Extended Outcomes and ctDNA Findings in the CLEVER Trial Targeting Disseminated Tumor Cells

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Background

- Breast cancer (BC) recurrence may follow a dormant phase in which quiescent cells reside in bone marrow (BM)
- Dormant disseminated tumor cells (DTCs) found in BM are independently associated with BC recurrence and death
- The CLEVER trial demonstrated feasibility, safety, and reduced DTCs with autophagy (hydroxychloroquine (HCQ)) and/or mTOR (everolimus (EVE)) inhibitors in DTC+ BC survivors (DeMichele, Nat Med, 2025)

Primary Objective: to present data on concurrent ctDNA testing and additional follow up among CLEVER trial participants

Methods

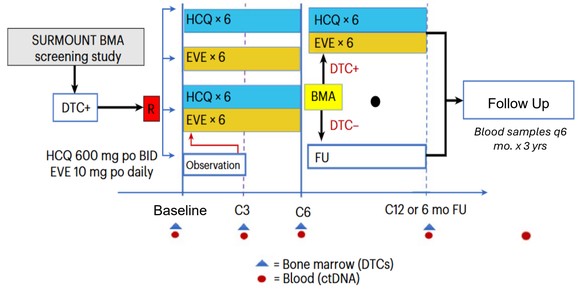
CLEVER is a randomized phase II trial for high-risk patients (pts) who had detectable DTCs via BM aspirate (BMA)

- **Eligibility:** Diagnosed within 5 years and completed definitive treatment (tx) (except endocrine therapy), either:
  - Triple negative disease
  - HER2+ or ER+ with either positive lymph nodes (LN) or residual disease (RD) after neoadjuvant chemotherapy
  - ER+ with Oncotype RS≥25 or high-risk MammaPrint

Study Procedures: BMA for DTC evaluation via immunohistochemistry (IHC); ctDNA assessed using tumor-informed, bespoke RaDaR assay (NeoGenomics)

- **DTC+** → Randomized to tx
- **DTC-** → Remain in surveillance cohort, yearly BMA and blood collection

Figure 1. CLEVER Trial Schema



Results

Figure 1. CLEVER Consort

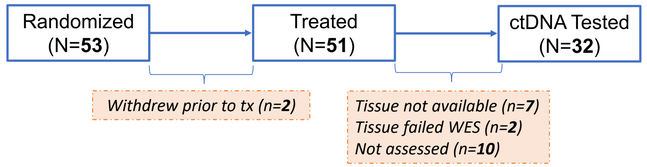


Table 1. CLEVER Population: Well-balanced by age (median 50), time since diagnosis (26 mo), Race/Ethnicity (89% Caucasian), LN+ (~50%) and chemo (~95% received)

	Total N=53	HCQ N=15	EVE N=15	HCQ+EVE N=23
Receptor Subtype				
ER+/Her2-	16 (30%)	6 (40%)	3 (20%)	7 (30%)
Her2+	6 (11%)	1 (7%)	2 (13%)	3 (13%)
TNBC	31 (59%)	8 (53%)	10 (67%)	13 (57%)

