Revista de Senología y Patología Mamaria 38 (2025) 100633

Sociedad Española de Senología y Patología Mamaria

Revista de Senología y patología mamaria
Journal of Senology and Breast Disease
www.elsevier.es/senologia

REVIEW

How can we integrate current adjuvant treatment options in triple negative patients with residual disease after neoadjuvant treatment?

M. Teresa Quintanar-Verdúguez[a,*], María Ballester Espinosa[b], Javier Pérez-Altozano[c], Álvaro Muñoz-Abad[a] and Álvaro Rodríguez-Lescure[a]

[a] *Hospital General Universitario de Elche, Alicante, Spain*
[b] *Hospital Vega Baja de Orihuela, Alicante, Spain*
[c] *IMED hospitales, Elche, Alicante, Spain*

Received 5 July 2024; accepted 8 August 2024
Available online 28 September 2024

KEYWORDS
Early triple negative breast cancer;
Adjuvant treatment;
Neoadjuvant treatment;
Pathological complete response

Abstract Triple negative breast cancer (TNBC) accounts for approximately 12%–20% of all breast cancers but usually has a more aggressive clinical course and worse prognosis than hormone receptor expressing breast cancers. Locoregional treatments as well as systemic chemotherapy are part of the therapeutic algorithm in early breast cancer. Currently, neoadjuvant treatment is the standard for TNBC T1c N0 or higher. This strategy allows treating the disease early as well as selecting subsequent adjuvant treatment based on the pathological response achieved. Those patients with early-stage TNBC who have residual disease after completing neoadjuvant therapy have a higher risk of relapse and worse survival than those who achieve pathological complete response. Different drugs (capecitabine, pembrolizumab, olaparib) have so far demonstrated their benefit in the adjuvant setting after previous neoadjuvant treatment without being comparable because their clinical trials differ in design and study population. This scenario is therefore a clinical challenge where the selection criteria are fundamental to identify those patients who can benefit from each of the available therapeutic strategies.

PALABRAS CLAVE
cáncer de mama triple negativo precoz;
tratamiento adyuvante;

¿Cómo podemos integrar las opciones de tratamiento adyuvante actuales en las pacientes con cáncer de mama triple negativo con enfermedad residual tras tratamiento neoadyuvante?

Resumen El cáncer de mama triple negativo (CMTN) representa aproximadamente 12–20% de todos los cánceres de mama pero suele tener un curso clínico más agresivo y peor pronóstico que

* Corresponding author.
E-mail address: quintanar_marver@gva.es (M.T. Quintanar-Verdúguez).

https://doi.org/10.1016/j.senol.2024.100633

tratamiento neoadyuvante; respuesta completa patológica

los cánceres de mama con expresión de receptores hormonales. Los tratamientos locorregionales así como la quimioterapia sistémica forman parte del algoritmo terapéutico en el cáncer de mama precoz. En la actualidad, el tratamiento neoadyuvante es el estándar para el CMTN T1c N0 o superior ya que permite tratar la enfermedad de forma temprana así como seleccionar el tratamiento adyuvante posterior en función de la respuesta patológica alcanzada. Aquellas pacientes con CMTN precoz que tienen enfermedad residual tras completar el tratamiento neoadyuvante, presentan mayor riesgo de recaída y peor supervivencia que aquellas que alcanzan respuesta completa patológica. Diferentes agentes (capecitabina, pembrolizumab, olaparib) han demostrado hasta el momento actual su beneficio en el contexto adyuvante tras tratamiento neoadyuvante previo sin poderse comparar entre ellos al diferir sus ensayos clínicos en diseño y población de estudio. Este escenario supone por tanto un reto clínico donde los criterios de selección son fundamentales para poder identificar a aquellas pacientes que pueden beneficiarse de cada una de las estrategias terapéuticas disponibles.

