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CLINICAL TRIAL

Addition of endocrine therapy to dual anti-HER2 targeted therapy in initial treatment of HER2 + /HR + metastatic breast cancer

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Abstract

Purpose Dual anti-HER2 targeted therapy and chemotherapy is the current first-line standard of care for HER2 + metastatic breast cancer (MBC), with endocrine therapy (ET) the backbone of treatment in hormone receptor positive (HR +) disease. The potential ET benefit in HER2 + /HR + patients is unknown as pivotal dual anti-HER2 clinical trials precluded ET use.

Methods Real-world data from a multi-site registry of consecutive HER2 + MBC patients treated at clinician discretion were examined. Patients that were HR + (ER + and/or PR +) and had received first-line chemotherapy alongside trastuzumab and pertuzumab were explored. Of 362 patients in the registry, 215 were excluded due to being HR- ($n = 210$) or not receiving chemotherapy ($n = 5$).

Results Of the 147 patients included, 91 (62%) received concurrent ET and 56 (38%) had not. Comparing the groups, there were no significant differences in age, performance status, metastatic sites, use of previous therapy and de novo metastatic disease. More patients with ER + PR + disease versus those with ER + PR- or ER-PR + received ET (73 vs 45%). The addition of ET was associated with significantly improved 5-year PFS (HR 0.58, CI 0.37–0.89, $p = 0.014$) and OS (HR 0.52, CI 0.31–0.90, $p = 0.018$), with no increase in adverse events noted.

Conclusion The addition of ET to first-line dual anti-HER2 therapy post chemotherapy in patients with HER2 + /HR + MBC was associated with major gains in PFS and OS with no safety concerns evident. Further studies of this combination are justified, along with studies of how best to integrate other agents that are active in this patient subset, including CDK4/6 inhibitors.

Keywords Metastatic breast cancer · Endocrine therapy · HER2 · Hormone receptor-positive

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Introduction

Breast cancer is the most frequently diagnosed solid organ cancer, impacting 12% of women worldwide over the course of their lifetime, and is a leading cause of cancer-related mortality globally [1]. Approximately 15–20% of all breast cancers are human epidermal growth factor receptor 2-positive (HER2 +) [2]. Approximately half of these are also hormone receptor positive (HR +) [3], resulting in 10–12% of all breast cancers having a HER2 + /HR + phenotype [2]. Tumours with HR + subtypes convey a better prognosis than HR- tumours, whereas those with HR- subtypes, particularly those with triple-negative disease, have the worst prognosis, likely due to the lack targeted therapy [4].

The hypothesis that HER2 and ER bidirectional crosstalk contributes to de novo and acquired resistance to both anti-HER2 therapy and ET is supported by clinical and laboratory evidence, suggesting that improved efficacy may be achieved by targeting both signalling pathways. This non-chemotherapy combined approach of ET with either trastuzumab [5, 6] or lapatinib [7] was shown to be safe and to improve progression free survival [5–8], but given the modest improvements, a non-chemotherapy approach did not become standard of care. The pivotal CLEOPATRA study demonstrated that comprehensive blockade of the HER2 receptor with pertuzumab and trastuzumab added to chemotherapy led to significantly improved survival outcomes in patients with HER2 + MBC [9, 10] but precluded the use of ET in the subset of patients that were also HR + [10, 11].

More recently, the PERTAIN [8] and ALTERNATIVE [12] trials explored the role of ET given with dual anti-HER2 therapy, again demonstrating superior progression free survival when compared with ET plus single agent anti-HER2 therapy, offering patients an effective chemotherapy-sparing regimen. In both instances however, no comparison was made between dual anti-HER2 blockade with or without the addition of ET. Current first-line standard of care treatment for HER2 + MBC includes either a combination of trastuzumab, pertuzumab and chemotherapy [13] or trastuzumab emtansine [14] depending on previous exposure and duration of disease free interval from previous anti-HER2 (neo) adjuvant therapy.

