The use of trastuzumab in New Zealand women with breast cancer

Running title: The use of trastuzumab in New Zealand

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Abstract.

Aim

Trastuzumab was first funded in New Zealand for use in HER2+ve stage I-III breast cancer in 2007. This observational study aims to ascertain the patterns of use of trastuzumab in women with invasive HER2+ve breast cancer, and assess the effectiveness of adjuvant trastuzumab in women with stage I-III HER2+ve breast cancer.

Methods

The Waikato and Auckland Breast Cancer Registries have clinical details of 12372 women diagnosed with invasive breast cancer between June 2000 and May 2013. The proportion of women with HER2+ve breast cancer treated with trastuzumab was examined by age, ethnicity, stage and year of diagnosis. Differences in outcomes including the development of metastases and death were assessed for women with stage I-III HER2+ve breast cancer treated with both chemotherapy and trastuzumab, compared to women treated with chemotherapy alone.

Results

Among the 1587 HER2+ve breast cancer patients, 888 (56.0%) women received trastuzumab. The probability of having trastuzumab decreased with higher age and co-morbidity score and increased with year of diagnosis, tumour size and cancer stage. Māori and Pacific women were less likely to be treated with trastuzumab. After adjustment for potential confounding factors the treatment with trastuzumab improved breast cancer-specific mortality (adjusted hazard ratio 0.57, 95% CI: 0.35-0.93).

Conclusion

Overall this observational study has shown a substantial improvement in survival for women with HER2+ve stage I-III breast cancer, and much of this improvement can be attributed to the

introduction of trastuzumab. Changes in chemotherapy also appear to have led to improved outcomes.

Key words: Breast Neoplasms, Epidermal Growth Factor, Mortality, Survival, Trastuzumab

Introduction

In New Zealand, the presence of the bio-marker human epidermal growth factor receptor 2 (HER2) in women with breast cancer has been commonly ascertained since 1998, and routinely since 2006. It has been found to be present in approximately 15-20% of breast cancers,(1, 2) presenting more commonly in breast cancers of younger women.(3) It is known that women who have HER2 positive (+ve) breast cancer have a poorer prognosis compared to women with HER2 negative (–ve) disease.(1)

Trastuzumab (Herceptin®) is a targeted therapy for patients with HER2+ve breast cancer. Randomised clinical trials have shown that trastuzumab reduced breast cancer recurrence and mortality in women with early stage HER2+ve breast cancer after surgery.(4-8) A study combining data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 clinical trials with a median follow-up time of 8 years, demonstrated a hazard ratio of 0.63 (95% CI: 0.54-0.73) in breast cancer-specific mortality and a hazard ratio of 0.60 (95% CI: 0.53-0.68) in all-cause mortality after adding 12 months trastuzumab to chemotherapy for HER2+ve stage I-III breast cancer.(4)

Trastuzumab was first licensed by the US FDA (Federal Drug Regulatory Authority) in 1998 for metastatic HER2+ve breast cancer and was funded for this indication in New Zealand since 2002 by PHARMAC, the national pharmaceutical funding agency.(9, 10) In 2006, 12 months of adjuvant therapy was licensed by the FDA for the treatment of stage I-III HER2+ve breast cancer.(11) In July 2007 PHARMAC also approved trastuzumab for stage I-III breast cancer but only funded 9 weeks of treatment.(10) From 1 July 2010, trastuzumab was funded for early stage disease for treatment of up to 12 months.(12) Trastuzumab for stage I-III HER2+ve breast cancer is only funded in conjunction with chemotherapy, either concomitantly with taxane chemotherapy or sequentially after chemotherapy.

Stage I breast cancer generally has an excellent prognosis. As the early adjuvant trastuzumab breast trials included only patients with stage I HER2+ve cancers more than 1cm in size, guidelines for adjuvant treatment with trastuzumab may not apply to stage 1 HER2+ve tumours smaller than 1cm.(6, 13) Stage II and III HER2+ve breast cancers are associated with a progressively poorer prognosis and greater risk of recurrence and these women should be offered trastuzumab as part of their adjuvant therapy (4, 5), as should women with metastatic HER2+ve breast cancers.

This study aims to 1) ascertain the patterns of use of trastuzumab in women with invasive HER2+ve breast cancer in New Zealand, 2) compare clinical outcomes between women with stage I-III HER2+ve breast cancer who received adjuvant trastuzumab versus those who did not.

