the conflict that may arise between the public interest in privacy and the public interest in medical research).

We applied for these exemptions to the current research programme. Individual consent for the release of data has been waived because:

- It is not possible or practical to obtain consent because of the large study population (more than 15,000 patients) and a large proportion of patients were likely to be deceased.
- Obtaining consent would prejudice the scientific value of the research due to the high participation rates required for unbiased samples (at least 90%) and the Australian evidence about the sociodemographic differences between participants who consent to data linkage research and those that do not.[73 74]

- The public interest in the research outweighs the public interest in privacy protection, as we know little about the way in which HER2-blockade medicines are used in the real-world marketplace.

DISSEMINATION PLAN

We will consult clinicians, policy makers and consumers where appropriate for guidance in interpreting and disseminating our results. The outcomes of this research will be submitted to international peer-reviewed journals; in particular oncology, general medical, and pharmacoepidemiology journals. We will also present our findings at national and international oncology and pharmacoepidemiology conferences. We will communicate study outcomes to relevant professional cancer/oncology societies such as the Clinical Oncology Society of Australia and the Medical Oncology Group of Australia; and policy groups such as the Pharmaceutical Benefits Advisory Committee and NPSMedicinewise. We will also develop lay summaries of research findings as needed.

In accordance with our DHS data agreement, we will submit all data that will be communicated in the public domain to the DHS for review and approval. Authorship will be based on the International Committee of Medical Journal Editors guidelines.[75] Outcomes will also be posted on the University of New South Wales web page of the lead investigator and the Centre for Big Data Research in Health website. Direct access to the data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

DISCUSSION

The programme of research outlined in this protocol will provide valuable evidence of the real-world, clinical use and outcomes of HER2-targeted therapies. The unique funding structure of these medicines in Australia has created one of the largest and only whole-of-country, HER2-targeted therapies datasets in the world. Observational studies of the kind described in this protocol are particularly important given many of the patients treated in routine practice would not meet typical clinical trial inclusion criteria. The existing observational research has highlighted the use of trastuzumab in populations significantly different from those in the clinical trials and at present there is limited information on the real-world use of lapatinib and no studies addressing T-DM1 or pertuzumab.

The strengths of this programme lie in the use of best practice methods to examine patterns of use and long-term outcomes associated with HER2-targeted therapy, this is particularly important for patients with survival times longer than the typical clinical trial follow-up period. Given these data come from a single payer and are national in scope, loss to follow-up is likely to be much lower than observational studies conducted in countries where health service provision and insurance is more fragmented. Due to the whole-of-population nature of the data, our findings are likely to be highly generalisable, and provide opportunities to extend knowledge on the population impact of HER2-targeted therapy.

ACKNOWLEDGEMENTS

This research is supported, in part, by a Cancer Australia Priority Driven Collaborative Support Scheme (ID: 1050648) and funding from the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA) (ID: 1060407). Benjamin Daniels is supported by an NHMRC Postgraduate Research Scholarship (ID: 1094325), the Sydney Catalyst Translational Cancer Research Centre, and a CREMA PhD scholarship top-up. We thank the Department of Human Services for providing the data for this research.

Contributorship Statement

BD, SJL, BEK, NH, PH, CYL, RLW, and SAP conceived of the study protocol. BD, RLW, and SAP contributed to the acquisition of the data. BD conducted the literature search and performed the data analyses. BD, SJL, BEK, NH, PH, CYL, RLW, and SAP contributed to the design of the work and interpretation of the data. All authors contributed to drafting and critical revisions of the manuscript and have agreed to the final content.

Competing Interests

BEK has received conference support and a speakers honorarium from Roche. The remaining authors declare no competing interests.

Funding

This research is supported, in part, by a Cancer Australia Priority Driven Collaborative Support Scheme (ID: 1050648) and funding from the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA) (ID: 1060407). Benjamin Daniels is supported by an NHMRC Postgraduate Research Scholarship (ID: 1094325), the Sydney Catalyst Translational Cancer Research Centre, and a CREMA PhD scholarship top-up.