International consensus guidelines suggest consideration of maintenance treatment with anti-HER2 therapy and ET for patients with HER2 + /HR + MBC treated with chemotherapy and anti-HER2 therapy in the first-line setting [13], and this combination approach has been widely used in routine care. Here we examine prescribing patterns for patients with HER2 + /HR + MBC in routine clinical practice, with an aim to evaluate the efficacy and safety of the combination of dual anti-HER2 blockade and ET versus anti-HER2 blockade alone.

Materials and methods

Eligibility and recruitment

Consecutive female patients with HER2 + /HR + MBC were identified in a search of the TABITHA® (*Treatment of Advanced Breast Cancer in the HER2 positive Australian Patient*) registry. TABITHA® is a prospective registry collecting data on consecutive patients with HER2 + MBC at 16 sites in Australia. Data collected includes patient demographics, tumour details including histology and staging, treatment lines, adverse events and survival outcomes. Patients with HR- tumours were excluded, including those who were HR + on primary biopsy but subsequently HR- on metastatic biopsy. All patients received treatment with dual anti-HER2 therapy (pertuzumab plus trastuzumab) and those who did not receive chemotherapy as first-line therapy were excluded from the analysis. This study received approval from the Institutional Human Ethics Committee at BioGrid, Melbourne.

Statistical analysis

Descriptive statistics were used to describe the clinical and disease characteristics, and treatment. Categorical variables are presented as observed counts and weight percentages, and continuous variables as a median with corresponding interquartile range. Survival was estimated by Kaplan–Meier method. Progression free survival (PFS) was defined as time from diagnosis of metastatic disease to date of documented progression or death. Overall survival (OS) was defined as the time from diagnosis of metastatic disease to death or censored at the date of last follow up. Univariate analyses of PFS and OS and multivariate analysis of PFS were performed using variables known to affect prognosis, including age, ECOG performance status, tumour hormone receptor profile, site of metastases (visceral/non-visceral, CNS) and receipt of ET.

Subgroup analyses were performed based on patient receipt of concurrent ET using relevant intergroup statistics. Statistical significance was defined as having a p value < 0.05. All statistical analyses were performed using Stata 12.

Results

Demographics and disease characteristics

From 1 January 2012 to 30 June 2020, 362 patients with newly diagnosed HER2 + MBC had been entered into the registry. Of these, 215 patients were excluded due to being

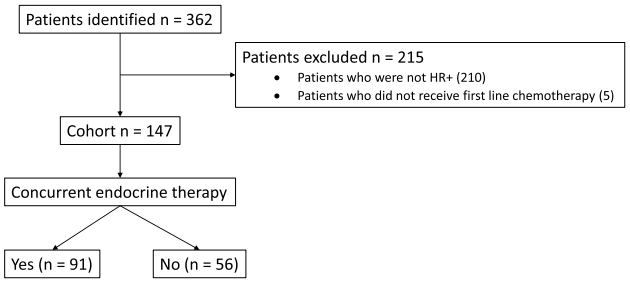

Fig. 1 Consort diagram describing TABITHA patients receiving dual anti HER2 therapy for HER2 + /HR + metastatic breast cancer

HR- ($n = 210$) or not receiving first-line chemotherapy ($n = 5$). Of the 147 patients included in the analysis, 91 (62%) had received concurrent ET and 56 (38%) had not (see Fig. 1).

Patient demographics and disease characteristics are presented in Table 1. The median age was 58 years (range: 27–95 years), with 95% of patients having a good performance status (ECOG 0–1). Most patients had ER positive disease (95%), with 5% being ER- PR + . Fifty two percent of patients had early stage disease at the time of initial diagnosis, and of these 59% had received trastuzumab and 72% had received ET in the adjuvant setting.

