TITLE PAGE

CLINICAL STUDY REPORT NO: ML28801STUDY INFORMATION

TITLE:	**A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	ML28801
VERSION NUMBER:	1.0
STUDIED MEDICINAL PRODUCT{S}:	All medicinal products used to treat metastatic breast cancer were considered studied in this local disease registry.
COUNTRY OF STUDY POPULATION:	Greece and Cyprus
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DATE FINAL:	See electronic date stamp below

CLINICAL STUDY REPORT APPROVAL

[This space is reserved for the electronic signature of Scientific Responsible. The author of the CSR can't sign the CSR.]

	Signature	Date
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3. SYNOPSIS/ABSTRACT

TITLE

A disease registry study to prospectively observe treatment patterns and outcomes in patients with HER2-positive (HER2+) unresectable locally advanced (LA) or metastatic (m) breast cancer (BC)

KEYWORDS

Effectiveness, HER2+ unresectable LA/mBC, real-world, treatment patterns

RESEARCH QUESTION AND OBJECTIVES

This study was designed to observe anticancer treatment regimens and clinical outcomes in patients with HER2+ unresectable LA/mBC.

Study objectives

- Primary objectives: treatment regimens and their sequencing; progression-free survival (PFS).
- Secondary objectives: OS; duration of response (DoR) per anticancer treatment regimen; overall response rate (ORR) per anticancer treatment regimen
  (Response was evaluated by the Investigator according to site-/country-specific medical practice).
- Safety objectives: safety outcomes of treatment regimens.
- Other objectives included HER2 testing results and HER2 re-testing rates, among others (such as patient-reported quality-of-life, work productivity loss and healthcare resource utilization) which are not presented in the report synopsis due to the limited sample sizes.

STUDY DESIGN

This observational disease registry was a multicentre non-interventional study involving primary data collection. Enrolled patients were prospectively followed after study enrolment, with only one "on study" observational period; no visit frequency was imposed. Enrolled patients received treatments and clinical assessments as determined by their treating physician, according to routine clinical practice at each site. Patients were considered "on study" until death, withdrawal of consent, loss to follow-up, or end of study, whichever came first.

TARGET POPULATION

Patients, males or females, aged ≥18 years, with HER2+ unresectable LA/mBC, initially diagnosed ⩽6 months prior to enrolment, and able to provide written informed consent and to comply with the study protocol.

STUDY SIZE

107 eligible patients were enrolled across 10 sites (9 in Greece and 1 in Cyprus).

STUDIED MEDICINAL PRODUCT

All medicinal products used to treat mBC were considered studied in this local disease registry.

DATA SOURCES

Data collection was carried out by means of a web-based data capture system (eCRF). Patient charts/medical records and patient-reported questionnaires (paper-and-pencil self-administered format) were used as data sources.

STATISTICAL AND EPIDEMIOLOGICAL METHODS

Statistical analyses were performed using SAS® software Version 9.4 [SAS Institute Inc., Cary, NC, USA]. Methods pertaining to the results presented in the report synopsis were as follows: summary statistics were calculated for continuous variables, and frequencies for categorical variables; for time-to-event analyses, the Kaplan-Meier (KM) method was implemented; PFS was censored at the last response assessment; OS was censored at the last date known to be alive/date of last contact/date of last visit; no imputation of missing values was applied.

RESULTS

From 12-October-2016 (First Patient In) to 27-December-2018 (Last Patient In), 108 patients were consecutively enrolled; one patient did not fulfill all eligibility criteria thus was excluded from the analysis set. Patients participated in the study for a median (IQR) of 33.7 (16.9, 58.3) months, with main reasons for study completion being 'physician decision' (31.8%; 34/107), 'lost to follow-up' (30.8%; 33/107) and 'death' (27.1%; 29/107). Key patient characteristics, primary and secondary outcomes, and safety analysis results are presented in the table below. The KM-estimated median follow-up time was 38.1 months. The number of PD events recorded for each patient was ≤1, therefore PFS analysis was performed in the 1L setting only.