Data Sharing Statement

Direct access to the data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

REFERENCES

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235(4785):177-82.
2. Harris CA, Ward RL, Dobbins TA, et al. The efficacy of HER2-targeted agents in metastatic breast cancer: a meta-analysis. *Ann Oncol* 2011;22(6):1308-17. doi: 10.1093/annonc/mdq593
3. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;4:CD006243. doi: 10.1002/14651858.CD006243.pub2
4. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2014;6:CD006242. doi: 10.1002/14651858.CD006242.pub2
5. Valachis A, Nearchou A, Lind P, et al. Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence. *Breast Cancer Res Treat* 2012;135(3):655-62. doi: 10.1007/s10549-012-2189-z
6. Hicks M, Macrae ER, Abdel-Rasoul M, et al. Neoadjuvant dual HER2-targeted therapy with lapatinib and trastuzumab improves pathologic complete response in patients with early stage HER2-positive breast cancer: a meta-analysis of randomized prospective clinical trials. *Oncologist* 2015;20(4):337-43. doi: 10.1634/theoncologist.2014-0334
7. Sun J, Chen C, Yao X, et al. Lapatinib combined with neoadjuvant paclitaxel-trastuzumab-based chemotherapy in patients with human epidermal growth factor receptor 2-positive breast cancer: A meta-analysis of randomized controlled trials. *Oncol Lett* 2015;9(3):1351-58. doi: 10.3892/ol.2015.2848
8. Kawalec P, Lopuch S, Mikrut A. Effectiveness of targeted therapy in patients with previously untreated metastatic breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer* 2015;15(2):90-100 e1. doi: 10.1016/j.clbc.2014.10.006
9. Broglio KR, Quintana M, Foster M, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. *JAMA Oncol* 2016;2(6):751-60. doi: 10.1001/jamaoncol.2015.6113
10. Kumler I, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2-positive breast cancer. *Cancer Treat Rev* 2014;40(2):259-70. doi: 10.1016/j.ctrv.2013.09.002
11. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366(2):109-19. doi: 10.1056/NEJMoa1113216
12. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367(19):1783-91. doi: 10.1056/NEJMoa1209124

13. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341(27):2061-7. doi: 10.1056/NEJM199912303412706
14. Avorn J. In defense of pharmacoepidemiology--embracing the yin and yang of drug research. *N Engl J Med* 2007;357(22):2219-21. doi: 10.1056/NEJMp0706892
15. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. *Lancet* 2008;372(9656):2152-61. doi: 10.1016/s0140-6736(08)61930-3 [published Online First: 2008/12/23]
16. Banks E, Pearson SA. A life-cycle approach to monitoring benefits and harms of medicines. *Med J Aust* 2012;197(6):313-4.
17. Kelman CW, Pearson SA, Day RO, et al. Evaluating medicines: let's use all the evidence. *Med J Aust* 2007;186(5):249-52.
18. Kaufman PA, Brufsky AM, Mayer M, et al. Treatment patterns and clinical outcomes in elderly patients with HER2-positive metastatic breast cancer from the registHER observational study. *Breast Cancer Res Treat* 2012;135(3):875-83. doi: 10.1007/s10549-012-2209-z
19. Tripathy D, Kaufman PA, Brufsky AM, et al. First-line treatment patterns and clinical outcomes in patients with HER2-positive and hormone receptor-positive metastatic breast cancer from registHER. *Oncologist* 2013;18(5):501-10. doi: 10.1634/theoncologist.2012-0414
20. Yardley DA, Kaufman PA, Brufsky A, et al. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2014;145(3):725-34. doi: 10.1007/s10549-014-2916-8
21. Yardley DA, Tripathy D, Brufsky AM, et al. Long-term survivor characteristics in HER2-positive metastatic breast cancer from registHER. *Br J Cancer* 2014;110(11):2756-64. doi: 10.1038/bjc.2014.174
22. Jackisch C, Schoenegg W, Reichert D, et al. Trastuzumab in advanced breast cancer--a decade of experience in Germany. *BMC Cancer* 2014;14:924. doi: 10.1186/1471-2407-14-924
23. Jackisch C, Welslau M, Schoenegg W, et al. Impact of trastuzumab treatment beyond disease progression for advanced/metastatic breast cancer on survival - results from a prospective, observational study in Germany. *Breast* 2014;23(5):603-8. doi: 10.1016/j.breast.2014.06.003
24. Hamy-Petit AS, Belin L, Bonsang-Kitzis H, et al. Pathological complete response and prognosis after neoadjuvant chemotherapy for HER2-positive breast cancers before and after trastuzumab era: results from a real-life cohort. *Br J Cancer* 2016;114(1):44-52. doi: 10.1038/bjc.2015.426
25. Seferina SC, Lobbezoo DJ, de Boer M, et al. Real-Life Use and Effectiveness of Adjuvant Trastuzumab in Early Breast Cancer Patients: A Study of the Southeast Netherlands Breast Cancer Consortium. *Oncologist* 2015;20(8):856-63. doi: 10.1634/theoncologist.2015-0006
26. Mustacchi G, Puglisi F, Molino AM, et al. Observational study on adjuvant trastuzumab in HER2-positive early breast cancer patients. *Future Oncol* 2015;11(10):1493-500. doi: 10.2217/fon.15.34

