End of enrollment and initial oncologic outcomes of the NEONOD2 Trial: A prospective Italian multicenter study on axillary de-escalation in ypN1mi breast cancer patients after neoadjuvant chemotherapy

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Background: The optimal axillary management of initially node-positive (cN+) breast cancer (BC) patients downstaged to cN0 after neoadjuvant chemotherapy (NAC) but presenting residual sentinel lymph node (SLN) micrometastasis (ypN1mi) remains controversial. NEONOD2 is a prospective multicenter trial investigating the safety of omitting axillary lymph node dissection (ALND) in this setting.

Methods: Eligible patients were cT1-3/cN+ BC patients treated with NAC who achieved ycN0 status and subsequently underwent SLNB. Patients with ypN1mi SLN involvement were included in the experimental group, ypN0 patients in the standard group, and patients with residual macrometastatic disease (ypN+) in the control group. Primary endpoint was recurrence-free survival (RFS); secondary endpoints included overall survival (OS), loco-regional and distant recurrence rates. Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed.

Results: Enrollment was completed in December 2025. Overall, 595 patients from 29 Italian centers were enrolled. After exclusions for dropout, loss to follow-up, screening failures, and unavailable data, the ITT population included 538 patients: 81 ypN1mi (15.1%), 346 ypN0 (64.3%), and 111 ypN+ macrometastatic patients (20.6%). Median follow-up was 25 months (range 6–79). In the ypN1mi group, 7/81 patients (8.6%) experienced recurrence: 2 loco-regional, 3 distant, and 2 combined loco-regional and distant recurrences. Only one isolated ipsilateral axillary recurrence was observed. In the ypN0 group, 16/346 patients (4.6%) recurred, including 2 ipsilateral axillary recurrences. In the control group, 13/111 patients (11.7%) experienced recurrence, including 1 ipsilateral axillary relapse. One death occurred in the ypN1mi group, compared with 7 deaths in both the ypN0 and ypN+ groups. The PP population included 466 patients. Recurrence rates were 9.9% in the experimental group, 4.1% in the standard group, and 14.1% in the control group.

Conclusions: Initial NEONOD2 results suggest that omission of ALND in selected ypN1mi patients after NAC is associated with low rates of isolated axillary recurrence and acceptable short-term oncologic outcomes.

Keywords: Breast Cancer, Neoadjuvant Chemotherapy, Sentinel Lymph Node Biopsy

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