REVIEW ARTICLE

Systemic treatment of HER2-positive metastatic breast cancer: A systematic review

Nicholas WILCKEN,1 Nicholas ZDENKOWSKI,2 Michelle WHITE,3 Ray SNYDER,4 Ken PITTMAN,5 Paul MAINWARING,6 Michael GREEN,7 Prudence FRANCIS,8 Richard DE BOER,9 Maree COLOSIMO,6 Sue CHUA,10 Jacque CHIRGWIN,11 Jane BEITH12 and Richard BELL13

1Westmead Hospital, 2Australia & New Zealand Breast Cancer Trials Group, and 12Chris O’Brien Lifehouse, New South Wales, 3Cabrini Hospital, 4St Vincent’s Hospital, 7Western Health, 8Peter MacCallum Cancer Centre, 9Royal Melbourne Hospital, 10Epworth Eastern Hospital, 11Box Hill Hospital, and 13Deakin University, Victoria, 5The Queen Elizabeth Hospital, South Australia, and 6Mater Private Breast Cancer Centre, Queensland, Australia

Abstract

Aim: We aimed to systematically review and summarize data from the available clinical trials that examined the treatment of HER2-positive metastatic breast cancer.

Methods: We reviewed phase 2 and 3 studies in which an anti-HER2 agent was used in one or both arms of the study.

While formal meta-analysis was not possible for such a heterogeneous group of trials, resulting forest plots outline some generalizable findings.

Results: There is strong evidence that the addition of an anti-HER2 agent to standard chemo- or endocrine therapy improves clinically relevant measurable outcomes. There is also consistent evidence that initial treatment with trastuzumab alone (and subsequent use of a cytotoxic) is inferior to the initial combination of trastuzumab plus chemotherapy, and that either T-DM1 or dual anti-HER2 agents are superior to single anti-HER2 agent regimens. There is no strong evidence that the use of more than one cytotoxic agent together with an anti-HER2 agent confers any benefit over a single cytotoxic, anti-HER2 combination.

Conclusion: This review provides a strong evidence base for current clinical practice with a discussion of treatment in the Australian setting.

Key words: anti-HER2 agent, breast cancer, metastatic, review, systematic.

INTRODUCTION

The development of targeted biological agents has improved survival for women with HER2-positive met-

static breast cancer.1 However, as more targeted agents are being developed and approved for use both as single agents and in combination with other agents, it is challenging to translate this evidence into optimal clinical practice.

Current guidelines on the treatment of HER2-positive metastatic breast cancer are at risk of becoming outdated, and may not include newly approved anti-HER2 agents.2 The anti-HER2 agents, trastuzumab, lapatinib, pertuzumab and trastuzumab emtansine (T-DM1), are approved for use in many parts of the world, including Australia.3–6 At the time of writing, trastuzumab

Correspondence: Associate Professor Nicholas Wilcken PhD FRACP, Crown Princess Mary Cancer Care Centre, Westmead Hospital, University of Sydney, Hawkesbury Road, Westmead, NSW 2145, Australia. Email: nicholas.wilcken@sydney.edu.au

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and lapatinib are the only anti-HER2 agents reimbursed by the Australian government for the treatment of metastatic HER2-positive breast cancer. In the first-line setting, trastuzumab may be used in combination with a taxane. Second-line options include trastuzumab monotherapy, and for patients whose disease has progressed on trastuzumab, lapatinib in combination with capecitabine.7

We are a group of oncologists from different health care settings in Australia who specialize in the treatment of breast cancer. Collectively and systematically, we selected and reviewed all available phase 2 and 3 randomized controlled trials evaluating anti-HER2 agents in metastatic breast cancer. Here, we present the results of this systematic review.

Clinically relevant questions are not always tractable systematic review questions and therefore there is an accompanying paper in this supplement addressing what we consider the most important clinical issues in the management of patients with HER2-positive metastatic breast cancer. In the second publication, we have built on the findings of this systematic review, gathered relevant published reports and applied our combined clinical experience to provide guidance in a number of common clinical scenarios challenging clinicians treating patients with HER2-positive metastatic breast cancer in Australia.

