Poster FPN#203P

Real-world treatment patterns in patients with HER2 positive unresectable or metastatic breast cancer: HER2 Real study final analysis in Asia-Pacific (APAC) and Brazil

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Aim

- The HER2 REAL (NCT04857619) study explored treatment practices and survival outcomes in human epidermal growth factor receptor 2 (HER2)-positive (+) unresectable (u) or metastatic (m) breast cancer (BC) patients treated in routine clinical practice in countries from the APAC region and Brazil.

Conclusions

- In our study, <50% of HER2+ u/mBC patients received guideline recommended therapy.
- Importantly, real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) were suboptimal even for patients who were treated with the preferred regimen of pertuzumab (PTZ) plus trastuzumab (TRA) in combination with chemotherapy (CT) in the first line of therapy (LOT1), and trastuzumab emtansine (T-DM1) in LOT2 as compared with randomized clinical trial data and other real-world studies.
- Missing data due to retrospective study design, enrolment criteria, and shorter follow-up duration may limit the generalizability of our results.
- The substantial attrition rates and enrollment of patients who had progressed after the second line may partially explain the poor survival results. However, since the reasons for attrition were not clearly defined, the data on attrition rates may be biased.
- Nonetheless, the results indicate that optimization of standard-of-care practices is urgently needed to improve survival outcomes in this group of patients.

Plain language summary

Why did we perform this research?
HER2+ metastatic breast cancer (mBC) expresses higher-than-normal levels of the HER2 protein and can spread from its original site to other parts of the body. The treatment for HER2+ mBC is evolving with several novel drugs approved in recent years. In this study, we attempt to better understand the treatment patterns and use of new and established drugs in patients with HER2+ unresectable (a tumor that cannot be completely removed with surgery) mBC in the real world.

How did we perform this research?
Available data of patients diagnosed with HER2+ mBC was obtained from medical records or from patients themselves. The data was collected from the date of diagnosis of unresectable mBC (index) to the end of follow-up (ie. until death, the last medical record entry, or date of data extraction, whichever was earlier). This study was conducted in six countries outside the US and European regions (Australia, Brazil, Hong Kong, the Republic of Korea, Singapore, and Taiwan.

What were the findings of this research?
Treatment patterns varied greatly in the real world among patients with HER2+ mBC, possibly due to the differences in accessibility of treatments in the different countries included in this study.

What are the implications of this research?
Our study shows that standard of care (recommended most appropriate treatment) practices and adherence to generally accepted guidelines for treatment of patients with HER2+ mBC needs improvement in the real world.

Where can I access more information?
Clinicaltrials.gov (NCT04857619).

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Introduction

- HER2+ BC comprises 15%–30% of all BC cases and is characterized by higher recurrence rates and metastatic potential and lower OS as compared to the more frequent luminal subtypes[1].
- Identification of the role of HER2 overexpression in the pathophysiology of this subtype of BC led to the development of HER2-targeted therapies which have drastically improved the survival outcomes in both early and advanced stages of HER2+ BC[2].
- Consistently, clinical trials have demonstrated superiority of dual HER2 blockade, involving a combination of HER2-directed agents, over single HER2-targeted therapy approaches[3,4,5].
- While new treatment alternatives for these patients have been recently introduced in many countries, presently, PTZ plus TRA in combination with a taxane represents the preferred first-line treatment in HER2+ mBC. The antibody-drug conjugate trastuzumab emtansine (T-DM1) is generally considered for second-line treatment[6,7].
- Although multiple treatment options have shown improved survival outcomes in different LOTs in clinical trials, their utilization and associated outcomes in the real-world setting remain to be fully explored.

Methods

- A multicountry, multicenter, retrospective, non-interventional study spanning 6 countries (Australia, Brazil, Hong Kong, the Republic of Korea, Singapore, and Taiwan)
- The analyses were performed on the overall study population as well as at the country level. The data analysis involved descriptive statistics for clinico-demographic characteristics and treatment patterns. Categorical variables were presented using frequencies, percentages, and corresponding 95% CI. Continuous variables were presented as mean (SD) or median (range).