Figure 2. RFS by Receptor Group, n=51

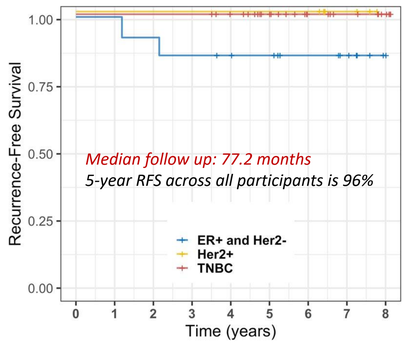


Figure 3. RFS by Drug Regimen, n=51

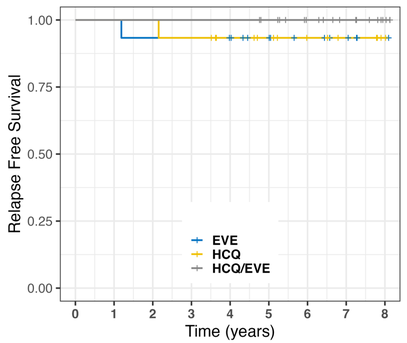


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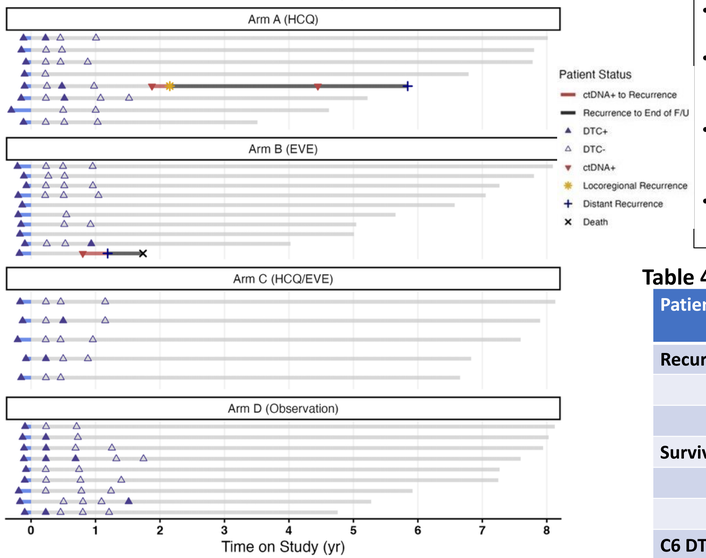
CLEVER	ER+/Her2-	TNBC	Her2+
5-year RFS	86.7%	100%	100%
Hazard Ratio	3.64 (0.33, 40.5)	1 (ref)	0 (0, inf)

Table 3. DTC/ctDNA Concordance*

CLEVER	ctDNA+	ctDNA-
DTC+	0	12
DTC-	0	67

*at dual collection timepoints

Figure 4. ctDNA results by Arm (n=32)



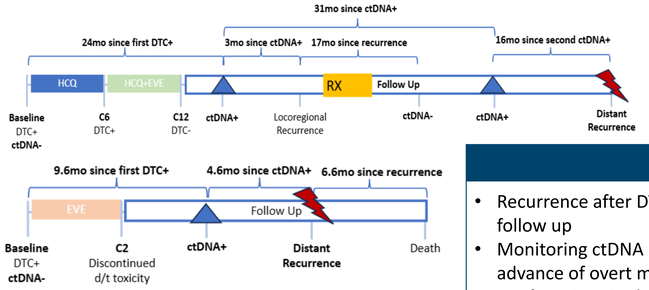
Summary

- 32/51 (63%) pts had samples submitted for ctDNA testing.
- Concordance was 85% among all timepoints where both DTCs and ctDNA were assessed.
- 234 ctDNA samples tested from 32 pts
  - 3/234 (1.3%) samples were ctDNA+
  - 2/32 (6.25%) pts had ctDNA+ result
- There were two recurrences within the population, and both pts were ctDNA+.

Table 4. ctDNA Outcomes

Patient Group	ctDNA+ (n=2)	ctDNA– (n=30)
Recurrence		
Local	1 (100%)	0 (0%)
Distant	2 (100%)	0 (0%)
Survival at 3yrs		
Alive	1 (3%)	30 (97%)
Deceased	1 (100%)	0 (0%)
C6 DTC Outcome		
DTC-	0 (0%)	24 (100%)
DTC+	1 (25%)	3 (75%)
Post-baseline DTC Outcomes		
All DTC-	0 (0%)	18 (100%)
Any DTC+	1 (9%)	10 (91%)
No Tests	1 (33%)	2 (67%)

Figure 5: Trajectories of ctDNA Positive Patients



Conclusions

- Recurrence after DTC-targeted tx remains low with 77.2 month follow up
- Monitoring ctDNA post-tx identified both pts with recurrences in advance of overt metastasis
- Confirmatory trials enrolling: NCT04523857 and NCT04841148

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For further information about this project, contact angela.demichele@pennmedicine.upenn.edu

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