Table 1 Demographics and disease characteristics

Characteristic	Total cohort $n = 147$	With endocrine $n = 91$ (62%)	Without endocrine $n = 56$ (38%)	p value
Age				
Median (IQR)	58 (48–68)	56 (48–65)	61 (50–71)	0.566
Gender				
Male	1 (0.7%)	1 (1.1%)	0 (0%)	1.000
Female	146 (99%)	90 (99%)	56 (100%)	
ECOG				
0–1	140 (95%)	87 (96%)	53 (95%)	1.000
> 2	7 (5%)	4 (4%)	3 (5%)	
Metastatic at diagnosis				
Yes	71 (48%)	38 (42%)	33 (59%)	0.061
No	76 (52%)	53 (58%)	23 (41%)	
Adjuvant HER2 therapy	$n = 76$	$n = 53$	$n = 23$	
Yes	45 (59%)	33 (62%)	12 (52%)	0.454
No	31 (41%)	20 (38%)	11 (48%)	
Adjuvant ET	$n = 76$	$n = 53$	$n = 23$	
Yes	54 (72%)	41 (78%)	13 (63%)	0.098
No	22 (28%)	12 (22%)	12 (37%)	
Site of metastases				
Visceral	99 (67%)	56 (62%)	43 (77%)	0.070
Bone	90 (61%)	59 (65%)	31 (55%)	0.297
Nodal	80 (54%)	51 (56%)	29 (52%)	0.733
Brain/leptomeningeal	20 (14%)	9 (10%)	11 (20%)	0.136
Hormone receptor status				
ER + ve, PR + ve	91 (62%)	66 (73%)	25 (45%)	**0.001**
ER + ve, PR − ve	49 (33%)	24 (26%)	25 (45%)	
ER − ve, PR + ve	7 (5%)	1 (1%)	6 (11%)	
ER positivity	$n = 140$	$n = 90$	$n = 63$	
1 +	18 (13%)	9 (10.0%)	9 (19%)	0.167
2 +	29 (21%)	20 (22.2%)	9 (16%)	
3 +	68 (49%)	50 (55.6%)	18 (38%)	
Unknown	25 (18%)	11 (12.2%)	14 (27%)	
PR positivity	$n = 98$	$n = 67$	$n = 31$	
1 +	22 (22%)	11 (16%)	11 (36%)	0.075
2 +	21 (21%)	16 (24%)	5 (16%)	
3 +	39 (49%)	30 (45%)	9 (29%)	
Unknown	16 (16%)	10 (15%)	6 (19%)	

Bold values denote significant p values

When comparing patients who received ET to those who did not, there was no significant difference in median age (56 vs 61 years), ECOG 0–1 (96 vs 95%), number of lines of therapy received in the metastatic setting (52% one line, 29% two lines), weeks on chemotherapy in the first-line setting (13 vs 15 weeks), use of adjuvant trastuzumab (62 vs 52%), use of adjuvant ET (78 vs 63%) or site and distribution of metastases (see Table 1). Patients with both ER + and PR + disease were more likely to receive ET (73%, $p = 0.001$), whereas those with only ER + or PR + disease were less likely to receive ET (45%, $p = 0.001$). The degree of ER positivity as defined by strength of staining (weak/moderate/strong) was similar across both cohorts.

Of those who received ET, median duration from chemotherapy cessation to commencement of ET was 35 days. 73% were treated with an aromatase inhibitor (86% non-steroidal vs 14% steroidal) and 27% with tamoxifen. Median duration of ET was 18 months in the first-line setting, with the majority (54%) either still on ET at census or continued into second line, 37% ceasing ET due to progressive disease and 9% ceasing due to toxicity or patient request.

Survival outcomes

Progression free survival was significantly prolonged in patients who received ET over those who did not (33.0 vs 17.9 months, $p = 0.014$) and those with a better performance status (30.0 vs 17.9 months, $p = 0.050$) (Table 2, Fig. 2a). On multivariate analysis, receipt of ET ($p = 0.031$) remained significant (Table 3).

The addition of ET (67.5 vs 46.3 months, $p = 0.018$) was associated with a significant improvement in overall survival (Table 4, Fig. 2b).

Adverse event profile

Nausea and vomiting were more common in those who did not receive ET (7 vs 21%, $p = 0.010$), otherwise safety data was similar across both groups, with 70% of all patients documented as experiencing at least one side effect during first-line treatment (Table 5). The most commonly reported adverse event was diarrhoea (33%). The addition of hormone therapy did not significantly increase any documented adverse events.

