Use and results of systemic treatments for de novo and recurrent metastatic breast cancer: a population-based cohort study

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ABSTRACT

AIMS: To describe the systemic treatments in patients with de novo metastatic breast cancer (dnMBC, initial metastatic diagnosis) and recurrent metastatic breast cancer (rMBC).

METHODS: Women diagnosed with dnMBC and rMBC in 2010–2017 were identified. Adjusted odds ratios of receiving systemic treatments were estimated by logistic regression model. Cox proportional hazards regression was used to estimate adjusted hazard ratio of breast cancer-specific mortality by treatments.

RESULTS: The adjusted odds ratio of having chemotherapy and trastuzumab (for human epidermal growth factor receptor 2 positive (HER2+) disease) for Pacific women was 0.43 and 0.13 compared to European women. Patients receiving chemotherapy had improved survival for HER2+ non-luminal and triple negative metastatic breast cancer (MBC) (hazard ratios: 0.30, 0.66). Those with endocrine therapy was associated with better survival for luminal A and luminal B HER2+ MBC (hazard ratio: 0.25, 0.26). Trastuzumab was associated with superior survival in luminal B HER2+ and HER2+ non-luminal disease (hazard ratio: 0.34, 0.40).

CONCLUSIONS: Pacific women with MBC were less likely to receive chemotherapy and trastuzumab than non-Pacific women. Chemotherapy was associated with improved survival in HER2+ non-luminal and triple negative MBC. Endocrine therapy improved survival in luminal A and luminal B HER2+ disease. Trastuzumab was associated with improved survival in luminal B HER2+ and HER2+ non-luminal disease.

Breast cancer is the second most common cause of cancer death in New Zealand.[1] The prognosis for patients diagnosed with early breast cancer is excellent, but the prognosis for patients diagnosed with metastatic breast cancer (MBC) is poor.[2] Thanks to treatment advances over the last three decades, the survival of patients with MBC has improved.[3] New medications introduced for MBC in the last three decades include taxanes, vinca-alkaloids, pyrimidine analogs, capecitabine, human epidermal growth factor receptor 2 (HER2) targeted drugs and HER2 drug conjugates, aromatase inhibitors, selective estrogen receptor downregulators (SERDs) and CDK4/6 inhibitors.[3]

Multiple lines of chemotherapy, endocrine therapies, HER2-targeted therapies and immunotherapies are now available for MBC and have proven beneficial for specific breast cancer subtypes. It is known that women who have HER2 positive (HER2+) breast cancer have a poorer prognosis compared to women with HER2 negative (HER2-) disease.[4] Trastuzumab was first licensed by the US Food and Drug Administration (FDA) in 1998 for metastatic HER2+ breast cancer and was funded for metastatic HER2+ breast cancer in New Zealand since

2002 by PHARMAC, the national pharmaceutical funding agency.[5,6]

There are differences in the features and survival between patients with de novo MBC (dnMBC, initial metastatic diagnosis) and patients who develop recurrent MBC (rMBC) following an initial non-metastatic diagnosis.[7] For instance, more luminal A and triple-negative breast cancers are found among those with dnMBC compared to rMBC.[8] The median survival is 2–3 years for dnMBC but less than two years for rMBC.[2,7,9–11]

This observational study aims to describe the use and results of systemic treatments for patients with dnMBC and rMBC in New Zealand, and to examine the equity in access to systemic treatments by ethnic group. This study is an extension of an earlier study[7] that demonstrated the characteristics and survival of dnMBC and rMBC.

