Top 3 abstracts concerning hormone-receptor-positive early breast cancer

Post San Antonio 2020 Update

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Summary  The three top abstracts at the 2020 virtual San Antonio Breast Cancer Symposium regarding hormone-receptor-positive early breast cancer, from our point of view, were the long-awaited results from Penelope® and RxPONDER as well as the data from the ADAPT trial of the West German Study Group. Penelope® failed to show any benefit by adjuvant palbociclib when added to standard endocrine therapy in patients without pathologic complete response after neoadjuvant chemotherapy. RxPONDER demonstrated that postmenopausal patients with early hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) breast cancer, 1–3 positive lymph nodes and an Oncotype DX Recurrence Score of less than 26 can safely be treated with endocrine therapy alone. In contrast, in premenopausal women with positive nodes, adjuvant chemotherapy plays still a role even in case of low genomic risk. Whether the benefit by chemotherapy is mainly an indirect endocrine effect and if ovarian function suppression would be similarly effective, is still a matter of debate. The HR+/HER2– part of the ADAPT umbrella trial investigated the role of a Ki-67 response to a short endocrine therapy before surgery in addition to Oncotype DX—performed on the pretreatment biopsy—to identify low-risk patients who can safely forgo adjuvant chemotherapy irrespective of menopausal status.

Keywords Metastatic breast cancer · San Antonio Breast Cancer Symposium · SABCS · Highlights · Review

Review

Within this short review we discuss the, from our point of view, three top abstracts at the 2020 virtual San Antonio Breast Cancer Symposium regarding hormone-receptor-positive (HR+)/HER2 negative (HER2–) early breast cancer (EBC).

Penelope® trial: endocrine therapy +/- palbociclib as postneoadjuvant therapy for high-risk early breast cancer [10]

Two phase III trials investigating CDK4/6 inhibitors as adjuvant therapy in HR+/HER2– EBC were already presented at the 2020 virtual congress of the European Society of Medical Oncology (ESMO) [1, 2]. The PALLAS trial investigated a 2-year treatment with the first-in-class CDK4/6 inhibitor palbociclib in combination with endocrine therapy in 5760 patients with HR+/HER2– stage II and III breast cancer. Compared to endocrine therapy alone, palbociclib did not prolong invasive disease-free survival (iDFS: hazard ratio [HR] 0.93; 95% confidence interval [CI] 0.76–1.15; P= 0.51) [2]. In contrast, the MonarchE trial, including only lymph-node-positive patients, showed a statistically significant benefit in iDFS from a 2-year therapy with abemaciclib in combination with endocrine therapy compared to endocrine therapy alone. The difference in iDFS was already statistically significant at the ESMO presentation of the second interim analysis, despite a very short follow-up of 15.5 months. At the 2020 San Antonio Breast Cancer Symposium the primary outcome iDFS analysis of MonarchE was presented with a slightly longer median follow-up of...
Fig. 1 Invasive disease-free survival (iDFS) of the Penelope\textsuperscript{a} trial at a median follow-up of 42.8 months [10]. With kind permission from S. Loibl. This figure is not included under the Creative Commons CC BY license of this publication.

Invasive disease-free survival (iDFS) of the Penelope\textsuperscript{b} trial at a median follow-up of 42.8 months [10]. With kind permission from S. Loibl. This figure is not included under the Creative Commons CC BY license of this publication.

19.1 months. A risk reduction for an iDFS event of 28.7% was shown by the addition of abemaciclib (HR 0.71; 95% CI 0.58–0.87; \(P<0.001\)), resulting in an absolute iDFS gain of 3.0% at year two (92.3 vs. 89.3%) [3]. At data cut-off, however, 58% of patients were still on treatment and only 26% completed the 2-year treatment period.

Considering the conflicting PALLAS and Monarch\textsuperscript{E} results, the first results from the Penelope\textsuperscript{b} trial, presented at the virtual SABCS 2020, were eagerly awaited. In contrast to the former two trials, the double-blind, placebo-controlled, phase III Penelope\textsuperscript{b} study recruited only HR+/HER2– breast cancer patients without pathologic complete remission (pCR) after neoadjuvant chemotherapy. To select patients with a high risk for recurrence, patients had to have a CPS-EG (pretreatment Clinical stage, posttreatment Pathologic Stage, Estrogen receptor status, nuclear Grade) score [4] of greater than 3 or—in case of persistent nodal-positivity—a score of greater than two. Patients were randomized 1:1 to palbociclib at standard dose for 1 year or to placebo for the same length of time. All patients were treated with endocrine therapy according to local standards. The median follow-up of Penelope\textsuperscript{b} at the data cut-off was 42.8 months, which is considerably longer than those of PALLAS (23.7 months) or Monarch\textsuperscript{E} (19.1 months). Even though patient adherence was much better than in PALLAS (20% early discontinuations compared to 42%), Penelope\textsuperscript{b} could not demonstrate a statistically significant benefit in iDFS (HR 0.93; 95% CI 0.74–1.17; \(P=0.525\); Fig. 1). Interestingly, at year 2 and 3, the iDFS rate was meaningfully higher in the palbociclib arm (88.3 vs. 84.0% and 81.2 vs. 77.7%, respectively); however these advantages disappeared at year 4 (73.0 vs. 72.4%). In subgroup analysis, no patient group could be identified which seemed to have a benefit from the CDK4/6 inhibition. In addition, the types of iDFS events were similar between the two treatment arms with distant recurrences representing 74% of all events. Similar to iDFS, overall survival (OS) was not significantly different between the palbociclib and the placebo arm (HR 0.87; 95% CI 0.61–1.22; \(P=0.420\)). Palbociclib was generally well tolerated with a known toxicity profile of mainly hematologic adverse effects (73% G3/4 neutropenia).