Discussion

This study builds on the previous registry-based studies exploring the management and outcomes of HER2 + / HR + MBC patients who received standard dual anti-HER2 therapy and ET in routine clinical practice [15], and specifically focussing on the impact of the addition of ET to dual anti-HER2 therapy post chemotherapy. It confirms the progression free survival benefit and safety parameters of this combination found in previous studies and presents the novel finding of significantly improved progression free survival and overall survival with the combination of anti-HER2 therapy and ET in the first-line setting. Consistent with historical data related to the safety of combining HER2 + and HR targeted therapy, no new safety signals were identified.

This study confirms the findings of previous clinical trials in our real-world patient population. The demographics of the HER2 + /HR + registry patients that we examined were those of a relatively young population with good performance status, not dissimilar to the population enrolled in typical large randomised controlled trials. Consistent with this, the overall survival data observed for the registry patients not treated with ET (median OS 46 months) was similar to that reported in the practice changing CLEOPATRA trial (median OS 41 months), which demonstrated the superiority of pertuzumab added to trastuzumab and chemotherapy with docetaxel [10]. This demonstrates the reproducibility of the seminal findings with dual anti-HER2 therapy in routine clinical practice. In our cohort, the age range extended to 95, signalling the reasonable safety profile of dual anti-HER2 therapy.

Table 2 Univariate analysis for 5-year progression free survival

Variable	mOS (months)	*P* value	HR (95% CI)
Age			
< 65 years	28.8	0.945	0.98 (0.60–1.62)
≥65 years	28.8		
ECOG			
0–1	30.0	**0.050**	0.40 (0.16–1.00)
≥ 2	17.9		
Metastatic at diagnosis			
Yes	28.4	0.380	1.21 (0.79–1.87)
No	31.3		
Hormone receptor status			
ER + ve, PR + ve	28.8	0.799	1.05 (0.72–1.55)
ER + ve, PR − ve	30.0		
ER − ve, PR + ve	28.4		
Visceral metastases			
Yes	28.8	0.367	0.81 (0.52–1.27)
No	30.0		
CNS metastases			
Yes	20.3	0.127	
No	30.9		1.59 (0.88–2.88)
Endocrine therapy			
Yes	33.0	**0.014**	0.58 (0.37–0.89)
No	17.9		

Bold values denote significant *p* values

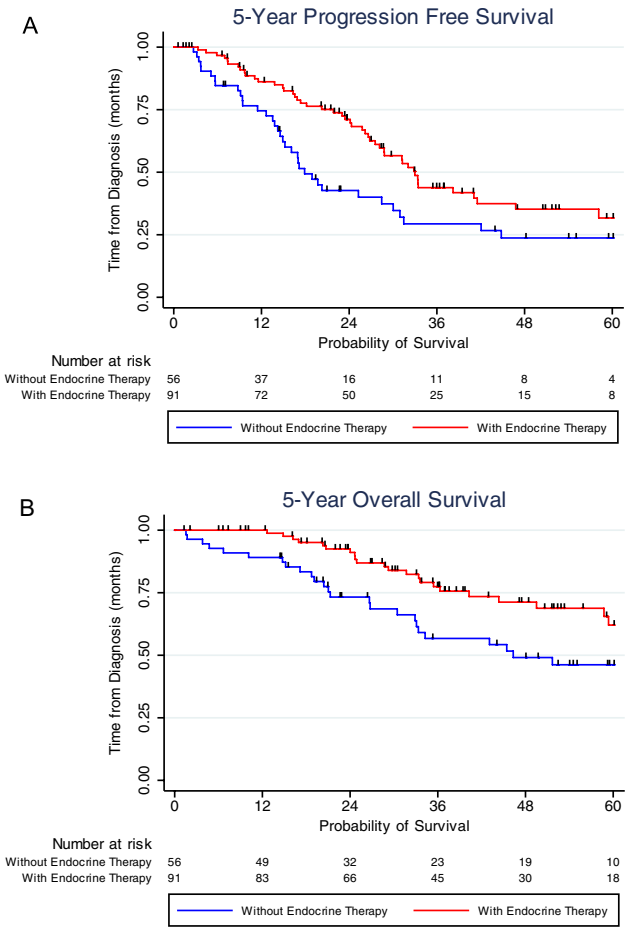

Fig. 2 **A** 5-year progression free survival for patients who received endocrine therapy versus those who did not. **B** 5-year overall survival for patients who received endocrine therapy versus those who did not

