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Original article

Efficacy of Late line Pertuzumab with Trastuzumab and Chemotherapy in HER2-positive metastatic breast cancer: an Australian case series

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Efficacy of late line pertuzumab

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Abstract

Background

Pertuzumab, when combined with trastuzumab and chemotherapy, is a highly active human epidermal growth factor receptor 2 (HER2) targeting agent in the neoadjuvant, adjuvant and first line metastatic HER2-positive breast cancer setting. The efficacy of late line (after first line) pertuzumab in combination with trastuzumab and chemotherapy is unknown.

Aims

To establish pertuzumab efficacy by performing an audit of patients who received pertuzumab after first line HER2 directed therapy. We sought to establish whether efficacy differed by clinicopathological factors.

Methods

The primary end point was progression-free survival (PFS) and the secondary endpoint, overall survival (OS). Clinico-pathological factors, PFS and OS data were collated and clinicopathological factors associated with PFS were evaluated using Cox regression models.

Results

Fourteen women were identified. Six (43%) had hormone receptor (HR) negative and eight (57%) had HR-positive, metastatic HER2+ breast cancer. Median follow up was 22.8 months, median prior lines of therapy were 5 (range 1-9). Median time from diagnosis of metastatic disease to receiving pertuzumab was 4.5 years (range 4.2-5.8). All patients received initial chemotherapy with pertuzumab and trastuzumab (taxane-based 71%). Median PFS was 9 months (95% confidence interval (CI): 7-not estimable (NE)) and median OS was not reached (95% CI: 16 months-NE). Univariable analysis demonstrated that HR-negative patients had a significantly longer PFS than HR positive patients (hazard ratio 0.11, 95% CI 0.01-0.88, $P=0.04$).

Conclusion

This small cases series reports a favourable PFS and OS for pertuzumab with trastuzumab and chemotherapy in the later line metastatic setting. This finding warrants further study.

Key words:

HER2 positive

Metastatic breast cancer

Pertuzumab

Trastuzumab

Late line HER2 targeted therapy

Introduction

In 2019 breast cancer is expected to be the most common malignancy diagnosed in Australia ¹. Approximately 18-20% of these tumours will over-express human epidermal growth factor receptor 2 (HER2) ^{2 3} and thus be eligible for Pharmaceutical Benefits Scheme (PBS) funded HER2-targeted therapy in the course of their systemic treatment in Australia.

Trastuzumab, a recombinant humanised monoclonal antibody that inhibits ligand independent HER2 and HER3 signalling ⁴ has been established as the cornerstone of treatment of early and advanced HER2 positive breast cancer for over a decade. Recently, the phase III CLEOPATRA clinical trial has further advanced the paradigm for first line treatment of HER2-positive metastatic breast cancer. The addition of the monoclonal antibody pertuzumab to trastuzumab and docetaxel chemotherapy saw a remarkable improvement in overall survival (OS) (median 56.5 versus 40.8 months; hazard ratio 0.68; 95% CI: 0.56-0.75) and progression-free survival (median 18.7 versus 12.4 months; hazard ratio 0.68; 95% CI: 0.58-0.8) ⁵ when compared with placebo. Pertuzumab prevents ligand induced HER2/HER3 dimerization of the HER2 receptor, in a manner complementary to trastuzumab ⁶. Pertuzumab has also been analysed in combination with trastuzumab and vinorelbine ⁷, trastuzumab-emtansine ⁸, trastuzumab and paclitaxel ⁹ and trastuzumab and capecitabine ¹⁰ in first and second line therapy for metastatic HER2-positive disease.

Pertuzumab has also been studied extensively in the management of HER2 positive early breast cancer with trastuzumab and chemotherapy. Impressive pathological complete response (pCR) rates after neoadjuvant pertuzumab ^{11 12 13 14 15} and improved rates of disease-free survival after adjuvant pertuzumab ¹⁶ have confirmed its integral role. These neoadjuvant and adjuvant studies also highlight the excellent survival rates associated with early HER2-positive breast cancer. The APHINITY trial reported a 3-year invasive disease-free survival (iDFS) of 92.3% in the arm receiving adjuvant pertuzumab compared with 93.2% in the placebo arm ¹⁶ and the NeoSPHERE study reported a five year event-free survival (EFS) of 86% (95% CI: 77-91%) after exposure to just 12 weeks of neoadjuvant pertuzumab, trastuzumab and chemotherapy ¹¹. Despite these advances in both early and advanced disease, HER2 positive metastatic disease remains incurable.

