Prevalence and dynamics of circulating tumor DNA among patients with triple-negative breast cancer undergoing preoperative systemic therapy with or without immunotherapy

Poster #PS2-07-06

Tae-Kyung Robyn Yoo* [1,2,3,4], Stefania Morganti* [1,2,3,6], Qingchun Jin[5], Ashka Patel[1], Craig Snow[1], Katheryn Santos[1], Catherine Stever[1], Olivia Cunningham[1], Tasnim Rahman[1], Jorge Gomez Tejeda-Zanudo[6], Joanna Baginska[1], Jad Bsat[1], Melinda Luo[1], Isabella G. Martino[1], Bridget Drummey[1], Sarina Virani[1], Karen Howarth[7], Christopher Rushton[7], Sofia Birkeälv[7], Samuel Woodhouse[7], Girish Putcha[7], Effie Christoforou[8], Sophie Kirschner[8], Agrin Moeini[8], Nisar Ahmad[9], Nadine Tung[3,10], Natalie Sinclair[1,2], Meredith Faggen[1,2], Sarah Sinclair[11], Maria Constantinou[12], Steve Lo[13], Jane L. Meisel[14], Eric P. Winer[1,2,3,15], Elizabeth A. Mittendorf[16], Nabihah Tayob[1], Nancy U. Lin[1,2,3], Sara M. Tolaney[1,2,3], Ana C. Garrido-Castro[1,2,3], Heather A. Parsons[1,2,3,6]

[1]Breast Oncology Program, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Harvard Medical School, Boston, MA, USA; [4]*Present affiliation:* Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [5]Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; [6]Broad Institute, Cambridge, MA, USA; [7]SAGA Diagnostics, Morrisville, North Carolina; [8]Oncology R&D, AstraZeneca, Cambridge, United Kingdom; [9]Phelps Cancer Center, Pittsfield, MA; [10]Division of Hematology-Oncology, Beth Israel Deaconess Medical Center, Boston, MA; [11]Eastern Maine Medical Center, Brewer, ME; [12]Lifespan Cancer Institute, The Rhode Island Hospital, Providence, RI; [13]Stamford Hospital, Stamford, CT; [14]Department of Hematology and Medical Oncology, Glenn Family Breast Center, Winship Cancer Institute, Emory University, Atlanta, GA; [15]*Present affiliation:* Yale University, New Haven, CT, USA; [16]Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA, USA

Key Findings and Conclusions

- MRD detection rate was high among patients with early-stage TNBC undergoing preoperative systemic therapy.
- MRD detection rate during preoperative systemic therapy did not differ according to treatment regimen (chemo only vs chemo + IO).
- MRD not detected or showing clearance within 7 weeks of preoperative systemic therapy is associated with a higher pCR rate and excellent survival, irrespective of pCR status.
- Postoperative MRD detection status is a strong predictor for recurrence independent of pCR status.
- This study highlights ctDNA as a promising biomarker for personalized risk assessment and systemic treatment guidance in patients with early-stage TNBC receiving modern preoperative systemic therapy.
- Further studies are needed to determine if ctDNA-guided intervention can alter clinical outcomes in patients undergoing preoperative systemic therapy for early-stage TNBC.

References

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Contact

Presenting author: Tae-Kyung Robyn Yoo, MD, PhD
(tkyoo@amc.seoul.kr)
Corresponding author: Heather Parsons, MD, MPH
(hparsons@fredhutch.org)

Introduction

- Preoperative systemic therapy (PST) with immunotherapy (IO) is the current standard-of-care for patients with early-stage triple-negative breast cancer (TNBC).
- Circulating tumor DNA (ctDNA) persistence in the (neo)adjuvant setting is associated with residual disease at surgery and a higher risk of recurrence.[1,2,3]
- Studies of ctDNA in TNBC have not yet reflected treatment in the modern IO era.