Methods

Data source

The combined Waikato and Auckland Breast Cancer Registers have clinical details of 12372 women diagnosed with invasive breast cancer between June 2000 and May 2013. Men diagnosed with breast cancer are included in the registers but were not included in this study. The collected information in the combined registers includes (but is not limited to): 1) patient characteristics: age and ethnicity; 2) tumour biology: diagnosis date, cancer stage, grade, tumour size, oestrogen receptor (ER), progesterone receptor (PR) and HER2 status; 3) treatment: chemotherapy, trastuzumab, endocrine therapy, surgery and radiotherapy; and 4) cancer progression: metastases, date of death and cause of death. The presence of comorbidities was ascertained by data linkage to the National Minimum Dataset (NMDS) that records clinical data for inpatients and day patients.

Mortality information including date of death and cause of death were from both the combined registers and New Zealand national mortality collection. The mortality collection is maintained by the Ministry of Health and records all deaths in New Zealand. Ethical approval for the study was granted through the Northern A Health and Disability Ethics Committee, reference: 12/NTA/42/AM01.

Pattern of trastuzumab use in HER2+ve invasive breast cancers

Of this group, 9504 female breast cancers (76.8%) were tested for HER2 receptor status, and 1587 (16.7%) invasive breast cancers were HER2+ve (FISH amplified or IHC 3+). The usage of trastuzumab for HER2+ve breast cancer was examined by age, year of diagnosis, ethnicity and cancer stage at diagnosis. The differences between subgroups were explored by chi-square test and logistic regression.

Outcomes in women with stage I-III HER2+ve breast cancer treated with trastuzumab

Trastuzumab is only funded in conjunction with chemotherapy for stage I-III HER2+ve breast disease in New Zealand. The benefit of trastuzumab for women with HER2+ve stage I-III breast cancer was explored by comparing the clinical outcomes of women treated with chemotherapy and trastuzumab (adjuvant and/or neo-adjuvant trastuzumab) and women treated with chemotherapy but without trastuzumab. The studied cohort included women diagnosed with stage I-III HER2+ve breast cancer at the age of less than 75 years, with a tumour size equal to or larger than 1cm.(6, 13) Patients who had inflammatory breast cancer, or developed metastatic disease or local recurrence within 3 months of diagnosis were excluded. Eligible women who received chemotherapy without trastuzumab for their primary breast cancer within 12 months of cancer

diagnosis were considered to be the control group (chemotherapy only group: 275 women), and women who started chemotherapy and trastuzumab for their primary breast cancer within 12 months of cancer diagnosis were considered to be the intervention group (trastuzumab treated group: 604 women). The characteristics of women in these two groups were studied.

Kaplan-Meier method and Cox proportional hazards model were used to examine the breast cancer-specific survival, all-cause survival and metastasis-free survival between women in the chemotherapy only group and women in the trastuzumab treated group. For all-cause survival analyses, patients without mortality information were considered to be censored on the last updated date for Mortality Collection which was 31 December 2014. For cancer-specific analyses, deaths from other causes were censored on the date of death. The censor date for metastasis-free survival was the last follow-up date for an individual patient in the Waikato and Auckland Breast Cancer Registers.

In the Cox proportional hazards model, hazard ratios between the chemotherapy only group and the trastuzumab treated group were estimated after adjustment for age, ethnicity, comorbidity (we applied a C3 score retrospectively to breast cancer patients (14)), stage, grade, tumour size, ER/PR status (ER and PR negative, ER and/or PR positive), endocrine therapy, surgery type (mastectomy, breast conserving surgery, no primary surgery), radiotherapy and chemotherapy. The chemotherapy regimens were classified into four groups: 1) anthracycline and taxane based, 2) anthracycline based, 3) taxane based and 4) non-anthracycline and non-taxane based.

Outcomes in women treated with 9 weeks and 12 months of trastuzumab

Trastuzumab is expensive and not without side effects. If a shorter treatment is equivalent with regards outcomes then it will be more cost effective. New Zealand was unique in approving a 9

week course of treatment which resulted in a natural experiment. While we are underpowered to "prove" equivalence we believe it is worthwhile reporting the observational findings. Thus we explored the difference in breast cancer-specific survival between women in the intervention group who received 9 weeks (22-126 days: 175 women) of trastuzumab and women who received 12 months (316-441 days: 342 women) of trastuzumab. Five women who received trastuzumab for less than 3 weeks, 27 women who had trastuzumab for 127-315 days, and 55 women on trastuzumab for more than 442 days were not included in this analysis. The survival difference between subgroups was considered significant if the two-tailed p-value was less than 0.05. All data analyses were performed in IBM SPSS statistics 23 (New York, United States).