The main objective of this study was to investigate if pertuzumab (with trastuzumab and chemotherapy) had demonstrable efficacy beyond first line therapy for metastatic HER2-positive disease. This report describes a retrospective case series on the Australian experience in this context.

Methods

Patients

Patients were from New South Wales and Victoria and had to have HER2-positive metastatic breast cancer defined by *in situ* hybridisation (ISH) with progression on prior trastuzumab-based therapy. Pertuzumab was administered with the standard loading (840 mg) and then maintenance (420 mg) doses on day one of each 21-day cycle. Pertuzumab was administered in combination with trastuzumab and chemotherapy at per investigator discretion. Treatment was provided until disease progression, or unacceptable toxicity. The number of chemotherapy cycles provided was also as per investigator's discretion. In the absence of disease progression or unacceptable toxicity, pertuzumab and trastuzumab were continued even if chemotherapy was ceased. Seventeen patients were identified who had received later line pertuzumab and had treatment between 2014 and 2018. Case report data including clinical and pathological information on 14 of 17 (82%) were available for this analysis.

Statistical Analysis

The primary endpoint for the study was PFS, defined as the time of pertuzumab commencement to disease progression, or death from any cause, whichever occurred first. The secondary endpoint was OS, defined as the time from pertuzumab commencement to death of any cause.

Cohort survival estimates for PFS and OS were obtained using the Kaplan-Meier method. For exploratory survival analyses of patient subgroups, we performed univariable Cox proportional hazards regression models. Kaplan-Meier survival curves were generated for visualisation with comparisons made by log-rank test. Given the limited patient numbers and events, multivariable Cox analysis was not performed. Subgroups were defined using arbitrary cut-off values that were deemed clinically relevant or approximating the median. Variables and cut off values were: age at commencement pertuzumab [≥ 60 years vs < 60 years]; HR status [negative vs positive]; de novo metastatic disease [yes vs no]; number of prior lines of therapy in the advanced setting [≥ 5 vs < 5]; time from diagnosis of metastatic disease to pertuzumab commencement [≥ 5 years vs < 5 years]. Patients who had recurrent metastatic disease, were further sub-grouped by recurrence-free interval (≥ 5 years vs < 5 years). These results are exploratory given the small number of patients and events. Statistical analyses were performed in R software version 3.5.1 and a two-sided p value of less than 0.05 was deemed significant.

Results

Patient characteristics

Demographics for the 14 women included in this analysis can be seen in **Table 1**. 57% (8/14) had HR-positive disease, and 43% (6/14) had HR-negative disease. 50% (7/14) of women had prior early stage disease and 50% (7/14) had de novo metastatic disease. Of those with early stage disease, five had prior HER2-positive disease and had received adjuvant trastuzumab (two had unknown HER2 status at diagnosis). The median recurrence-free interval for those with recurrent metastatic disease was 3.7 years (range 0.7-13.3 years).

Prior to treatment with late line pertuzumab, patients had received a median of 5 (range 1-9) lines of prior chemotherapy and HER2 targeted therapy. All 14 women had visceral metastatic disease at the time of pertuzumab commencement. The median time from diagnosis of metastatic disease to pertuzumab commencement was 4.5 years (range: 4.2-5.8 years). At the time of this analysis, four women (4/14=29%) remained on pertuzumab therapy (**Figure 1**).

After a median follow-up of 22.8 months (95% CI 14- NE), there were nine PFS events, and four deaths. There were no deaths attributable to pertuzumab therapy and no patients stopped pertuzumab due to toxicity. Where reported, observed toxicities were similar to those noted in the landmark clinical trials, namely diarrhoea, fatigue and rash.

Pertuzumab efficacy

The median PFS for the whole cohort was 9 months (95% CI: 7-NE). The 6-month PFS estimate was 71% (95% CI: 51-100), and the 12-month PFS estimate was 29% (95% CI: 11-72). There were three patients that remained on therapy after more than 12 months without disease progression, all of whom had de novo metastatic disease and were HR-negative. With only 4 deaths, median OS was not reached (95% CI 16-NE). The 12-month OS estimate was 73% (95% CI: 51-100), and the 18-month OS estimate was 61% (95% CI: 37-100).

