SUMMARY

- Trastuzumab (Herceptin™) is a recombinant humanised monoclonal antibody that inhibits the proliferation of human tumour cells that overexpress the human epidermal growth factor receptor 2 (HER2). In patients with metastatic breast cancer whose tumours overexpress HER2, trastuzumab is licensed as monotherapy or combination therapy with other chemotherapy or hormonal agents until progression of disease. It is not licensed for use following disease progression.

- There is a great deal of controversy and practice variation in the UK regarding the continued use of trastuzumab at the time of disease progression; this may be because there is uncertainty as to the mechanisms of resistance and whether this is partial or absolute.

- In their clinical guidance on advanced breast cancer, NICE have recommended that for patients who are receiving treatment with trastuzumab for advanced breast cancer, treatment with trastuzumab should be discontinued at the time of disease progression outside the central nervous system on the basis that there is limited evidence of clinical benefit and there is no robust evidence for its cost effectiveness. If disease progression is within the central nervous system alone, treatment with trastuzumab should be continued. NICE note within the guideline that they were aware of limited, very recent evidence (Von Minckwitz study; not included in NICE evidence appraisal but discussed below) of clinical benefit for the use of trastuzumab on disease progression but made the recommendation on the basis that it would not be appropriate to recommend the use of trastuzumab on disease progression without robust evidence of the cost effectiveness of this high cost treatment.

- As NICE note, there are very limited data supporting the continued use of trastuzumab after disease progression. One post-RCT analysis showed that the efficacy and incidence of adverse events were comparable between the group that continued on trastuzumab compared to the group that had trastuzumab for the first time after disease progression. Results of the von Minckwitz study found the overall response and time to progression to be statistically superior with the combined therapy compared to capecitabine alone with no additional significant toxicity. In this trial the median time to progression in patients continuing to receive trastuzumab (plus capecitabine) was 8.2 months vs 5.6 months – a difference of 2.6 months. However the study was underpowered, there may have been potential for bias in the assessment of response rates by the unblinded investigator, patients in the capecitabine group may have had an on-going exposure to trastuzumab because of the drugs long half-life and the trial did not show that the difference in progression-free survival resulted in a statistically significant impact on overall survival (25.5 months vs 20.4 months). A phase II study and six retrospective case series provide some additional evidence in support of continuing trastuzumab therapy beyond disease progression but because the data are uncontrolled it is difficult to set the results described into clinical context.

- NICE estimate that annual savings of £11,717,000 in England and Wales, equating to a saving around £21,500 per 100,000 population, could be realised if trastuzumab was discontinued in women whose disease progresses. This saving is based on an estimate that there are currently 777 patients (or between 1 and 2 per 100,000 population) are being treated every year with trastuzumab for disease that has progressed outside the CNS.
Continued use of trastuzumab following disease progression in metastatic breast cancer

BACKGROUND

Trastuzumab (Herceptin™; Roche) is a recombinant humanised monoclonal antibody that inhibits the proliferation of human tumour cells that overexpress the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 has been observed in 20% to 30% of primary breast cancers and studies have demonstrated that patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not over express HER2.1

The introduction of trastuzumab (TRZ) has revolutionised the management of metastatic breast cancer (MBC). In patients whose tumours overexpress HER2, TRZ is licensed:

- As monotherapy for the treatment of those patients who have received at least two chemotherapy regimens (at least an anthracycline and a taxane) for their metastatic disease. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- In combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- In combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.1

There is no agreed standard treatment for patients whose disease progresses after treatment with TRZ. Treatment options that are usually considered include TRZ-, capecitabine- and vinorelbine-containing regimens.

Preclinical studies have demonstrated that TRZ is effective as a cytostatic agent as long as it is present, whereas TRZ withdrawal results in rapid tumour growth.2 Furthermore preclinical data suggest that cells retain sensitivity to the chemotherapy potentiating effects of TRZ and therefore continued administration of TRZ with a different, second-line chemotherapy agent may result in better clinical outcomes compared to using the chemotherapy agent alone.3,4 TRZ has an added advantage over chemotherapy agents in the long term management of MBC; cumulative toxicity has not been demonstrated.5

There is a great deal of controversy and practice variation regarding the continued use of TRZ when chemotherapy is stopped or changed at the time of disease progression; this may be because there is ambiguity on the primary mechanism of action of TRZ, the possibility of development of resistance and the optimal use of TRZ. Many oncologists have continued TRZ beyond progression of disease, although this trend is based on preclinical data and retrospective analyses rather than randomised controlled trial data.

