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REVIEW ARTICLE

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News and updates in the treatment of localized stage triple-negative breast cancer

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ABSTRACT

Compared to other breast cancer subtypes, triple-negative breast cancer presents a worse prognosis and higher mortality. Even in localized stages, the risk of relapse is high, especially in patients with ≥ cT2 and/or ≥ cN1. We know that those patients who achieve a complete pathologic response after neoadjuvant treatment have better disease-free survival. Therefore, many research efforts have been made to try to optimize neoadjuvant chemo/immunotherapy to increase pathologic complete response rates. The available evidence related to that subject matter is summarized in this article. In the field of adjuvant therapy, the challenge of improving disease-free survival in those patients who do not achieve pathologic complete response after neoadjuvant therapy stands out. The second part of this article will deal with the challenges inherent to this issue.

Key words: adjuvant treatment, disease-free survival, early breast cancer, neoadjuvant treatment, pathological complete response, treatment personalization, triple-negative breast cancer

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Introduction

In the treatment of early-stage triple-negative breast cancer (TNBC), guidelines distinguish between two major therapeutic branches: 1) in those tumors with clinical stage cT1N0, they recommended performing upfront surgery with the possibility of subsequent adjuvant treatment depending on the pathological stage and 2) in those tumors with clinical stage ≥ cT2 and/or ≥ cN1, they recommend neoadjuvant therapy followed by surgery and subsequent adjuvant treatment [1].

Compared to other subtypes of breast cancer, TNBC has a worse prognosis and higher mortality, even when it debuts in a localized form. We know that those patients who achieve a complete pathologic response after neoadjuvant therapy have better disease-free survival. Therefore, research efforts have been oriented towards the optimization of neoadjuvant chemo/immunotherapy to increase pathological complete response (pCR) rates without disregarding the issue of toxicity accumulation that can limit successive lines as well as the selection of patient profiles based on biomarkers that determine their risk of relapse to individualize treatment in terms of adoption of escalation and de-escalation strategies.

We also know that patients who do not achieve pCR have lower disease-free survival (DFS: invasive iDFS or distant DDFS) despite the available adjuvant treatments. In the field of adjuvant therapy, the challenge of improving survival parameters in this subgroup of patients and exploring new drugs as well as escalation strategies stands out.

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Optimizing the search for complete pathologic response in neoadjuvant therapy

Nuances in the management of cT1N0 tumors

In tumors with clinical stage cT1N0, the guidelines initially recommend performing surgery. If the pathologic stage is pT1aN0, follow-up is recommended. However, in all patients whose pathological stage results are ≥ pT2 and/or ≥ pN1 and, generally speaking, also in those with pT1b-c pN0, they recommended performing adjuvant treatment [with chemotherapy (QT) or with targeted therapy (TD) with PARP inhibitors in the case of *BRCA* mutations] [1].

In the case of patients with minimal tumor disease in the pathologic specimen (pT1b-cN0), the question is what parameters are indicative of good prognosis that would allow for individualized management and selection of those patients who may be exempt from the toxicity of adjuvant treatment that can be detrimental to their long-term survival.

The European Society for Medical Oncology (ESMO) 2022 guidelines distinguish four histology types which are associated with good prognosis: apocrine, secretory, medullary, and cystic adenoid. They point out that, within these histology types, follow-up could be considered due to their 5-year overall survival (OS) of more than 92% [1].

However, the frequency of these histologies is low, which has led to the search for other markers that can guide de-escalation, such as the proliferation index (ki67) or tumor-infiltrating lymphocytes (TILs). The prognostic role of TILs is indisputable (level of evidence 1B) and has been demonstrated in several studies [1].

Park et al. [2] reviewed a cohort of 476 patients from 4 centers (1989–2015) with resected TNBC without perioperative QT. Retrospectively, they assessed the percentage of TILs in the surgical specimen, stratifying into two groups: TILs < 30% and TILs ≥ 30%. They concluded that stage I TNBC patients with TILs ≥ 30% form a subgroup with excellent prognosis without adjuvant chemotherapy [at 5 years: DFS 91% (95% CI 84–96), D-DFS 97% (95% CI 93–100), OS 98% (95% CI 95–100)] [2].