Methods

We included women diagnosed with dnMBC and women who developed rMBC during the period 2010–2017. Patients were identified from the New Zealand Breast Cancer Register (NZBCR). We linked patients via their National Health Index (NHI) numbers to the New Zealand Mortality Collection (including free-text mortality for more recent deaths not yet coded in the Mortality Collection) to obtain mortality data for survival analysis. The Pharmaceutical Collection dataset (PHARMS) was also linked to identify the use of endocrine therapy, chemotherapy and trastuzumab and was cross-checked with the NZBCR treatment data. From the combined dataset, the following data were collected: (1) patient characteristics: age, ethnicity and deprivation quintile; (2) tumour information: date of primary diagnosis, date of metastatic diagnosis, sites of metastases at diagnosis and biomarkers (estrogen receptor (ER), progesterone receptor (PR) and HER2); (3) treatments: surgery, radiotherapy, endocrine therapy, chemotherapy and trastuzumab; (4) outcomes: cause of death and date of death. The register records self-identified ethnicity collected as a part of the WBCR consent process, as per the Ministry of Health's Ethnicity Data Protocols. In accord with to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual,[12] women who had presented with distant metastases at diagnosis or within four months of primary diagnosis were considered to have dnMBC, and women who had developed metastatic disease more than four months after a primary diagnosis were considered to have rMBC.

Based on the metastasis-free interval (MFI), which is the time between initial non-MBC diagnosis and diagnosis of rMBC, we stratified patients with rMBC into four groups: recurrent in <2 years, recurrent in 2–4 years, recurrent in 5–7 years and recurrent in 8+ years. First site(s) of metastases at metastatic diagnosis were classified into three groups: non-visceral (including bone and all nodal areas except ipsilateral axillary, internal mammary and supraclavicular areas), visceral (liver, lung, brain, pleura/peritoneum and others) and both (both visceral and non-visceral). The treatment option depended on subtype and the survival varies by subtype.[13–16] Breast cancer subtypes were categorised into five groups according to biomarker status, based on the modified St. Gallen Consensus recommendation, which excludes Ki67[13–16]: (1) luminal A: ER+, PR+ and HER2-; (2) luminal B HER2-: ER or PR+, HER2-; (3) luminal B HER2+: ER+ and/or PR+, HER2+; (4) HER2 non-luminal: ER-,PR-,HER2+; (5) triple negative: ER-, PR-, HER2-. In this study, HER2+ was defined as FISH amplified or 3+ staining on immunohistochemistry (IHC) according to the 2013 American Society of Clinical Oncology Guidelines.[17] As recommended in the 2001 St. Gallen Consensus, ER+ or PR+ was assessed as any degree of IHC positivity (at least 1+ intensity and 1% staining of nuclei).[18]

Characteristics of the study cohort and use of systemic treatments were compared between dnMBC and rMBC. The use of endocrine therapy was examined for ER+ or PR+ cases only, and use of trastuzumab was examined for HER2+ cases only. Adjusted odds ratios for receiving chemotherapy, endocrine therapy and trastuzumab were estimated by logistic regression model after adjustments for age, ethnicity, year of metastatic diagnosis, deprivation quintile, type of MBC (dnMBC and rMBC with different MFIs), site of metastases and biomarker subtype. Cox proportional hazards regression was used to estimate the adjusted hazard ratio of

breast cancer-specific mortality by treatments after adjustment for age, ethnicity, year of metastatic diagnosis, deprivation quintile, site of metastases and type of MBC, and after stratification by biomarker subtype. Analyses of breast-cancer-specific survival were censored at either date of death or 31 December 2018 (the last date of update of the Mortality Collection). All data analyses were performed in IBM SPSS 25 (New York, United States). Ethics approval for the study was granted through the Northern A Health and Disability Ethics Committee (reference: 19/CEN/14/AM01).

Results

We identified 2,177 patients diagnosed with MBC in 2010–2017, with 30.6% of cases (667) being de novo and 69.4% recurrent (1,510) (Table 1). Overall, 70.2% of the patients with MBC were New Zealand European and 47.7% were aged under 60 years. Among the dnMBC cases, 17.3% of them were luminal B HER2+ disease and 9.4% were triple-negative disease, compared to 9.5% and 19.6% in rMBC. Most of the rMBC cases were found within four years after the primary non-metatsatic diagnosis: 31.9% in less than two years, and 37.4% in 2–4 years.