Results

Pattern of trastuzumab use in HER2+ve invasive breast cancers

Among the 1587 patients with HER2+ve breast cancer, 888 (56.0%) women had trastuzumab in 2000-2013 (Table 1). The probability of having trastuzumab decreased with higher age (from 68.7% for women aged <50 to 5.8% for women aged 75+ years) and co-morbidity score (from 60.7% for C3 score 0 to 30.3% for C3 score 2+), increased with tumour size (from 45.0% for tumour size <10 mm to 62.3% for tumour size 30+ mm) and cancer stage (from 46.8% for stage I to 66.6% for stage III) except stage IV (51.5%). In 2000-2006, 30.4% of women diagnosed with HER2+ve breast cancer received trastuzumab, compared to 72.3% of women with HER2+ve disease diagnosed in 2007-2013. The chi-square test showed no significant difference in the treatment with trastuzumab between Māori women (50.5%), Pacific women (49.7%) and others (57.6%). However, after adjustment for age, cancer stage, grade, year of diagnosis, tumour size and C3 score, the respective odds ratios of Māori women (184) and Pacific women (171) having

trastuzumab compared to others (1232) were 0.44 (95% CI: 0.29-0.67) and 0.31 (95% CI: 0.20-0.50).

Outcomes in women with HER2+ve stage I-III breast cancer treated with trastuzumab

Of the 1455 women with HER2+ve stage I-III breast cancer, 27 developed metastatic disease or local recurrence in less than 3 months of initial diagnosis, 2 had inflammatory breast cancer, 185 had a tumour size less than 10mm, and 103 women were 75+ years old (Figure 1). These 317 women were excluded from further analyses. A total of 275 women who received chemotherapy without trastuzumab for their primary breast cancer within 12 months of cancer diagnosis were included in the chemotherapy only group, and 604 women who received chemotherapy and trastuzumab were included in the trastuzumab treated group. The rest of women were not included either because they did not start chemotherapy for primary breast cancer in no more than 12 months of initial diagnosis (237), or because they started trastuzumab in more than 12 months of initial diagnosis (18) or the start date of trastuzumab was not available (4).

Over 90% women in the chemotherapy only group were diagnosed in 2000-2006, and 90% women in the trastuzumab treated group were diagnosed in 2007-2013 (Table 2). In the trastuzumab treated group, 559 (92.5%) women received trastuzumab in 2007-2013, and 45 (7.5%) women received trastuzumab in 2000-2006. There was no significant difference in age between the chemotherapy only group and the trastuzumab treated group. The trastuzumab treated group has a higher proportion of stage I breast cancers, a lower proportion of Māori patients, and a lower proportion of ER and PR negative cancers than the chemotherapy only group. The majority (73.5%) of women in the chemotherapy only group received anthracycline based chemotherapy while 86.3% of women in the trastuzumab treated group received both anthracycline and taxane based chemotherapy. Anthracycline based chemotherapy was more

commonly used in the early years, anthracycline and taxane based chemotherapy was more commonly used in recent years (Appendix Table 1).

The median follow-up time was 107 months for women in the chemotherapy only group and 53 months for women in the trastuzumab treated group. Breast cancer-specific survival, all-cause survival and metastases free survival in the trastuzumab treated group were all significantly better (log-rank test: p-values all less than 0.001) (Figure 2, Appendix Table 2). The unadjusted hazard ratios in breast cancer-specific mortality, all-cause mortality and metastases- (distant recurrences) in the trastuzumab treated group compared to the chemotherapy only group were 0.44, 0.48 and 0.56, respectively (Table 3). After adjustment for age, ethnicity, comorbidity score, stage, grade, tumour size, ER/PR status, endocrine therapy, surgery type, radiotherapy and chemotherapy regimens (in particular to allow for the effect of adding taxanes to the chemotherapy regimen), the hazard ratios changed to 0.58, 0.65 and 0.66, respectively. The adjusted hazard ratio of breast cancer-specific mortality for women who received anthracycline and taxane based chemotherapy was 0.60 (95% CI: 0.36-0.99) compared to women who received anthracycline based chemotherapy.

Outcomes in women treated with 9 weeks and 12 months of trastuzumab

Women (175) who received 9 weeks of trastuzumab were older and diagnosed in earlier years than women (342) who received 12 months of trastuzumab (Appendix Table 3). There were no significant differences in age, ethnicity, cancer stage, ER/PR status or chemotherapy regimens between these two groups. 54.9% of women in the 9 weeks treatment group were diagnosed in 2006-2009 and 64.3% of women in the 12 months treatment group were diagnosed in 2010-2013. The Kaplan-Meier analysis showed no significant difference in breast cancer-specific survival between women receiving 9 weeks of trastuzumab and women receiving 12 months of trastuzumab (Appendix Figure 1, log-rank test p-value: 0.246). The adjusted hazard ratios in

breast cancer-specific mortality and all-cause mortality in women receiving 12 months of trastuzumab were 0.62 (95% CI: 0.29-1.30, p-value=0.202) and 0.52 (95% CI: 0.25-1.07, p-value=0.074) compared to women receiving 9 weeks of trastuzumab, respectively.