The concept of continuing HER-2 blockade in patients with HER-2 positive disease has been explored in a randomised trial of lapatinib versus lapatinib and capecitabine which demonstrated a significant improvement in time to progression (4.3 months versus 6.2 months, p<0.001) in patients in favour of lapatinib and capecitabine.6 Lapatinib (in combination with capecitabine), within its licensed indication, has not yet been approved by NICE for the routine treatment of women with previously treated advanced or MBC whose tumours overexpress HER2.7

NICE have recommended that for patients who are receiving treatment with TRZ for advanced breast cancer, treatment with TRZ should be discontinued at the time of disease progression outside the central nervous system on the basis that there is limited evidence of clinical benefit and there is no robust evidence for its cost effectiveness. However, in patients whose disease progression is within the central nervous system alone, NICE recommend that treatment with TRZ should be continued. NICE note that they were aware of limited, very recent evidence of clinical benefit for the use of TRZ on disease progression but made the recommendation on the basis that it would not be appropriate to recommend the use of TRZ on disease progression without robust evidence of the cost effectiveness of this high cost treatment.8

NICE state that continued TRZ in patients with progressive MBC should be investigated as part of a randomised controlled trial with a high-quality cost effectiveness analysis. Nonetheless, despite the limited evidence from randomised controlled trials, many clinicians continue TRZ beyond disease progression in clinical practice.8
Epidemiology of metastatic breast cancer

There are no published national data on the incidence of advanced breast cancer; therefore it is difficult to estimate the burden of disease. Only one cancer register, the West Midlands Cancer Intelligence Unit, collects information on all cases of secondary breast cancer (Secondary Breast Cancer Taskforce 2007). The data indicate that approximately 5% of women and men diagnosed with breast cancer between 1992 and 1994 had metastases at the time of their primary diagnosis. The data also suggest that a further 35% of all those with a primary diagnosis went on to develop metastases in the 10 years following diagnosis. However there are few data to quantify the number of cases of secondary breast cancer developing after the 10-year time period.

In the costing template for advanced breast cancer NICE estimate that there are 10,786 presentations of advanced breast cancer each year in England – 1907 new presentations and 8879 in patients that have progressed. About 25% of these will be HER2 positive, therefore NICE estimate that there are around 2697 women per year for whom this guidance is relevant which equates to around 5 per 100,000 population.

Clinical evidence

Studies evaluating continuing TRZ post progression

In a pivotal Phase III trial, the addition of TRZ to chemotherapy significantly improved response rate, time to disease progression and overall survival in women with previously untreated HER2-overexpressing MBC (HO648g; n=469). In an extension study to this trial, 247 patients were given the opportunity to continue weekly TRZ treatment at the time of progression, to provide additional safety information (HO659g). TRZ-naïve patients (group 1, n=154) from the initial pivotal trial were given TRZ alone (n=105) or with chemotherapy (n=49). Patients in group 2 (n=93) who had received chemotherapy and TRZ in the initial trial either continued with TRZ alone (n=22) or continued with TRZ in addition to chemotherapy (n=71). Patients from group 1 entered the extension study earlier than those from group 2 (median time to progression [TTP] 30 months vs 45 months). Most of the patients entering the extension phase had high burden disease, but with more of the patients in the group that continued TRZ after disease progression having more than three sites of disease compared to the group of patients that had TRZ for the first time after disease progression. The median duration of TRZ treatment was 30 weeks and 26 weeks, objective response rates (ORR=CR+PR) were 14% and 11%, and the median duration of response was 7.4 and 6.7 months for groups 1 and 2, respectively.

