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Long-term Response Patterns in HER2-Positive Advanced Breast Cancer within the GEICAM/2014-03 (RegistEM) study

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INTRODUCTION

- Breast cancer (BC) is a heterogeneous disease with distinct subtypes, each having different prognosis and treatment responses (1).
- Significant advances have led to better median overall survival (OS) in patients (pts) with HER2+ BC (2).
- Targeted anti-HER2 therapies have changed the management and prognosis of HE2+ advanced BC (ABC), although there is a lack of data from long-term responders (LTRs) (3, 4).
- The RegistEM (GEICAM/2014-03) study aims to understand the distribution of subtypes in ABC and their clinical implications. This is a multicenter, retrospective and prospective, non-interventional observational study, recruiting ABC patients, with either recurrent early BC (EBC) or de novo metastatic BC (*dn*MBC), diagnosed from Jan-16, and with ≥5 years of follow-up (ClinicalTrials.gov NCT02819882) (5).

OBJECTIVES OF THE CURRENT ANALYSIS

- To better characterize LTRs among HER2+ ABC patients with 1st-line (1L) or 2nd-line (2L) based on anti-HER2 targeted therapies.

MATERIAL AND METHODS

- Female and male ABC patients from the RegistEM study diagnosed since Jan-2016 to Dec-19 were enrolled in this analysis.
- Biological samples from primary tumors, metastatic lesions, and blood were collected.
- BC subtype was assessed by immunohistochemistry (IHC) with or without *in situ* hybridization (ISH), in the most recent tumor sample before 1L, at local laboratory.
- In the current analysis, 1900 evaluable patients enrolled at 38 GEICAM sites were considered (database ongoing, cut-off date 17-Mar-2025).
- 341/1900 (18%) patients had HER2+ ABC; 11 patients excluded caused by lack of data or because they did not receive treatment for ABC.
- We defined LTR when progressive disease (PD) was not reported to 1L for >35 months (mo.) and/or 2L for >16 mo.

LTR	1L	2L	1L and 2L	Total
n (%)	82 (62%)	38 (29%)	13 (9%)	133 (100%)

- Oligometastatic disease was considered when ≤2 organs were involved, with up to 5 lesions per organ (further analysis with this definition).
- Median follow-up (FU) at cut-off date was of 46 mo (range: 0,8-108).

RESULTS

Table 1. Characteristics at ABC diagnosis[A] (1L and/or 2L LTR)

	LTR n=133 (40%)	NLTR n=197 (60%)
Age at ABC diagnosis, years		
Median	56	56
Q1; Q3	47; 65	48; 70
Menopausal status at ABC diagnosis, n (%)		
Postmenopausal	84 (67)	138 (72)
Premenopausal	41 (33)	55 (28)
Extension of BC at ABC diagnosis, n (%)[B]		
Recurrent EBC	64 (48)	119 (60)
de novo MBC	69 (52)	78 (40)
Hormone receptor (ER and/or PgR) status, n (%)		
Positive	92 (69)	122 (62)
Negative	41 (31)	75 (38)
HER2 status by IHC, n (%)		
IHC 0*	2 (2)	0
IHC 1+*	4 (3)	6 (3)
IHC 2+*	23 (17)	43 (22)
IHC 3+	89 (67)	140 (71)
IHC not done (ND)*	15 (11)	8 (4)
HER2 status by ISH, n (%)		
Amplified by ISH	55 (41)	81 (41)
Organs involved, n (%)[C]		
Visceral (+/- bone)	77 (58)	149 (76)
Bone (non-visceral)	36 (27)	32 (16)
Soft tissue only	20 (15)	15 (8)
Most common metastatic locations (≥10%), n (%)		
Lymph node	69 (52)	106 (54)
Bone	66 (50)	102 (52)
Liver	40 (30)	79 (40)
Lung	37 (28)	69 (35)
Skin and sc tissue	16 (12)	11 (6)
Number of metastatic locations, n (%)		
1	40 (30)	39 (20)
2	27 (20)	57 (29)
3	43 (32)	52 (27)
4	17 (13)	38 (19)
≥5	6 (5)	10 (5)

[A] All patients were female. [B] The difference between LTR and NLTR was statistically significant (P=0.0276). [C] A different pattern of metastatic spread was observed between LTR and NLTR (P=0.002, X^2 test). *: All amplified by ISH.

