Advances in Breast Cancer Treatment – three major trials

Recent advances in breast cancer research have shown practice changing findings. This review article wants to highlight key insights from three major breast cancer trials presented at the last 2024 ESMO congress: the HypoG-01 trial, which evaluated hypofractionated radiotherapy in localized breast cancer requiring nodal irradiation, the KEYNOTE-522 trial, which investigated the addition of pembrolizumab to chemotherapy in localized node positive triple-negative breast cancer (TNBC), and the NATALEE trial, which assessed adjuvant ribociclib in hormone receptor-positive high risk early breast cancer. These studies contribute to ongoing developments in personalized treatment strategies across various breast cancer subtypes.

HypoG-01 Study

The HypoG-01 trial evaluated the non-inferiority of hypofractionated radiotherapy compared to normofractionated radiotherapy in patients with localized breast cancer requiring nodal irradiation (1). While previous studies support the use of lower doses for breast-only irradiation, evidence in the context of nodal irradiation was lacking before this trial. Up to now patients needing nodal irradiation underwent treatment with a standard dose of 50 Gy over 25 fractions over five weeks, which involves larger irradiation volumes.

HypoG-01 is a multicenter, open-label, randomized phase 3 trial including participants with stage T1-3, N0-3 breast cancer requiring regional nodal radiotherapy. Patients were randomized to receive either hypofractionated radiotherapy (40 Gy in 15 fractions over three weeks) or normofractionated radiotherapy (50 Gy in 25 fractions over five weeks). The primary endpoint was the 3-year cumulative incidence of arm lymphoedema, defined by a ≥10% increase in arm circumference at specific distances from the olecranon. The study met its primary endpoint, establishing that hypofractionated radiotherapy is non-inferior to normofractionated radiotherapy for patients requiring nodal irradiation. The 5-year cumulative incidence of lymphoedema was 33.3% in the hypofractionated group versus 32.8% in the normofractionated group. Secondary endpoints, including overall survival (OS), locoregional-free survival (LRFS), distant disease-free survival (DDFS), and breast cancer-specific survival (BCSS), also resulted to be non-inferior, further confirming the efficacy and non-inferirority of hypofractionated therapy in this patient population.

The safety profile was consistent across treatment groups, with only minor differences in radiation skin injuries, which were clinically insignificant.

Hypofractionated radiotherapy is now positioned as the new standard of care for patients with localized breast cancer requiring nodal irradiation, providing an effective, less burdensome treatment option.

KEYNOTE-522 Trial

KEYNOTE-522 is a prospective, randomized, placebo-controlled trial enrolling patients with stage T1cN1-2 or T2-4N0-2 TNBC (2). Participants received pembrolizumab alongside chemotherapy in the pre-operative setting, followed by adjuvant pembrolizumab for up to 9 cycles after surgery.

Primary endpoints have been met and discussed at previous EMSO congresses and published in the New England Journal of Medicine, these being an increase in pathologic complete response (pCR) and event-free survival (EFS). Prof. Peter Schmid presented the secondary endpoint results, being the 5-year overall survival (OS), at this last ESMO congress 2024.

The addition of pembrolizumab led to a 5% improvement in 5-year OS, corresponding to a hazard ratio of 0.66, indicating a 34% reduction in the risk of death. The correlation between pCR and OS was also confirmed, with improved OS in patients achieving pCR post-chemotherapy. Among patients not achieving pCR, those who completed 18 cycles of pembrolizumab showed a 71.8% 5-year OS, compared to 65.7% in those not receiving immunotherapy. Safety profiles were similar between the groups, with most toxicities being attributable to chemotherapy rather than pembrolizumab. Pembrolizumab has therefore now solidified its role in the treatment of high-risk, early-stage TNBC and is confirmed to be recommended as a standard of care.

NATALEE Trial

The NATALEE trial investigates adjuvant ribociclib in hormone receptor-positive early breast cancer patients at high risk of recurrence (3). The trial included patients with stage IIA, node-positive disease or node-negative disease with additional risk factors, as well as patients with stages IIB and III. Patients received as adjuvant treatment either ribociclib, a CDK4/6 inhibitor, at a dose of 400 mg/day, three weeks on - one week off, in association to hormone therapy or hormone therapy alone. The study's primary endpoint is invasive disease-free survival (iDFS). The 3-year results were discussed at a previous congress, and the 4-year results were discussed at this year's ESMO.

At 4 years, ribociclib showed a 4.9% improvement in iDFS, with survival curves continuing to separate across all evaluated subgroups, including stage II and III disease. The positive trend suggests an ongoing benefit in terms of both DFS and OS, which results are still awaited.

As we could expect, ribociclib was associated with an increase rate of adverse events compared to hormone therapy only, including neutropenia, liver-related toxicities, QTc prolongation, and gastrointestinal effects. Such results suggest that ribociclib represents a valuable option in the adjuvant setting for selected high-risk hormone receptor-positive breast cancer patients.

Take-Home-Messages

The findings from the HypoG-01, KEYNOTE-522, and NATALEE trials collectively affirm advancements in breast cancer treatment. Hypofractionated radiotherapy is now recommended as standard for patients requiring nodal irradiation, pembrolizumab is confirmed as the standard of care in early-stage high-risk TNBC, and the addition of ribociclib can be considered for adjuvant treatment in selected hormone receptor-positive breast cancer patients at high risk of recurrence.

These results underscore the importance of tailored, evidence-based approaches in the management of breast cancer. □

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