METHODS

Literature searches

The protocol for this systematic review was prospectively registered with PROSPERO (Registration No. 20130820). We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Reviews of Effect, the Cochrane Database of Systematic Reviews, Embase, Health Technology Assessment, Medline, Medline Daily, NHS Economic Evaluations Database, Web of Science and the ASCO meeting library using a predefined search strategy.8 We included phase 2 and 3 randomized clinical trials of systemic treatments for HER2-positive (HER2 over-expressing, or amplified) metastatic breast cancer. We excluded studies of adjuvant therapy as we wished to focus on metastatic breast cancer treatments. Records from the start of each database to January 2014 were retrieved. We hand-searched the abstracts from the European Society of Medical Oncology, the European Breast Cancer Conference and the San Antonio Breast Cancer Symposium for the years 2009–2013.

Eligibility criteria

Studies were eligible if they were randomized, included patients with metastatic or incurable locally advanced HER2-positive breast cancer, and there was an anti-HER2 agent(s) in one or both arms of the trial.

Outcomes

The primary outcome for the review was progression-free survival (PFS). PFS was defined as the time from the date of randomization to the date of tumor progression or patient death. Time to progression (TTP) was included as a surrogate for PFS where PFS was not reported. TTP was defined as the time elapsed between randomization and tumor progression only.9 Given that few patients die without documentation of disease progression, PFS and TTP are considered sufficiently similar endpoints for the purpose of this review.9

Secondary outcomes were overall survival (OS), objective response rate (ORR), quality of life (QOL) and safety, using standard definitions. QOL was assessed using any validated QOL instrument. Our safety review focused on grade 3 or 4 events (as defined by NCI-CTC), with a particular focus on cardiac events.

Study selection

We screened all retrieved abstracts for eligibility and reviewed a full copy of the publication for each eligible abstract. Publications that met the eligibility criteria were included, and these were grouped together where multiple publications of a study were found.

Data extraction

We developed and piloted a standard extraction form to capture the study details and outcomes of the review as defined in the protocol. Data extraction included: the number of participants and eligibility criteria; interventions studied; comparators used; study design; hazard ratio for PFS or TTP as a surrogate for PFS, for the intervention versus control; hazard ratio for OS for the intervention versus control; ORR; QOL data; and toxicity data including cardiac events and other grade 3 and 4 events of interest.

The authors cross-checked all abstracts, publications and data extraction forms to ensure the quality of the data included in the review.

Data analysis

We did not plan to conduct a meta-analysis of the data due to the expected heterogeneity of the studies. Instead, we aimed to present summary statistics in table and plot form, together with some narrative interpretation.
The studies were grouped to represent the type of intervention used: Group 1: comparison of an anti-HER2 containing regimen with a non-anti-HER2 containing control regimen; Group 2: both arms contained different anti-HER2 regimens; Group 3: comparison of different chemotherapy regimens in combination with the same anti-HER2 agent; Group 4: miscellaneous studies that compared different doses or schedules of either an anti-HER2 agent or a chemotherapeutic regimen. The data were stratified into studies of first-line treatment, second-line or later lines and any line of treatment.

Data used in the development of summary figures and tables were extracted directly from the studies. In several cases, the hazard ratios for PFS or OS were not reported. As mentioned earlier, where TTP hazard ratios and confidence intervals were reported, these were imputed as surrogates for missing PFS values. In the case of the pivotal Marty trial (M77001), we imputed TTP and OS hazard ratios. The TTP hazard ratio was calculated as the median TTP in the control arm divided by the median TTP in the experimental arm. The OS hazard ratio was calculated as the OS in the control arm divided by the OS in the experimental arm. Only a point estimate is provided, as confidence intervals around the median TTP in the control arm. The OS in the control arm divided by the median TTP in the experimental arm. The OS hazard ratio was calculated as the OS in the control arm divided by the median TTP in the experimental arm. The OS in the control arm divided by the median TTP in the experimental arm. Only a point estimate is provided, as confidence intervals around the median TTP and OS survival times were not reported in the paper.

Assessment of bias

Given the presentation of hazard ratios without formal meta-analysis, we did not consider that a formal assessment of bias was warranted.

RESULTS

Study selection

We identified 2380 abstracts, of which 833 were duplicate records. We screened all 1547 abstracts and excluded 1186 that did not meet the eligibility criteria. After a full-text review of the remaining 361 publications, we identified 100 eligible publications. The final 100 publications were reviewed and grouped according to the study they reported, giving a total of 34 studies for data extraction. Reasons for exclusion are presented in Figure 1.