A prospective phase II study assessed consecutive patients with MBC who had experienced disease progression after first-line TRZ based therapy at a single centre based in Austria. Follow up started in May 2002 and data were analysed in May 2005; median length of follow up was 24 months (range: 7-51 months). Fifty four patients (one male) received an initial dose of 8mg/kg TRZ on the first day of treatment followed by 6mg/kg every three weeks. Thirty one patients were previously treated with adjuvant chemotherapy, commonly vinorelbine, docetaxel, capecitabine, gemcitabine, platinum derivatives and others, and fifteen patients received adjuvant endocrine therapy (tamoxifen, anastrazole). The most common combination partners with TRZ were: vinorelbine (n=55), docetaxel (n=28), capecitabine (n=28), gemcitabine (n=25), platinum derivatives (n=13), others (n=28). The response rates for all TRZ- containing treatment lines are tabulated below (table 1).

Table 1: Response rates and TTP for TRZ- containing treatment lines (Bartsch et al, 2006)

<table>
<thead>
<tr>
<th>TRZ combination treatment line</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Stable disease (%)</th>
<th>Progressive disease (%)</th>
<th>Clinical benefit rate (%)</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line (n=54)</td>
<td>7.4</td>
<td>35.2</td>
<td>42.6</td>
<td>14.8</td>
<td>85.2</td>
<td>6</td>
</tr>
<tr>
<td>Second line (n=54)</td>
<td>3.7</td>
<td>22.2</td>
<td>42.6</td>
<td>31.5</td>
<td>68.5</td>
<td>6</td>
</tr>
<tr>
<td>Beyond second line *</td>
<td>1.7</td>
<td>28.3</td>
<td>28.3</td>
<td>41.4</td>
<td>58.3</td>
<td>6</td>
</tr>
</tbody>
</table>

3⁷ line n=33, 4⁷ line n=18, 5⁷ line n=6, 6⁷ line n=2, 7⁷ line n=1.
Investigators in an Italian oncology treatment centre have published a retrospective analysis of treatment response rates in 59 women treated at their centre who continued TRZ despite disease progression and compared survival rates with 23 patients that changed treatment centre and stopped TRZ. They state that the median overall survival was 70 months for patients that continued TRZ and 56 months for those that stopped (HR: 0.87, 95% CI: 0.51 to 1.18, p=0.52). Obviously it is not possible to control for confounding variables in this analysis and that includes the effect of the treatment centre itself. Within this analysis the following results are presented for women who continued TRZ – at a median follow up period of 39.6 months and a median duration of TRZ treatment of 16.5 months (table 2).

<table>
<thead>
<tr>
<th>TRZ combination treatment line</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Stable disease (%)</th>
<th>Clinical benefit (%)</th>
<th>Median TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line (n=57)</td>
<td>10.5</td>
<td>24.5</td>
<td>39</td>
<td>74</td>
<td>7.25 (1.5 to 46.5)</td>
</tr>
<tr>
<td>Second line (n=55)</td>
<td>3.5</td>
<td>12.5</td>
<td>36</td>
<td>53</td>
<td>5.25 (1.25 to 34.2)</td>
</tr>
<tr>
<td>Third line (n=26)</td>
<td>0</td>
<td>15</td>
<td>42</td>
<td>60</td>
<td>5.25 (1 to 33.5)</td>
</tr>
<tr>
<td>Fourth line (n=12)</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>17</td>
<td>3.75 (1 to 7)</td>
</tr>
</tbody>
</table>

There are at least five other retrospective case series and abstract data which have assessed the safety and efficacy of continuing TRZ beyond disease progression (appendix 1). Pooling the data from these studies is difficult because of heterogeneity in the patient population, interventions and treatment outcomes. Overall, these studies offer little additional evidence to support continuing therapy and are prone to selection bias as data are only chosen from those fit enough to continue treatment after progression or have not stopped TRZ because of toxicity. At best, they point towards further investigation through a randomised controlled trial.