Patient and disease characteristics at screening/enrolment.	
	% (n/N)
Overweight/obese (BMI >25 kg/m^2)	63.0 (63/100)
Ever smoker (i.e., current or ex-smoker)	30.8 (33/107)
Postmenopausal	75.5 (80/106)
ECOG PS ≥1	26.2 (28/107)
Ductal histology at the time of initial diagnosis	80.4 (78/97)
De novo stage IIIB-C / IV	17.5 (18/103) / 44.7 (46/103)
HR+ (ER+ and/or PgR+)	57.0 (57/100)
Neoadjuvant and/or adjuvant treatment for early stage BC	32.7 (35/107)
mBC at enrolment/screening	84.0 (89/106)
Most common (reported in ≥20.0%): Bone metastasis	38.7 (41/106)
Liver metastasis	38.7 (41/106)
Lung metastasis	21.7 (23/106)
Number of HER2 testings at enrolment/screening (N_{pt}= 107)	115 (min-max: 1-2; ISH in 27 and IHC in 88)
Number of testings with IHC result 1+ / 2+ / 3+	1 / 3 / 84
HER2 re-testing rate during the observation period, % (n/N)	11.2% (12/107); positive in 9 of 10 evaluable patients
Anticancer treatment regimen *(defined as any anticancer medication, used as a single agent or as part of a combination of medications given from the date of initiation until the date of PD)*	
1L therapy setting *(i.e., prior to 1st PD)*	**% (n/N)**
TRASTU + PERTU + ChT (± other TT)	57.9% (62/107)
TRASTU + PERTU + ChT + HT (± other TT)	26.2% (28/107)
TRASTU (± PERTU) + HT	5.6% (6/107)
TRASTU (± PERTU) + ChT	3.7% (4/107)
TRASTU + HT + ChT (± other TT)	2.8% (3/107)
ChT only	1.9% (2/107)
TRASTU + HER2 TKI	0.9% (1/107)
T-DM1 + HT	0.9% (1/107)
>1L therapy setting *(i.e., after 1st PD until end of study participation, as no other PD was recorded)*	**% (n/N)**
T-DM1-based without HER2 TKI	41.0% (16/39)
T-DM1-based with HER2 TKI	33.3% (13/39)
Other/non-T-DM1-based	25.6% (10/39)
Relevant sequences of treatment regiments *(among those proceeding to >1L in this study)*	**% (n/N)**
1L TRASTU ± any other therapy → T-DM1 ± any other therapy	71.8% (28/39)

1L TRASTU+PERTU ± any other therapy → T-DM1 ± any other therapy						64.1% (25/39)
PFS in the 1L setting						
		PFS		**ORR**	**DoR**	
		% censored	**Median (95% CI), months**	**% ($n_{CR/PR}/N_{with\ ≥1\ assessment}$)**	**N[a]**	**Median (IQR), months**
Overall		35.5	23.5 (14.3-27.5)	73.9 (68/92)	39	11.3 (4.9, 24.2)
1L treatment subgroups	TRASTU+PERTU+ChT	25.8	13.5 (8.8-22.3)	70.0 (35/50)	27	11.0 (4.9, 21.3)
	TRASTU+PERTU+ChT+HT	57.1	37.7 (27.4-N/A)	89.3 (25/28)	6	25.1 (22.8, 33.6)
	Other	35.3	27.1 (7.5-30.5)	57.1 (8/14)	6	6.9 (2.5, 20.7)

OS				
	% censored	**Median (95% CI), months**	**3-year rate, % (95% CI)**	**5-year rate, % (95% CI)**
Overall	72.9	Not reached (N/A)	74.6 (64.0-82.5)	62.4 (49.4-72.9)

Adverse events and adverse reactions		
	n_{events}	**n_{pt} (%)**
At least one (N)SAE	541	81 (75.7)
At least one SAE	37	20 (18.7)
At least one (N)SADR	257	60 (56.1)
At least one SADR	5	5 (4.7)
MedDRA PT: Diarrhoea[a]	2	2 (1.9)
MedDRA PT: Acute kidney injury[a], Febrile neutropenia[a], Hypersensitivity[b]	1, each	1 (0.9), each
(N)SAEs of special interest	.	.
(N)SADRs of specific interest[c]	6	5 (4.7)
(N)SAEs leading to anticancer treatment dose adjustment	23	12 (11.2)
(N)SAEs leading to anticancer treatment dose interruption	17	12 (11.2)
(N)SAEs leading to anticancer treatment discontinuation	6	6 (5.6)
(N)SAEs that led to death	4	4 (3.7)
Deaths during the observation period	29	29 (27.1)

[a]Related to docetaxel. [b]Related to paclitaxel. [c]Ejection fraction decreased (related to PERTU/TRASTU in 2 patients; related to PERTU/TRASTU/docetaxel in 2 patients) and pneumonitis (related to 'other TT' in 1 patient); all events were non-serious. Abbreviations: 1L, first-line; BC, breast cancer; BMI, body mass index; ChT, chemotherapy; CI, confidence interval; CR, complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HT, hormonal therapy; HC, immunohistochemistry; IQR, interquartile range (Q1, Q3); mBC, metastatic BC; MedDRA PT, Medical Dictionary for Regulatory Activities Preferred Term; (N)SADR, (non)serious adverse drug reaction; (N)SAE, (non)serious adverse event; ORR, overall response rate; OS, overall survival; PERTU, pertuzumab; PFS, progression-free survival; PgR, progesterone receptor; PR, partial response; SADR, serious adverse drug reaction; SAE, serious adverse event; T-DM1, ado-trastuzumab emtansine; TKI, tyrosine kinase inhibitor; TRASTU, trastuzumab; (other) TT, targeted therapy other than anti-HER2 (i.e., bevacizumab and/or denosumab).

CONCLUSIONS

The majority of HER2+ unresectable LA/mBC patients were treated with guideline-recommended therapies as 1L treatment, accompanied by a high response rate and half of patients being free of disease progression/death at 2 years after treatment initiation.