Discussion

Since funding of adjuvant trastuzumab in conjunction with chemotherapy was approved for HER2+ve stage I-III breast cancer in New Zealand, it has become widely used. Sixty nine percent of women with HER2+ve non-metastatic breast cancer were treated with trastuzumab between 2007 and 2013. The use of trastuzumab varied by age, cancer stage and ethnicity. Older women were less likely to be treated with chemotherapy and trastuzumab, while women with more advanced disease were more likely to receive adjuvant trastuzumab. Within ethnic groups, although the sample size is relatively small, Māori and Pacific women were less likely to receive neo-adjuvant/adjuvant trastuzumab and chemotherapy. Māori and Pacific women tend to be younger, have more advanced disease and are more likely to have comorbidities. After adjustment for these factors we have shown that both groups are less likely to be treated with trastuzumab than are other New Zealanders. This apparent differential use of a potentially life-saving treatment needs further research to better understand this inequity.

Our study suggests that outcomes for women with HER2+ve breast cancer have improved. Although expensive, the introduction of trastuzumab has provided a substantial benefit to women with HER2+ve early stage disease with 5-year breast cancer-specific survival improving from 75.6% to 89.5% (adjusted hazard ratio: 0.58). This is in line with the NSABP B-31 and the NCCTG N9831 clinical trials demonstrating a 0.60 hazard ratio in breast cancer-specific mortality by adding 12 months trastuzumab to chemotherapy for HER2+ve stage I-III breast cancer after a median follow-up time of 8 years.(4) We have shown that during this time there has also been a change in the chemotherapy regime for women with stage I-III breast cancer with more women

being treated with combined anthracycline and taxane based treatment. This has led to further reductions in mortality with an adjusted HR of 0.60 compared to the mortality in women treated with only anthracycline based chemotherapy.

The Finland Herceptin (FinHer) trial(15) showed a 35% relative reduction in rates of distant disease using 9 weeks of trastuzumab compared to no trastuzumab. As noted above in New Zealand only 9 weeks of trastuzumab was funded for women with non-metastatic breast cancer between 2007 and 2010. When we compared the survival between women treated with 9 weeks of trastuzumab and women treated with 12 months of trastuzumab, no significant difference was identified, with an adjusted HR of 0.62 (95% CI 0.29 – 1.30). This may be because our study was underpowered to show a difference and further research is needed to demonstrate whether there is a worthwhile benefit of 12 months treatment over 9 weeks. A 9-week course of trastuzumab is associated with a smaller risk of side effects and lower costs.(16, 17) but if this regime is significantly less effective, then the 12 month course should be preferred. The results of the SOLD trial, which has been powered to compare 9 weeks with 12 months of trastuzumab are eagerly awaited.(18)

The strength of this study is that it is based on real world data. The patients in clinical trials are highly selected and may not represent the diversity of patients who may benefit from trastuzumab. This study is based on the Waikato and Auckland population-based Breast Cancer Registers that collect good quality data on all breast cancer patients. The data have been shown to be highly complete and accurate.(19) The limitations of this study are associated with the nature of an observational study. The characteristics of patients in the chemotherapy only group and those in the trastuzumab treated group are not evenly distributed. Although we adjusted for a number of factors in the multivariate analyses, there may be still some residual confounding. However, our findings are in line with the large randomized trials.(4-8) and support the belief that the use of trastuzumab has significant benefit for women with HER2+ve breast cancer.

Conclusions

Overall this observational study has shown a substantial improvement in survival for women with HER2+ve stage I-III breast cancer, and this improvement can be attributed to the treatment of trastuzumab. Changes in chemotherapy also appear to have led to improved outcomes. Further research is needed to establish the benefit of 12 months treatment of trastuzumab over 9 weeks.