Studies evaluating TRZ and capcitabine

There is only one published phase III randomised controlled study comparing TRZ and capcitabine versus capcitabine alone in patients with HER2 positive locally advanced or MBC that progressed during TRZ treatment. In this open-label study, patients with at least 12 weeks of previous treatment with TRZ were randomised to capcitabine 2500mg/m² daily on days 1-14 of a 21 day cycle (n=78) or TRZ 6mg/kg every 21 days in addition to the previous capcitabine dose (n=78). The primary endpoint was TTP.

The study required 482 patients to identify a significant difference between the two arms but was prematurely terminated due to poor accrual and the registration of lapatinib, so that only 156 patients were eventually recruited over 45 months. The study was originally designed with 80% power to detect 27.5% improvement in TTP from 4 to 5.1 months for continuing TRZ beyond progression. The trial recruited 78 patients per arm and those who continued TRZ beyond progression demonstrated a 46% improvement in median TTP from 5.6 to 8.2 months (HR=0.69; 2-sided p=0.034; 1-sided p=0.015) and 5 month (25%) improvement in OS despite being underpowered (from 20.4 to 25.5 months, HR 0.76; P value: 2-sided p=0.026; 1-sided p=0.13) versus patients who stopped TRZ on progression.

ORR were reported in 20 (27.0%) patients in the capcitabine group and in 37 (48.1%) patients in the combined treatment group (OR 2.5; p= 0.0115). A further 20 patients in the capcitabine group and 21 patients in the combined treatment group had stable disease for greater than 24 weeks, resulting in clinical benefit rates of 54.1% in the capcitabine group and 75.3% in the combined treatment group. Brain metastases occurred in 5 and 8 patients, respectively.

There are two published phase II studies of capcitabine and TRZ in heavily pre-treated patients with HER2 positive advanced breast cancer. Both are small scale studies and have demonstrated an overall response rate of 20-42%, median TTP of 4-8 months and median OS of 16-24 months depending on the line of capcitabine and TRZ therapy (appendix 2).

Studies evaluating TRZ and vinorelbine

There are no phase III randomised controlled studies comparing TRZ with vinorelbine. Interim results from one phase II study have been presented at conference (appendix 3).

Adverse events/Safety issues

When TRZ is used alone, common adverse effects (>10% patients) include abdominal pain, asthenia, chest pain, chills, fever, headache, pain, diarrhoea, nausea, vomiting, arthralgia, myalgia and rash. Compared to conventional chemotherapy, myelosuppression and alopecia are rare (>1 % and < 10 %; 1) but TRZ is associated with cardiotoxicity and infusion related reactions.

All patients in the Tripathy et al study were included in the safety analysis and adverse effects were similar those observed in the pivotal study; 76% of group 1 and 55% of group 2 experienced at least one adverse event. Nineteen patients experienced a serious adverse event possibly related to TRZ, 10 of these were reported to be cardiac dysfunction. Other serious adverse events were allergic reaction, asthenia, pericardial effusion, acute leukae mia, sepsis, dyspnea, fever, pulmonary embolus and infuson reactions. No antibodies against TRZ occurred in either group and there was no clear trend of increased adverse events when patients were examined over a longer time frame (>12 months).

In the Von Minckwitz et al study, 49 patients in the capcitabine group and 49 patients in the combined treatment group experienced grade 3 or 4 toxicities; anaemia (2.8% vs 0%), neutropenia (4.3% vs 5.3%), febrile neutropenia (0% vs 2.6%), vomiting (4.0% vs 1.3%), diarrhoea (18.9% vs 15.6%), mucositis (2.7% vs 1.3%), sensory neuropathy (5.4% vs 2.6%).