Table 2 demonstrates the associations with PFS by subgroup in univariable analyses. Patients with HR-negative disease had significantly longer PFS compared with patients with HR-positive disease (median

not reached for HR-negative disease vs 7 months for HR-positive disease; Hazard ratio 0.11, 95% CI 0.01-0.88, $P=0.04$) (**Figure 2**). All other subgroup analyses did not demonstrate statistical significance, although numerically longer PFS values were particularly noted for patients with de novo metastatic disease.

Discussion

Over the past two decades, the treatment of HER2-positive metastatic breast has enjoyed much success. Multiple active agents have become available and survival has improved significantly. Despite this, challenges remain. Whilst early-stage disease is now associated with excellent survival, many patients present with Stage 4 de novo metastatic disease and are considered incurable. The landmark CLEOPATRA study found that OS was significantly prolonged relative to PFS¹⁷ which suggested that early addition of pertuzumab altered the natural history of this disease. Given this, it is of interest to determine if pertuzumab can alter disease biology and hence impact on survival in the late line setting, especially amongst women who didn't receive the agent first line. Supporting this hypothesis, the PHEREXA study evaluated the addition of pertuzumab to capecitabine and trastuzumab after first line trastuzumab-based treatment failure and observed a PFS improvement from 9 to 11.1 months (stratified hazard ratio 0.82; 95% CI: 0.65 - 1.02; log-rank $p = 0.0731$) and a relatively larger numerical 8 month increase in OS (28.1 vs 36.1 months; hazard ratio 0.68; 95% CI, 0.51 to 0.90) at a median follow-up of 19.5 months¹⁰. These results and clinical trial data outlined in **Table 3** of pertuzumab in the metastatic, albeit earlier line setting, highlight that our reported median PFS of 9 months in the later line setting would seem of interest for those patients to consider if they did not receive pertuzumab first line.

Our data shows that pertuzumab was an active and tolerable agent in the later line setting, after progression on multiple HER2-targeted and chemo-therapy (**Figure 1**). Although the numbers used for this case series are small, there was a statistically significant difference in PFS according to HR status, with a longer duration of response observed in the HR-negative patients (**Figure 2**). This was also seen in the first line setting as CLEOPATRA reported a numerically superior hazard ratio for OS and PFS in the HR-negative compared to the HR-positive subgroup but importantly, hormonal therapy was not allowed as per protocol in this study⁵.

Clinical benefit of pertuzumab has been noted in trastuzumab-resistant disease previously. In a study of 11 patients the pertuzumab and trastuzumab combination (without chemotherapy) was considered safe with a median time to progression of six weeks (range: 3-54 weeks)¹⁸. A single arm, open label study of 66 patients reported a median PFS of 5.5 months (80% CI: 18-31months)¹⁹. Both of these studies

enrolled patients who had less than three prior lines of HER2 directed therapy. A single-institution study of 19 patients reported a median PFS of 4.5 months (range: 1.5-8.7 months) with a mean 3 prior lines of therapy²⁰. These are important distinctions as the patients in our case series had a mean 5 lines of prior therapy (**Table 1**) and our case series suggests that efficacy stretches beyond third line. Our results here also compare favourably to the median PFS of 6.2 months (95% CI: 5.59-6.87) vs 3.3 months (95% CI: 2.89-4.14 months) and median OS of 22.7 months (95% CI: 19.4-27.5 months) vs 15.8 months (95% CI: 13.5-18.7 months)²¹ in the TH3RESA study of TDM-1 vs physician's choice chemotherapy and trastuzumab. Importantly, all patients in the TH3RESA study had progressed on at least two prior lines of therapy.

There are limitations to this retrospective descriptive case series. The cases are highly selected and outline the experience of a small group of women treated in large, metropolitan centres. According to current Australian PBS guidelines, in the metastatic setting, pertuzumab is only available for first line treatment and none of the patients included in this series received pertuzumab neither in this setting nor in the adjuvant setting. There is no control group, the findings are descriptive and hence exploratory in nature. Regardless, this case series is hypothesis generating.

Conclusion

The treatment of HER2-positive breast cancer has seen remarkable successes over the past decade with the introduction of effective HER2 targeted agents that confer a substantial survival advantage. Early-stage disease is now highly curable. Pertuzumab with trastuzumab and taxane-based chemotherapy is now available on the Australian PBS as treatment in the first line metastatic setting in Australia. It is also Therapeutic Goods Administration (TGA) approved by the Australian Government for neo-adjuvant treatment and is undergoing evaluation for the adjuvant treatment of high-risk early-stage disease. Despite this, the addition of pertuzumab to trastuzumab and chemotherapy has only shown convincing OS gains in the metastatic setting. This case series outlines the Australian experience of pertuzumab use in the later line setting and suggests that pertuzumab in combination with trastuzumab and chemotherapy is efficacious, well tolerated and thus warrants further investigation and consideration in those patients who didn't receive pertuzumab first line or in the adjuvant setting.

