I would like to congratulate the authors for putting together this extremely important population-based research regarding the use and outcomes of anti HER-2 therapy in "real-world" Australian breast cancer patients. The strengths of this research are well described by the authors. I would suggest to emphasize in the introduction the potential ability of the proposed research to give clues on many issues that the clinical trials are not able to answer e.g. predictors of time to discontinuation and time to death, characterizing differences between patients who die during or soon after first-line treatment, and those who survive for many years (relevant mainly in MBC patients).

It is a pity that the main outcome concerning anti HER-2 adjuvant treatment in early breast cancer patients (disease-free-survival) will not be able to be retrieved because of limitations of the Australian data-set. This fact will leave us with a limited answer whether the 52 weeks of adjuvant anti HER-2 treatment is providing the expected benefits as in the HERA trial. As of so, the main outcome results in this proposed population-based study will be actually regarding mainly MBC patients rather than EBC patients. I would suggest the authors to emphasize this point in the limitations chapter.

An important strength of this research is its ability to provide data about patients who received HER-2 targeted therapies in both EBC and MBC settings. Since trastuzumab was already regulatory approved for MBC a few years before it was approved for EBC, such data is lacking in the clinical trials. The authors plan to evaluate characteristics of and survival between this group of patients and other patients who received trastuzumab for EBC but not in the metastatic setting and a third group of patients who received trastuzumab in MBC, but were "trastuzumab" naïve. I would suggest dividing this later group to two subgroups: 1. patients who were diagnosed with EBC and received adjuvant treatment before 2006. 2. Patients who were initially diagnosed with a metastatic disease and therefore did not receive any adjuvant therapy.

I would also suggest the authors to consider adding to this comparison also the groups of patients who received lapatinib or T-
DM1 while receiving or within 6 months of completing adjuvant trastuzumab (not clear whether lapatinib was approved in Australia in such a setting).

One typo: on the bottom of page 14 in “study population” chapter—characteristics of patient population are in table 4 (not table 3).

I wish the authors success in this research and eager to see its first results.

REVIEWER
Giorgio Mustacchi
Professor Emeritus of Medical Oncology
University of Trieste
Italy

REVIEW RETURNED
29-Nov-2016

GENERAL COMMENTS
Reviewed paper:

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

This is a very interesting experience: the review of an ongoing observational study about targeted anti-HER2 drugs use in Australia, in any setting. Absolutely agree with the relevance of observational studies aiming to give to oncologists, health economy experts and governements, informations about whath happens in the “real life”, outside clinical trials.

Furthermore, it seems to me there is just one observational papers on this matter related to the Australian scenario, cited and well commented by Authors.

I have some suggestion:

1) References could be updated/improved by citing not only reviews but also the pivotal papers, at least:

Neoadjuvant papers

1) Buzdar AU et al. on behalf of the American College of Surgeons Oncology Group investigators. Fluourouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. Lancet Oncol 2103; published online Nov 13. http://dx.doi.org/10.1016/S1470-2045(13)70502-3.

2) Gianni L et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus adjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative


Review Neoadjuvant


Review Adjuvant


Review Dual targeting HER2


2) In introduction:

Introduction and/or Discussion could be more extensive:

Authors should better discuss that observational studies are a very inhomogeneous matter: the “clinical ones”, based on the true clinical data from real patients have usually a small sample size, are reliable on “Who” “Whay” “Whay not” “How”, about treatment and safety, PFS, but there is no reliable information about the costs.

I suggest reading and cite the following observational studies

Anne-Sophie Hamy-Petit et al. Pathological complete response and
<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
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<tr>
<td>JP Spano, S Vignot, X Dung Ho et al.</td>
<td>Outcome of HER2-positive breast cancer patients following metastatic relapse after adjuvant trastuzumab treatment since EMA regulatory approval. J Clin Oncol 30, (suppl; abstr 641)</td>
</tr>
<tr>
<td>IM Vaz Duarte Luis, RA Ottesen, Melissa E Hughes.</td>
<td>Impact of hormone receptor (HR) status on clinicopathological features, patterns of recurrence, and clinical outcomes among patients (pts) with human epidermal growth factor receptor-2 positive (HER2) breast cancer (BC) in the National Comprehensive Cancer Network (NCCN). J Clin Oncol 30 (suppl; abstr 599)</td>
</tr>
</tbody>
</table>
trastuzumab in the northeast of Italy: Preliminary data from a multicenter observational study in a clinical setting. J Clin Oncol 30 (suppl; abstr 586)


3) The “database-based” observational studies, like this one, are rich in economical informations but poor in the clinical ones, as correctly Authors state.