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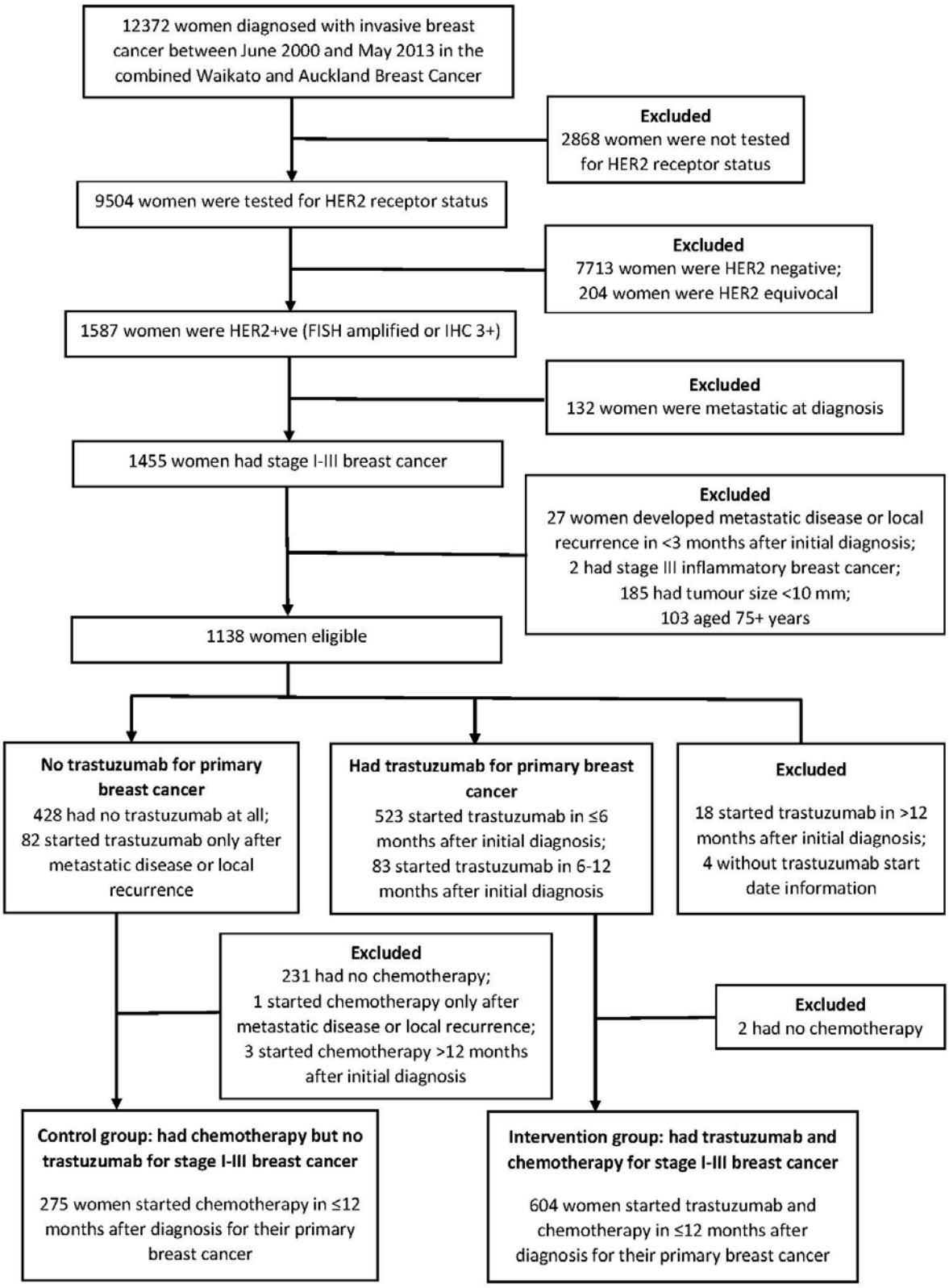
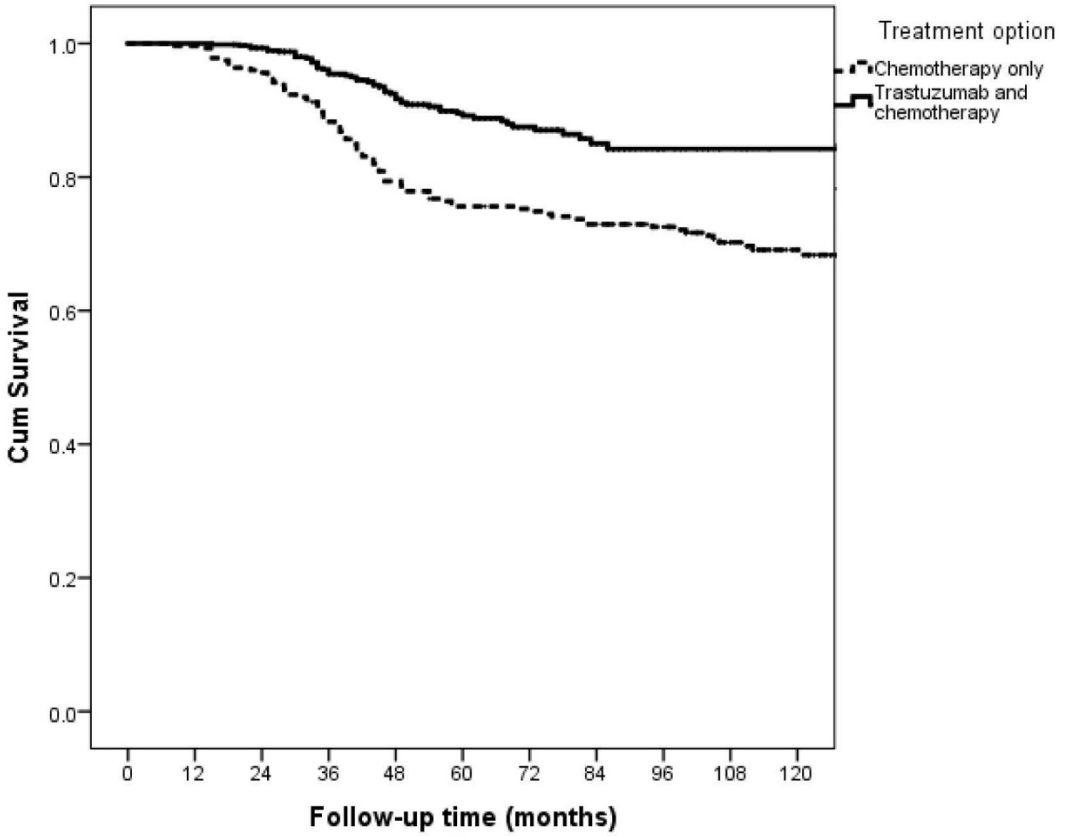


