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Prognostic impact of postoperative ctDNA surveillance on relapse-free survival and molecular lead time in high-risk breast cancer: JCOG1204A1

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Background

The phase III trial, JCOG1204, prospectively compared intensive vs. standard postoperative follow-up in patients with high-risk breast cancer (BC). The ancillary study, JCOG1204A1, incorporated serial circulating tumor DNA (ctDNA) monitoring, enabling precise evaluation of relapse-free survival (RFS) and the molecular lead time from ctDNA detection to clinical recurrence under structured surveillance. We investigated the prognostic impact of ctDNA and quantified lead time.

Methods

JCOG1204A1 enrolled patients from JCOG1204 who were within 4 years from the date of surgery and had no recurrence. Serial plasma samples were collected every 3–6 months and analyzed using a personalized, tumor-informed assay (Signatera™, Natera Inc.) for up to 5 years in estrogen receptor (ER)-positive and 2 years in ER-negative BC. ctDNA positivity was defined as ≥1 positive result. Lead time was defined as the interval between first ctDNA positivity and radiologic or clinical diagnosis of recurrence.

Results

Among 210 evaluable patients, 28 (13.3%) became ctDNA positive during a median follow-up period of 72.3 months. ctDNA positivity was strongly associated with inferior RFS. Five-year RFS was 99.5% in ctDNA-negative patients vs. 53.6% in ctDNA-positive patients. ctDNA positivity markedly increased the risk of recurrence (hazard ratio [HR] 60.3, 95% confidential interval [CI] 20.5–177.5), and this association was also observed in the time-dependent Cox model (HR 27.7, 95% CI 10.1–75.4). The prognostic impact was most pronounced in ER-positive/HER2-negative disease, with 7-year RFS of 94.1% versus 15.9% in ctDNA negative and positive patients, respectively (HR 32.0, 95% CI 10.8–95.3). Among 21 patients with ctDNA positivity and recurrence or death, ctDNA detection preceded clinical recurrences by a median of 6.9 months (range 0.3-29.9, interquartile range 4.1–12.5).

Conclusions

Within a randomized intensive follow-up trial, postoperative ctDNA positivity was strongly associated with inferior RFS, providing a molecular lead time of approximately 7 months. These findings support integrating ctDNA surveillance into structured follow-up strategies, particularly for luminal BC.

Clinical trial identification

Main study, JCOG1204 trial (UMIN000012429; Registration: 2013 - 2020, N = 1034), a randomized phase3 trial evaluating whether intensive follow-up is superior to standard follow-up, with primary endpoint of overall survival. The results are expected in 2027. Data on ctDNA

assessment in the intensive follow-up group are also planned to be reported after 2027.

Legal entity responsible for the study

JCOG.

Funding

Natera Inc. provides test fee.

Disclosure

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