Table 2. Characteristics of pts with recurrent EBC (1L and/or 2L LTR)

	LTR n=64 (35%)	NLTR n=119 (65%)
Stage at EBC diagnosis, n (%)		
	n=56	n=113
I	10 (18)	11 (10)
IIA	14 (25)	30 (27)
IIB	13 (23)	32 (28)
IIIA	10 (18)	18 (16)
IIIB	6 (11)	9 (8)
IIIC	3 (5)	13 (12)
Time to recurrence (at distance), years		
Median (IQR)	4.6 (2.5 – 9)	4 (2.1 – 8.5)
Prior therapy for EBC, n (%)		
AT	36 (59)	55 (49)
NAT + AT	20 (33)	46 (41)
NAT	5 (8)	11 (10)

Table 3. Stage at 1st diagnosis in 1L LTR

	1L LTR (n=95, 29%)	1L NLTR (n=235, 71%)
Extension of disease at ABC diagnosis, n (%)		
Recurrent EBC	44 (46)	139 (59)
de novo MBC + ULABC	51 (54)	96 (41)
Time to recurrence for EBC patients, n (%)		
≤ 1 year	4 (9)	11 (8)
> 1 year	40 (91)	128 (92)

Table 4. PFS and OS for LTR and NLTR (1L and/or 2L)

	LTR		NLTR	
No. of patients	**133**	**77**	**197**	**142**
Median FU from ABC, mo.	**77**		**31**	
Line	**1L**	**2L**	**1L**	**2L**
Median PFS, mo. and 95% CI	50 42–64	23 19–30	12 10–13	5 4–7
Median OS from ABC, mo. and 95% CI	Not reached		34 31 – 38	
Deaths, %	23% (PD 65%)		76% (PD 77%)	

Figure 1. Type of therapies for 1L and 2L (LTR vs. NLTR)

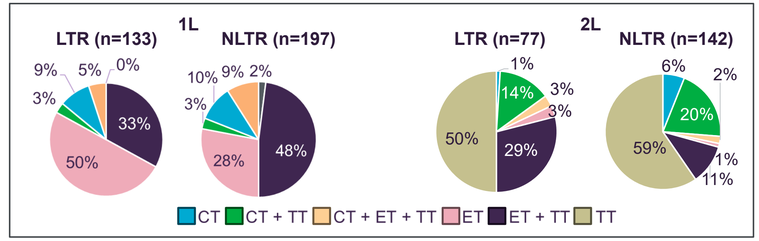


Figure 2. Type of anti-HER2 therapies for 1L and 2L in LTR vs. NLTR patients (%)

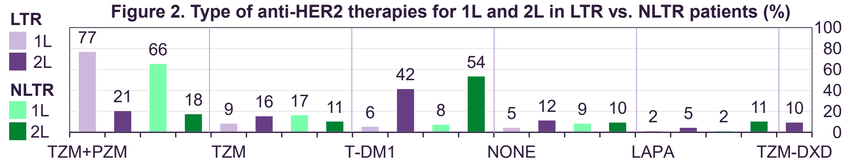


Figure 3. 1L PFS (mo.) by anti-HER2 therapy

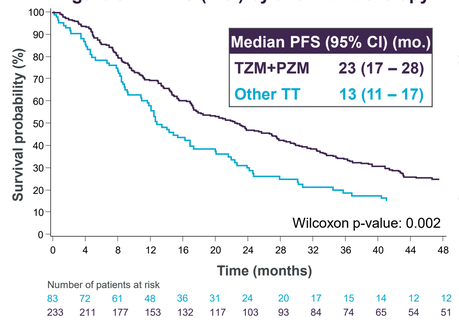
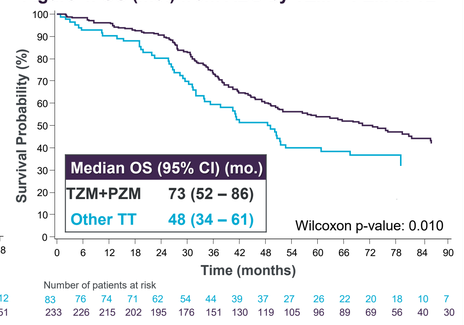


Figure 4. OS (mo.) from ABC by TZM + PZM in 1L



Multivariate logistic regression analysis (LTR vs. NLTR)

- Variables: stage at 1st diagnosis, menopausal status, HR status, metastatic locations, presence of oligometastatic disease and age at ABC diagnosis.
- Stage at 1st diagnosis, metastatic locations and oligometastatic disease demonstrated a statistically significant association with LTR. Specifically, *de novo* MBC (compared to EBC), non-visceral disease and oligometastatic disease had increased odds of LTR.

Abbreviations: AI= aromatase inhibitors; AT= adjuvant therapy; BT= biological therapy; CI = confidence interval; CT= chemotherapy; ER = estrogen receptor; ET= endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IQR = interquartile range; LAPA = Lapatinib; NA = not applicable; NAT= neoadjuvant therapy; NLTR: non LTR; NR = not reached; PgR = progesterone receptor; PZM = pertuzumab; Q = quartile; SC=subcutaneous; T-DM1= trastuzumab emtansine; TT= Targeted therapy; TZM= trastuzumab.

CONCLUSIONS

- **In our cohort, HER2+ ABC patients classified as LTR, more frequently had bone or soft tissue-only metastases compared to visceral disease.**
- **No significant differences were observed between LTR vs. NLTR in terms of HR, HER2-IHC score (3+ vs. 2+).**
- **Patients with de *dn*MBC (compared to EBC), and with oligometastatic disease had increased odds of being LTR.**

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