Introduction

Triple negative breast cancer (TNBC) accounts for approximately 12%–20% of all breast cancers[1,2] but usually has a more aggressive clinical course and worse prognosis than hormone receptor expressing breast cancers due to its higher histological grade and lack of target drugs. Locoregional treatments (surgery and radiotherapy) as well as systemic chemotherapy are part of the therapeutic algorithm in early breast cancer. Currently, neoadjuvant treatment is the standard for TNBC T1c N0 or higher. This strategy allows treating the disease early as well as selecting subsequent adjuvant treatment based on the pathological response achieved. Neoadjuvant chemotherapy in early breast cancer achieves pathological complete response (pCR) rates of approximately 22%–51%.[3–5] *The Collaborative Trials in Neoadjuvant Breast Cancer* (CTNeoBc) pooled meta-analysis demonstrated a strong association between pCR (defined as no residual disease in the breast or nodes) and disease-free survival (DFS) (HR 0.24; 95% CI 0.18–0.33) and overall survival (OS) (HR 0.16; 95% CI 0.11–0.25) in patients with early-stage TNBC receiving neoadjuvant therapy followed by surgery.[6] This association was greater in patients with TNBC who achieved pCR. Those patients with early-stage TNBC who have residual disease after completing neoadjuvant therapy have a higher risk of relapse and worse survival than those who achieve pCR. Patients with residual nodal involvement after neoadjuvant chemotherapy have a risk of recurrence in the following 5–10 years of approximately 40%–60%.[7] Because of these differences in the risk of recurrence depending on the response achieved, adjuvant therapy is recommended for patients with residual disease after completing neoadjuvant and surgical treatment.[8,9] Different drugs (capecitabine, pembrolizumab, olaparib) have so far demonstrated their benefit in the adjuvant setting after previous neoadjuvant treatment without being comparable because their clinical trials differ in design and study population. This scenario is therefore a clinical challenge where the selection criteria are fundamental to identify those patients who can benefit from each of the available therapeutic strategies (see Table 1).

Capecitabine

In the last decade, capecitabine has been the adjuvant treatment recommended by clinical practice guidelines in patients with TNBC without pCR after neoadjuvant chemotherapy based on anthracyclines, taxanes, and/or platinum. Several studies have attempted to demonstrate the benefit of using capecitabine in the adjuvant setting with different results depending on the study population, but showing that adding capecitabine to standard treatment improves DFS and OS outcomes in TNBC patients.[10]

CREATE-X

The recommendation for the use of adjuvant capecitabine in TNBC is based on the results of this study[11] which showed benefit in DFS and OS at 5 years in patients receiving capecitabine versus surgery alone. The study randomized 1:1910 patients with HER 2 negative invasive breast cancer with residual disease after neoadjuvant chemotherapy (anthracycline, taxane, or both) to receive standard post-surgical treatment with or without capecitabine. Patients in the treatment arm received capecitabine 2500 mg/m^2 D1–14 every 21 days for 8 cycles. The primary endpoint was DFS. The secondary endpoint was OS. The final analysis of the study demonstrated impact on DFS in favor of the group receiving capecitabine (74.1% vs 67.6%, HR 0.70 95% CI 0.53–0.92, $p = .01$) as well as OS (89.2% vs 83.6%, HR 0.59 95% CI 0.39–0.90 $p = .01$). 32.2% of the included patients had TNBC. In this subgroup, the DFS rate was 69.8% in the capecitabine group vs 56.1% in the control group (HR 0.58; 95% CI, 0.39–0.87), and the OS rate was 78.8% vs 70.3% (HR 0.52; 95% CI, 0.30–0.90). One of the aspects to be highlighted in the CREATE-X study is the selection criterion for patients based on the absence of pCR, which makes them a group with a very high risk of recurrence.

Table 1 Adjuvant clinical studies in TNBC.

