Free-HER: Discontinuation of Maintenance HER-2 Directed Therapy in Long-Term Survivors of Metastatic HER-2 Positive Breast Cancer: A Trial Update

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INTRODUCTION

While metastatic breast cancer (BC) is considered incurable, HER-2 directed therapy has enabled a subset of patients with metastatic HER-2 positive (HER2+) BC to maintain a complete radiographic (CRR) remission for years. The current standard of care is to continue anti-HER-2 therapy indefinitely, despite its associated toxicity, cost, and inconvenience. This study evaluates if maintenance HER2-directed therapy can be safely discontinued in patients with metastatic HER2+ breast cancer who have remained in CRR for ≥36 months and assesses the potential for durable remission or cure.

METHODS

- IRB-approved, single-site pilot study which seeks to enroll 20 subjects with stage IV HER2+ BC in CRR ≥36 months who have negative ctDNA at the time of enrollment.
- Financial toxicity and QOL assessments are performed.
- Study patients are monitored with ctDNA testing at 6 and 12 weeks after treatment discontinuation, and once every 12 weeks thereafter. If sufficient tissue available, Signatera ctDNA testing is used, and if not, Guardant Reveal
- Standard of care radiologic imaging occurs at 3 months after treatment discontinuation and then every 6 months.
- Patients are continued on study for a total of three years or until evidence of disease recurrence, defined as ctDNA positivity or radiographic progression of disease.
- Patients with hormone receptor positive (HR+) disease are recommended to continue hormonal treatment during the trial.

RESULTS

Table 1. Patient Demographic and Clinical Information.

Age, yr: median (range)	62 (41-86)
Duration of CRR at Enrollment, yr: Median(Range)	7 (3-17)
HER2 Status	
IHC 3+	14 (82%)
IHC 2+, FISH Positive	3 (18%)
ER Status	
ER Positive	10 (59%)
ER Negative	7 (41%)
ctDNA Testing Method	
Signatera	7 (59%)
Guardant Reveal	10 (41%)
Onset of Metastases	
De Novo	12 (71%)
Relapsed	5 (29%)
Number of Metastases	
Oligometastatic (<5)	12 (71%)
Widely Metastatic (5+)	5 (29%)

- 17 patients enrolled at this time
- At baseline, 12 of the 17 had oligometastatic disease defined as <5 metastatic sites. Sites of metastases included bone (8), liver (4), distant lymph nodes (4), lung (2), and brain (2).
- 11 patients had induction therapy with docetaxel, trastuzumab and pertuzumab (HP) and maintenance HP
- 3 patients had targeted therapy alone
- 11 patients had only been on one line of metastatic therapy prior to maintenance HER2-directed therapy, but 6 had received two or more.
- Of the 12 patients with de novo metastatic disease, 9 had local therapy to the primary breast lesion.
- 2 patients had local therapy (surgery and/or radiation) to all sites of disease; three had no local therapy to breast or metastatic sites.

RESULTS CONTINUED

Key Clinical Findings

- 2 patients developed a positive ctDNA(at 12 and 60 weeks). Both had oligometastatic disease at baseline.

12-Week Recurrence Patient:

  - CRR for 4.5 years; ER-negative.
  - ctDNA intermittently positive despite resuming HP, but no definitive radiologic PD and remains in CRR 18 months later.

60-Week Recurrence:

  - Spontaneously reverted to ctDNA-negative without restarting therapy; remains negative and disease-free for 9 months.

- One patient withdrawn due to lung nodule that was not amenable to biopsy with negative ctDNA (history of lung cancer).
- The maximum length of time on trial for any patient in the study is 29 months.
- No deaths have occurred on trial.

CONCLUSIONS

- Early findings suggest HER2-directed maintenance therapy may be safely discontinued in carefully selected metastatic HER2+ breast cancer patients who have remained in CRR for ≥36 months.
- Baseline ctDNA may help identify patients suitable for therapy discontinuation and guide intensified surveillance.

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