Pacific women were the least likely to receive chemotherapy for MBC, and also the least likely to receive trastuzumab for HER2+ MBC (Table 2, Table 3), for both dnMBC and rMBC. After adjustment for age, year of metastatic diagnosis, deprivation quintile, type of metastases, site of metastases and biomarker subtype, the adjusted odds ratio of having chemotherapy was 0.43 (95% confidence interval (CI): 0.30–0.60, p-value<0.001) for Pacific women, and the adjusted odds ratio of having trastuzumab (for HER2+ disease only) was 0.13 (95% CI: 0.06–0.29, p-value<0.001) for Pacific women, compared to New Zealand European women. After adjustment, there was no significant difference in use of endocrine therapy for ER+ and/or PR+ MBC between different ethnic groups. The use of chemotherapy and endocrine therapy has been found to be decreasing over time, with adjusted odds ratios per year of 0.95 (95% CI: 0.91–0.99, p-value<0.05) and 0.90 (95% CI: 0.84–0.96, p-value<0.001).

Compared to those with dnMBC, patients with rMBC were less likely to receive endocrine therapy and trastuzumab. Patients with visceral metastases and patients with both visceral and non-visceral metastases were less likely to have endocrine therapy than patients with non-visceral metastases only (adjusted odds ratios: 0.34 (95% CI: 0.24–0.48, p-value<0.001) and 0.60 (95% CI: 0.41–0.87, p-value<0.01)). Compared to luminal A disease, patients with luminal B HER2+, HER2+ non-luminal and triple-negative disease were more likely to be treated with chemotherapy, with adjusted odds ratios of 1.67 (95% CI: 1.20–2.32, p-value<0.01), 2.50 (95% CI: 1.64–3.82, p-value<0.001) and 1.64 (95% CI: 1.22–2.20, p-value<0.001), respectively.

After adjustment for age, ethnicity, year of metastatic diagnosis, deprivation quintile, site of metastases and type of MBC, patients receiving chemotherapy showed improved survival for MBC patients with aggressive subtype disease after a median follow-up time of 16 months (adjusted hazard ratio of 0.30 (95% CI: 0.16–0.55, p-value<0.001) for HER2+ non-luminal and 0.66 (95% CI: 0.50–0.86, p-value<0.01) for triple-negative disease (Table 4). Patients with endocrine therapy had improved survival for patients with luminal A and luminal B HER2+ MBC, with an adjusted hazard ratio of 0.25 (95% CI: 0.20–0.31, p-value<0.001) and 0.26 (95% CI: 0.18–0.39, p-value<0.001). Patients with HER2+ disease treated with trastuzumab showed a substantial benefit, with adjusted hazard ratios of 0.34 (95% CI: 0.21–0.56, p-value<0.001) for luminal B HER2+ disease and 0.40 (95% CI: 0.24–0.68, p-value<0.001) for HER2+ non-luminal disease.

Discussion

This observational study found that systemic treatments are associated with differing MBC survival for different biomarker subtypes. Chemotherapy was associated with a significant survival benefit but only in HER2+ non-luminal and triple-negative disease. No significantly different outcomes in other subgroups were observed between those treated with and without chemotherapy where endocrine therapy and trastuzumab have benefits.

Table 1: Characteristics of metastatic breast cancer.

Subgroup	dnMBC		rMBC		P-value (Chi-square test)	Total	
Ethnicity							
European	435	(65.2%)	1093	(72.4%)		1528	(70.2%)
Māori	72	(10.8%)	159	(10.5%)		231	(10.6%)
Pacific	89	(13.3%)	132	(8.7%)	<0.001***	221	(10.2%)
Asian	42	(6.3%)	96	(6.4%)		138	(6.3%)
Others	29	(4.3%)	30	(2.0%)		59	(2.7%)
Age group							
<50	163	(24.4%)	378	(25.0%)		541	(24.9%)
50–59	125	(18.7%)	372	(24.6%)		497	(22.8%)
60–69	112	(16.8%)	286	(18.9%)	<0.001***	398	(18.3%)
70–79	149	(22.3%)	247	(16.4%)		396	(18.2%)
80+	118	(17.7%)	227	(15.0%)		345	(15.8%)
Deprivation quintile							
1 (least deprived)	71	(18.2%)	225	(19.0%)		296	(18.8%)
2	59	(15.1%)	201	(17.0%)		260	(16.5%)
3	78	(20.0%)	222	(18.7%)		300	(19.0%)
4	68	(17.4%)	236	(19.9%)	0.477	304	(19.3%)
5 (most deprived)	114	(29.2%)	301	(25.4%)		415	(26.3%)
Unknown	277		325			602	
Site of metastases							
Non-visceral	246	(39.1%)	551	(37.9%)		797	(38.2%)
Visceral	206	(32.8%)	528	(36.3%)		734	(35.2%)
Both	177	(28.1%)	376	(25.8%)	0.271	553	(26.5%)
Unknown	38		55			93	