Additionally, our study shows a survival benefit when ET is added to the current standard of dual targeted anti-HER2 therapy in the subset of patients that are also HR+, noting that HR therapy was precluded for these patients in CLEOPATRA. The benefit of combining anti-HER2 therapy with ET has been demonstrated in preclinical studies. These studies have demonstrated that inhibition of HER2 pathways upregulates ER-mediated signalling pathways, which impacts growth regulation and response to therapy, and leads to resistance to either endocrine or anti-HER2 therapy [16–19]. It has therefore been postulated that inhibiting both pathways concurrently could potentially prevent this upregulation [18] and provide further clinical benefit to either therapy alone. Subsequent clinical trials have indicated a progression free survival advantage with this combination [5, 6]. Our study extends upon this and for the first time demonstrates a significant overall survival advantage with this combination. The improvement in survival cannot be explained by any measured difference between the

Table 3 Multivariate analysis for 5-year progression free survival

Variable	Hazard ratio	*P* value	95% CI
Age			
< 65 years	1.1	0.714	0.65–1.86
> 65 years	1		
ECOG			
0–1	0.46	0.148	0.16–1.31
≥ 2	1		
Metastatic at diagnosis			
Yes	1.12	0.630	0.71–1.78
No	1		
Hormone receptor status			
ER + ve, PR + ve	0.97	0.893	0.64–1.48
ER + ve, PR − ve	1		
ER − ve, PR + ve	1		
Visceral metastases			
Yes	0.82	0.419	0.50–1.33
No	1		
CNS metastases			
Yes	1.47	0.237	
No	1		0.78–2.77
Endocrine therapy			
Yes	0.59	**0.031**	0.36–0.95
No	1		

Bold values denote significant *p* values

Table 4 Univariate analysis for 5-year overall survival

Variable	mOS (months)	*P* value	HR (95% CI)
Age			
< 65 years	67.2	**0.014**	0.50 (0.28–0.87)
≥ 65 years	43.1		
ECOG			
0–1	65.8	**0.033**	0.33 (0.12–0.91)
≥2	17.0		
Metastatic at diagnosis			
Yes	67.2	0.812	0.94 (0.55–1.60)
No	59.4		
Hormone receptor status			
ER + ve, PR + ve	67.5	0.543	1.15 (0.73–1.80)
ER + ve, PR − ve	65.8		
ER − ve, PR + ve	63.2		
Visceral metastases			
Yes	64.1	0.805	1.07 (0.61–1.88)
No	65.8		
CNS metastases			
Yes	67.5	0.896	
No	64.1		0.94 (0.40–2.2)
Endocrine therapy			
Yes	67.5	**0.018**	0.52 (0.31–0.90)
No	46.3		

Bold values denote significant *p* values

Table 5 Adverse events (any grade)

Toxicity	With endocrine $N=91$	Without endocrine $N=56$	P value
Overall	64 (70%)	42 (75%)	0.575
Diarrhoea	30 (33%)	20 (36%)	0.858
Neuropathy	29 (32%)	14 (25%)	0.456
Haematological	14 (15%)	12 (21%)	0.379
Cardiotoxicity	8 (9%)	4 (7%)	1.000
Nausea/vomiting	6 (7%)	12 (21%)	**0.010**

Bold values denote significant p values

patient groups and was maintained irrespective of age or performance status, suggesting that all patients should be considered for the addition of ET to dual anti-HER2 therapy.

Importantly, our study also demonstrates the variable practice of Australian oncologists. Comparing the registry patients who did and did not receive ET, there are no major differences that would be considered likely to impact the clinical decision to utilise ET; the main reason to omit or delay ET is the concurrent use of chemotherapy. The patients who received ET were of similar age and performance status to those not treated with ET, and prior adjuvant therapy and rates of presentation with de novo metastatic disease were also similar. It is evident from this study that ER + and PR + patients are more likely to receive ET as opposed to either ER + or PR + alone. However, subset analyses for survival were not conducted due to limited power.