Similarly, De Jong et al. [3] retrospectively reviewed a sample of 441 patients from the German registry (1989–2000), younger than 40 years at diagnosis, with pT1-3N0 and without perioperative chemotherapy. They stratified TILs into three groups: < 30%, 30–75%, and ≥ 75%. At 15 years, the cumulative incidence of distant metastases or death was 2.1% for the subgroup with high TILs ≥ 75% (95% CI: 0–5) and 38.4% for the subgroup of low TILs <30%. Furthermore, each 10% increase in TILs correlated with a 19% decrease in the risk of death [adjusted hazard ratio (HR) = 0.81; 95% CI 0.76–0.87]. They concluded, therefore, that young, QT-naive, N0 TNBC patients with sTILs ≥ 75% have an excellent long-term prognosis, and prospective clinical trials investigating (neo)adjuvant QT de-escalation strategies should be considered in this subgroup [3]. Because of the aforementioned lack of prospective clinical trials, there is still no evidence to make therapeutic decisions based solely on this parameter, and, therefore, it is not currently recommended in the clinical practice guidelines. However, this is an emerging line of research that will provide new developments in the coming years.

Triple-negative breast cancer with ≥ cT2 and/or ≥ cN1: gainig further knowledge of neoadjuvant therapy

For the treatment of TNBC ≥ cT2 and/or ≥ cN1, the NCCN 2022 guidelines issue multiple recommendations regarding options for therapeutic schemes which they classify under three headings: “preferred regimens”, “regimens useful in certain circumstances” “other recommended regimens” [4].

The NCCN 2022 guidelines lay out fundamental concepts according to which: 1) the recommended schedule with the most evidence is AC > T biweekly or weekly (where “A” indicates doxorubicin, “C”, cyclophosphamide, and “T”, paclitaxel) 2) for high-risk TNBC, the guidelines recommend combining QT with pembrolizumab in neoadjuvant treatment according to the KEYNOTE 522 scheme 3) the combination of carboplatin with paclitaxel/docetaxel is mentioned in the preoperative setting but is not routinely recommended for most patients 4) bevacizumab has no place in (neo)adjuvant therapy and is recommended in combination with chemotherapy only for selected patients with recurrent or stage IV disease [4]. The ESMO 2022 guidelines reinforce the same concepts [1].

Neoadjuvant chemotherapy

Classically, three fundamental questions have been considered around the issue of neoadjuvant chemotherapy in TNBC ≥ cT2 and/or ≥ cN1: 1) should carboplatin be added? 2) what is the role of bevacizumab? 3) are anthracyclines necessary? We will try to answer them below.

Should carboplatin be added?

There are subgroups within TNBC (such as those associated with *BRCA* mutations), in which the inherent defect in DNA repair based on homologous recombination increases sensitivity to alkylating agents, such as carboplatin [5]. Table 1 [6–12] summarizes the most important characteristics of the main clinical trials related to the study of the addition of carboplatin to neoadjuvant chemotherapy. Several issues are noteworthy:

1. All trials are phase II except the GeparOcto/GBG84 trial [10] and BrighTNess trial [11, 12], which are phase III;
2. There is great variability in the design of the trials, including combinations and sequencing of different chemotherapy agents, with variability in doses. Some also include targeted therapies (veliparib) or antiangiogenics (bevacizumab). The heterogeneity in the design makes the results difficult to compare;
3. The primary endpoint for all of them was pCR, with significant differences in favor of carboplatin use of around 25% in both BrighTNess [11, 12] and ISPY-2 [9] and around 15% in GeparSixto/GBG66 [8] and CALGB 40603 [7];
4. Regarding survival data, it is remarkable that no trial achieved significant differences in OS. In contrast, in GeparSixto/GBG66 [8] and BrighTNess [11, 12], significant differences in DFS in favor of carboplatin were achieved.

Of all the trials mentioned, BrighTNess [11, 12] is noteworthy for its relevance. It is a three-arm phase III trial that randomized women > 18 years, with ECOG 0–1, with stage II/III TNBC and potential surgical candidates to receive: paclitaxel (first arm), carboplatin (second arm), with the addition of veliparib to the previous combination (third arm), followed by AC and subsequent surgery. It was a positive trial in terms of pCR and DFS (as shown in Tab. 1). Its authors conclude that:

1. adding carboplatin improved pCR ,and this, in turn, translated into improved DFS with no impact on OS;
2. the increase in hematologic toxicity with the addition of carboplatin and the consequent delay in treatment did not worsen end-point outcomes;
3. adding veliparib did not impact pCR, DFS, or OS [11, 12].