Table 1: Characteristics of metastatic breast cancer (continued).

Subgroup	dnMBC		rMBC		P-value (Chi-square test)	Total	
Subtype							
Luminal A	276	(43.9%)	718	(49.3%)	<0.001***	994	(47.7%)
Luminal B HER2-	52	(8.3%)	69	(4.7%)		121	(5.8%)
Luminal B HER2+	109	(17.3%)	138	(9.5%)		247	(11.9%)
HER2+ non-Luminal	53	(8.4%)	103	(7.1%)		156	(7.5%)
Triple negative	59	(9.4%)	285	(19.6%)		344	(16.5%)
Unknown	118		197			315	
MFI							
<2 years	-		482	(31.9%)		-	
2–4 years			565	(37.4%)			
5–7 years			231	(15.3%)			
8+ years			232	(15.4%)			
Total	**667**	(30.6%)	**1,510**	(69.4%)		**2,177**	

dnMBC: de novo metastatic breast cancer; rMBC: recurrent metastatic breast cancer

* <0.05, **<0.01, ***<0.001; All p-values were estimated after excluding the unknown group.

Table 2: Treatment pattern for metastatic breast cancer.

Subgroup	Use of chemotherapy				Use of endocrine therapy (for ER+ and/or PR+ only)				Use of trastuzumab (for HER2+ only)			
	dnMBC		rMBC		dnMBC		rMBC		dnMBC		rMBC	
	n	%†	n	%	n	%	n	%	n	%	n	%
Ethnicity												
European	203	46.6%	586	53.7%	274	91.0%	594	78.3%	78	78.8%	91	57.2%
Māori	43	59.7%	90	56.6%	44	84.6%	94	81.0%	20	90.9%	25	73.5%
Pacific	39	43.8%	64	48.5%	60	87.0%	87	88.8%	15	65.2%	8	25.8%
Asian	26	61.9%	56	58.3%	23	79.3%	53	77.9%	9	81.8%	12	75.0%
Others	15	51.7%	17	56.7%	20	87.0%	15	65.2%	9	75.0%	3	75.0%
p-value	0.088		0.573		0.257		0.064		0.335		<0.001***	
Age group												
<50	125	76.7%	283	74.9%	109	90.8%	213	80.1%	61	89.7%	61	70.1%
50–59	86	68.8%	239	64.2%	75	87.2%	205	79.5%	25	86.2%	44	74.6%
60–69	56	50.0%	176	61.5%	67	88.2%	173	80.8%	27	79.4%	19	47.5%
70–79	51	34.2%	91	36.8%	100	86.2%	135	79.4%	17	63.0%	13	43.3%
80+	8	6.7%	24	10.6%	70	92.1%	117	75.0%	1	11.1%	2	7.1%
p-value	<0.001***		<0.001***		0.680		0.727		<0.001***		<0.001***	
Deprivation quintile												
1 (least deprived)	33	46.5%	133	59.1%	47	92.2%	130	79.3%	13	72.2%	19	54.3%
2	28	47.5%	116	57.7%	28	75.7%	109	76.2%	8	80.0%	14	48.3%
3	32	41.0%	129	58.1%	48	84.2%	137	83.0%	10	83.3%	25	62.5%
4	40	58.8%	132	55.9%	46	93.9%	147	83.1%	15	78.9%	16	51.6%
5 (most deprived)	53	46.5%	147	48.8%	78	86.7%	181	81.9%	22	78.6%	34	55.7%
Unknown	140	50.4%	156	48.1%	174	91.6%	139	71.6%	63	78.8%	31	64.6%
p-value	0.300		0.106		0.098		0.483		0.964		0.808	

Table 2: Treatment pattern for metastatic breast cancer (continued).