Ultimately, over half of the identified patients with HER2 + /HR + MBC received ET in addition to dual anti-HER2 therapy. Our impression is that clinicians have concluded from the available limited data that the addition of ET in this subset of patients is appropriate in the routine care setting, an approach which is cautiously supported by guidelines. This is presumably due in part to the relative tolerability of ET and the established benefit in the HR + MBC population in general, as reflected in our findings of only a very small subset of patients ceasing endocrine therapy due to toxicity.

We would propose that there are challenges in addressing whether the addition of ET improves survival outcomes by conducting a standard randomised Phase III clinical trial, not the least of which is the difficulty of enrolling patients to a standard of care arm with no ET in the HER2 + /HR + population, given current practice. The phase III Detect V/CHEVENDO study (NCT02344472) is currently prospectively evaluating dual anti-HER2 blockade combined with either chemotherapy or ET, with the primary endpoint of safety and secondary endpoints of survival. However, this will still not answer whether the addition of ET following chemotherapy with dual anti-HER2 therapy is beneficial.

There are limitations to this study. Firstly, this is a small unplanned retrospective analysis of prospectively collected data. We did not capture data as to why clinicians chose to use or not to use ET. Whilst registry data is collected across a number of sites, validation in an independent prospective cohort would be desirable. Secondly, the number and severity of adverse events in a registry is potentially under reported with ET-specific toxicity not routinely reported in this registry, so further studies of the safety of this combination in a trial setting are warranted. Finally, standard of care for HER2-/HR + MBC has evolved over the last decade. The combination of CDK4/6 inhibitors with ET has led to significant improvements in survival in several studies [20, 21] and is now a standard of care in HR + breast cancer. The role of CDK4/6 inhibitors with ET and anti-HER2 therapy in HER2 + / HR + MBC is unknown at present. However the triplet combination has shown strong preclinical activity. Preliminary efficacy results of the phase 1b/II trial NCT03054363 and the phase II PATRICIA trial have been positive, with the role of CDK4/6 inhibitors in this setting being further evaluated in the phase I/II trial (NCT 03,304,080) and the PATINA Phase III trial (NCT 02,947,685).

Conclusion

This study demonstrates that the addition of ET to dual anti-HER2 therapy as maintenance therapy post chemotherapy provides clinically and statistically significant gains in both progression free and overall survival, without an increase in adverse events. We encourage further studies, including further registry analyses, to independently support this finding. Based on our data, the use of ET in combination with dual anti-HER2 + therapy following chemotherapy in HER2 + /HR + MBC should be encouraged. Further research into the role of CDK4/6 inhibitors in this patient group is also warranted.

Author contributions ML, SWL, PG and LG: contributed to conceptualization, methodology and design. All authors contributed to material preparation and data collection. ML: analysis and the first draft was performed and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The dataset generated during and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest SWL has received institutional research grants from Novartis and royalty payments. RDB is on the advisory board for AstraZeneca, Novartis and Gilead, has received speaker honoraria from Gilead and Eli Lilly and research grants from Pfizer, Novartis and AstraZeneca. BY is on the advisory board for Roche/Genetech, and has received speaker honoraria and travel grant from Roche. AA has received institutional research funding from Bayer, AstraZeneca, Amgen, Astellas, Janssen, MSD and Mundipharma, and honoraria from Amgen, Janssen and Eisai. VW has received institutional research funding from Pierre Fabre, Amgen, Roche, MSD, AstraZeneca and Merck, and speaker honoraria from Amgen and Janssen. JM is on the advisory board for GSK and AstraZeneca and has received support for virtual education meeting attendance from GSK, AstraZeneca and Novartis. ML, LM, SG, MN, LN, IC, JT, FB, PG and LG have no conflicts of interest to disclose.

Ethical approval This study received ethics approval for the collection and utilization of de-identified patient data from individual sites and from the ethics committee overseeing the TABITHA registry.

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