In the Bartsch et al, 2006 study, TRZ- based therapy was reasonably well tolerated. WHO grade III toxicities included neutropenia (25.9%), anaemia (11.1%), hand-foot syndrome (5.8%), stomatitis (3.7%), thrombocytopenia (3.7%) and nausea (1.9%). A WHO grade IV neutropenia was observed in five patients (9.3%).
Health economics

We are working in conjunction with the Yorkshire Cancer Network who has commissioned York Health Economics Consortium (YHEC) to provide a review of the economic evidence of whether TRZ should be made available for the treatment of post-progression HER2 positive breast cancer. Below is a statement of their overall findings:

Roche submitted to YHEC a cost-utility analysis of trastuzumab compared to capecitabine monotherapy in post-progression HER2 positive metastatic breast cancer. The model used the clinical survival data from the German Breast Group (GBG26) trial (von Minckwitz et al, 2009). The results from the model reported an incremental cost per quality adjusted life year (QALY) of £54,137. This is well above the normal threshold of £20,000 to £30,000 per QALY accepted by NICE. The sensitivity analysis showed the results were robust. YHEC judged that the economic model itself, and the values used to populate it, were in the main acceptable and thus the result was valid to use for decision making purposes.

Economic/cost implications per 100,000 population

NICE have calculated that the cost per patient of continuing TRZ treatment is £15,080 including administration and cardiac monitoring costs. Based on their guidance to discontinue TRZ in the event of disease progression, NICE estimate that annual savings of £11,717,000, would be realised in England and Wales, equating to a cost of £21,500 per 100,000 population. This saving is based an estimate that there are currently 777 patients are being treated with TRZ for disease that has progressed outside the CNS. NICE propose that if all these patients currently being treated with TRZ were to discontinue TRZ, a significant cost saving would be made, although this would vary annually as disease progression will differ from patient to patient.

Discussion points/Issues for consideration

- The Tripathy et al extension study needs to be interpreted with caution. It was primarily a safety analysis that had limited efficacy analysis i.e. it did not require formal cardiac evaluation or tumour assessment. Furthermore, the extent of the therapeutic contribution of TRZ and optimal duration of treatment cannot be ascertained from this extension study, since a wide variety of agents were used.

- Results of the Von Minckwitz et al study found a significant improvement in overall response and time to progression with the combined therapy compared to capecitabine alone. However the study had various limitations; it was underpowered, there may have been potential for bias in the assessment of response rates by the unblinded investigator, and patients in the capecitabine group may have had an on-going exposure to TRZ because of the drugs long half-life and the trial did not show that the difference in progression-free survival resulted in a significant impact on overall survival (20.4 months vs 25.5 months).

- In the Bartsch et al 2006 study, the authors comment a clinical benefit rate of nearly 60% demonstrates that some patients benefit from treatment continuation without excess toxicity. However this study is limited by the very small patient numbers and the lack of control arm to for comparisons means that the findings need to be interpreted with caution.

- Several retrospective case series in women with MBC have shown promising results for continuing TRZ alone or with other chemotherapy agents (appendix 1). However these data need to be interpreted with extreme caution because of selection bias whereby patients with rapidly progressing disease after initial TRZ therapy are likely to have been excluded from any analysis.

- Due to the lack of sufficient clinical data, the optimal schedule, dose and duration of TRZ treatment still remains unknown and its use beyond disease progression remains controversial. The long-term tolerability of TRZ and preclinical evidence of efficacy account for its widespread use among oncologists. However, based on the lack of evidence of its cost-effectiveness, NICE did not recommend its use beyond disease progression outside the central nervous system in their clinical guidelines for advanced breast cancer. They have also highlighted this advice in their cost saving guidance.

The document reflects the views of LCNDG and may not reflect those of the reviewers.

Please direct any comments to Sheetal Ladva, London & South East Medicines Information Service, Guy’s Hospital, Great Maze Pond, London SE1 9RT
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Continued use of trastuzumab following disease progression in metastatic breast cancer

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2. Pietras RJ, Pegram MD, Finn RS et al. Remission of human breast cancer xenografts on therapy with humanised monoclonal antibody to HER-2 receptor and DNA reactive drugs. Oncogene 1998; 17: 2235-2249


10. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. NEJM 2001; 344: 783-792


17. Montemurro F, Donadio M, Clavarezzza M et al. Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. The Oncologist 2006; 11: 318-324