Study	*n*	Drug	Population	Selection criteria	Primary endpoint	Secondary endpoint	Results
CREATE-X, Phase 3	910	Adjuvant capecitabine vs no treatment (1:1)	Her 2 negative BC 32.2% TNBC	No pCR after neoadjuvant chemotherapy	DFS	OS	TNBC population **5-y DFS**: 69.8% vs 56.1% (HR 0.58, 0.39–0.87) **5-y OS:** 78.8% vs 70.3% (HR 0.52, 0.30–0.90)
CIBOMA, Phase 3	876	Adjuvant capecitabine vs no treatment (1:1)	TNBC, tumor size ≥1 cm	Prior neo/adjuvant chemotherapy	DFS	OS	**5-y DFS:** 79.6% vs 76.6% (HR 0.82, 0.63–1.06) **5-y OS:** 86.2% vs 85.9% (HR 0.92, 0.66–1.28)
ECOG-ACRIN, Phase 3	410	Adjuvant platinum salt vs capecitabine (1:1)	TNBC, stage II–III	No pCR after neoadjuvant chemotherapy (>1 cm in breast)	iDFS	OS	**3-y iDFS**: 46% vs 69% (HR 1.94, 0.69–5.45) **3-y OS:** 58% vs 66%, (HR 1.13, 0.71–1.79)
CARE, Retrospective	270	Adjuvant capecitabine	TNBC	No pCR after neoadjuvant chemotherapy	DFS	OS	**DFS:** 62% **OS 2y:** 84% **OS 3y:** 76.2%
KEYNOTE 522, Phase 3, double-blind	1174	Neo and adjuvant Pembrolizumab vs placebo (2:1)	TNBC	Untreated Stage II–III	pCR EFS	OS	**pCR:** 64.8% vs 51.2% **3-y EFS:** 84.5% vs 76.8% **3-y EFS in pCR:** 94.4% vs 92.5% **Estimated 3-y OS:** 89.7% vs 86.9%
OlympiA, Phase 3, double-blind	1836	Olaparib vs placebo (1:1)	Her 2 negative BC and BRCA 1–2 mutation 82% TNBC	Prior neo/adjuvant chemotherapy	iDFS	OS	**4-y iDFS:** 82.7% vs 75.4% (p<.001) **4-y OS:** 89.8% vs 86.4% (p=.009)

BC: breast cancer; TNBC: triple negative breast cancer; DFS: disease-free survival; OS: overall survival; iDFS: invasive disease free survival; pCR: pathological complete response; EFS: event-free survival.

CIBOMA

One of the first randomized phase III studies attempting to demonstrate the benefit of adjuvant capecitabine in TNBC is the GEICAM/2003-11_CIBOMA/2004–01 Clinical Trial.[12] In this trial, 876 patients with operable, node-positive or node-negative TNBC and tumor size ≥1 cm who had received prior anthracycline and/or taxane-based chemotherapy were eligible for 1:1 randomization to receive capecitabine 2000 mg/m^2/d 14 days every 21 days for 8 cycles or observation. Approximately, 20% of the included patients had received neoadjuvant chemotherapy. The primary objective of the study was to compare DFS between the 2 arms. 55.9% of the patients had no lymph node involvement and 74% had a basal-like phenotype (staining for epidermal growth factor receptor and/or cytokeratins 5/6). The CIBOMA study failed to demonstrate the benefit of adding capecitabine to these patients. The 5-year DFS rate was 79.6% (95% CI 75.8–83.4) in the capecitabine arm versus 76.8% (95% CI, 72.7%–80.9%) in the observation arm. In the preplanned subgroup analysis, it is noteworthy that patients without basal-like phenotype appeared to benefit more from capecitabine administration both in terms of DFS (HR 0.53, 95% CI 0.31–0.91, p=.022) and OS (HR 0.42, 95% CI 0.21–0.81, p=.0095). This finding suggests that capecitabine activity in the basal TNBC subgroup is lower due to their higher proliferative index which makes them more sensitive to other drugs such as platinum salts, taxanes, and eribulin, while it presents higher activity in the non-basal subgroup. However, this hypothesis should be confirmed in subsequent studies. Likewise, the results of the CIBOMA study cannot be compared with those of the CREATE-X study, as they present populations with different relapse risk and different designs.

ECOG-ACRIN EA1131[13]

In this study, patients with stage II–III TNBC with >1 cm of residual disease in the breast regardless of nodal response after receiving neoadjuvant chemotherapy (taxane with or without anthracyclines) were randomized 1:1 to receive 3-weekly platinum (carboplatin or cisplatin) for 4 cycles or capecitabine at a dose of 2000 mg/m^2/day for 6 cycles. TNBC subtype (basal vs non-basal) was determined by PAM50 in residual disease. A non-inferiority design with alternative superiority (hybrid design) was chosen in an attempt to demonstrate that in patients with basal subtype TNBC, the use of platinum would improve iDFS (time from random assignment to the earliest disease recurrence (locoregional or distant), invasive contralateral cancer, second primary cancer, or death) compared with capecitabine (4-year iDFS of 67% with capecitabine based on the results of the X-Create study). Between 2015 and 2021, 410 patients of the 775 planned participants were randomized to receive platinum or capecitabine. Of the total patients, 308 (78%)