Subgroup	Use of chemotherapy				Use of endocrine therapy (for ER+ and/or PR+ only)				Use of trastuzumab (for HER2+ only)			
	dnMBC		rMBC		dnMBC		rMBC		dnMBC		rMBC	
	n	%†	n	%	n	%	n	%	n	%	n	%
Site of metastases at diagnosis												
Non-visceral	123	50.0%	291	52.8%	181	93.8%	387	87.2%	45	83.3%	39	50.0%
Visceral	109	52.7%	278	52.8%	104	83.9%	215	70.5%	49	81.7%	47	52.8%
Both	89	50.3%	228	60.6%	121	87.7%	221	80.1%	36	70.6%	50	69.4%
Unknown	5	13.2%	16	29.1%	15	78.9%	20	51.3%	1	50.0%	3	60.0%
p-value	0.804		0.030*		0.015*		<0.001***		0.221		0.034*	
Subtype												
Luminal A	112	40.4%	384	53.6%	253	91.3%	581	81.0%	-	-	-	-
Luminal B HER2-	19	36.5%	35	50.7%	48	92.3%	50	72.5%	-	-	-	-
Luminal B HER2+	80	73.4%	83	60.1%	89	81.7%	98	71.0%	82	75.2%	78	56.5%
HER2+ non-Luminal	44	83.0%	71	68.9%	-	-	-	-	45	84.9%	60	58.3%
Triple negative	44	74.6%	163	57.2%	-	-	-	-	-	-	-	-
Unknown	27	22.9%	77	39.1%	31	86.1%	114	81.4%	4	80.0%	1	33.3%
p-value	<0.001***		0.030*		0.017*		0.012*		0.160		0.788	
MFI												
<2 years	-		247	51.4%		-	218	77.0%	-		38	50.7%
2–4 years			342	60.5%			305	77.6%			79	64.2%
5–7 years			128	55.4%			155	81.2%			15	50.0%
8+ years			96	41.4%			165	83.8%			7	43.8%
p-value			<0.001***				0.232				0.133	
Total	326	48.8%	813	53.9%	421	88.8%	843	79.2%	131	78.4%	139	57.0%

dnMBC: de novo metastatic breast cancer; rMBC: recurrent metastatic breast cancer

* <0.05, **<0.01, ***<0.001; All p-values were estimated after excluding the unknown group.

† Percentage of patients having that systemic treatment over all dnMBC patients or over all rMBC patients.

Table 3: Adjusted odds ratios[†] of having treatment for metastatic breast cancer.

