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Unraveling Trastuzumab emtansine (T-DM1) resistance in HER2+ advanced breast cancer GEICAM/2017-04-KATIA study: biomarker analyses

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GEICAM 30 years researching breast cancer

BACKGROUND AND OBJECTIVE

- T-DM1 (Trastuzumab emtansine; Kadcyla) remains a relevant therapeutic option for patients with HER2-positive metastatic breast cancer (HER2+ MBC), particularly for those who have previously received trastuzumab and taxane-based therapies.
- Despite its clinical utility, the mechanisms underlying both primary and acquired resistance to T-DM1 remain largely uncharacterized, limiting the ability to optimize treatment strategies and identify patients most likely to benefit from this therapy[1-3].
- The aim was to perform a comprehensive and integrated characterization of the mechanisms of primary and acquired resistance to T-DM1 in a prospective cohort of progressive/recurrent HER2+ Breast Cancer (BC) patients[4].

MATERIALS AND METHODS

- The KATIA study (NCT03829306) was a prospective, multicenter study in progressive/recurrent HER2+ MBC patients treated with second-line T-DM1 (Figure 1).
- Tumor and plasma samples were collected from 32 (100%) patients.
- Genomic profiling was performed on pre-treatment baseline (BL) metastatic tumors (n=18, 56%), and on liquid biopsies at BL (n=20, 62,5%) and at disease progression (n=12, 37,5%) using the FoundationOne CDx and FoundationOne liquid CDx assays (324-gene NGS panels; Foundation Medicine).
- Additionally, we analyzed a 77-gene NGS panel on circulating tumor DNA (AVENIO ctDNA Expanded Kit V2, Roche, n=31, 97%).
- HER2, Ki67, Estrogen and Progesterone Receptors (ER and PR) status and the tumor immune microenvironment markers (PD-L1 (PD-L1 CPS score ≥1 were considered positive), PD1, CD3, CD8, tumor-infiltrating lymphocytes) were analyzed on BL tumors (n=26, 81%) by immunohistochemistry (IHC).
- We examined the association of biomarkers and mutations detected with Objective Response Rates (ORR), as independent variables, by Fisher test for categorical variables, and Mann-Whitney for continuous variables (adjusting for multiple comparisons by Bonferroni method).
- The Kaplan-Meier method estimated median progression free survival (PFS) and overall survival (OS). Hazard ratios (HR) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models.

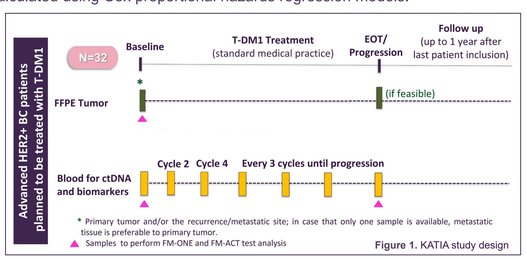


Figure 1. KATIA study design

RESULTS

Patient disposition and demography

- ✓ Between November 2018 and March 2021, 33 women were included in the study (1 of them withdrew consent for participation in the study before receiving treatment).
- ✓ The median age was 60 years; 91% were postmenopausal.
- ✓ Primary tumors: 48.5% had histologic grade 3, and 15.2% had histologic grade 2 and 12.1% had histologic grade 1 tumors. 69.7% were M0 at initial diagnosis.
- ✓ Metastatic tumors: 18.2% had histologic grade 3, and 18.2% had histologic grade 2 and 3% had histologic grade 1 tumors.
- ✓ 61% of patients were ER+, 27% were PgR+, and 67% of patients had Ki67 index ≥ 30%.

Primary endpoint: Objective Response Rate (ORR)

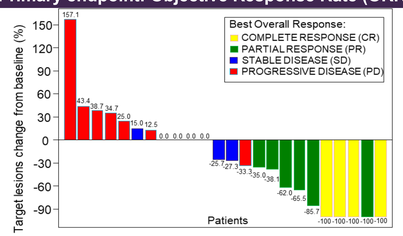


Figure 2: Waterfall plot indicating % change of target lesions from BL in the efficacy population (n=31). CR: n=4 (12.9%); PR: n=7 (22.6%); SD: n=7 (22.6%); PD: n=8 (25.8%). No post-baseline Response assessment: n=5 (16.1%). The ORR was 35.5% (n=11) Complete Response + Partial Response (95% CI:19.2%–54.6%). The Clinical benefit rate (CBR) was 58.1% Complete Response + Partial Response + Stable Disease of any duration (95% CI:39.1%–75.5%).