had basal subtype TNBC. In this population, after a median follow-up of 20 months and 120 iDFS events (61% of complete data), the 3-year iDFS for platinum was 42% (95% CI, 30–53) vs 49% (95% CI, 39–59) for capecitabine (HR 1.06, 95% CI 0.62–1.81). The study was closed prematurely as long-term follow-up was unlikely to show non-inferiority or superiority of platinum and also had a higher incidence of grade 3–4 toxicities than capecitabine. As for OS at 3 years, it was 58% (95% CI, 45–68) in the platinum arm vs 66% (95% CI, 56–74) in the capecitabine arm (HR 1.13, 95% CI 0.71–1.79). Meanwhile, the subgroup of patients with non-basal phenotype (n=88, 22% of the total), the 3-year iDFS was 46% for the platinum arm vs 69% in patients receiving capecitabine (HR 1.94, 95% CI 0.69–5.45). Patients with basal subtype TNBC had worse iDFS than patients with non-basal subtype (HR 1.71; 95% CI 1.10–2.67). Therefore, the use of platinum as adjuvant treatment in TNBC patients with residual disease after neoadjuvant chemotherapy does not improve the outcome of these patients and is associated with increased toxicity. The iDFS results in the study population at 3 years were globally lower than expected, which highlights the need to improve oncological therapies in this population at high risk of relapse.

CaRe[14]

Multicenter, observational, retrospective study of adjuvant capecitabine in patients with early TNBC with residual invasive disease after surgery and neoadjuvant chemotherapy. In total, 270 patients were retrospectively identified. Of the patients, 50.4% had positive residual nodal disease, 7.8% had large residual tumor (ypT3/ypT4), 81.9% had G3 residual tumor, and 80.4% had Ki-67 >20%. Capecitabine treatment was initiated within 4 months of definitive surgery in all patients. The median number of capecitabine cycles administered was 6 (range 1–8). 12.6% of patients discontinued capecitabine treatment due to disease relapse and 10.4% discontinued due to toxicity. In the overall population, with a median follow-up of 15 months, DFS at 2 years was 62%, and OS at 2 and 3 years was 84.0% and 76.2%, respectively. In 129 patients with a median follow-up of 25 months, DFS at 2 years was 43.4% and OS at 2 and 3 years was 78.0% and 70.8%, respectively. Six or more cycles of capecitabine were associated with more favorable outcomes than fewer than 6 cycles. The CaRe study shows unexpectedly good tolerability of adjuvant capecitabine in a real-world setting, although efficacy appears to be lower than that observed in the CREATE-X study. However, this is a retrospective study, which limits its comparability with the CREATE-X trial.