27. Menard S, Balsari A, Tagliabue E, et al. Biology, prognosis and response to therapy of breast carcinomas according to HER2 score. *Ann Oncol* 2008;19(10):1706-12. doi: 10.1093/annonc/mdn369
28. Dall P, Lenzen G, Gohler T, et al. Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany. *J Geriatr Oncol* 2015;6(6):462-9. doi: 10.1016/j.jgo.2015.06.003
29. Outcome of HER2-positive breast cancer patients following metastatic relapse after adjuvant trastuzumab treatment since EMA regulatory approval. ASCO Annual Meeting Proceedings; 2012.
30. Krell J, James CR, Shah D, et al. Human epidermal growth factor receptor 2-positive breast cancer relapsing post-adjuvant trastuzumab: pattern of recurrence, treatment and outcome. *Clin Breast Cancer* 2011;11(3):153-60. doi: 10.1016/j.clbc.2011.03.012
31. First-line patterns of care and outcomes of HER2-positive breast cancer patients who progressed after receiving adjuvant trastuzumab in the outpatient community setting. ASCO Annual Meeting Proceedings; 2010.
32. Vaz-Luis I, Seah D, Olson EM, et al. Clinicopathological features among patients with advanced human epidermal growth factor-2-positive breast cancer with prolonged clinical benefit to first-line trastuzumab-based therapy: a retrospective cohort study. *Clin Breast Cancer* 2013;13(4):254-63. doi: 10.1016/j.clbc.2013.02.010
33. Marla S, Cardale J, Dodwell DJ, et al. HER2-positive early breast cancers: What proportion are receiving adjuvant trastuzumab therapy? A multicenter audit. *Journal of Clinical Oncology* 2010;28(15_suppl):668-68. doi: doi:10.1200/jco.2010.28.15_suppl.668
34. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Impact of hormone receptor status on patterns of recurrence and clinical outcomes among patients with human epidermal growth factor-2-positive breast cancer in the National Comprehensive Cancer Network: a prospective cohort study. *Breast Cancer Res* 2012;14(5):R129. doi: 10.1186/bcr3324
35. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol* 2013;31(33):4222-8. doi: 10.1200/JCO.2013.48.7884
36. Shih YC, Xu Y, Dong W, et al. First do no harm: population-based study shows non-evidence-based trastuzumab prescription may harm elderly women with breast cancer. *Breast Cancer Res Treat* 2014;144(2):417-25. doi: 10.1007/s10549-014-2874-1
37. Tsai HT, Isaacs C, Fu AZ, et al. Risk of cardiovascular adverse events from trastuzumab (Herceptin((R))) in elderly persons with breast cancer: a population-based study. *Breast Cancer Res Treat* 2014;144(1):163-70. doi: 10.1007/s10549-014-2836-7
38. Vaz-Luis I, Keating NL, Lin NU, et al. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. *J Clin Oncol* 2014;32(9):927-34. doi: 10.1200/JCO.2013.51.1261
39. Rossi M, Carioli G, Bonifazi M, et al. Trastuzumab for HER2+ metastatic breast cancer in clinical practice: Cardiotoxicity and overall survival. *Eur J Cancer* 2016;52:41-9. doi: 10.1016/j.ejca.2015.09.012