Study characteristics

Of the 34 studies, 68% (n = 23) compared first-line treatments, 21% (n = 6) were in second-line or later, and 9% (n = 3) were in any line of treatment. Two recently published studies compared treatments used either first or second line. About one quarter (26%, n = 9) of the studies (Group 1) compared a treatment regimen including an anti-HER2 agent with a control regimen that did not contain an anti-HER2 agent. In 24% (n = 8) of the studies (Group 2), each arm contained a different anti-HER2 regimen and 32% (n = 11) of the studies (Group 3) compared different chemotherapy regimens in combination with the same anti-HER2 agent. The remaining studies (Group 4) were classified as miscellaneous (Table 1).

Trastuzumab was the anti-HER2 agent used in 54% of experimental and 38% of control arms demonstrating a change in use of experimental and control agents over time (Figure 2). The most commonly used chemotherapy was taxane based (41% of experimental and 43% of control arms). In keeping with our planned analysis, PFS and TTP were the primary endpoints used for most studies (57%, n = 21, Table 1).

While our search included studies from the start of each database, the studies meeting the eligibility criteria for the systematic review were predominantly those published since 2010 (62%), with the earliest publication dating to 2001 (Table 1).

Outcomes

Prior to reviewing the collated outcomes data, we reviewed the study designs for consistency. To allow a meaningful comparison of outcomes, the data for the experimental and control arms in studies JO17360, BCIRG007 and Hernata were reversed, for the purpose of comparing hazard ratios in a consistent way, to show the experimental arm as the combination of an anti-HER2 agent with chemotherapy, in keeping with the majority of the other studies in the review.

Data for Group 4 (miscellaneous) are not shown on forest plots as they are individual studies not appropriate for comparison and were not clinically relevant to the questions being considered in this review. Details of the studies are shown in Table 1.

Two small studies, looking at scheduling of chemotherapy with an anti-HER2 agent, demonstrated the importance of using an anti-HER2 in combination with chemotherapy upfront. The first study (HERTAX trial) compared the upfront combination of trastuzumab with docetaxel with trastuzumab alone followed by docetaxel alone after disease progression. The other study (JO17360 trial) compared the combination of trastuzumab with docetaxel with trastuzumab alone followed by the addition of docetaxel. In both studies, the sequential use of an anti-HER2 agent and chemotherapy was inferior to the combination arm.
**Progression-free survival**

Two pivotal studies (Marty\textsuperscript{14} and Slamon\textsuperscript{12}) established that trastuzumab and a taxane are superior to chemotherapy alone. These studies established trastuzumab as the first-line treatment for HER2-positive metastatic breast cancer. Similarly, for hormone receptor positive, HER2-positive metastatic breast cancer, trastuzumab and an aromatase inhibitor are superior to an aromatase inhibitor alone, both in the first-line\textsuperscript{11,29–33,37,38} and second-line\textsuperscript{36} settings. Only one small study\textsuperscript{11} of an aromatase inhibitor with or without trastuzumab had confidence intervals that crossed unity (HR 0.67, CI 0.35–1.29) (Fig. 3, panel 1).

In second-line studies, HER2 blockade with lapatinib in combination with capecitabine is more effective than chemotherapy alone.\textsuperscript{13,21–26,34,35} Overall, addition of an anti-HER2 agent to chemotherapy was consistently superior to chemotherapy alone (HR 0.52–0.71).

Consistent benefit was also seen in Group 2 experimental arms, when T-DM1 or dual anti-HER2 therapy was compared with standard single anti-HER2 agent regimens (HR 0.53–0.74). Lapatinib-taxane was inferior to trastuzumab/taxane (HR 1.33)\textsuperscript{48,49} and neratinib was inferior to lapatinib-capecitabine (HR 1.19; Fig. 3, panel 2).\textsuperscript{54,55,59} No clear benefit was seen when a second chemotherapy agent was added to chemotherapy and an anti-HER2 agent, with the exception of the Robert study\textsuperscript{61} that showed addition of carboplatin to trastuzumab and three weekly paclitaxel improved PFS. Trastuzumab/vinorelbine and trastuzumab/docetaxel were of similar benefit\textsuperscript{10} (Fig. 3, panel 3).

