PS4-01-07 Prospective Validation of HER2DX in Early HER2+ Breast Cancer: Operational Feasibility of Centralized Genomic Screening in the DEFINITIVE Trial. Real-Time Insights from the First 122 Screened Patients

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Background

- HER2-positive breast cancer (BC) accounts for approximately 20% of all breast tumors. Despite major advances in HER2-targeted therapies, many patients with early-stage HER2-positive BC remain over treated, leading to unnecessary toxicity and increased healthcare costs.
- HER2DX is a genomic diagnostic tool that stratifies patients by risk of recurrence and likelihood of achieving pathological complete response (pCR) after neoadjuvant therapy.
- The DEFINITIVE trial (www.thedefinitivetrial.eu) evaluates the clinical utility of HER2DX to guide treatment de-escalation or escalation in early-stage HER2-positive BC. We report preliminary feasibility and performance metrics from the first 122 screened patients.

Methods

- DEFINITIVE (NCT06446882) is an international, multicenter, randomized, open-label, two-arm clinical trial designed to evaluate the impact of HER2DX-guided treatment versus standard of care on health-related quality of life, safety, and efficacy outcomes. Eligible patients include premenopausal or postmenopausal women and men with stage II–IIIA HER2-positive BC suitable for neoadjuvant therapy.
- This interim analysis includes all patients screened from study initiation on October 30, 2024, through October 9, 2025. All patients underwent centralized screening with HER2DX using formalin-fixed paraffin-embedded (FFPE) tumor samples shipped to a reference laboratory.
- Operational endpoints included the number of samples received, HER2DX testing success rate, and turnaround time (TAT) from sample receipt to result delivery. All data were collected prospectively as part of the trial workflow.

Objective & Results

To characterize the baseline clinical and molecular profiles of the first patients included in the DEFINITIVE trial, and to evaluate critical operational timelines throughout the diagnostic pathway, including intervals from biopsy, informed consent, laboratory processing, and result delivery.

- As of the data cutoff, 122 patients had been screened across 14 sites in 3 countries. A total of 122 samples were received by the central laboratory, and HER2DX testing was successfully completed in 115 cases, yielding a success rate of 94.3%. Test failures were due to insufficient tumor content or low RNA purity (Table 1).
- The median TAT (turnaround time) was 7 working days (interquartile range [IQR] 5–8; range 4–15), confirming the feasibility of rapid centralized testing. The median time from tumor diagnostic biopsy to sample reception at the central lab was 23 days (IQR 16–31) with a range of 2-54 days, reflecting real-world variability in local processing and logistics (Figure 2 and 3)

Figure 1. HER2DX scores of the first patients screened. Percentages calculated over the total cohort (N=115).

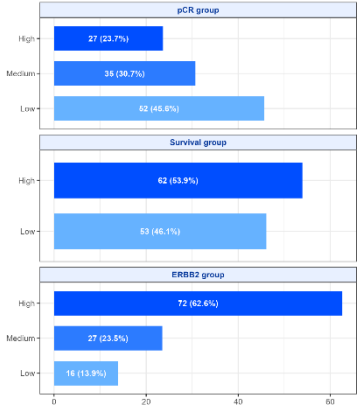
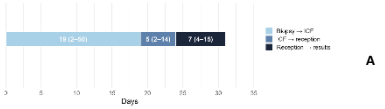


Table 1. Baseline characteristics of the first patients screened
n: number of patients. [IQR]: interquartile-range. Percentages calculated over the total cohort (N=115).

Age at diagnosis, mean (SD)	56.8 (11.8)
Histology, n (%)	
Ductal	107 (93.0)
Lobular	1 (0.9)
Other	7 (6.1)
Tumor size, n (%)	
T1	15 (13.0)
T2	90 (78.3)
T3	10 (8.7)
Nodal status, n (%)	
N0	58 (50.4)
N1	49 (42.6)
N2	7 (6.1)
N3	1 (0.9)
Estrogen receptor expression	
Estrogen receptor, median [IQR]	85 [0.0–98.0]
Positive, n (%)	80 (69.6)
Negative, n (%)	35 (30.4)
HER2 IHC, n (%)	
HER2 +2	20 (17.5)
HER2 +3	94 (82.5)
NA	1 (0.9)
Grade, n (%)	
G1	6 (5.2)
G2	58 (50.4)
G3	48 (41.7)
Ki67 median, [IQR]	30 [22.2–40.0]

Figure 2. Operational timelines. Median (range) for each interval



Operational swimmers plot

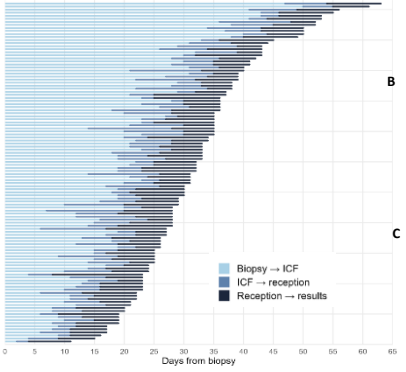
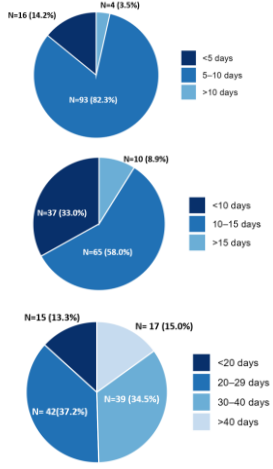


Figure 3 . Operational timelines
A. From sample reception to result
B. From ICF signature to result
C. From biopsy to result



Conclusions

Centralized HER2DX-based screening in the DEFINITIVE trial has proven operationally feasible on an international scale. High testing success rates, acceptable TAT, and biologically informative distributions support the integration of genomic classifiers into real-time treatment decision-making in prospective (neo)adjuvant clinical trials.

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