References

1. www.aihw.gov.au Canberra: Australian Institute of Health and Welfare [updated 11/12/2018; cited 17/01/2019]. Australian Government. Available from: <http://www.aihm.org.au/reports/cancer/cancer-data-in-australia/contents/rankings>.
2. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987 Jan 9;235(4785):177–82.
3. Wolff AC, Hammond MEH, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Archives of Pathology & Laboratory Medicine*. 2007 Jan 1;131(1):18–43.
4. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001 Mar 15;344(11):783–92.
5. Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015 Feb 19;372(8):724–34.
6. Capelan M, Pugliano L, de Azambuja E, Bozovic I, Saini KS, Sotiriou C, et al. Pertuzumab: new hope for patients with HER2-positive breast cancer. *Ann Oncol*. 2012 Aug 21;24(2):273–82.
7. Perez EA, López-Vega JM, Petit T, Zamagni C, Easton V, Kamber J, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res*. 2016;18(1):126.
8. Perez EA, Barrios C, Eiermann W, Toi M, Im Y-H, Conte P, et al. Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. *J Clin Oncol*. 2017 Jan 10;35(2):141–8.
9. Smyth LM, Iyengar NM, Chen MF, Popper SM, Patil S, Wasserheit-Lieblich C, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. *Breast Cancer Res Tr*. 2016 Jul 1;158(1):91–7.
10. Urruticoechea A, Rizwanullah M, Im S-A, Ruiz ACS, Láng I, Tomasello G, et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. *J Clin Oncol*. 2017 Sep 10;35(26):3030–8.
11. Gianni L, Pienkowski T, Im Y-H, Tseng L-M, Liu M-C, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or

early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol.* 2016 Jun;17(6):791–800.

12. Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero J-M, Verrill M, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol.* 2018 Mar 1;29(3):646–53.
13. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol.* 2013 May 22;24(9):2278–84.
14. Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang C-S, Thompson AM, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2018 Jan;19(1):115–26.
15. Loibl S, Jackisch C, Schneeweiss A, Schmatloch S, Aktas B, Denkert C, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. *Ann Oncol.* 2017 Mar 1;28(3):497–504.
16. Minckwitz von G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med.* 2017 Jul 13;377(2):122–31.
17. Swain SM, Kim S-B, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2013;14(6):461–71.
18. Portera CC, Walshe JM, Rosing DR, Denduluri N, Berman AW, Vatas U, et al. Cardiac Toxicity and Efficacy of Trastuzumab Combined with Pertuzumab in Patients with Trastuzumab-Insensitive Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *Clin Cancer Res.* 2008 May 1;14(9):2710–6.
19. Baselga J, Gelmon KA, Verma S, Wardley A, Conte P, Miles D, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol.* 2010 Mar 1;28(7):1138–44.
20. Dao BD, Ho H, Quintal LN. Combination pertuzumab, trastuzumab, and taxane for metastatic breast cancer after first progression: a single institution's experience. *J Oncol Pharm Pract.* 2016 Apr;22(2):261–4.
21. Krop IE, Kim S-B, González-Martín A, LoRusso PM, Ferrero J-M, Smitt M, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *The Lancet Oncol.* 2014 Jun;15(7):689–99.

Figure 1. Time from pertuzumab commencement to progression (PFS) and survival in 14 women with metastatic HER2-positive breast cancer (green bar: time on pertuzumab; purple bar: time from pertuzumab to death or censoring; thatched bars: HER2-positive and HR-positive; filled bars: HER2-positive and HR-negative; blue dot: death; blue arrow: ongoing pertuzumab therapy)

Figure 1

Figure 2. Kaplan Meier progression free survival of patients (PFS) curves according to HR status (HR-negative: hormone receptor negative; HR-positive: hormone receptor positive; HR: hazard ratio). Log rank p value is given

Figure 2

Table 1. Demographics for all patients analysed after commencement of pertuzumab (HER2: human epidermal growth factor receptor 2; HR+: hormone receptor positive; HR-: hormone receptor negative; OG: ongoing treatment at time of study reporting)