What is the role of bevacizumab?

The 2022 NCCN and ESMO guidelines do not consider the use of bevacizumab in the (neo)adjuvant setting [1, 4]. This is because although clinical trials of bevacizumab in the neoadjuvant setting are positive for the primary end-point (pCR), this does not translate into a significant increase in DFS/OS [7, 13–15]. Likewise, in the adjuvant setting, the BEATRICE trial also did not

Table 1. Main trials related to the study of carboplatin in combination in neoadjuvant therapy for the treatment of early triple-negative breast cancer

Trial	Phase	N	Design	pCR [%]	DFS/OS (HR)
GEICAM 2006/03 [6]	II	94	EC × 4 > T_{100} × 4 T_{75} Cb × 4	30% *vs.* 30%	—
CALGB 40603 [7]	II	443	wP ± Cbq3w > AC × 4 ± Bev	41% *vs.* 54% (increase 13%)*	5 yr DFS: 70.1% *vs.* 70.4% HR = 0.94 (NS) **5 yr OS: 75.6% *vs.* 74.4% HR = 1.12 (NS)**
GeparSixto/ /GBG66 [8]	II	315	wP + wN-PLD ± Bev ± wCb	37% *vs.* 53% (increase 16%)*	3 yr DFS: 86.1% *vs.* 75.8% HR = 0.56* **3 yr OS: 91.9% *vs.* 86% HR = 0.60 (NS)**
ISPY-2 [9]	II	60	wP ± Cb + V > AC × 4	26% *vs.* 51%* (increase 25%)	—
GeparOcto/ /GBG84 [10]	III	403	wP NPLD Cb *vs.* EP q2w × 3 > Cq2w × 3	48,5% *vs.* 51.7%	—
BrighTNess [11, 12]	III	634	wP ± Cb ± V > AC × 4	31% *vs.* 58% (Cb) *vs.* 53% (CbV) (increase 26%)*	**4.5 yr DFS: 68.5% *vs.* 78.2% *vs.* 79.3% 4.5 yr OS: 86.1% *vs.* 88% *vs.* 90% HR = 0.82 (NS) HR = 0.63 (NS) HR = 1.25 (NS)**

*Statistically significant value; > — followed by; A — doxorubicin; Bev — bevacizumab; C — cyclophosphamide; Cb — carboplatin; DFS — disease-free survival; E — epirubicin; HR — hazard ratio; NPLD — non-pegylated liposomal doxorubicin; NS — not significant; NS — not significant; OS — overall survival; P — paclitaxel; pCR — pathological complete response; q — dose; T — docetaxel; V — veliparib; w — weekly; yr — year

Table 2. Main trials related to the study of bevacizumab in combination with ?? in neoadjuvant therapy for the treatment of early triple-negative breast cancer

Trial	Phase	N	Design	pCR [%]	DFS/OS (HR)
In the neoadjuvant setting					
CALGB 40603 [7, 14]	II	443	wP ± Cbq3w > AC × 4 ± Beva	41% *vs*. 54% (increase 13%)*	5 yr DFS: 70.1% *vs*. 70.4% HR = 0.94 (NS) **5 yr OS: 75.6% *vs*. 74.4% HR = 1.12 (NS)**
GeparQuinto/ /GBG44 [13]	II	315	ECq3w × 4 > Dq3w × 4 ± Beva	27.9% *vs*. 39.3% (increase 11%)*	3 yr DFS: 75.5% *vs*. 72.9% (NS) **3 yr OS: 85.5% *vs*. 80.9% (NS)**
ARTemis [15]	III	800	T × 3 > CEF × 3 ± Beva	45% *vs*. 31% (increase 14%)*	3.5 yr DFS: 74% *vs*. 78% HR = 1.18 (NS) 3.5 yr OS: 81% *vs*. 84% HR = 1.26 (NS)
In the adjuvant setting					
BEATRIZE [16]	III	2591	AT ± Beva × 4	—	3 yr DFS: 82.7% *vs*. 83.7% HR = 0.87 (NS)

*Statistically significant value; > — followed by; A — doxorubicin; Bev — bevacizumab; C — cyclophosphamide; Cb — carboplatin; DFS — disease-free survival; E — epirubicin; F — fluorouracil; HR — hazard ratio; NPLD — non-pegylated liposomal doxorubicin; NS — not significant; NS — not significant; OS — overall survival; P — paclitaxel; pCR — pathological complete response; q — dose; T — docetaxel; V — veliparib; yr — year

demonstrate a significant increase in survival parameters [16]. The results of the main trials are summarized in Table 2 [7, 13 –16].