40. Bonifazi M, Franchi M, Rossi M, et al. Trastuzumab-related cardiotoxicity in early breast cancer: a cohort study. *Oncologist* 2013;18(7):795-801. doi: 10.1634/theoncologist.2013-0065
41. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst* 2012;104(17):1293-305. doi: 10.1093/jnci/djs317
42. Goldhar HA, Yan AT, Ko DT, et al. The Temporal Risk of Heart Failure Associated With Adjuvant Trastuzumab in Breast Cancer Patients: A Population Study. *J Natl Cancer Inst* 2016;108(1) doi: 10.1093/jnci/djv301
43. Chen J, Long JB, Hurria A, et al. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol* 2012;60(24):2504-12. doi: 10.1016/j.jacc.2012.07.068
44. Pearson SA, Ringland CL, Ward RL. Trastuzumab and metastatic breast cancer: trastuzumab use in Australia--monitoring the effect of an expensive medicine access program. *J Clin Oncol* 2007;25(24):3688-93. doi: 10.1200/jco.2007.11.2516 [published Online First: 2007/08/21]
45. Lu CY, Srasuebkul P, Drew AK, et al. Positive spillover effects of prescribing requirements: increased cardiac testing in patients treated with trastuzumab for HER2+ metastatic breast cancer. *Intern Med J* 2012;42(11):1229-35. doi: 10.1111/j.1445-5994.2011.02604.x
46. Lu CY, Srasuebkul P, Drew AK, et al. Trastuzumab therapy in Australia: which patients with HER2+ metastatic breast cancer are assessed for cardiac function? *Breast* 2013;22(4):482-7. doi: 10.1016/j.breast.2013.04.011
47. Gallagher CM, More K, Masaquel A, et al. Survival in patients with non-metastatic breast cancer treated with adjuvant trastuzumab in clinical practice. *Springerplus* 2016;5:395. doi: 10.1186/s40064-016-2008-9
48. Bonifazi M, Franchi M, Rossi M, et al. Long term survival of HER2-positive early breast cancer treated with trastuzumab-based adjuvant regimen: a large cohort study from clinical practice. *Breast* 2014;23(5):573-8. doi: 10.1016/j.breast.2014.05.022
49. Negri E, Zambelli A, Franchi M, et al. Effectiveness of trastuzumab in first-line HER2+ metastatic breast cancer after failure in adjuvant setting: a controlled cohort study. *Oncologist* 2014;19(12):1209-15. doi: 10.1634/theoncologist.2014-0227
50. Parkinson B, Viney R, Haas M, et al. Real-World Evidence: A Comparison of the Australian Herceptin Program and Clinical Trials of Trastuzumab for HER2-Positive Metastatic Breast Cancer. *Pharmacoeconomics* 2016 doi: 10.1007/s40273-016-0411-2
51. Vaz-Luis I, Lin NU, Keating NL, et al. Treatment of early-stage human epidermal growth factor 2-positive cancers among medicare enrollees: age and race strongly associated with non-use of trastuzumab. *Breast Cancer Res Treat* 2016;159(1):151-62. doi: 10.1007/s10549-016-3927-4
52. Guerin A, Lalla D, Gauthier G, et al. Comparison of treatment patterns and economic outcomes in metastatic breast cancer patients initiated on trastuzumab versus lapatinib: a retrospective analysis. *Springerplus* 2014;3:236. doi: 10.1186/2193-1801-3-236