Trying to quantify the benefits of anti-HER2 agents in prolonging PFS, while of great clinical importance,
Table 1 Study characteristics

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*aThe Marty et al. [14] trial did not report hazard ratios for PFS or TTP. AC, anthracycline plus cyclophosphamide; Anas, anastrozole; Cape, capecitabine; Carbo, carboplatin; Cyclo, cyclophosphamide; Doce, docetaxel; EC, epirubicin plus cyclophosphamide; Epi, epirubicin; Gem, gemcitabine; Let, letrozole; Ner, neratinib; Pac, paclitaxel; Paz, pazopanib; Per, pertuzumab; Plac, placebo; Tras, Trastuzumab; Vin, vinorelbine.*
is difficult to do given all the variables across different trials. With that caveat in mind, it is interesting to look at three trials where there is a common arm of trastuzumab and docetaxel (Marty, CLEOPATRA and Hurvitz). In the Marty trial, adding trastuzumab to docetaxel improved median PFS from around 6 to 12 months. In the CLEOPATRA study, median PFS for trastuzumab/docetaxel (now the control arm) was also 12 months, and the addition of pertuzumab increased median PFS to 18 months. The hazard ratio for PFS with T-DM1 compared with trastuzumab/docetaxel was very similar to that in the CLEOPATRA study. Therefore, it seems likely that adding anti-HER2 agents to standard chemotherapy improves median PFS by at least 6 months and perhaps between 6 and 12 months for “modern” anti-HER2 treatments (trastuzumab plus pertuzumab or T-DM1 alone).

Figure 2  Balloon plot of included studies. AC, anthracycline plus cyclophosphamide; Anas, anastrozole; Cape, capecitabine; Carbo, carboplatin; Cyclo, cyclophosphamide; Doce, docetaxel; EC, epirubicin plus cyclophosphamide; Epi, epirubicin; Gem, gemcitabine; Let, letrozole; Ner, neratinib; Pac, paclitaxel; Paz, pazopanib; Per, pertuzumab; Plac, placebo; Tras, trastuzumab; Vin, vinorelbine.
Figure 3  Forest plot for progression-free survival. Panel 1: Group 1: anti-HER2 versus no anti-HER2 agent trials; Panel 2: Group 2: anti-HER2 agent comparison trials; Panel 3: Group 3: anti-HER2 agent with additional chemotherapy trials; Panel 4: Group 4: miscellaneous trials of anti-HER2 agents. †Denotes TTP as a surrogate for PFS. ‡Denotes point estimate only (no confidence intervals provided). †Denotes chemotherapy with doxorubicin or epirubicin plus cyclophosphamide or paclitaxel.
Overall survival

Available OS data from Group 1, comparing an anti-HER2 containing regimen with a non-anti-HER2 containing control regimen, demonstrated an advantage in the two first-line studies (HR 0.73–0.74), but no advantage in second-line studies (HR 0.87–0.94; Fig. 4, panel 1). Group 2 (comparing anti-HER2 agents) demonstrates a survival advantage of T-DM1 in the two second- or later-line studies (HR 0.55–0.68), but not in the first-line setting when compared with trastuzumab-docoltaxel (HR 1.06; Fig. 4, panel 2). However, these first-line OS results are not mature at a median follow-up of 23 months. Dual anti-HER2 agents were more effective than single anti-HER2 agents in first- and second-line studies (HR 0.66–0.74; Fig. 4, panel 2). Using a second chemotherapy agent with anti-HER2 therapy was no better than single-agent chemotherapy with anti-HER2 therapy, with the exception of a small improvement with carboplatin added to trastuzumab and paclitaxel in the Robert study (Fig. 4, panel 3).