Are anthracyclines necessary?

Anthracyclines are chemotherapeutics with widely demonstrated efficacy in the treatment of TNBC. However, they carry cardiovascular risks and the risk of secondary leukemias in the long term [5]. Especially in localized stages, where the fundamental curative pillar is surgery, it is advisable to try to reduce as much as possible the toxicity derived from neoadjuvant treatment that may be detrimental, in the long term, to the quality of life of the patients and therapeutic possibilities in successive lines. For this reason, de-escalation trials have been designed to try to evaluate the benefit-toxicity balance that anthracyclines bring to perioperative treatment. Some of them include an anthracycline arm in the design. Others, however, omit them and compare them with the results available in the literature. Table 3 [17–21] lists the main trials in this regard.

None of the trials listed in Table 3 conclude in favor of anthracyclines although only two (the NCT01276769 trial [18] and the NeoCART trial [20]) obtain higher pCR rates with the alternative scheme. The remaining trials highlight the non-inferiority of omitting anthracyclines and the resulting benefits in tolerability. The phase II trial NCT01276769 compared paclitaxel plus carboplatin versus epirubicin plus paclitaxel [18]. It concluded the superiority of carboplatin with a significant difference in terms of pCR and DFS at 4 years [18]. However, it should be remembered that the chemotherapy scheme recommended with the most evidence in the 2022NCCN guidelines is anthracycline plus cyclophosphamide followed by taxane [4]. The design of the study NCT01276769 can, therefore, be questioned for not comparing the taxane-platinum combination with the standard combination. The phase II NeoCART trial, on the other hand, was designed to compare the taxane-platinum combination with AC followed by taxane [20]. A significant pCR benefit in favor of carboplatin was maintained, however, no differences in survival parameters were obtained [20].

Conclusions regarding neoadjuvant chemotherapy

Heterogeneity in the study design makes it difficult to draw clear conclusions. In this regard, Li J. et al. [22] designed a meta-analysis comparing different chemotherapy schedules for the treatment of stage I–III TNBC. They included randomized trials with the control group, published in English. From an initial search of more than 2000 references, they finally selected 35 clinical trials. As the primary objective, they compared pCR, and as the secondary objective they compared the aggregate adverse effects (AEs), defined as total adverse effects grade 3 or higher. They concluded that adding platinum to neoadjuvant TNBC treatment, both in regimens in which it is combined with taxanes alone (TCb; OR = 2.16; 95% CI 1.20–3.91) and in those that also include anthracyclines (ATPt; OR = 2.04; 95% CI 1.69–2.48), significantly increases the pCR rate with respect to AT regimens. Furthermore, without anthracyclines, it improves tolerance without worsening the pCR rate, although no significant differences were obtained in the incidence of severe ALE (OR = 0.66; 95% CI 0.23–1.72) [22].

Table 3. Main trials related to the possibility of omitting anthracyclines in neoadjuvant treatment of early triple-negative breast cancer

Trial	Phase	N	Design	pCR [%]	DFS/OS (HR)
PROGECT (NCT01560663) Compare results with available literature [17]	—	190	TCb q3w × 6	55% Similar rate to ACb but better safety profile.	3 yr DFS: 79% **3 yr OS: 87%**
NCT01276769 [18]	II	91	PCb q3w *vs*. EP q3w × 6	14.0% (EP) *vs.* 38.9% (PCb)*	4 yr DFS: 52.8% (EP) *vs.* 71.1% (PCb)*; p = 0.080 **4 yr OS: 70.1% *vs.* 72.5% (NS); p = 0.980**
TBCRC030 [19]	II	139	wPx12 *vs.* CDDP q3w × 4	11.9% P *vs.* 15.3% CDDP	—
NeoCART [20]	II	93	TCb q3wx6 *vs.* EC × 4 > T × 4	61.4% *vs.* 38.6% *	3 yr DFS: 88.3% *vs.* 90.8% (NS); HR = 0.76 **3 yr OS: 92.8% *vs.* 93.1% (NS); HR = 0.96**
NeoSTOP [21]	II	100	wP ± Cb q3w × 4 > AC × 4 *vs.* TCb q3w × 6	54% *vs.* 54%	3 yr DFS and OS: NS between both arms and significantly higher in those achieving pCR regardless of treatment received pCR 3 yr DFS: 100% *vs.* 81% **pCR 3 yr OS: 100% *vs.* 86%**