Factors	Chemotherapy	Endocrine therapy (for HR+ only)	Trastuzumab (for HER2+ only)
Age (continuous)	0.93 (0.93–0.94)***	1.00 (0.99–1.01)	0.93 (0.91–0.95)***
Ethnicity			
European	Reference	Reference	Reference
Māori	0.80 (0.57–1.11)	0.96 (0.61–1.53)	1.21 (0.51–2.85)
Pacific	0.43 (0.30–0.60)***	1.55 (0.91–2.65)	0.13 (0.06–0.29)***
Asian	0.77 (0.52–1.15)	0.83 (0.48–1.43)	1.12 (0.38–3.34)
Others	1.11 (0.61–2.03)	0.66 (0.31–1.37)	0.98 (0.25–3.85)
Year (continuous)	0.95 (0.91-–0.99)*	0.90 (0.84–0.96)***	1.04 (0.92–1.16)
Deprivation quintile			
1 (least deprived)	Reference	Reference	Reference
2	1.14 (0.77–1.67)	0.68 (0.41–1.13)	1.53 (0.57–4.12)
3	1.06 (0.73–1.54)	1.04 (0.62–1.76)	1.55 (0.60–3.95)
4	1.16 (0.80–1.68)	1.29 (0.76–2.20)	1.40 (0.55–3.56)
5 (most deprived)	0.78 (0.55–1.12)	0.94 (0.57–1.54)	1.78 (0.74–4.31)
Type of metastases			
De novo	Reference	Reference	Reference
Recurrent in <2 years	0.86 (0.65–1.14)	0.37 (0.24–0.56)***	0.26 (0.13–0.52)***
Recurrent in 2-4 years	1.22 (0.93–1.60)	0.40 (0.27–0.59)***	0.39 (0.20–0.73)**
Recurrent in 5-7 years	1.26 (0.89–1.79)	0.47 (0.29–0.77)**	0.22 (0.08–0.59)**
Recurrent in 8+ years	0.89 (0.62–1.28)	0.67 (0.39–1.16)	0.21 (0.06–0.70)*
Site of metastases			
Non-visceral	Reference	Reference	Reference
Visceral	1.08 (0.86–1.38)	0.34 (0.24–0.48)***	1.15 (0.63–2.11)
Both	1.27 (0.99–1.63)	0.60 (0.41–0.87)**	1.42 (0.75–2.68)
Subtype			
Luminal A	Reference	Reference	-
Luminal B HER2-	1.09 (0.70–1.70)	0.77 (0.46–1.29)	-
Luminal B HER2+	1.67 (1.20–2.32)**	0.50 (0.35–0.72)***	Reference
HER2+ non-Luminal	2.50 (1.64–3.82)***	-	1.27 (0.74–2.16)
Triple negative	1.64 (1.22–2.20)***	-	-

dnMBC: de novo metastatic breast cancer; rMBC: recurrent metastatic breast cancer

[†] All the above factors were included in the logistic regression model, and the respective odds ratios were adjusted for other factors.

* <0.05, **<0.01, ***<0.001

Table 4: Adjusted hazard ratios[†] of treatments on breast cancer-specific mortality by subtype.

Treatment	Luminal A (994)	Luminal B HER2- (121)	Luminal B HER2+ (247)	HER2+ non-luminal (156)	Triple negative (344)
Chemotherapy					
No chemo-therapy	Reference	Reference	Reference	Reference	Reference
Had chemo-therapy	1.11 (0.93–1.32)	0.61 (0.32–1.15)	0.82 (0.52–1.30)	0.30 (0.16–0.55)***	0.66 (0.50–0.86)**
Endocrine therapy					
No endocrine therapy	Reference	Reference	Reference		
Had endo-crine therapy	0.25 (0.20–0.31)***	0.60 (0.32–1.15)	0.26 (0.18–0.39)***	-	-
Trastuzumab					
No trastuzumab			Reference	Reference	
Had trastu-zumab	-	-	0.34 (0.21–0.56)***	0.40 (0.24–0.68)***	-

dnMBC: de novo metastatic breast cancer; rMBC: recurrent metastatic breast cancer.

[†] Adjusted for age, ethnicity, deprivation quintile, year of metastatic diagnosis, type of MBC (dnMBC and rMBC with different MFIs) and site of metastases.

* <0.05, **<0.01, ***<0.001.

As expected, trastuzumab was associated with improved outcome in HER2+ breast cancers, which confirms the outcomes of clinical trials[19–23] and that application in New Zealand reflects the positive clinical trial results.

Pacific women were less likely to have chemotherapy for MBC and less likely to have trastuzumab (for HER2+ disease only). Our previous paper investigating the use of trastuzumab for patients with stage I–III HER2+ breast cancer also found that Pacific women were less likely to receive trastuzumab.[13] This was partly because Pacific patients had more comorbidities[24] and were more likely to decline chemotherapy and trastuzumab.[13,25] Further research is needed to identify the reasons why Pacific women with metastatic breast cancer were less likely to receive treatments, and further efforts will be needed to ensure equal access to treatments. We did not find a significant difference in endocrine therapy and trastuzumab between Māori and New Zealand European women. These achievements are probably associated with the all advocations and efforts on reducing inequity for Māori patients with cancer in New Zealand.[26–28] There was a lower use of chemotherapies for Māori compared to European women, but this was probably because of the small number of patients and is likely insignificant; a larger sample size is needed for confimation.