Pembrolizumab

In the double-blind, randomized, phase 3 KEYNOTE 522 trial,[15] a total of 1174 patients with stage II–III TNBC were randomized in a 2:1 ratio to receive neoadjuvant treatment with chemotherapy–pembrolizumab (784 patients) or chemotherapy–placebo (390 patients). The chemotherapy schedule contained weekly paclitaxel, carboplatin, and anthracycline with cyclophosphamide sequentially. After definitive surgery, patients received adjuvant pembrolizumab or placebo every 3 weeks for up to 9 cycles. No cross-over was allowed during the study, nor was adjuvant capecitabine allowed in patients with residual disease since the study design was conducted before the data from the CREATE-X study were known.[11] The primary objectives of the study were pCR at the time of surgery (defined as ypT0/Tis ypN0) and event-free survival (EFS) in the intention-to-treat population. In the first interim analysis, among the first 602 randomized patients, the percentage of patients with a pCR was 64.8% (95% CI: 59.9%–69.5%) in the pembrolizumab chemotherapy group and 51.2% (95% CI: 44.1%–58.3%) in the placebo chemotherapy group (estimated difference 13.6 percentage points; 95% CI: 5.4–21.8; p<.001). These differences were consistent across the different predetermined groups, including different PD-L1 expression. Approximately, 80% of the included patients had overexpression of this biomarker. In the subgroup of patients with PD-L1 overexpression, the pCR rate was 68.9% in patients receiving pembrolizumab vs 54.9% in the placebo group, while in patients without overexpression, it was 45.3% vs 30.3%. At long-term follow-up EFS at 3 years was 84.5% (95% CI 81.7%–86.9%) in the combination arm with pembrolizumab vs 76.8% (95% CI 72.2%–80.7%) in the placebo arm with chemotherapy (HR for event or death, 0.63; 95% CI 0.48–8.82; p<.001). In those patients who achieved pCR, EFS at 3 years was 94.4% in the chemotherapy–pembrolizumab arm vs 92.5% in the chemotherapy–placebo group (HR 0.73; 95% CI 0.39–1.36), while in patients with residual disease it was considerably lower (64.7% vs 56.8%, HR 0.7; 95% CI 0.52–0.95).[15] However, the study was not designed to determine the relative contribution of pembrolizumab in the neoadjuvant or adjuvant setting, but rather in a global manner according to the trial design. The most frequent event in the EFS analysis was distant recurrence, which occurred in 7.7% of patients in the chemotherapy–pembrolizumab group and in 13.1% in the chemotherapy–placebo group. These differences were consistently observed in the different prespecified subgroups including subgroups defined according to PD-L1 expression and nodal involvement. The estimated 3-year survival was 89.7% (95% CI 87.3–91.7) in the pembrolizumab group and 86.9% (95% CI 83–89) in the placebo group. Long-term follow-up of the study, with a median follow-up of 63.1 months, the addition of pembrolizumab to chemotherapy provided an absolute benefit of a 7.2% higher pCR and a 9% increase in EFS.[16] Data from the exploratory analysis of EFS based on residual cancer burden (RCB) have recently been reported with a lower follow-up than previously reported data (39.1 months).[17] In the pembrolizumab arm, there were more patients with RCB-0 (pCR, HR 0.70 (0.38–1.31)) and fewer patients in the RCB-1 (HR 0.92, 0.39–2.20), RCB-2 (0.52, 0.32–0.82), and RCB-3 (HR 1.24, 0.69–2.23) groups. Thus, the maximum benefit was observed in the RCB-2 group (20% at 3 years, compared with 2% and 1% for the RCB-0 and RCB-1 groups). The loss of benefit in the RCB-3 subgroup needs further validation because of the small sample size. The most frequent first EFS event was distant recurrence, with lower numbers in all RCB subgroups in the pembrolizumab arm (3-year EFS in the RCB-1, RCB-2, and RCB-2 groups depending on treatment arm was 84.4% vs 83.8%, 75.7% vs 55.9%, and 26.2 vs 34.4%, respectively). Among patients with RCB-0/1, 55.3% of all

events occurred at the central nervous system level (59.1% in the pembrolizumab arm and 50% in the placebo group), so this remains a therapeutic challenge in these patients. In light of these data, it seems important to be able to identify those patients with RCB-3 treated with neoadjuvant pembrolizumab–chemotherapy in order to consider which is the best therapeutic alternative in the adjuvant context, as well as to incorporate new biomarkers such as pretreatment stromal tumor-infiltrating lymphocytes that have been associated with better prognosis in patients with TNBC treated with neoadjuvant chemotherapy or chemoimmunotherapy.[18–20]

Olaparib

OlympiA is a randomized, double-blind, phase 3 clinical trial[21] in patients with human epidermal growth factor receptor 2-negative early breast cancer with pathogenic or probably pathogenic germline BRCA1 or BRCA2 variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. The study was initially designed for BRCA-mutated TNBC, but an amendment was subsequently made to allow the inclusion of hormone receptor-positive patients. Patients included had to have received at least 6 cycles of prior chemotherapy containing taxanes, anthracyclines, or both, and prior platinum use was allowed (stratification factor). Patients did not receive adjuvant capecitabine. In the case of TNBC, patients were considered high-risk if they had residual disease after neoadjuvant chemotherapy or they had to have lymph node involvement or a tumor size of at least 2 cm if they had received adjuvant treatment. Patients were randomized 1:1 to receive 1 year of treatment with oral olaparib 300 mg twice daily or placebo. The primary endpoint of the study was IDFS (defined as the time from randomization until the date of first occurrence of one of the following events: ipsilateral invasive breast tumor, locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, second primary invasive cancer, or death from any cause). A total of 1836 patients were randomized, of whom 1509 had TNBC. In the first prespecified analysis, with a median follow-up of 2.5 years, 3-year IDFS was 85.9% in the olaparib group and 77.1% in the placebo group (95% CI, 4.5–13.0; HR of invasive disease or death, 0.58; 99.5% CI, 0.41–0.82; $p < .001$). The 4-year IDFS was 82.7% in the olaparib group and 75.4% in the placebo group (95% CI, 3.0–11.5). In terms of OS at 4 years,[22] patients receiving olaparib had an absolute benefit of 3.4% (89.8% vs 86.4%, 95% CI 0.1%–6.8%; HR 0.68; CI 98.5% 0.47–0.97, $p = .009$). In the analysis by preplanned subgroups, the improvement in survival contributed by olaparib was independent of BRCA mutation type, hormone receptor status, prior platinum use, and neoadjuvant/adjuvant setting of prior treatment. In the subgroup of TNBC patients, the relative HR for olaparib vs placebo was for IDFS HR 0.62 vs 0.68 for luminal disease.