Objectives

The primary goal of this study is to:

- Investigate the prevalence and clearance of molecular residual disease (MRD) during PST and its association with pathologic complete response (pCR) in patients
  - ✓ pCR was defined as the absence of invasive and in situ cancer in both the breast and axillary lymph nodes
- Examine the prognostic significance of MRD status and its change during PST and surgery

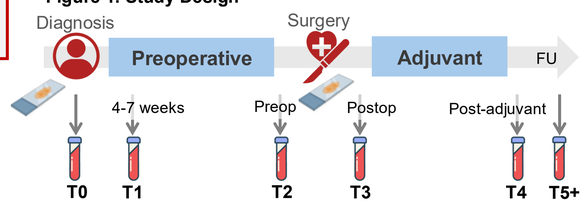
Primary endpoints are:

- ❖ Negative predictive value of MRD clearance for pCR
- ❖ Recurrence-free survival (RFS)

Methods

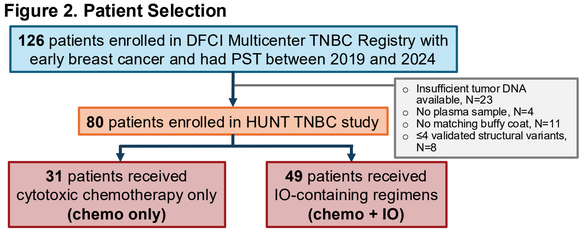
- The DFCI Multicenter TNBC Registry is a prospective multi-center cohort study enrolling early-stage TNBC patients.
- Within the registry, patients diagnosed with stage I-III TNBC who received PST were retrospectively identified.

Figure 1. Study Design



- Circulating tumor DNA (ctDNA) assay
  - Tumor-informed assay, primarily applied tumor tissue from diagnosis
  - 15x whole-genome sequencing of tumor samples
  - Tracking up to 16 structural variants to detect and quantify MRD
  - ✓ Samples requirements • Tumor DNA: 150ng, minimum 100ng • Buffy coat • Plasma: 4mL, minimum 2mL

Figure 2. Patient Selection



Results

Table 1. Baseline characteristics

- Patients receiving chemo+IO had higher clinical stage. (Fisher's exact p=0.004)
- pCR rate did not differ according to PST regimen. (Chi-square p=0.539)

		Overall (n=80), N (%)	Chemo only (n=31), N (%)	Chemo + IO (n=49), N (%)
Age at diagnosis	Median (IQR)	50.4 (40.7-60.4)	54.6 (40.5-57.9)	48.7 (41.0-60.8)
Clinical T stage	T1	17 (21.3)	11 (35.5)	6 (12.2)
	T2	53 (66.3)	17 (54.8)	36 (73.5)
	T3/4	10 (12.5)	3 (9.7)	7 (14.3)
Clinical N stage	N0	48 (60.0)	25 (80.6)	23 (46.9)
	N1	25 (31.3)	5 (16.1)	20 (40.8)
	N2/3	7 (8.8)	1 (3.2)	6 (12.3)
Clinical stage	I	14 (17.5)	11 (35.5)	3 (6.1)
	II	31 (38.8)	11 (35.5)	20 (40.8)
	III	34 (42.5)	9 (29.0)	25 (51.0)
	Missing	1 (1.3)	0 (0)	1 (2.0)
Hormone receptor	Negative	70 (87.5)	27 (87.1)	43 (87.8)
	Positive low	10 (12.5)	4 (12.9)	6 (12.2)
pCR (invasive & in situ)	Yes	46 (57.5)	16 (51.6)	30 (61.2)
	No	34 (42.5)	15 (48.4)	19 (38.8)
RCB class	0	49 (61.3)	18 (58.1)	31 (63.3)
	I	3 (3.8)	0 (0)	3 (6.1)
	II	12 (15.0)	8 (25.8)	4 (8.2)
	III	4 (5.0)	1 (3.2)	3 (6.1)
	Unknown	12 (15.0)	4 (12.9)	8 (16.3)
PST regimen	A only	2 (2.5)	0 (0)	2 (4.1)
	T only	1 (1.3)	1 (3.2)	0 (0)
	A and T	10 (12.5)	4 (12.9)	6 (12.2)
	P and T	23 (23.8)	23 (74.2)	0 (0)
A, anthracycline T, taxane P, platinum	A, T, and P	43 (53.8)	2 (6.5)	41 (83.7)
	Missing	1 (1.3)	1 (3.2)	0 (0)