We did not find any significant difference in survival between Māori and European women with MBC.[7] This is inconsistent with the Breast Cancer Foundation report for advanced breast cancer,[29] which found a 5% five-year survival rate for Māori and a 15% five-year survival rate for Europeans, and the viewpoint by Kereama-Royal et al [30] on wose outcome on MBC for Māori patients. This inconsistency may be because the Breast Cancer Foundation report included data from 2000 to 2015, whereas our study included data from 2010 to 2017. This study and our published study[7] show that equal outcomes for MBC have been achieved between Māori and Europeans in recent years.

There was less chemotherapy and endocrine therapy use recorded for patients diagnosed with MBC in 2016–2017 than in the previous years. This is probably because 19% of patients started their chemotherapy more than two yearsafter the metastatic diagnosis (based on the 2010–2015 data), and 18% of patients only started endocrine therapy more than two years after the metastatic diagnosis. We assumed that another 18–19% of patients diagnosed in 2016–2017 might have received chemotherapy and endocrine therapy more than two years after their metastatic diagnosis, but these data were not available when we conducted our study and therefore the use of chemotherapy and endocrine for patients diagnosed in 2016–2017 was underestimated. With the new targeted therapies being funded including pertuzumab (funded since January 2017) and trastuzumab emtansine (funded since December 2019), further research with a longer follow-up time is needed to find out the benefits of these new treatments.

We found that 78.4% of dnMBC HER2+ patients received trastuzumab, whereas only 57% of rMBC HER2+ patients received trastuzumab. The difference may be because 54% of rMBC HER2+ patients were treated with trastuzumab for their primary non-metastatic breast cancer. (Trastuzumab cannot be started at the time of the metastatic breast cancer diagnosis if the HER2+ breast cancer recurred within 12 months of completing adjuvant trastuzumab.) The Special Authority criteria by PHARMAC requires that interval between adjuvant and metastatic trastuzumab is more than 12 months. As expected, women with visceral metastases were significantly less likely to receive endocrine therapy (odds ratio of 0.34 for visceral metastases compared to non-visceral metastases). Previous literature has demonstrated both a greater chance of response and a more rapid response when chemotherapy is used for visceral disease.[31,32] In our study, compared to women with non-visceral metastases, women with visceral metastases and both metastases were slightly more likely to have chemotherapy, but the difference is not significant.

The strength of this work is that it is a population-based study with detailed data from the NZBCR, including biomarker status. Treatment information from NZBCR was cross-checked with the PHARMS data to make sure the treatment data

were relatively complete. However, as mentioned above, for patients diagnosed in 2016–2017, the short follow-up time available likely led to underestimation of treatments used. Also, our study was not based on randomised data, and patients were selected for each of these treatments based on a multitude of disease and patient factors, not all of which have necessarily been adequately adjusted for in our models. In our models, we have adjusted factors that were recorded in NZBCR, including age, ethnicity, deprivation quintile, year of metastatic diagnosis, type of MBC and site of metastases.

Conclusion

This observational population-based study found that Pacific women with MBC were less likely to receive chemotherapy and trastuzumab than other ethnic groups. Māori had equal access to systemic treatment as compared with Europeans. Chemotherapy was associated with improved survival in HER2+ non-luminal and triple negative MBC but not other subtypes. Endocrine therapy improved survival in luminal A MBC and luminal B HER2+ disease, and trastuzumab was associated with improved survival in luminal B HER2+ and HER2+ non-luminal disease.

Competing interests:
Nil.
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REFERENCES