Figure 1. Patient inclusion criteria for examining the treatment effect of trastuzumab



Follow-up time (months)		0	12	24	36	48	60	72	84	96	108	120
Number of women at risk	Chemotherapy only	275	274	262	241	212	200	197	190	177	134	94
	Trastuzumab + Chemotherapy	604	602	551	440	342	251	183	112	53	28	18

Figure 2. Breast cancer-specific survival between the chemotherapy only group and the trastuzumab treated group by Kaplan-Meier method

Table 1. The treatment pattern of trastuzumab in HER2+ve breast cancers

	Total	No Trastuzumab	Had Trastuzumab		Unadjusted Odds Ratio	Adjusted Odds Ratio
Age						
<50	616	193	423	68.7%	Ref	Ref
50-59	477	189	288	60.4%	0.70 (0.54-0.89)**	0.53 (0.39-0.74)***
60-74	374	204	170	45.5%	0.38 (0.29-0.50)***	0.23 (0.16-0.34)***
75+	120	113	7	5.8%	0.03 (0.01-0.06)***	0.01 (0.01-0.03)***
Ethnicity						
Others	1232	522	710	57.6%	Ref	Ref
Māori	184	91	93	50.5%	0.75 (0.55-1.02)	0.44 (0.29-0.67)***
Pacific	171	86	85	49.7%	0.73 (0.53-1.00)	0.31 (0.20-0.50)***
Cancer stage						
I	462	246	216	46.8%	Ref	Ref
II	574	249	326	56.8%	1.49 (1.16-1.90)**	1.87 (1.28-2.72)**
III	419	140	278	66.3%	2.27 (1.73-2.98)***	3.37 (2.17-5.22)***
IV	132	64	68	51.5%	1.21 (0.82-1.78)	2.86 (1.38-5.91)**
Grade						
1	52	38	14	26.9%	Ref	Ref
2	554	285	269	48.6%	2.56 (1.36-4.83)**	3.62 (1.63-8.03)**
3	914	336	578	63.2%	4.67 (2.49-8.74)***	6.96 (3.14-15.44)***
Unknown	67	40	27	40.3%	-	-
Tumour size						
<10 mm	189	104	85	45.0%	Ref	Ref
10~30 mm	791	347	444	56.1%	1.57 (1.14-2.15)**	2.17 (1.40-3.38)***
30+ mm	517	195	322	62.3%	2.02 (1.44-2.83)***	1.91 (1.12-3.28)*
Unknown	90	53	37	41.1%	-	-
C3 score						
0	1279	503	776	60.7%	Ref	Ref
1	133	74	59	44.4%	0.52 (0.36-0.74)***	0.89 (0.55-1.44)
2+	175	122	53	30.3%	0.28 (0.20-0.40)***	0.41 (0.25-0.68)***
Year of diagnosis						
2000-06	619	431	188	30.4%	Ref	Ref
2007-13	968	268	700	72.3%	5.99 (4.80-7.47)***	15.24 (11.13-20.86)***
Total	1587	699	888	56.0%		