53. Delea TE, Kartashov A, Sharma PP. Retrospective Study of the Prevalence, Predictors, and Consequences of Nonadherence With Lapatinib in Women With Metastatic Breast Cancer Who Were Previously Treated With Trastuzumab. *Journal of Pharmacy Technology* 2013:8755122513513428.
54. Gallagher CM, More K, Kamath T, et al. Delay in initiation of adjuvant trastuzumab therapy leads to decreased overall survival and relapse-free survival in patients with HER2-positive non-metastatic breast cancer. *Breast Cancer Res Treat* 2016;157(1):145-56. doi: 10.1007/s10549-016-3790-3
55. DaCosta Byfield S, Buck PO, Blauer-Peterson C, et al. ReCAP: Treatment Patterns and Cost of Care Associated With Initial Therapy Among Patients Diagnosed With Operable Early-Stage Human Epidermal Growth Factor Receptor 2-Overexpressed Breast Cancer in the United States: A Real-World Retrospective Study. *J Oncol Pract* 2016;12(2):159-67. doi: 10.1200/JOP.2015.004747
56. Pharmaceutical Benefits Advisory Committee 2015 [updated October 22, 2015. Available from: http://www.pbs.gov.au/info/industry/listing/participants/pbac accessed April 05 2016.
57. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC research notes* 2015;8(1):634.
58. Public Summary Document for Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Nov 2008 2009 [updated March 25, 2009. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-trastuzumab-nov08 accessed April 5 2016.
59. Budget briefs. *Sunday Tasmanian* 2002 May 19, 2002.
60. Cooke G. Govt to make breast cancer treatment drug free of charge. *Canberra Times* 2001 October 13, 2001;19.
61. Metherell M. Free drug for women with breast cancer. *Sydney Morning Herald* 2001 October 12, 2001;3.
62. Public Summary Document -- November 2014 PBAC Meeting. In: Committee PBA, ed. Australia, 2014.
63. Transitioning of Herceptin Subsidy to the Pharmaceutical Benefits Scheme (PBS). In: Health Do, ed. http://www.pbs.gov.au/info/news/2015/07/transitioning-of-herceptin-subsidy-to-pbs: Department of Health, 2015.
64. Kearny B, Smith M. Response to the Senate Select Committee on Health. In: Australia Po, ed. http://www.aph.gov.au/DocumentStore.ashx?id=f263db77-ba89-466e-8edb-ae95b880ce72, 2014.
65. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC). Statistical Local Area (SLA). [Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/2901.0Chapter23002011 accessed April 5 2016.
66. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC) [Available from: http://www.abs.gov.au/websitedbs/D3310114.nsf/home/Australian+St

andard+Geographical+Classification+%28ASGC%29 accessed April 5 2016.
67. Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care* 2003;41(6):761-74. doi: 10.1097/01.MLR.0000064641.84967.B7
68. Srasuebkul P, Dobbins TA, Elements of Cancer Care I, et al. Validation of a proxy for estrogen receptor status in breast cancer patients using dispensing data. *Asia Pac J Clin Oncol* 2014;10(2):e63-8. doi: 10.1111/ajco.12015
69. Lu CY, Barratt J, Vitry A, et al. Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting. *J Clin Epidemiol* 2011;64(2):223-8. doi: 10.1016/j.jclinepi.2010.02.015
70. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes* 2015;8:634. doi: 10.1186/s13104-015-1616-8
71. Do pharmaceutical claims accurately reflect oncology prescribing practice? Evidence from an Australian HER2+ early breast cancer cohort (HER2EBC). ASCO Annual Meeting Proceedings; 2013.
72. A Proxy of Cancer Progression in Dispensing Claims: Validation and Performance. Pharmacoepidemiology and Drug Safety; 2013. John Wiley & Sons.
73. Young AF, Dobson AJ, Byles JE. Health services research using linked records: who consents and what is the gain? *Aust N Z J Public Health* 2001;25(5):417-20.
74. Holman CD. The impracticable nature of consent for research use of linked administrative health records. *Aust N Z J Public Health* 2001;25(5):421-2.
75. Internation Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. December 2015 ed, 2015.