Ultrasensitive ctDNA Tracking Predicts Exceptional Response in HER2+ Metastatic Breast Cancer

Morganti S.[1-3*], Song C.[3*], Zhou N.[1], Santos K.[1,3], Jain P.[3], Walsh L.[3], Rhoades J.[3], Gilligan K.[3], Kirkner G.[1], Stever C.[1], Patel A.[1], Hughes M.E.[4], Priedigkeit N.[1-3], Krop I.[4], Curigliano G.[5,6], Winer E.P.[4], Tolaney S.M.[1,2], Tayob N.[1,2], Li T.[1], Heiling H.[1], Xiong K.[3], Lin N.U.[1,2], Adalsteinsson V.A.[3^], Parsons H.A.[1-3,7^]

1. Dana-Farber Cancer Institute, Boston, MA; 2. Harvard Medical School, Boston, MA; 3. Broad Institute of MIT and Harvard, Boston, MA; 4. Yale Cancer Center, New Haven, CT; 5. University of Milan, Milan, Italy; 6. European Institute of Oncology IRCCS, Milan, Italy; 7. Fred Hutch Cancer Center, Seattle, WA (current affiliation)

*these authors contributed equally; ^these authors contributed equally

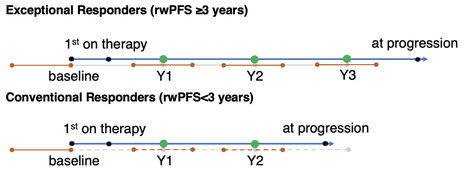
BACKGROUND

- HER2-targeted therapies have transformed the trajectory of HER2-positive (HER2+) metastatic breast cancer (MBC), with a subgroup of responders remaining on first line (1L) therapy for many years[1].
- The treatment paradigm for MBC is still palliative, with patients receiving therapy indefinitely[2].
- Detection of minimal residual disease (MRD) via ctDNA to guide tx is promising but data supporting its use in HER2+ MBC are virtually absent.

METHODS

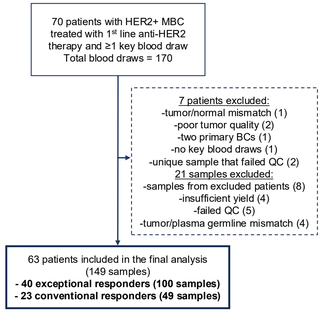
- **Inclusion Criteria:**
- HER2+ MBC treated with 1L HER2 targeted therapy seen at Dana-Farber Cancer Institute and consented to the EMBRACE cohort study.
- Archival tumor tissue, buffy coat and plasma at ≥1 key timepoints while on 1L therapy (year [Y] 1 landmark [L], Y2L, Y3L). If available, samples collected at baseline, first-on-therapy, and at time of disease progression (PD) were also analyzed.
- **Primary objective:** To assess the association between Y1L MRD status (plasma samples collected 1 yr from 1L start +/- 3 months) and exceptional response.
- Exceptional responders were patients without PD that led to treatment switch, or death, for ≥3 years from 1L start (real-world progression-free survival [rwPFS] ≥3 years). Late Progressors were Exceptional responders with PD or death occurring after Y3.
- Conventional responders were patients with PD that led to treatment switch, or death, within 3 years of 1L start (rwPFS<3 yrs).
- Baseline clinicopathological features were compared between exceptional and conventional responders. Median rwPFS and overall survival were estimated via the Kaplan-Meier method and with a landmark analysis at year 3 for Exceptional Responders. P values <0.05 were statistically significant.
- Tumor fraction (TFx), limit of detection (LOD95), and MRD status were determined using MAESTRO* (Minor Allele Enriched Sequencing Through Recognition Oligonucleotides), an ultrasensitive, whole-genome, tumor-informed, mutation enrichment sequencing assay, in a pooled testing format in which all bespoke assays are applied to all samples from all patients (MAESTRO-Pool)[3,4].
- TFx was defined as the fraction of tumor-derived cfDNA fragments; LoD95 as the minimal TFx estimated to be detected with 95% probability based on the number of cfDNA molecules and tumor mutations assayed in a given sample.