29. NICE. Cost saving guidance 2009 http://www.nice.org.uk/usingguidance/benefitsofimplementation/costsavingguidance.jsp
Appendix 1: Retrospective case series and abstract data assessing the efficacy of continuing TRZ beyond disease progression; 1st, 2nd and 3rd lines (adapted from NICE evidence review)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Interventions</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fountzilas et al</td>
<td>N=80</td>
<td>Women with HER2+ve MBC previously treated with TRZ and chemotherapy</td>
<td>TRZ loading dose: 4mg/kg &lt;br&gt; TRZ maintenance dose: 2mg/kg three weekly.</td>
<td>1st line (n=80) = 40 &lt;br&gt; 2nd line (n=80)= 23.7 &lt;br&gt; 3rd line (n=49) = 14</td>
<td>1st line = NR &lt;br&gt; 2nd line = 5.2 &lt;br&gt; 3rd line = 3.5</td>
<td>NR</td>
</tr>
<tr>
<td>Gelmon et al</td>
<td>N=105,</td>
<td>Women with HER2+ve MBC previously treated with more than two TRZ-containing regimens</td>
<td>NR</td>
<td>1st line (n=77) = 39 &lt;br&gt; 2nd line (n=85) = 32 &lt;br&gt; 3rd line = NR</td>
<td>1st line = 5.9 &lt;br&gt; 2nd line = 6.5 &lt;br&gt; 3rd line = NR</td>
<td>29</td>
</tr>
<tr>
<td>Garcia-Saenz et al</td>
<td>N=58</td>
<td>Women with MBC previously treated with at least one TRZ-containing regimen</td>
<td>TRZ loading dose: 4mg/kg &lt;br&gt; TRZ maintenance dose: 2mg/kg weekly.</td>
<td>1st line (n=23) = 39.6 &lt;br&gt; 2nd line (n=31) = 25.8 &lt;br&gt; 3rd line (n = 8) = 12.5</td>
<td>1st line = 6 &lt;br&gt; 2nd line = 3 &lt;br&gt; 3rd line = 2</td>
<td>NR</td>
</tr>
<tr>
<td>Montemurro et al</td>
<td>N = 184</td>
<td>Women with HER2+ve MBC previously treated with at least one TRZ-containing regimen</td>
<td>NR</td>
<td>1st line (n=102) = 55.4 &lt;br&gt; 2nd line (n=40) = 17.5 &lt;br&gt; 3rd line = NR</td>
<td>1st line = 9 &lt;br&gt; 2nd line = 6.3 &lt;br&gt; 3rd line = NR</td>
<td>30.1</td>
</tr>
<tr>
<td>Stemmler et al</td>
<td>N = 136</td>
<td>Women with HER2+ve MBC</td>
<td>TRZ loading dose: 4mg/kg &lt;br&gt; TRZ maintenance dose: 2mg/kg weekly.</td>
<td>1st line (n=77) = 56.6 &lt;br&gt; 2nd line (n=23) = 39.1</td>
<td>1st line = 7.4 &lt;br&gt; 2nd line = NR</td>
<td>NR</td>
</tr>
<tr>
<td>Extra et al (abstract data)</td>
<td>N=177</td>
<td>Women with HER2+ve MBC treated with hormonal therapy or chemotherapy</td>
<td>Group A (N=107): once weekly TRZ with loading dose of 4mg/kg – no further dose details available Group B (n=70): Discontinued TRZ</td>
<td>NR</td>
<td>Group A: 10.2 &lt;br&gt; Group B: 7.1</td>
<td>Group A: not yet reached at 27.8 &lt;br&gt; Group B: 16.8</td>
</tr>
<tr>
<td>Metro et al (abstract data)</td>
<td>N=69</td>
<td>Women with HER2+ve MBC, treated with ≥ 2 TRZ-based therapies (either TRZ alone or in combination with chemo- and/or endocrine therapy).</td>
<td>NR</td>
<td>1st line (n=77) = 27.5</td>
<td>1st line= 6.5</td>
<td>NR</td>
</tr>
<tr>
<td>Del Bianco et al (abstract data)</td>
<td>N=12</td>
<td>Women with HER2+ve MBC, median 2 lines of TRZ-based therapies (either TRZ alone or in combination with chemo- and/or endocrine therapy).</td>
<td>NR</td>
<td>1st line (n=8) = 50 &lt;br&gt; 2nd line (n=8) = 62.5 &lt;br&gt; 3rd line (N=8) - 50</td>
<td>1st line = 8 &lt;br&gt; 2nd line = 9 &lt;br&gt; 3rd line = NR</td>
<td>33.5</td>
</tr>
<tr>
<td>Tripathy et al; registHER (most recent analysis; abstract data)</td>
<td>N=1023</td>
<td>Women with HER2+ve MBC 879 treated with 1st line TRZ 539 treated with 2nd line TRZ 347 treated with 3rd or later line TRZ.</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Inclusion criteria</td>
<td>Interventions</td>
<td>ORR (%)</td>
<td>Median TTP (months)</td>
<td>Median OS (months)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------</td>
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<td>--------------------</td>
</tr>
<tr>
<td>Fabi et al</td>
<td>N=59</td>
<td>Women (and 2 men) with HER2 +ve MBC, treated with TRZ-based therapies (either TRZ alone or in combination with chemo- and/or endocrine therapy).</td>
<td>TRZ loading dose: 8mg or 4mg/kg TRZ maintenance dose: 2mg/kg weekly or 6mg/kg every three weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median age: 51 years Follow up: NR</td>
<td></td>
<td>1st line (n =37) = 27% 2nd line (n = 16) = NR 3rd line (N=9) =NR</td>
<td></td>
<td>1st line = 6.7 2nd line = 4.0 3rd line = 4.5</td>
<td>37</td>
</tr>
<tr>
<td>Tokajuk et al</td>
<td>N=27</td>
<td>Women with HER2 +ve MBC, median 2 lines of TRZ-based therapies</td>
<td>NR</td>
<td></td>
<td>1st line (n=14) = 50 2nd-5th line (n = 6) = 28.5</td>
<td>1st line = 5.1</td>
</tr>
<tr>
<td></td>
<td>Median age: 52 years Follow up: NR</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Appendix 2: Phase II studies assessing the efficacy of continuing TRZ and capecitabine beyond disease progression; 1st, 2nd and 3rd lines