Primary Outcomes
- To describe the treatment patterns in patients with HER2+ u/mBC

Secondary Outcomes
- To describe the demographic and clinicopathological characteristics of patients with HER2+ u/mBC
- To describe the effectiveness of different treatment regimens for HER2+ u/mBC
- To assess the safety and tolerability of different treatment regimens in patients with HER2+ u/mBC

763 patients enrolled

Inclusion Criteria*
- Adult patients (≥18 years) diagnosed with HER2+ u/mBC since the available date of T-DM1 or 01 January 2017, whichever was earlier
- Availability of ≥12 months of follow-up data from the index date unless the patient died within the first 12 months
- Completed ≥1 LOT in the advanced setting
- Patient or legal representative having provided written informed consent

*Patients diagnosed between Jan 2017 and Dec 2019 who had already progressed on two prior LOTs during study enrollment were included before the protocol amendment.

684 (89.6%) patients included in the final analysis set

Australia	Brazil	Hong Kong	Republic of Korea	Singapore	Taiwan
N = 76	N = 152	N = 97	N = 174	N = 110	N = 154

Reasons for exclusion
- Not meeting protocol-defined index date = 10
- Did not have ≥12 months of follow-up data from the index date = 21
- Didn't have confirmed HER2+ status = 7
- Didn't complete ≥1 LOT from the index date = 20
- Concomitant cancer = 1
- Deemed screen failures by the site staff and marked SF in the EDC = 20

79 patients were excluded from the final analysis

Exclusion Criteria
- Patients with HER2- negative u/mBC
- Change in HER2 status from positive to negative during disease progression
- Concomitant cancer at the time of diagnosis
- Patients participating in an interventional study that remains blinded at the time of enrolment

Results and interpretation

- A total of 684 HER2+ BC patients with a median (range) age of 55 (20–91) years were analyzed (Table 1).
- Overall, 681 (99.6%) were female of whom 379 (55.7%) were postmenopausal at the index date.
- Hypertension (146/301 [48.5%]) and diabetes (83/301 [27.6%]) were the most prevalent comorbidities.
- The top regimen overall in LOT1 was TRA + PTZ + CT (321/670 [47.9%]) and in LOT2 was T-DM1 (254/596 [42.6%]), while patients received diverse regimens from LOT3 onwards (Table 2).

Table 1: Demographics and Baseline Clinical Characteristics at Index Date

Demographic characteristics	Overall (N = 684)	Australia (N = 62)	Brazil (N = 120)	Hong Kong (N = 92)	Rep of Korea (N = 157)	Singapore (N = 105)	Taiwan (N = 148)
Age (years)#	55 (20-91)	58 (29-91)	53 (25-85)	57 (35-81)	51 (20-84)	58 (31-80)	55 (21-81)
Site of metastasis†							
Visceral	465 (68.0)	50 (80.6)	62 (51.7)	67 (72.8)	100 (63.7)	77 (73.3)	109 (73.6)
Visceral only	156 (22.8)	7 (11.3)	28 (23.3)	21 (22.8)	36 (22.9)	16 (15.2)	48 (32.4)
Non-visceral	427 (62.4)	49 (79.0)	60 (50.0)	62 (67.4)	106 (67.5)	81 (77.1)	69 (46.4)
Non-visceral only	126 (18.4)	4 (6.5)	28 (23.3)	17 (18.5)	43 (27.4)	20 (19.0)	14 (9.5)
CNS	149 (21.8)	27 (43.5)	20 (16.7)	13 (14.1)	31 (19.7)	12 (11.4)	46 (31.1)
CNS only	31 (4.5)	4 (6.5)	7 (5.8)	5 (5.4)	5 (3.2)	2 (1.9)	8 (5.4)
NA*	39 (5.7)	1 (1.6)	20 (16.7)	2 (2.2)	3 (1.9)	4 (3.8)	9 (6.1)
Time from Initial BC diagnosis to the index date duration (mo)#	26 (0-424)	37 (3-268)	18 (0-424)	29 (0-222)	29 (0-177)	34 (2-183)	25 (0-99)
< 2 years	171 (25.0)	8 (12.9)	54 (45.0)	19 (20.7)	37 (23.6)	14 (13.3)	39 (26.4)
2-5 years	142 (20.8)	13 (21.0)	24 (20.0)	23 (25.0)	34 (21.7)	14 (13.3)	34 (23.0)
> 5 years	75 (11.0)	7 (11.3)	18 (15.0)	7 (7.6)	20 (12.7)	13 (12.4)	10 (6.8)
NA*	296 (43.3)	34 (54.9)	24 (20.0)	43 (46.8)	66 (42.0)	64 (60.9)	65 (43.9)
Follow-up duration (mo)#	30.1 (1-167)	33 (5-67)	31.7 (1-167)	26.8 (11-64)	29.4 (5-68)	32.3 (7-99)	28.8 (1-64)
Family history of BC							
Yes	117 (17.1)	20 (32.3)	24 (20.0)	19 (20.7)	16 (10.2)	18 (17.1)	20 (13.5)
No	464 (67.8)	28 (45.2)	62 (51.7)	62 (67.4)	120 (76.4)	72 (68.6)	120 (81.1)
NA*	103 (15.1)	14 (22.6)	34 (28.3)	11 (12.0)	21 (13.4)	15 (14.3)	8 (5.4)
Estrogen receptor							
Positive	218 (31.9)	25 (40.3)	23 (19.2)	30 (32.6)	53 (33.8)	49 (46.7)	38 (25.7)
Negative	205 (30.0)	12 (19.4)	12 (10.0)	38 (41.3)	64 (40.8)	37 (35.2)	42 (28.4)
NA*	261 (38.2)	25 (40.3)	85 (70.8)	24 (26.1)	40 (25.5)	19 (18.1)	68 (45.9)
Progesterone receptor							
Positive	145 (21.2)	20 (32.3)	12 (10.0)	13 (14.1)	37 (23.6)	42 (40.0)	21 (14.2)
Negative	272 (39.8)	16 (25.8)	23 (19.2)	53 (57.6)	80 (51.0)	41 (39.0)	59 (39.9)
NA*	267 (39.0)	26 (41.9)	85 (70.8)	26 (28.3)	40 (25.5)	22 (21.0)	68 (45.9)