Objective response rate

A clear improvement in ORR was seen in all Group 1 studies, comparing chemotherapy with chemotherapy plus anti-HER2 therapy (HR 1.32–3.03; Fig. 5, panel 1). Overall response rates in the anti-HER2 arms ranged from 24 to 75%, with ORR in the control arms ranging from 13 to 57%. In Group 2, overall response rates ranged from 10 to 80% in the experimental arm, and between 7 and 69% in the control arm, probably reflecting differences in patient selection and the rigor and method of HER2 status determination (immunohistochemistry (IHC) vs in situ hybridization (ISH), changes in antibodies and other variations in assessment). Both second-line T-DM1 studies demonstrated improved ORR (HR 1.41–3.63; Fig. 5, panel 2). Dual anti-HER2 agents were not shown to improve ORR. The study comparing neratinib to lapatinib-capcitabine was unable to demonstrate inferiority or non-inferiority and was therefore inconclusive. In the Group 3 scheduling studies, the ORR in the experimental arms ranged from 30 to 61% in the experimental arms, and from 7 to 64% in the control arm (Fig. 5, panel 3). Divergent results were seen: better ORR with trastuzumab alone followed by docetaxel alone compared with the combination; and better ORR with combination trastuzumab and docetaxel compared with trastuzumab followed by trastuzumab and docetaxel. No ORR difference was seen in any of the studies that compared anti-HER2
1

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental</th>
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<th>RR (95% CI)</th>
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<tr>
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<td>Marty</td>
<td>Tris + Doce</td>
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<td>Tris + Pac</td>
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<td>EGF104535</td>
<td>Lap + Pac</td>
<td>1.38 (1.18, 1.62)</td>
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<tr>
<td>Electra</td>
<td>Tris + Let</td>
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2

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<td></td>
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2nd line or later

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<td>Emilia</td>
<td>T-DM1</td>
<td>Lap + Cape</td>
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<td>Thressia</td>
<td>T-DM1</td>
<td>Physician’s choice</td>
<td>3.63 (2.25, 5.85)</td>
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Any line

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<th>Control</th>
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<tbody>
<tr>
<td>Tandem</td>
<td>Tris + Ansa</td>
<td>Anas</td>
<td>3.03 (1.35, 6.81)</td>
</tr>
</tbody>
</table>

Safety

Safety data are summarized in Table 2. The median percentage of patients experiencing each adverse event of interest was calculated from those studies in which a percentage was reported. The data are grouped according to the type of agent used in the treatment arm and split by line of treatment.

The safety data are difficult to summarize and interpret given the wide range of study designs, the varying chemotherapeutic agents, doses, schedules and variability of prior lines of treatment. This renders between-trial comparisons hazardous. For example, data for all events in studies of first-line anti-HER2 agents suggest that patients receiving trastuzumab experience more grade 3 or 4 adverse events than those receiving lapatinib, a finding not in keeping with clinical experience. This likely reflects the fact that the trials with lapatinib were mostly in combination with non-myelosuppressive drugs like capcitabine or endocrine agents while the trastuzumab trials were mainly with taxanes.

Cardiac events

Unlike adjuvant treatment trials, cardiac toxicity was not consistently reported in metastatic breast cancer studies. The grade 3 or 4 cardiac events reported in a small number of studies did not provide sufficient data to be meaningfully pooled. Therefore, a narrative synthesis is presented.

In the majority of studies, anthracyclines were not used in combination with the anti-HER2 agent and patients with previous cardiac events were excluded from entry into most of the studies. Using a variety of definitions of cardiac toxicity, most trials in Group 1 reported a numerically higher rate of cardiac events in the anti-HER2 arm when compared with the non-anti-HER2 arm. The excess cardiac toxicity seen in the Slamon trial was predominantly in the patient group treated with concurrent anthracycline and trastuzumab. Patients in the Hercules trial experienced a higher cardiac event rate with 90 mg/m² compared with 60 mg/m² epirubicin, when given concurrently with cyclophosphamide and trastuzumab.

Quality of life

QOL data were infrequently measured and inconsistently reported across the studies in this review. We were unable to draw any meaningful conclusions from these data.

Figure 5 Forest plot for objective response rate. Panel 1: Group 1: anti-HER2 versus no anti-HER2 agent trials; Panel 2: Group 2: anti-HER2 agent comparison trials; Panel 3: Group 3: anti-HER2 agent with additional chemotherapy trials. Denotes chemotherapy with doxorubicin OR epirubicin plus cyclophosphamide OR paclitaxel.
In Group 2, cardiac toxicity from T-DM1 appears no worse than other anti-HER2 agents.50,56,60 Cardiac toxicity was not increased with a dual anti-HER2 treatment using pertuzumab and trastuzumab.44 On the other hand, the combination of lapatinib and trastuzumab may cause more cardiac toxicity than lapatinib alone, although rates were low in both arms of that study.19 In Group 3, additional non-anthracycline-based chemotherapy did not appear to increase the rate of cardiac events. Within Group 4, bevacizumab appeared to cause additional cardiac toxicity,80,81 as did pazopanib when added to lapatinib.83 Most cardiac events were asymptomatic and reversible.