STUDY DESIGN

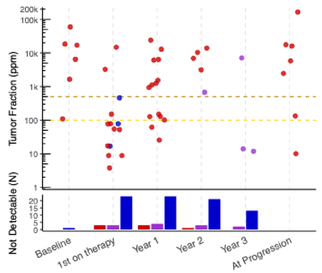


REFERENCES: 1. Swain S, et al., Lancet Oncol, 2020; 2. Gennari A. et al., Ann Oncol 2022; 3. Gydush G et al., Nat Biomed Eng, 2022. 4. Blewett T et al., Clin Chem 2024

RESULTS



REMARK diagram of the study cohort



Tumor fraction distribution at the key timepoints



- A median of 1,382 (range 138-4,635) tumor-specific mutations were tracked per patient.
- 49 (32.9%) samples were MRD+ (median TFx 936.4 ppm; range 3.79-164,068 ppm).
- 23 (46.9%) of MRD+ samples had TFx <500 ppm (LOD95 of tumor-agnostic MBC assays).
- 15 (30.6%) of MRD+ samples had TFx <100 ppm (LOD95 of 1st generation tumor-informed MRD tests).

Variable	Total (63)	Exceptional Responders (40)	Conventional Responders (23)	p value
Median age	48.5(26.0-72.8)	48.0(26.0-72.3)	50.4(26.9-72.8)	0.392
Tumor Stage				
I-II-III	25(39.7%)	12(30.0%)	13(56.5%)	0.060
De novo metastatic	38(60.3%)	28(70.0%)	10(43.5%)	
Racial Background				
White	52(82.5%)	34(85.0%)	18(78.3%)	
African American	5(7.9%)	1(2.5%)	4(17.4%)	0.244
Asian, Pacific Islander	4(6.3%)	3(7.5%)	1(4.3%)	
Other	2(3.2%)	2(5.0%)	0(0.0%)	
1st line regimen				
chemotherapy + HP	50(79.4%)	33(82.5%)	17(73.9%)	0.511
others	13(20.6%)	7(17.5%)	6(26.1%)	
1L maintenance ET (if ER+)	19(79.2%)	14(87.5%)	5(62.5%)	0.300
HER2 status				
2+/FISH amplified	10(15.9%)	4(10.0%)	6(26.1%)	0.238
3+	51(81.0%)	34(85.0%)	17(73.9%)	
Unknown	2 (3.2%)	2(5%)	0(0%)	
ER status				
Negative	39(61.9%)	24(60.0%)	15(65.2%)	0.800
Positive	24(38.1%)	16(40.0%)	8(34.8%)	
Visceral disease	39(61.9%)	24(60.0%)	15(65.2%)	0.783
Brain metastases	11(17.5%)	6(15.0%)	5(21.7%)	0.738

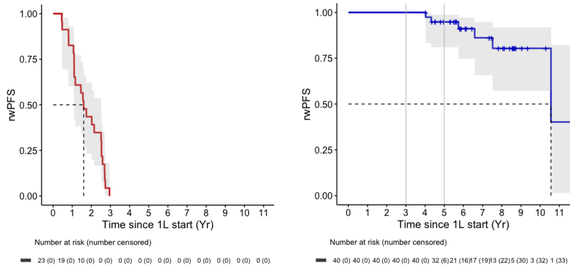
Clinicopathological characteristics and treatment patterns

- Most patients had *de novo* MBC at diagnosis, high (3+ by IHC) HER2 expression, ER-negative disease, and had visceral metastases at diagnosis.
- All features were similar between exceptional and conventional responders.
- Most patients in both groups had 1L chemotherapy/HP and maintenance endocrine therapy if ER-positive.