MRD detection rate and clearance rate during and after PST

- 444 plasma samples were evaluated, median 5 (range, 1-11) samples per patient.
- Personalized ctDNA assays were designed targeting 5-16 (median 12) structural variants

Figure 3. MRD detection rate during and after PST

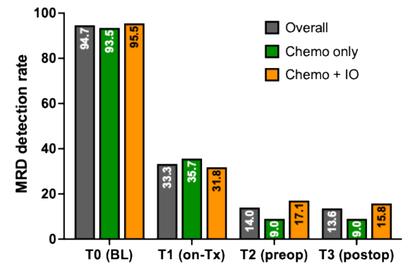
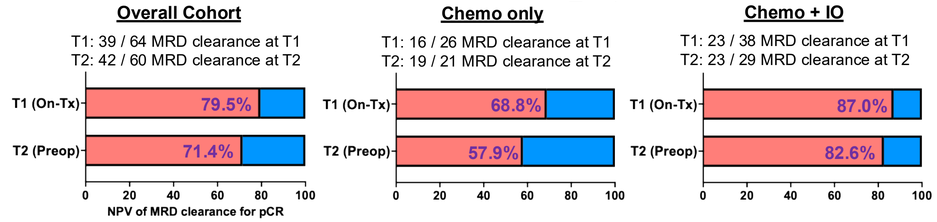


Table 2. MRD detection rate according to pCR status

	MRD Detected	MRD Not Detected	Odds Ratio of pCR (MRD detected vs not detected)	p value
T0 (Baseline; N=75)				
pCR	42 (100%)	0 (0.0%)	NA	NA
non-pCR	29 (87.9%)	4 (12.1%)		
T1 (On-Treatment; N=72)				
pCR	8 (18.6%)	35 (81.4%)	0.19 (0.06, 0.60)	0.002
non-pCR	16 (55.2%)	13 (44.8%)		
T2 (Preop; N=57)				
pCR	0 (0.0%)	33 (100%)	NA	NA
non-pCR	8 (33.3%)	16 (66.7%)		

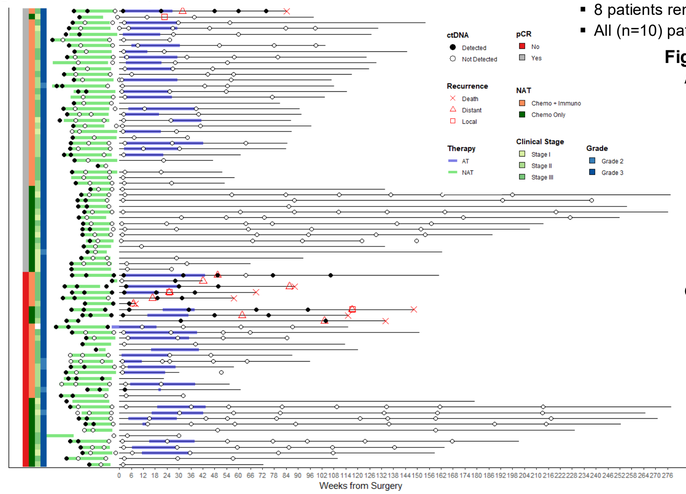
Figure 4. Negative predictive value of MRD clearance for pCR

* Note that not all patients have T0, T1, and T2 samples available.



Prognostic significance of MRD status and its change during PST and surgery

Figure 5. Swimmer plot of the overall cohort



- Median postoperative follow-up duration was 26.2 months (IQR 18.6, 37.3)
  - Chemo Only: 43.2 months (IQR: 28.1, 58.1)
  - Chemo+IO: 21.1 months (IQR: 13.3, 27.0)
- 8 patients remained ctDNA(+) after surgery → 7 (87.5%) had recurrence (median lead time 10.9 [IQR 6.1, 16.4] months)
- All (n=10) patients experiencing distant recurrence had MRD detected prior to the event

Figure 6. Kaplan-Meier survival curves (RFS)