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Interventions</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamamoto et al</td>
<td>N=56</td>
<td>Women with HER+ve MBC previously treated with other agents except TRZ</td>
<td>TRZ loading dose: 4mg/kg TRZ maintenance dose: 2mg/kg weekly or 6mg/kg every three weeks Capecitabine dose 1,657mg/m2 twice daily on days 1-21 every 4 weeks.</td>
<td>1st or 2nd line: 41.7</td>
<td>1st or 2nd line: 4.3</td>
<td>1st or 2nd line: 16</td>
<td>Grade 3 toxicities: Hand-foot syndrom e (n=1); diarrhoe a (n=1); nausea (n=3), stomatitis (n=1)</td>
</tr>
<tr>
<td>Bartsch et al</td>
<td>N=40</td>
<td>Women with HER+ve MBC previously treated with other agents and at least one line of TRZ therapy</td>
<td>TRZ loading dose: 8mg/kg TRZ maintenance dose: 6mg/kg every three weeks Capecitabine dose 1,250mg/m2 twice daily on days 1-14 every 3 weeks.</td>
<td>1st line (n=21): 19 2nd-4th line (n=19): 21.1</td>
<td>1st line: 7 months 2nd-4th line: 8 months</td>
<td>24</td>
<td>Grade 3 toxicities: Hand-foot syndrom e (n=6); diarrhoe a (n=2);</td>
</tr>
</tbody>
</table>
### Appendix 3: Phase II study assessing the efficacy of continuing TRZ and vinorelbine beyond disease progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Interventions</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chollet et al (abstract data)</td>
<td>N=17</td>
<td>Women with HER2 +ve MBC previously treated with other agents including TRZ</td>
<td>Initial TRZ dose of 4mg/kg then weekly at 2mg/kg or three weekly at 6mg/kg. Vinorelbine dose 30mg/m2 on days 1-8 every 3 weeks.</td>
<td>29</td>
<td>NR</td>
<td>NR</td>
<td>Grade 3/4 toxicities: neutropenia (n=4)</td>
</tr>
</tbody>
</table>