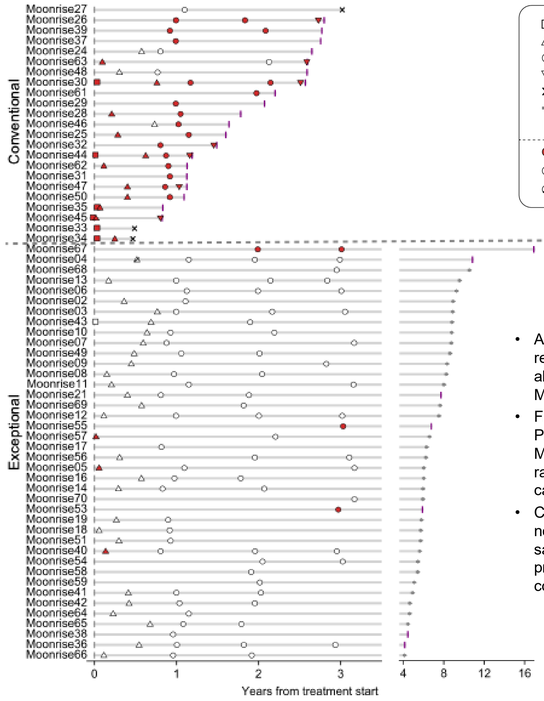
- Y1L MRD status was associated with exceptional vs conventional response (p<0.001).

	Exceptional Responders (N=27)	Conventional Responders (N=12)	p value
Y1 MRD status			
Positive	0 (0.0%)	9 (75.0%)	<0.001
Negative	27 (100.0%)	3 (25.0%)	

- With 289.9 person-yrs of follow up, 7/40 exceptional responders had late PD.
- In a landmark analysis at Y3, the 2-yr rwPFS was 94.9% (95%CI 81.%-98.7%) (5 yrs from 1L start); 5-yr overall survival (OS) was 88.7% (95%CI 67.6%-96.4%) (8 yrs from 1L start).
- For conventional responders, total follow up was 101.3 person-yrs, median rwPFS was 1.6 yrs (95%CI 1.1-2.51), median OS was 4.58 yrs (95%CI 3.78-6.48).



Real World PFS for conventional responders (left) and exceptional responders (right)



- All exceptional responders who remained progression-free were always MRD- (n=30) or cleared MRD by Y1L (n=3).
- Five of the 7 patients who had late PD had a Y3L sample, which was MRD+ in 3 out of 5 cases (lead time range 2.77-13.47 yrs). One MRD- case had breast-only progression.
- Considering only progression and not death as events, the last sample collected before progression was MRD+ for 18/20 conventional responders.

Swimmer plot of the study cohort

CONCLUSIONS

- We report, to our knowledge, the first data showing a significant association between ultrasensitive MRD detection and duration of response to 1L therapy for HER2+ MBC.
- MRD status at Y1L was highly predictive of exceptional response.
  - All (100%) exceptional responders had cleared MRD at the Y1L timepoint; whereas 75% of conventional responders were MRD+.
- All but one exceptional responders with late distant progression were MRD+ at the Y3L timepoint.
- 15 (30.1%) MRD+ samples had TFx<100ppm and would have been misclassified by 1st generation MRD tests.
- Prospective clinical trials implementing ultrasensitive MRD tracking as integral biomarker to guide treatment tailoring for patients with HER2+ MBC are warranted.

Acknowledgments: METAvivor, AIRC/Gianni Bonadonna Foundation, Susan G. Komen, National Cancer Institute, Gerstner Philanthropies, Saverin Family, American Association for Cancer Research (Scholar–in-Training Award).
Financial Disclosure (Morganti S): Daiichi-Sankyo (consultancy, not related to this project), AstraZeneca (expense reimbursement; not related to this project), Precede Biosciences (research funding to the Institution, not related to this project), Merck (research funding to the Institution, not related to this project).
*V. Adalsteinsson is a co-inventor of MAESTRO, which has been licensed to Exact Sciences.

#PS5-11

This presentation is the intellectual property of the author/presenter. Contact them at stefania_morganti@dfci.harvard.edu for their permission to reprint and/or distribute.