Data presented as n (%) for all categories except age, initial BC diagnosis to the index date, and follow-up durations. #Data presented as median (range)
*Not applicable (contains de novo patients) and includes not reported, not available, unknown, and missing categories.
†Site of metastasis for "visceral only" category contains only patients with metastasis in this location, while "visceral" includes both these patients, as well as those with visceral + any other location. Corresponding logic applies to the "non-visceral" and "CNS" categories. Non-visceral metastases include tumors located in the bone, bone marrow, lymph nodes, skin, and soft tissues. CNS metastases include tumors located in the brain, spinal cord, or meninges. All other locations are classified as visceral disease.

Table 3: Median rwOS and rwPFS for the top regimen in LOT1, LOT2, and LOT3 by country

Country	LOT1 (PTZ+TRA+CT)		LOT2 (T-DM1)		LOT3	
	rwOS (95% CI), months	rwPFS (95% CI), months	rwOS (95% CI), months	rwPFS (95% CI), months	rwOS (95% CI), months	rwPFS (95% CI), months
Australia (N=62)	41.5 (29.4–53.3)	15.5 (12.5–22.3)	NC	NC	T-Dxd	
					NC	NC
Brazil (N=120)	NC	13.0 (6.8–26.0)	NC	NC	TRA + CT	
					NC	NC
Hong Kong (N=92)	35.9 (23.2–NC)	13.3 (9.0–17.7)	16.4 (11.2–NC)	6.0 (4.5–8.2)	Lapatinib + CT	
					7.0 (2.9-10.9)	NC
Rep of Korea (N=157)	46.8 (33.9–55.5)	9.6 (8.3–12.4)	22.4 (18.7–27.4)	6.8 (4.3–8.4)	CP	
					13.5 (7.4–NC)	2.8 (1.4–4.4)
Singapore (N=105)	49.1 (30.6–NC)	8.8 (7.3–14.6)	NC	6.2 (2.3–9.7)	TRA + CT	
					NC	NC
Taiwan (N=148)	42.2 (30.7–NC)	9.1 (6.9–11.0)	NC	7.1 (4.4–28.3)	TRA + CT	
					NC	NC

rwOS: the time from the index date or date of initiation of LOT to the date of death due to any cause; rwPFS: the time from the index date or date of initiation of LOT to the first documented real-world disease progression or death, whichever occurs first.
One patient from Rep of Korea had negative follow-up time (death date earlier than index date) and was thus excluded from the Km curve analysis. A regimen is presented only if it is taken by >10% of the patients in a country.