Progression Free Survival (PFS)

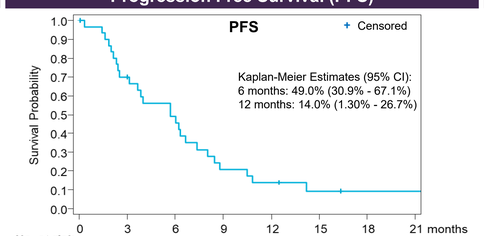


Figure 3: Kaplan-Meier survival analysis. In the secondary analysis of PFS for the ITT population (n=33), 84.4% of patients (n=27) had events and 15.6% (n=5) were censored. The median PFS was 5.7 months (95% CI: 3.2–7.4).

Overall survival (OS)

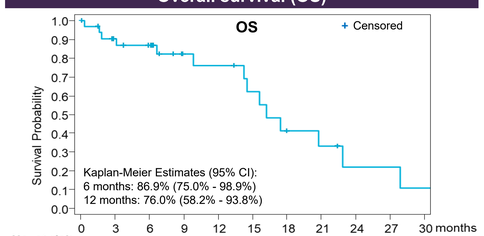
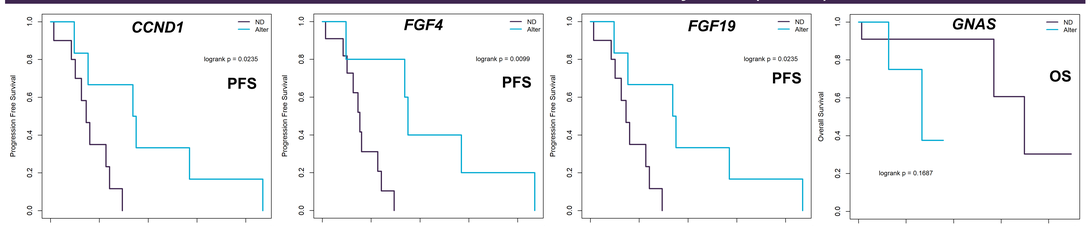


Figure 4: Kaplan-Meier survival analysis. In the secondary analysis of OS for the ITT population, 45.5% (n=15) of patients had events and 54.5% (n=18) were censored. The median OS was 16.2 months (95% CI: 14.2–22.9).

Biomarker results: alterations detected in tumors by F-ONE (PFS/OS)



#mut	N	Events	mPFS
0 (ND)	10	9(90%)	3.65
1 (Alter)	6	6(100%)	8.61

HR (CI95%): 0.19 (0.04-0.92); P=0.039

#mut	N	Events	mPFS
0 (ND)	11	10(90.9%)	3.84
1 (Alter)	5	5(100%)	8.77

HR (CI95%): 0.1 (0.01-0.79); P=0.0298

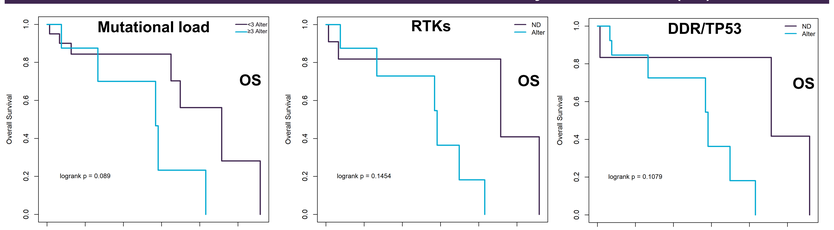
#mut	N	Events	mPFS
0 (ND)	10	9(90%)	3.65
1 (Alter)	6	6(100%)	8.61

HR (CI95%): 0.19 (0.04-0.92); P=0.039

#mut	N	Events	mOS
0 (ND)	11	3(27.3%)	17.45
1 (Alter)	5	2(40%)	6.67

HR (CI95%): 4.63 (0.42-51.09); P=0.2111

Biomarker results: alterations detected in ctDNA by F-ACT/AVENIO (OS)