**DISCUSSION**

There is clear evidence that anti-HER2 agents are effective treatment for patients with metastatic HER2-positive breast cancer in terms of PFS, OS and ORR. Combinations of anti-HER2 agents with both chemotherapy and endocrine therapy are efficacious. Dual anti-HER2 agents are superior to single anti-HER2 agent, when combined with chemotherapy. Single-agent anti-HER2 therapy without chemotherapy initially is generally a less effective option, although antibody-chemotherapy conjugate T-DM1 alone has similar or superior efficacy to a combination treatment.

The lack of benefit from adding a second chemotherapy to an anti-HER2 agent with chemotherapy suggests that anti-HER2 control remains the primary objective. Using anti-HER2 therapy with single-agent cytotoxic or endocrine therapy is in line with consensus statements in the metastatic setting which recommend that the minimum number of effective agents should be used.85 However, there is insufficient evidence to guide sequencing of anti-HER2 agents beyond first line. The efficacy of other anti-HER2 agents after initial failure of trastuzumab (T-DM1, trastuzumab plus lapatinib, lapatinib plus capecitabine) argues for continued HER2 blockade after first-line treatment where feasible from both a regulatory and a financial perspective.

There are several limitations to our review. Because of the heterogeneity of the data in this systematic review, a meta-analysis was not appropriate, and the data are therefore presented descriptively. Given this is a rapidly developing area of clinical research and while every effort has been made to ensure the data are up to date, emerging results will likely further change the landscape that we have presented here.

Several challenges for the future remain. As the number of available agents grows, determining the

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**Table 2**

| Table 2 Median proportion of patients with grade 3 or 4 events by line and type of treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **First line**                  | **All events**  | **Febrile neutropenia** | **Diarrhea** | **Fatigue** |
| **Anti-HER2 antibody**-based arms | 6.8 (46–91)  | 9.75 (0–37)   | 4 (0–14)    | 5.3 (0–14)  |
| **Chemotherapy-alone**-based arms | 30.3 (39)  | 39.6 (0–37)   | 4 (0–14)    | 5.3 (0–14)  |
| **Aromatase inhibitor** alone arms | 32.2 (14–42) | 57.7 (57)     | 2 (0–3.5)   | 7 (0–3.5)   |

**Beyond first line**

| **All events**  | **Febrile neutropenia** | **Diarrhea** | **Fatigue** |
| **Anti-HER2 antibody**-based arms | 30.2 (28–63.6) | 1.4 (0–2.7) | 0.3 (0–1.7) |
| **Chemotherapy-alone**-based arms | 16.3 (16.3) | 0.5 (0–2) | 0.3 (0–1.7) |
| **Aromatase inhibitor** alone arms | 1 (1) | 1 (1) | 0 (0) |

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most appropriate agents to use, in what combinations and in which order remains problematic. In Australia, anti-HER2 agent use is likely to be limited by reimbursement criteria, which may restrict use of agents to certain lines of therapy, or in combination with certain agents. Furthermore, in order to limit health expenditure, reimbursement may be limited to single-lifetime use of an agent, or discourage sequential use of particular anti-HER2 agents. While this is understandable from a health care expenditure point of view, it may mean that the best outcome for the patient is not achieved.

While the discovery of the HER2 gene revolutionized treatment outcomes for patients with HER2-positive disease, there is still a lot to learn about the nuances of HER2-positive metastatic breast cancer. Dissecting out different HER2-positive subtypes may become important in order to guide therapeutic options. Furthermore, a better understanding of how to predict and treat resistance to anti-HER2 agents is required.

CONCLUSION

The development of trastuzumab and subsequent anti-HER2 agents has revolutionized the treatment of HER2-positive disease. While effective use of these drugs in the adjuvant setting will thankfully make HER2-positive metastatic disease less and less common, it will still remain a disease needing treatment. As outlined above, there are now a number of effective options and we encourage further research into mechanisms of resistance to anti-HER2 agents and how to overcome this problem.

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