Table 2: Real-world treatment patterns for the top regimens by LOT and country

Regimen	Overall (N=684)	Australia (N = 62)	Brazil (N = 120)	Hong Kong (N = 92)	Rep of Korea (N = 157)	Singapore (N = 105)	Taiwan (N = 148)
LOT1 (N1 [%])	**670 (98.0)**	**62 (100)**	**107 (89.2)**	**92 (100)**	**157 (100)**	**105 (100)**	**147 (99.3)**
Duration$ (mo)	8.3 (0–62)	11.0 (0–62)	7.9 (0–54)	9.3 (1–47)	8.3 (0–55)	7.7 (0–55)	7.3 (0–43)
Regimen 1				**TRA+PTZ+CT**			
n/N1 (%)	321 (47.9)	37 (59.7)	38 (35.5)	43 (46.7)	118 (75.2)	28 (26.7)	57 (38.8)
Regimen 2	**TRA+CT**	**TRA+PTZ+CT+HT**	**TRA+CT**	**TRA+PTZ+CT+HT**	**T-DM1**	**TRA+CT**	**TRA+CT**
n/N1 (%)	103 (15.4)	10 (16.1)	31 (29.0)	19 (20.7)	13 (8.3)	27 (25.7)	25 (17.0)
LOT2 (N1 [%])	**596 (87.1)**	**47 (75.8)**	**81 (67.5)**	**88 (95.7)**	**148 (94.3)**	**101 (96.2)**	**131 (88.5)**
Duration$ (mo)	5.1 (0–47)	8.3 (0–41)	10.3 (0–47)	5.1 (0–30)	4.5 (0–26)	4.3 (0–26)	4.4 (0–34)
Regimen 1				**T-DM1**			
n/N1 (%)	254 (42.6)	23 (48.9)	13 (16.0)	58 (65.9)	103 (69.6)	30 (29.7)	27 (20.6)
Regimen 2	**TRA+CT**	**Anti-HER2*+HT**	**TRA+CT**	**Lapatinib+CT**	**Lapatinib+CT#**	**TRA+CT**	**TRA+PTZ+CT**
n/N1 (%)	54 (9.1)	6 (12.8)	12 (14.8)	12 (13.6)	14 (9.5)	18 (17.8)	22 (16.8)
LOT3 (N1 [%])	**381 (55.7)**	**26 (41.9)**	**36 (30.0)**	**56 (60.9)**	**104 (66.2)**	**68 (64.8)**	**91 (61.5)**
Duration$ (mo)	3.5 (0–36)	2.9 (1–36)	5.3 (1–12)	2.9 (0–12)	3.5 (0–31)	4.9 (0–31)	2.8 (0–26)
Regimen 1	**TRA+CT**	**T-DXd**	**TRA+CT**	**Lapatinib+CT**	**CP**	**TRA+CT**	**TRA+CT**
n/N1 (%)	64 (16.8)	8 (30.8)	10 (27.8)	15 (26.8)	23 (22.1)	23 (33.8)	13 (14.3)
Regimen 2	**Lapatinib+CT**	**TRA+PTZ+CT^**	**T-DXd**	**T-DM1**	**DXR^**	**T-DM1$**	**TRA+PTZ+CT**
n/N1 (%)	53 (13.9)	3 (11.5)	6 (16.7)	10 (17.9)	22 (21.2)	8 (11.8)	12 (13.2)

$Data presented as median (range)
*Excluding TRA, PTZ, T-DM1, T-DXd, and lapatinib
#An equal proportion of patients received Cyclophosphamide (CP: 14/148 [9.5%]) as regimen 2 in LOT2 in the Republic of Korea
^An equal proportion of patients received TRA (3/26 [11.5%]) as regimen 2 in LOT3 in Australia
^ Doxorubicin/liposomal doxorubicin
$An equal proportion of patients received TRA + HT (8/68 [11.8%]) and lapatinib + CT (8/68 [11.8%]) as regimen 2 in LOT3 in Singapore