* p-value<0.05, ** p-value<0.01, *** p-value<0.001

Table 2. Characteristics of women in the chemotherapy only group and women in the trastuzumab treated group

	Chemotherapy only group		Trastuzumab treated group		P value (Chi-square test)	Total	
Age (years)	Mean: 49.6; Median: 50		Mean: 50.3; Median: 50				
<40	50	18.2%	88	14.6%	0.072	138	15.7%
40-49	80	29.1%	196	32.5%		276	31.4%
50-59	105	38.2%	197	32.6%		302	34.4%
60-69	36	13.1%	117	19.4%		153	17.4%
70-74	4	1.5%	6	1.0%		10	1.1%
Year of diagnosis							
2000-2003	95	34.5%	17	2.8%	<0.001	112	12.7%
2004-2006	154	56.0%	44	7.3%		198	22.5%
2007-2009	19	6.9%	220	36.4%		239	27.2%
2010-2013	7	2.5%	323	53.5%		330	37.5%
Ethnicity							
Māori	43	15.6%	61	10.1%	0.036	104	11.8%
Pacific	30	10.9%	56	9.3%		86	9.8%
Others	202	73.5%	487	80.6%		689	78.4%
Cancer stage							
Stage I	44	16.0%	141	23.3%	0.046	185	21.0%
Stage II	131	47.6%	260	43.0%		391	44.5%
Stage III	100	36.4%	203	33.6%		303	34.5%
ER/PR status							
ER and PR negative	131	47.6%	240	39.7%	0.002	371	42.2%
ER and/or PR positive	141	51.3%	364	60.3%		505	57.5%
Unknown	3	1.1%	0	0.0%		3	0.3%
Chemotherapy							
Anthracycline and taxane based	48	17.5%	521	86.3%	<0.001	569	64.7%
Anthracycline based	202	73.5%	37	6.1%		239	27.2%
Taxane based	4	1.5%	44	7.3%		48	5.5%
Non-anthracycline and non-taxane based	20	7.3%	1	0.2%		21	2.4%
Unknown	1	0.4%	1	0.2%		2	0.2%
Total	275		604			879	

Table 3. Hazard ratios in the trastuzumab treated group compared to the chemotherapy only group estimated with Cox proportional hazards model

	Unadjusted hazard ratio	P value	Adjusted hazard ratio†	P value
Breast cancer-specific mortality using end of 2014 as censor date	0.44 (0.31-0.63)	<0.001	0.58 (0.35-0.96)	0.025
All-cause mortality using end of 2014 as censor date	0.48 (0.34-0.67)	<0.001	0.65 (0.40-1.05)	0.064
Metastases using last follow-up date as censor date	0.56 (0.41-0.77)	<0.001	0.66 (0.42-1.04)	0.062

† Adjusted for age, ethnicity, C3 score, stage, grade, tumour size, ER/PR status, endocrine therapy, surgery type, radiotherapy and chemotherapy.