I suggest to read and discuss the many cost/effectiveness studies already published on the topic:


Mylonas C, Kourlaba G, Fountzilas G et al. Cost-Minimization Analysis of Trastuzumab Intravenous versus Trastuzumab Subcutaneous for the Treatment of Patients with HER2+ Early Breast Cancer and Metastatic Breast Cancer in Greece. Value in...
4) Methods

“Study Setting” and “Medicines of interest...” sections are long and boring, not particularly interesting outside Australia. They are probably necessary but may be cited in the paper and transferred to a detailed supplementary appendix. The same could be done for “Data Sources”: shorter in the text and well explained in appendix.

I hope the above suggestions could give more strength and international value to this paper, because in any paper Authors will find different way to do the evaluation, but with the same conclusions (look at how much is payed by patients and of how is much is the cost for operators).

This work is very important because of the planned observation time (until 2020). So an initial great effort will give a great result.

Two Typing mistakes:

Page 4 row 18: “Strenghts”
Page 12 row 23: “emtansine”

VERSION 1 – AUTHOR RESPONSE

REVIEWER ONE COMMENTS:

1. I would suggest to emphasize in the introduction the potential ability of the proposed research to give clues on many issues that the clinical trials are not able to answer e.g. predictors of time to discontinuation and time to death, characterizing differences between patients who die during or soon after first-line treatment, and those who survive for many years (relevant mainly in MBC patients).

We have added a line to the first paragraph on Page 7 specifically noting that we will be investigating issues that clinical trials are not designed to address.

2. It is a pity that the main outcome concerning anti HER-2 adjuvant treatment in early breast cancer patients (disease-free-survival) will not be able to be retrieved because of limitations of the Australian data-set. This fact will leave us with a limited answer whether the 52 weeks of adjuvant anti HER-2 treatment is providing the expected benefits as in the HERA trial. As of so, the main outcome results in this proposed population-based study will be actually regarding mainly MBC patients rather than EBC patients. I would suggest the authors to emphasize this point in the limitations chapter.

We share Reviewer One’s regret concerning our inability to assess disease-free-survival in the adjuvant setting and we have added a sentence to the Limitations section of the manuscript, in the
last paragraph on Page 23, in order to emphasize that the majority of results from the proposed programme of work will focus on metastatic patients.

3. An important strength of this research is its ability to provide data about patients who received HER-2 targeted therapies in both EBC and MBC settings. Since trastuzumab was already regulatory approved for MBC a few years before it was approved for EBC, such data is lacking in the clinical trials. The authors plan to evaluate characteristics of and survival between this group of patients and other patients who received trastuzumab for EBC but not in the metastatic setting and a third group of patients who received trastuzumab in MBC, but were "trastuzumab" naïve. I would suggest dividing this later group to two subgroups:

These are excellent suggestions and we thank the reviewer for them. We are currently performing the analyses related to this project and we will attempt to look at these subgroups. We addressed each individually below:

a. patients who were diagnosed with EBC and received adjuvant treatment before 2006.

Unfortunately, we lack specific data around diagnoses and we are unable to accurately discern exactly which patients were initially diagnosed with EBC and may have received non-trastuzumab adjuvant therapy prior to receiving trastuzumab for metastatic disease. We are able to detect cancer therapies prior to receipt of metastatic trastuzumab, but not the treatment setting for which they were dispensed.

b. Patients who were initially diagnosed with a metastatic disease and therefore did not receive any adjuvant therapy.

Similarly, we are unable to discern which patients were first diagnosed with metastatic disease. However, we know the dates of metastatic trastuzumab dispensings and we can use those dates to identify a group of patients that is perhaps similar to the one proposed above. For instance, patients whose first cancer medicine in the dispensing data was trastuzumab for metastatic disease could comprise a meaningful subgroup whose outcomes we can examine. We have edited the manuscript on Page 19 to reflect that we will investigate the outcomes of this subgroup.

c. I would also suggest the authors to consider adding to this comparison also the groups of patients who received lapatinib or T-DM1 while receiving or within 6 months of completing adjuvant trastuzumab (not clear whether lapatinib was approved in Australia in such a setting).

In Australia, lapatinib is only approved following progression while or after receiving trastuzumab for metastatic disease. There may be patients who initiate lapatinib within six months of completing adjuvant trastuzumab but this group is likely to be small in number. T-DM1 is approved for patients who progress to metastatic disease within six months of completing adjuvant trastuzumab, however, at present we do not have dispensing data for T-DM1. These data will be contained in our next data update which will arrive in 2017.

4. One typo: on the bottom of page 14 in "study population" chapter- characteristics of patient population are in table 4 (not table 3).