Figure 1: KM curves for rwOS for the top regimens in LOT1 by country

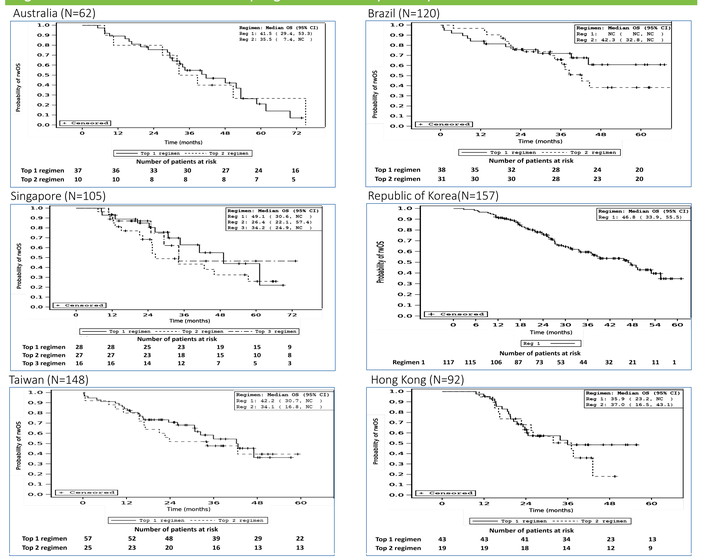
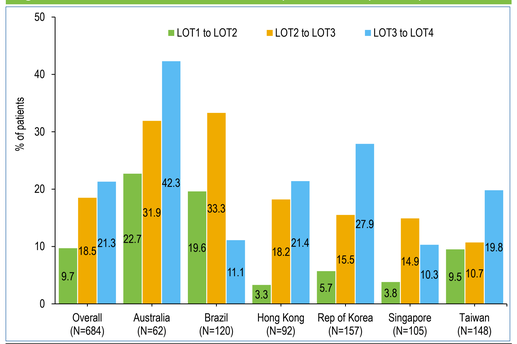


Figure 2: Real-world attrition rates for the top three LOTs by country



LOT (n [%])	Overall (N=684)	Australia (N=62)	Brazil (N=120)	Hong Kong (N=92)	Rep of Korea (N=157)	Singapore (N=105)	Taiwan (N=148)
LOT1	670 (98.0)	62 (100)	107 (89.2)	92 (100)	157 (100)	105 (100)	147 (99.3)
Patients ongoing	9/670 (1.3)	1/62 (1.6)	5/107 (4.7)	1/92 (1.1)	0	0	2/147 (1.4)
Attrition	65/670 (9.7)	14/62 (22.6)	21/107 (19.6)	3/92 (3.3)	9/157 (5.7)	4/105 (3.8)	14/147 (9.5)
LOT2	596 (87.1)	47 (75.8)	81 (67.5)	88 (95.6)	148 (94.3)	101 (96.2)	131 (88.5)
Patients ongoing	105/596 (17.6)	6/47 (12.8)	18/81 (22.2)	16/88 (18.2)	21/148 (14.2)	18/101 (17.8)	26/131 (19.8)
Attrition	110/596 (18.5)	15/47 (31.9)	27/81 (33.3)	16/88 (18.2)	23/148 (15.5)	15/101 (14.9)	14/131 (10.7)
LOT3	381 (55.7)	26 (41.9)	36 (30.0)	56 (60.9)	104 (66.2)	68 (64.8)	91 (61.5)
Patients ongoing	247/381 (64.8)	6/26 (23.1)	16/36 (44.4)	14/56 (25.0)	11/104 (10.6)	14/68 (20.6)	22/91 (24.2)
Attrition	83/381 (21.8)	11/26 (42.3)	4/36 (11.1)	12/56 (21.4)	29/104 (27.9)	7/68 (10.3)	18/91 (19.8)
LOT4	217 (31.7)	9 (14.5)	16 (13.3)	30 (32.6)	64 (40.8)	47 (44.8)	51 (34.5)

Algorithm for calculating attrition rates:
Attrition rate for LOTn = Patients receiving LOTn – (Patients ongoing at LOTn + Patients receiving LOTn+1)

- Median rwOS ranged from 36 to 49 months for all 6 countries for TRA + PTZ + CT regimen in LOT1, with a median (95% CI) follow-up duration of 30.1 (1–167) months (Table 3/Figure 1)
- Treatment attrition rate increased from 9.7% (65/670) in LOT1 to 21.3% (14/62) in LOT4 (Figure 2)

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Abbreviations: CNS, Central nervous system; CP, cyclophosphamide; CT, chemotherapy; DXR, doxorubicin; EDC, electronic data capture; HT, hormone therapy; KM, Kaplan-Meier; LOT, line of therapy; mo, months; N, the total number of patients per country; n, number of patients in the treatment; NA, not applicable; NC, not calculable; PFS, progression-free survival; PTZ, pertuzumab; rw, real-world; SF, screen failure; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TRA, trastuzumab.