Appendix Table 1. Chemotherapy regimens by year of diagnosis

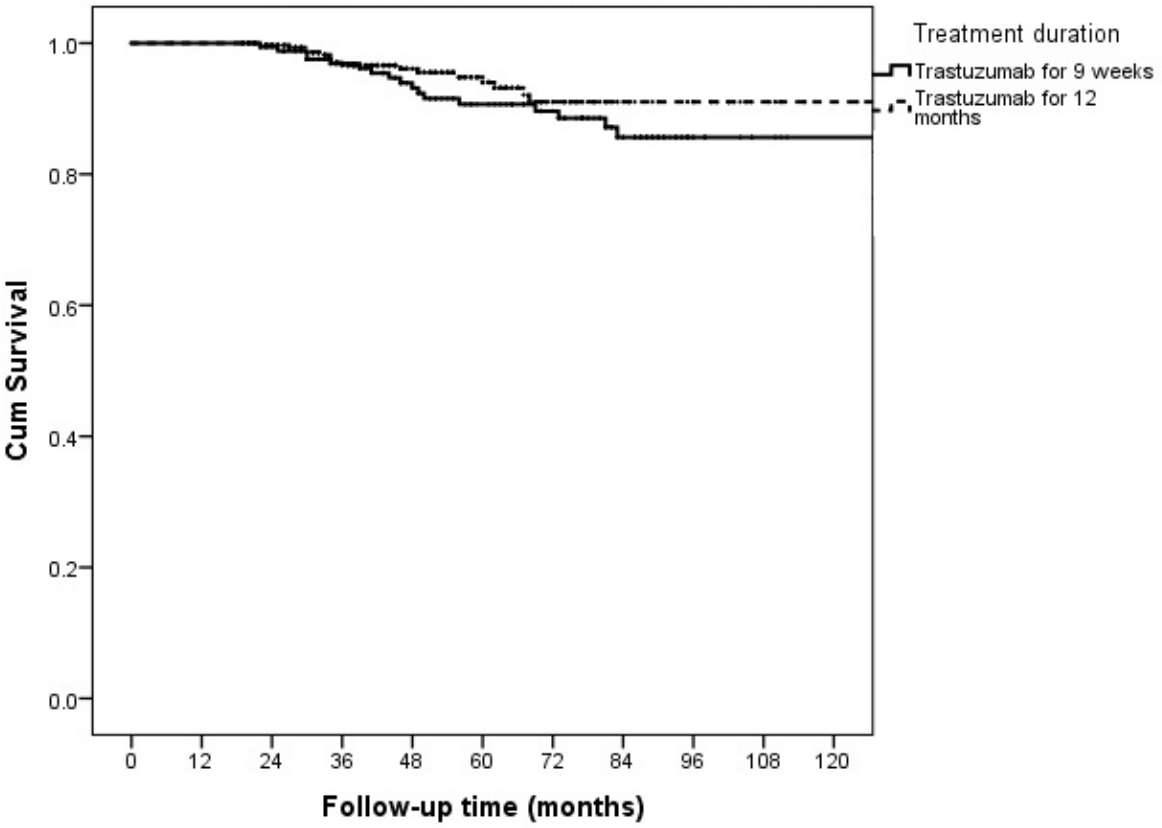
Year of diagnosis	Anthracycline and taxane based		Anthracycline based		Taxane based		Non-anthracycline and non-taxane based		Unknown	Total
2000-2003	8	7.1%	82	73.2%	6	5.4%	15	13.4%	1	112
2004-2006	58	29.3%	133	67.2%	3	1.5%	4	2.0%	0	198
2007-2009	206	86.2%	13	5.4%	17	7.1%	2	0.8%	1	239
2010-2013	297	90.0%	11	3.3%	22	6.7%	0	0.0%	0	330
Total	569	64.7%	239	27.2%	48	5.5%	21	2.4%	2	879

Appendix Table 2. 5-year clinical outcomes between the chemotherapy only group and the trastuzumab treated group

Chemotherapy only group		Trastuzumab treated group		P value (Log rank test)
Breast cancer-specific survival				
75.6%	(70.5% - 80.7%)	89.5%	(86.6% - 92.5%)	<0.001
All-cause survival				
74.6%	(69.4% - 79.8%)	88.2%	(85.0% - 91.3%)	<0.001
Metastases-free survival using last follow-up date as censor date				
72.6%	(67.3% - 77.9%)	83.0%	(79.4% - 86.7%)	<0.001

Appendix Table 3. Characteristics of women receiving 9 weeks of trastuzumab and women receiving 12 months of trastuzumab

	Women receiving 9 weeks trastuzumab		Women receiving 12 months trastuzumab		P-value (chi-square test)
Age (years)					
<40	19	10.9%	54	15.8%	0.061
40-49	47	26.9%	119	34.8%	
50-59	62	35.4%	102	29.8%	
60-69	44	25.1%	65	19.0%	
70-74	3	1.7%	2	0.6%	
Year of diagnosis					
2000-2003	0	0.0%	14	4.1%	<0.001
2004-2006	12	6.9%	19	5.6%	
2007-2009	96	54.9%	89	26.0%	
2010-2013	67	38.3%	220	64.3%	
Ethnicity					
Māori	19	10.9%	33	9.6%	0.868
Pacific	15	8.6%	27	7.9%	
Others	141	80.6%	282	82.5%	
Cancer stage					
Stage I	45	25.7%	76	22.2%	0.674
Stage II	75	42.9%	154	45.0%	
Stage III	55	31.4%	112	32.7%	
ERPR status					
ER and PR negative	73	41.7%	132	38.6%	0.493
ER and/or PR positive	102	58.3%	210	61.4%	
Chemotherapy					
Anthracycline and taxane based	147	84.0%	303	88.6%	0.068
Anthracycline based	8	4.6%	20	5.8%	
Taxane based	20	11.4%	18	5.3%	
Non-anthracycline and non-taxane	0	0.0%	1	0.3%	
Total	175		342		



Follow-up time (months)		0	12	24	36	48	60	72	84	96	108	120
Number of women at risk	9 weeks	175	174	164	142	119	99	85	55	12	4	1
	12 months	342	342	304	235	173	118	69	38	31	18	13

Appendix Figure 1. Breast cancer-specific survival between women receiving 9 weeks of trastuzumab and women receiving 12 months of trastuzumab by Kaplan-Meier method