

Raising the bar for patients with HR+/HER2- Early Breast Cancer

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So far, high-risk HR+/HER2- early breast cancer (EBC) has been an unmet medical need. Even though, standard locoregional therapy, together with endocrine therapy (ET) and also chemotherapy are sufficient to cure the majority of patients, there is still a substantial number of patients who will relapse in this setting. Loco-regional tumor burden as well as aggressive tumor biology (i.e. grade 3, high Ki67, high-risk result in a gene expression assay) do predict for poor outcome even after standard therapy.

Recently, two new systemic therapy have been approved by FDA and EMA in this setting – abemaciclib and Olaparib. They hold great promise of increasing cure rates in high-risk HR+/HER2- EBC.

The monarch-E trial assessed 2 years of abemaciclib together with standard ET in pre- and postmenopausal patients. The trial included patients with ≥ 4 involved lymph nodes (LN) or patients with 1-3 LN and tumors > 5 cm, grade 3 or Ki67 $\geq 20\%$. The use of abemaciclib increases iDFS and dDDFS significantly and in a clinically meaningful way.

The OLYMPIA trial assessed 1 year of olaparib in patients with high-risk HER2-negative EBC and a gBRCA mutation. Recently, the trial update showed a significant OS advantage for Olaparib given together with ET.

A number of ongoing international trials will provide additional insights into the optimal therapy approach in this disease setting. For example, the NATALEE trial will show whether ribociclib is also suited as an adjuvant therapy. WSG-ADAPTcycle will explore the effect of an endocrine-based approach (with ribociclib) vs. (neo-) adjuvant chemotherapy in tumors where ET alone is not sufficient. WSG-ADAPTlate is randomizing patients at high risk of recurrence who already have received more than one year of ET for adding abemaciclib vs. continuing ET alone to see whether adding abemaciclib in the adjuvant setting will also overcome secondary endocrine resistance. Lastly, POETIC-A explores the addition of abemaciclib to endocrine therapy in patients without endocrine response to a short preoperative endocrine therapy.

As relapses in HR+/HER2- EBC can occur over 10-20 years, long-term-follow-up of the practice-changing Monarch-E and OLYMPIA trials is needed to see the actual benefit over time from these advances for our patients.