1. Ministry of Health. Cancer: New registrations and deaths 2013. Wellington: Ministry of Health. 2016.
2. New Zealand Breast Cancer Foundation. Insights into living – and dying – with Advanced Breast Cancer in New Zealand. Auckland, New Zealand. 2018.
3. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review. JNCI Cancer Spectr. 2018;2:pky062-pky.
4. 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;235:177-82.
5. Ferrusi IL, Marshall DA, Kulin NA, Leighl NB, Phillips KA. Looking back at 10 years of trastuzumab therapy: What is the role of HER2 testing? A systematic review of health economic analyses. Personalized Medicine. 2009;6:193-215.
6. Metcalfe S, Evans J, Priest G. PHARMAC funding of 9-week concurrent trastuzumab (Herceptin) for HER2-positive early breast cancer. N Z Med J. 2007;120.
7. Lao C, Kuper-Hommel M, Elwood M, Campbell I, Edwards M, Lawrenson R. Characteristics and survival of de novo and recurrent metastatic breast cancer in New Zealand. Breast Cancer. 2021;28:387-97.
8. Malmgren JA, Mayer M, Atwood MK, Kaplan HG. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. Breast Cancer Res Treat. 2018;167:579-90.
9. den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK, Lohrisch CA. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat. 2017;161:549-56.
10. Lobbezoo DJ, van Kampen RJ, Voogd AC, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer. 2015;112:1445-51.
11. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012. Bethesda, MD. USA: National Cancer Institute. 2015.
12. Kalli S, Semine A, Cohen S, Naber SP, Makim SS, Bahl M. American Joint Committee on Cancer's Staging System for Breast Cancer, Eighth Edition: What the Radiologist Needs to Know. Radiographics : a review publication of the Radiological Society of North America, Inc. 2018;38:1921-33.
13. Lawrenson R, Lao C, Campbell I, et al. The use of trastuzumab in New Zealand women with breast

cancer. Asia Pac J Clin Oncol. 2018;14:e152-e60.

14. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of oncology: official journal of the European Society for Medical Oncology. 2015;26:1533-46.
15. Lawrenson R, Lao C, Campbell I, et al. The impact of different tumour subtypes on management and survival of New Zealand women with Stage I–III breast cancer. N Z Med J. 2018;131(1475):51-60.
16. Lawrenson R, Lao C, Campbell I, et al. Treatment and survival disparities by ethnicity in New Zealand women with stage I-III breast cancer tumour subtypes. Cancer causes & control : CCC 2017;28:1417-27.
17. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31:3997-4013.
18. Thuerlimann B. International consensus meeting on the treatment of primary breast cancer 2001, St. Gallen, Switzerland. Breast Cancer. 2001;8:294-7.
19. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2 - Positive breast cancer: Planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. Journal of Clinical Oncology. 2014;32:3744-52.
20. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369:29-36.
21. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. New England Journal of Medicine. 2005;353:1659-72.
22. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. Journal of Clinical Oncology. 2005;23:4265-74.
23. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. PLoS One. 2011;6:e21030.
24. Brown C, Lao C, Lawrenson R, et al. Characteristics of and differences between Pasifika women and New Zealand European women diagnosed with breast cancer in New Zealand. N Z Med J. 2017;130:50-61.
25. Seneviratne S, Campbell I, Scott N, et al. Adherence to adjuvant endocrine therapy: Is it a factor for ethnic differences in breast cancer outcomes in New Zealand? Breast. 2015;24:62-7.
26. Cormack D, Purdie G, Ratima M. Access to cancer services for Maori: A report prepared for the Ministry of Health. Wellington, New Zealand. 2005.
27. Gurney J, Campbell S, Jackson C, Sarfati D. Equity by 2030: achieving equity in survival for Māori cancer patients. N Z Med J. 2019;132:66-76.
28. Hobbs M, Ahuriri-Driscoll A, Marek L, Campbell M, Tomintz M, Kingham S. Reducing health inequity for Māori people in New Zealand. Lancet. 2019;394:1613-4.
29. Breast Cancer Foundation New Zealand. "I'm still here": Insights into living and dying- with Advanced Breast Cancer in New Zealand. Auckland, New Zealand. 2018.
30. Kereama-Royal I, Jones S, Wijohn EL, Doole C, Burgess EL, Came H. Resisting ethnic inequities in advanced breast cancer: a call to action. N Z Med J. 2019;132:83-9.
31. Pronzato P, Rondini M. First line chemotherapy of metastatic breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology 2006;17 Suppl 5:v165-8.
32. Hernandez-Aya LF, Ma CX. Chemotherapy principles of managing stage IV breast cancer in the United States. Chinese Clinical Oncology 2016;5:13.