Discussion

TNBC with residual disease after neoadjuvant treatment continues to be a therapeutic challenge given the risk of relapse and death that these patients present. Nowadays, there are 3 drugs available that have demonstrated benefit in terms of survival but they are not comparable with each other because there are no studies that compare them and their scientific evidence is derived from clinical trials with different designs and populations. The chemoimmunotherapy combination of the KEYNOTE-522 trial[15] has become the neoadjuvant standard for a high percentage of patients with TNBC (stage II–III). It should be taken into account that this study was not designed independently in the neoadjuvant and adjuvant phase, but rather a single initial randomization was carried out and all patients continued after the pembrolizumab intervention regardless of the response achieved in the surgical specimen. This makes it impossible to know the contribution of the drug separately in each of the treatment phases or the exact benefit of pembrolizumab in the adjuvant setting, a situation in which other studies with immunotherapy have not achieved favorable results.[23]

In addition, patients who did not achieve pCR with chemoimmunotherapy treatment did not receive capecitabine or olaparib in case of germline mutations in BRCA, drugs that have shown impact on OS in patients with TNBC and residual disease after neoadjuvant chemotherapy, so at present, we do not know what may be the impact of the combination or sequence of the different therapeutic strategies as well as their possible toxicity and impact on the quality of life of patients.

Therefore, the persistence of residual disease after neoadjuvant treatment in patients with TNBC continues to be a situation of high risk of recurrence for these patients in whom it is essential to search for and integrate new biomarkers and drugs that allow the most effective therapeutic strategy to be individualized after surgery.

Funding

None.

Ethical considerations

This review article has been carried out in compliance with all current ethical and legal guarantees. As this is a review article of the available scientific evidence, no animal experiments have been carried out, no patients have been involved in it and it is not a clinical trial.

Patients consent

The authors declare that they obtained the patient's consent for publication of the article.

Declaration of competing interest

M. Teresa Quintanar Verdúguez; Consultant or advisor fees from AstraZeneca and Daiichi Sankyo. Research funding for his institution from AstraZeneca, GEICAM, and Anthos Therapeutics. Speaker's fees from Novartis, Lilly, Leo Pharma and MSD. Travel grants from Novartis, Roche and MSD.

María Ballester Espinosa; Speaker's fees from: AstraZeneca, Gilead, Daichi-Sankyo. Travel grants from Astra Zeneca and Roche.

Javier Pérez Altozano; No conflict of interests.

Álvaro Muñoz Abad; No conflict of interests.

Álvaro Rodríguez Lescure; Consultant or advisor fees from Roche, Pfizer, Novartis, Lilly, AstraZeneca, Daiichi Sankyo, Gilead, Pierre Fabre, MSD, Organon and Seagen. Research funding for his institution from Roche, Novartis, Pfizer, Lilly, AstraZeneca, MSD, Radius, Zymeworks, Gilead,GEICAM, and Sanofi; Speaker's fees from Roche, Pfizer, Novartis, Lilly, AstraZeneca, Gilead, Daiichi Sankyo, Eisai, MSD, and Seagen Travel grants from Roche, Pfizer, and Novartis.