These results demonstrate the importance of a sufficient follow-up time for the final interpretation of adjuvant trials. The temporary separation of the survival curves of the Penelope\textsuperscript{b} trial in the first 3 years suggests that longer treatment with palbociclib may be beneficial. This question is partly addressed by the ongoing NATALEE trial, investigating 3 years of ribociclib.

**RxPONDER trial: Oncotype DX in patients with 1–3 positive lymph nodes [11]**

The TAILOR\textsuperscript{x} trial demonstrated that patients with node negative early HR+/HER2– breast cancer and an Oncotype DX Recurrence Score (RS) of <26 have generally an excellent prognosis with no benefit from adjuvant chemotherapy [5, 6]. The only exception from this finding were patients 50 years or younger with a RS of 21–25, who seemed to have a risk reduction for recurrence by adjuvant chemotherapy (~5.8% at 5 years) [7]. Based on these findings, the results of the RxPONDER trial, which included only patients with 1–3 positive lymph nodes, were long-awaited. Patients fit enough for adjuvant chemotherapy and a RS of 0–25 were randomized between chemotherapy fol-
**short review**

Fig. 2  
**a** Postmenopausal women with early HR+/HER2– breast cancer with 1–3 positive nodes did not benefit from adjuvant chemotherapy if the Oncotype DX Recurrence Score was <26.  
**b** Premenopausal women had a statistically significant better invasive disease-free survival if adjuvant chemotherapy was given [11]. With kind permission from K.M. Kalinsky. This figure is not included under the Creative Commons CC BY license of this publication.

RxPONDER and TAILORx show clearly that postmenopausal patients with early HR+/HER2– breast cancer, 0–3 positive lymph nodes and an Oncotype DX RS of 0–25 can safely be treated by endocrine therapy alone. Premenopausal women with a RS 16–25 or positive lymph nodes, tamoxifen monotherapy should definitely be avoided and either chemotherapy be added or OFS in combination with an aromatase inhibitor be used.

**WSG-ADAPT HR+/HER2: endocrine monotherapy in patients with RS<12 or RS 12–25 and Ki-67 response after 3 weeks of endocrine therapy [12]**

The ADAPT trial of the West German Study Group is a large umbrella trial including different breast cancer subtypes. In the endocrine part of the trial—similar to RxPONDER and TAILORx—Oncotype DX was used for primary risk stratification in patients with HR+/HER2– early breast cancer and a general indication for adjuvant chemotherapy (cT2 or G3 or Ki-67 ≥ 15% or N+). In contrast to the other trials, in ADAPT all patients received 3 weeks of endocrine therapy (tamoxifen or an aromatase inhibitor) before the diagnostic biopsy and surgery. The diagnostic biopsy was used to determine Oncotype DX RS and Ki-67. At surgery Ki-67 was retested and in case of a RS of 12–25 only patients with a Ki-67 response (defined as Ki-67 < 10% at surgery) were included in the trial. All patients received endocrine monotherapy according to the investigator. The primary goal of the trial was to show that patients with a RS 12–25 and a Ki-67 response do not have a lower iDFS at 5 years than patients with a RS <12. As assumed, the 5-year iDFS was noninferior (93.9 vs. 92.6%; P=0.05). Similarly, the distant disease-free survival (dDFS) and OS were also comparable between the two groups. There was also no difference in dDFS in patients ≤50 years (Fig. 3) or with positive lymph nodes. Only patients with a RS 12–25 and three or more involved lymph nodes had...
Distant disease-free survival (dDFS) at year 5 was not different between patients with RS 12–25 but Ki-67 response after 3 weeks of endocrine therapy and patients with a RS <12 both in patients below and above 50 years [12]. With kind permission from N. Harbeck. This figure is not included under the Creative Commons CC BY license of this publication.

Conclusion

Because of the negative results of PALLAS and PENELOPE, MonarchE remains currently the only positive phase III trial investigating adjuvant CDK4/6 inhibitors in early HR+/HER2– breast cancer. Longer follow-up is needed before 2 years of abemaciclib can be declared as new standard of care for lymph-node-positive, high-risk HR+/HER2– breast cancer. The results of the NATALEE trial investigating 3 years of ribociclib are still awaited.

The data of RxPONDER clearly strengthened the role of Oncotype DX in risk prediction and the choice of adjuvant chemotherapy for HR+/HER2– breast cancer. Postmenopausal women with less than 4 positive lymph nodes should only receive adjuvant chemotherapy if the RS is above 25. In premenopausal women with positive nodes, adjuvant chemotherapy plays still a role even in case of low genomic risk. Maybe a Ki-67 response to a short preoperative endocrine therapy could help to identify patients with an intermediate risk according to Oncotype DX, who can safely forgo adjuvant chemotherapy.

Conflict of interest

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