We have corrected this typo.
REVIEWER TWO COMMENTS:

1. References could be updated/improved by citing not only reviews but also the pivotal papers, at least:

   We have reviewed all of the papers suggested by Reviewer Two. Regarding citing the clinical trials—we have instead decided to cite meta-analyses or reviews for each of the medicines as these analyses are better able to demonstrate the efficacy of these medicines. However, we thank the reviewer for highlighting this issue as meta-analyses/reviews do not yet exist for pertuzumab or T-DM1. We have edited the first paragraph of the manuscript to cite the pivotal trials for these two medicines and we have also added the suggested reviews from Broglio et al and Kümler et al.

2. Introduction and/or Discussion could be more extensive:

   Authors should better discuss that observational studies are a very inhomogeneous matter: the “clinical ones”, based on the true clinical data from real patients have usually a small sample size, are reliable on “Who” “Whay” “Whay not” “How”, about treatment and safety, PFS, but there is no reliable information about the costs.

   We have reviewed all of the papers the reviewer suggests and cited them in our introduction. We agree with the reviewer that there exists a wide variety of observational research into HER2-targeted therapies. Our intention in the introduction, as well as Table 1, is to situate our programme of research within the existing group of studies that have used similar datasets to those that we will be using—routinely collected, population based administrative data—not the wider observational research context. We feel the latter would be a substantial undertaking more suitable for a formal systematic review or multiple systematic reviews. We had intentionally omitted a detailed discussion of the studies highlighted by the reviewer as they are based on data collected from hospitals. These are valuable studies that provide much needed evidence around the use and outcomes associated with these medicines in real-world patients, but we feel that they are beyond the scope of this protocol paper that focuses on defining our research using large population-based administrative datasets.

   Please note, the reviewer’s comment prompted us to do another literature search for studies that have used routinely collected, population-based administrative data and we have added four studies to the introduction and Table One (Chen 2012, Negri 2014, DaCosta Byfield 2016, and Vaz-Luis 2016).

3. The “database-based” observational studies, like this one, are rich in economical informations but poor in the clinical ones, as correctly Authors state. I suggest to read and discuss the many cost/efficacy studies already published on the topic:

   Similarly to the above response, we felt that the suggested economic studies were beyond the scope our brief introduction. We have cited two studies that have reported costs associated with HER2-targeted therapy (Guerin 2014 and DaCosta Byfield 2016); these studies reported economic results within the context of a ‘patterns of care’ analysis, which more closely aligns with the proposed programme of research. Again, economic cost/benefit analyses studies as suggested by the reviewer are absolutely necessary and provide insights around the economic burdens of treatment with these medicines, but we feel that they are beyond the scope of this paper.

4. Methods
“Study Setting” and “Medicines of interest...” sections are long and boring, not particularly interesting outside Australia. They are probably necessary but may be cited in the paper and transferred to a detailed supplementary appendix. The same could be done for “Data Sources”: shorter in the text and well explained in appendix.

We have edited the “Study Setting” and “Medicines of interest...” sections highlighted by the reviewer (Pages 8 and 9 of the manuscript). An appealing aspect of protocol papers is that they allow for a detailed presentation of datasets, which is often severely restricted by word limits in other types of papers. As such, we feel that the “Data Sources” section cannot be meaningfully reduced. The ideas discussed in these two paragraphs are essential to understanding idiosyncrasies of our data holdings and how these idiosyncrasies limit the types of questions we are able to answer using these data.

We also feel that Tables Two and Three convey important information about these data to the reader but we are happy to move these to the appendix at the discretion of the editor.

5. Two Typing mistakes:
Page 4 row 18: “Strenghts”
Page 12 row 23: “emtansine”

We have corrected these typos.

**VERSION 2 – REVIEW**

**REVIEWER**
Ariel Hammerman, PhD
Clalit Health Services Headquarters, Tel-Aviv
Israel

**REVIEW RETURNED**
18-Dec-2016

**GENERAL COMMENTS**
Thank you for sending me the resubmitted manuscript for review. I am indeed satisfied with the current version of this paper. All my previous remarks were adequately referred and discussed. I recommend accepting this paper as is.

**REVIEWER**
Giorgio Mustacchi
Prof Emeritus of Oncology
University of Trieste
Italy

**REVIEW RETURNED**
15-Dec-2016

**GENERAL COMMENTS**
Authors answer to any comment and suggestion by reviewers exhaustively and made the appropriate changes to the paper

**VERSION 2 – AUTHOR RESPONSE**

Thank you for your email of 20 December 2016 regarding our manuscript, bmjopen-2016-014439. We have made both changes as requested.
GENERAL COMMENTS

After the minor corrections, I recommend accepting for publication as is.

GENERAL COMMENTS