References

1. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010;363:1938–48.
2. Palma G, Frasci G, Chirico A, Esposito E, Siani C, Saturnino C, et al. Triple negative breast cancer: looking for the missing link between biology and treatments. Oncotarget. 2015;6:26560–74.
3. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008;26:1275–81.
4. R. Caparica, M. Lambertini, N. Pond, D. Fumagalli, E. Azambuja, M. Piccart. Post-neoadjuvant treatment and the management of residual disease in breast cancer: state of the art and perspectives, *Ther Adv Med Oncol*, **11**, 2019, 1758835919827714.
5. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810–21.
6. Cortazar P, Zhang L, Untch M, Mehta K, Constantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164–72.
7. J.R. Bellon, H.J. Burstein, E.S. Frank, EA. Mittendorfet, TA. King.Multidisciplinary considerations in the treatment of triple-negative breast cancer, *CA Cancer J Clin*, **70**, 2020, 432–442.
8. S. Loibl, F. Andr, T. Bachelot, CH. Barrios, J. Bergh, HJ. Hurstein, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, *Ann Oncol*, **35**, 2024, 159–182.
9. F. Ayala de la Pena, S.A. Novoa, J.G. Gregori, L. González Cortijo, F. Henao Carrasco, MT. Martínez Martínez, et al. SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (2022), *Clin Transl Oncol*, **25**, 2023, 2647–266
10. van Mackelenberg MT, Sither F, Volker M, O'Shaughnessy J, Martin M, Joenssu H, et al. Effects of capecitabine as part of neo –/adjuvant chemotherapy- a meta-analysis of individual breast cancer patient data from 13 randomised trials including 15993 patients. Eur J Cancer. 2022;166:185–201.
11. Masuda N, Lee S-J, Ohtani S, Im J-H, Lee E-S, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147–59.
12. A. Lluch, C.H. Barrios, L. Torrecillas, M. Ruiz Borrego, J. Bines, J. Segalla, et al. Phase III trial of adjuvant capecitabine after standard neo –/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM 2003-11_CIBOMA/2004-01), *J Clin Oncol*, **38**, 2019, 203–213.
13. I.A. Mayer, F. Zhao, C.L. Arteaga, J.F.Symmans, B.H. Park, B.L. Burnette, et al. Randomized phase III postoperative trial of platinum-based chemotherapy versus capecitabine in patients with residual triple-negative breast cancer following neoadjuvant chemotherapy: ECOG-ACRIN EA1131, *J Clin Oncol*, **39**, 2021, 2539–2551.
14. Di Lisa FS, Krasniqi E, Pizzuti L, Barba M, Cannita K, De Giorgi U, et al. Adjuvant capecitabine in triple negative breast cancer patients with residual disease after neoadjuvant treatment: realworld evidence from CaRe, a multicentric, observational study. Front Oncol. 2023;13:1152123.
15. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Berg J, et al. Pembrolizumab for early triple negative breast cancer. N Engl J Med. 2020;382:810–21.
16. Schmid P. LBA18. Ann Oncol. 2023;34(suppl 2):S1257.
17. L. Pusztai, C. Denkert, J. O'Shaughnessy, J. Cortes, R. Dent, H. McArthur, et al. Event-free survival by residual cancer burden with pembrolizumab in early-stage TNBC: exploratory analysis fron KEYNOTE-522, *Ann Oncol*, **35**, 2024, 429–436.
18. E. Agostineto, L. Buisseret, R. Salgado, M. Kok, M. Ignatiadis. Residual disease post neoadjuvant chemo-immunotherapy in early triple-negative breast cancer: does it help tailor adjuvant treatment?, *Ann Oncol*, **35**, 2024, 409–411.
19. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumour infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 2018;19:40–50.
20. Loibl S, Untch M, Burchadi N, Huober J, Sinn BV. J-H Blohmer, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30:1279–88.
21. Tutt A, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med. 2021;384:2394–405.
22. G.E. Geyer, J.E. Garber, R.D. Gelber, G. Yothers, M. Taboada, L. Ross, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA and high risk, early breast cancer, *Ann Oncol*, **33**, 2022, 1250–1268.
23. M. Ignatiadis, A. Bailey, H. McArthur, S. El Abed, E. Azambuja, O. Metzger, et al. GS01–03 Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase trial, Conference Proceeding Presented at the San Antonio Breast Cancer Symposium, 2023.