#mut	N	Events	mOS
<3 Alter	20	7(35%)	22.87
≥3 Alter	8	5(62.5%)	14.23

HR (CI95%): 2.85 (0.81-10.01); P=0.1032

#mut	N	Events	mOS
0 (ND)	11	4(36.4%)	22.87
1 (Alter)	8	6(75%)	14.55

HR (CI95%): 3.15 (0.62-16); P=0.1658

#mut	N	Events	mOS
0 (ND)	6	3(50%)	22.87
1 (Alter)	13	7(53.8%)	14.55

HR (CI95%): 4.98 (0.59-42.32); P=0.1416

Central biomarkers assessment by IHC in BL tumors:

- ✓ PD-L1 was positive in 12 (39%) patients and negative in 14 (45%).
- ✓ Median PD1 was 4% (0% - 35%)
- ✓ Median TILs were 5% (0% - 65%)
- ✓ Median CD3 was 25% (0% - 50%)
- ✓ Median CD8 was 27.5% (0% - 50%)
- ✓ Median Ki67 was 18.7% (2% - 65%)

The results showed no significant association of any of the biomarkers assessed by IHC with Objective Response.

Figure 5: Cox regression and Kaplan-Meier survival analysis from selected mutations/pathways assessed. Genomic profiling was performed on available pre-treatment BL tumor (by F-ONE) and plasma samples at BL and at progression by both F-ACT and AVENIO Expanded tests. Tumor BL mutations detected by F-ONE in *CCDN1*, *FGF4* or *FGF19* predicted better median PFS (*CCDN1*: 8.61 vs. 3.65 m. with no mutations detected (ND), HR 0.19; 95% CI 0.04-0.92, p=0.039; *FGF4*: 8.77 vs. 3.84 m., HR 0.1; 95% CI 0.01-0.79, p=0.0298; *FGF19*: 8.61 vs. 3.65m., HR 0.19; 95% CI 0.04-0.92, p=0.039). However, *GNAS* mutations in BL tumors showed a trend towards worse mOS (6.67 m. with mutations detected in GNAS vs. 17.45 m. with no mutations detected, HR 4.63; 95% CI 0.42-51.09, p=0.21). Tumor burden ctDNA analyses by AVENIO Expanded test revealed that having ≥3 BL mutations showed a trend towards worse mOS (14.23 m. with ≥3 mutations vs. 22.87 m. with <3 mutations, HR 2.85; 95% CI 0.91-10.01, p=0.1032). Additionally, ctDNA BL mutations detected by F-ACT in the following pathways showed a trend towards worse mOS: receptor tyrosine kinases (RTKs: 14.55 m. with mutations detected in RTKs pathway vs. 22.87 m. with no mutations detected, HR 3.15; 95% CI 0.62-16, p=0.17) or DNA damage response/TP53 (DDR/TP53: 14.55 m. with mutations detected in DDR/TP53 pathway vs. 22.87 m. with no mutations detected, HR 4.98; 95% CI 0.59-42.32, p=0.14).Similar results were obtained with mutations detected in the same pathways (RTKs and DDR/TP53) at disease progression (data not shown). The results showed no significant association of any of the alterations detected by genomic profiling with Objective Response (data not shown).

CONCLUSIONS

- ✓ Baseline tumor mutations in *CCDN1*, *FGF4* or *FGF19* genes were significantly associated with longer PFS in HER2+ MBC patients treated with second line T-DM1 (Trastuzumab emtansine; Kadcyla), suggesting their potential role as predictive biomarkers of treatment benefit.

REFERENCES

1. *Verma S, et al. N Engl J Med 2012; 367:1783-1791*
2. *Hunter FW. Br J Cancer. 2020;122(5):603-612.*
3. *Barok M, et al. Breast Cancer Res 2014;16(2):209.*
4. Rojo Todo F., et al. "354TiP Unraveling trastuzumab emtansine resistance in HER2-positive advanced breast cancer: GEICAM KATIA study". *Annals of Oncology, Volume 31, S391. https://www.annalsofoncology.org/article/S0923-7534(20)40452-1/fulltext*

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