Demographics		
Age at pertuzumab commencement	55 years (median); 38-81 years (range)	
Breast cancer characteristics		
Prior early breast cancer at diagnosis (Stage 1-3)	7/14 (50%)	
Advanced disease at diagnosis (de novo metastatic Stage 4)	7/14 (50%)	
HR-/HER2-positive disease at diagnosis	6/14 (43%)	
HR+/HER2-positive disease at diagnosis	8/14 (57%)	
Disease free interval	Median 3.6 years (range (0.67-13.3 years)	
Time from diagnosis of metastatic disease to pertuzumab commencement	Median 4.5 years (range 4.24-5.82 years)	
HER2 immunohistochemistry (IHC) (n=11 as 3/14 (21%) unknown)	3+	
HER2 copy number (n=10 as 4/14 (29%) unknown)	mean 16 copies; median 14.5 copies (range 12-24)	
Systemic treatment		
Patient identifier	Lines of chemotherapy prior to pertuzumab	Agents co-administered with pertuzumab & duration (weeks)
All	5 (mean & median) 1-8 lines (range)	Trastuzumab
Pmab01	1	nab-paclitaxel (15)
Pmab02	7	nab-paclitaxel (12)
Pmab03	2	nab-paclitaxel (18)
Pmab04	3	Paclitaxel (10)
Pmab05	5	Vinorelbine (18)
Pmab06	2	Paclitaxel (3)

Pmab07	6	Carboplatin (15)
Pmab08	6	Vinorelbine (6)
Pmab09	4	Docetaxel (9)
Pmab10	8	Paclitaxel (21)
Pmab11	6	Paclitaxel (15)
Pmab12	4	nab-paclitaxel (OG)
Pmab13	8	Paclitaxel (30)
Pmab14	2	Vinorelbine (OG)

Table 2 Univariable analysis for associations with PFS by subgroup (n=14 for each subgroup except recurrence free interval where n=7)

Variable	Hazard Ratio	95% CI	p value
Age at commencement pertuzumab (≥ 60 years vs < 60 years)	0.73	0.18-3.01	0.666
Hormone receptor status: negative vs positive	0.11	0.01-0.88	0.037
De novo metastatic disease vs recurrent metastatic disease	0.4	0.1-1.65	0.206
Recurrence free interval (≥ 5 years vs < 5 years)* (primary to metastatic)	0.65	0.11-3.92	0.637
Number of prior systemic lines of therapy for advanced disease (continuous)	1.13	0.87-1.45	0.363
Number of prior systemic lines of therapy for advanced disease (≥ 5 vs < 5 lines)	2.14	0.53-8.63	0.283
Time from diagnosis of metastatic disease to pertuzumab (≥ 5 years vs < 5 years)	1.4	0.37-5.28	0.619

Table 3 Comparative studies analysing use of pertuzumab after progression of trastuzumab based therapy for advanced HER2 positive breast cancer. (HR: hazard ratio; CI: confidence interval)

Trastuzumab and pertuzumab clinical trials name and patient numbers	Line of therapy	Investigational agent/s	Median PFS (months)	Median OS (months)
CLEOPATRA randomised phase III ⁵	1	Pertuzumab Trastuzumab Docetaxel	18.7 (pertuzumab) vs 12.4 (placebo) HR 0.68 (95% CI 0.58-0.80) p<0.001	56 (pertuzumab) vs 40.8 (placebo) HR 0.68 (95% CI 0.56-0.84) p< 0.001
VELVET cohort 1 ⁷ phase II N=106	First line	vinorelbine pertuzumab trastuzumab	14.3 (95% CI: 11.2-17.5)	NA
PHEREXA ¹⁰ Randomised phase III Arm A: n=224 Arm B: n=228	Second line	Arm A: trastuzumab & capecitabine Arm B: trastuzumab & capecitabine & pertuzumab	Arm A: 9 Arm B: 11 HR 0.82 (95%CI 0.65-1.02)	Arm A: 28.1 Arm B: 36.1 HR 0.68 (95% CI 0.51-0.9) (favouring Arm B)
Smyth LM ⁹ Phase II	First or second line	paclitaxel & trastuzumab &	All: 21.4 1 st line only: 25.7	All: 44 1 st line only: 44

n=69		pertuzumab &	2 nd line only: 16.9	2 nd line only: 37.5
Baselga J¹⁹	< 3 prior	Trastuzumab &	5.5	NA
Phase II	lines	pertuzumab	(80% CI:18-31)	
n=66

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