*Statistically significant value; > — followed by; A — doxorubicin; Bev — bevacizumab; C — cyclophosphamide; Cb — carboplatin; CDDP — cisplatin; DFS — disease-free survival; E — epirubicin; HR — hazard ratio; NPLD — non-pegylated liposomal doxorubicin; NS — not significant; NS — not significant; OS — overall survival; P — paclitaxel; pCR — pathological complete response; q — dose; T — docetaxel; V — veliparib; w — weekly; yr — year

Neoadjuvant immunotherapy

Figure 1 [23–28] summarizes the current immunotherapy (IT) landscape for neoadjuvant treatment in early-stage TNBC. Atezolizumab gained FDA approval in 2019 and EMA approval in 2020 in combination with paclitaxel-albumin based on the results of the IMPASSION 031 trial [22]. Pembrolizumab was approved in 2021 by the FDA in combination with chemotherapy as neoadjuvant treatment and in adjuvant monotherapy based on the results of the KEYNOTE 522 trial [24, 25]. The EMA also approved it in 2021 but only for CPS ≥10, rectifying the approval in 2022 when it became approved regardless of PDL1 levels. Nivolumab is not tested in early stages, but the phase II TONIC trial was designed for metastatic TNBC [28, 29].

The IMPASSION 031 phase III clinical trial randomized patients with cT2-T4 cN0-N3 cM0 TNBC who had not received prior treatment to receive paclitaxel albumin ± atezolizumab followed by anthracycline + cyclophosphamide ± atezolizumab in the neoadjuvant phase. After surgery, those patients in the IT arm continued with atezolizumab in adjuvant versus placebo in the control arm. It was a positive trial in favor of using atezolizumab in terms of its primary end-point, significantly improving pCR both in the overall sample and when stratifying by PDL1 (overall: 57.6% *vs.* 41.1%; Δ16.5%; 95% CI 5.9–27.1; PDL1 positive: 68.8% *vs.* 49.3%, Δ19.5%; 95% CI 4.2–39.8; PDL1 negative: 47.7% *vs.* 34.4%, Δ13.3%; 95% CI from –0.9 to 27.5). No significant differences were found in survival parameters [23].

The NeoTRIP phase III clinical trial was, in contrast, a pCR-negative trial at its primary endpoint. It randomized patients with previously untreated early-stage TNBC to receive carboplatin + taxane ± atezolizumab. After surgery, adjuvant treatment was performed in both arms with QT (AC/EP/FEC). They concluded that adding atezolizumab to the nab-paclitaxel + carboplatin scheme did not significantly increase the pCR rate [24].

The phase III GEPAR-DUOZE trial is still ongoing. Its design randomizes patients with early TNBC to receive carboplatin + taxane ± atezolizumab followed by epirubicin + cyclophosphamide ± atezolizumab. After surgery, adjuvant will be performed with atezolizumab for the IT arm versus placebo [25].

The phase III KEYNOTE 522 trial, in addition to achieving FDA and EMA approval of pembrolizumab in combination with QT for the perioperative treatment of early TNBC, positioned the scheme at ESMO 2021 as the new standard of care. Patients were randomized to receive carboplatin + taxol ± pembrolizumab sequenced with anthracycline + cyclophosphamide. After surgery, the IT arm maintained pembrolizumab in adjuvant vs. placebo in the control arm. The study concluded in favor of using pembrolizumab in (neo) adjuvant, with a significant increase in pCR rate (66.8% *vs.* 51.2%; p = 0.00055) as well as DFS at 36 months (84.5% *vs.* 76.8%; HR = 0.63; 95% CI 0.43–0.82). The benefit was maintained in all subgroups, being independent of PDL1 [26, 27].

The results in DFS stratified by pCR of KEYNOTE 522 are interesting. Those patients who achieve

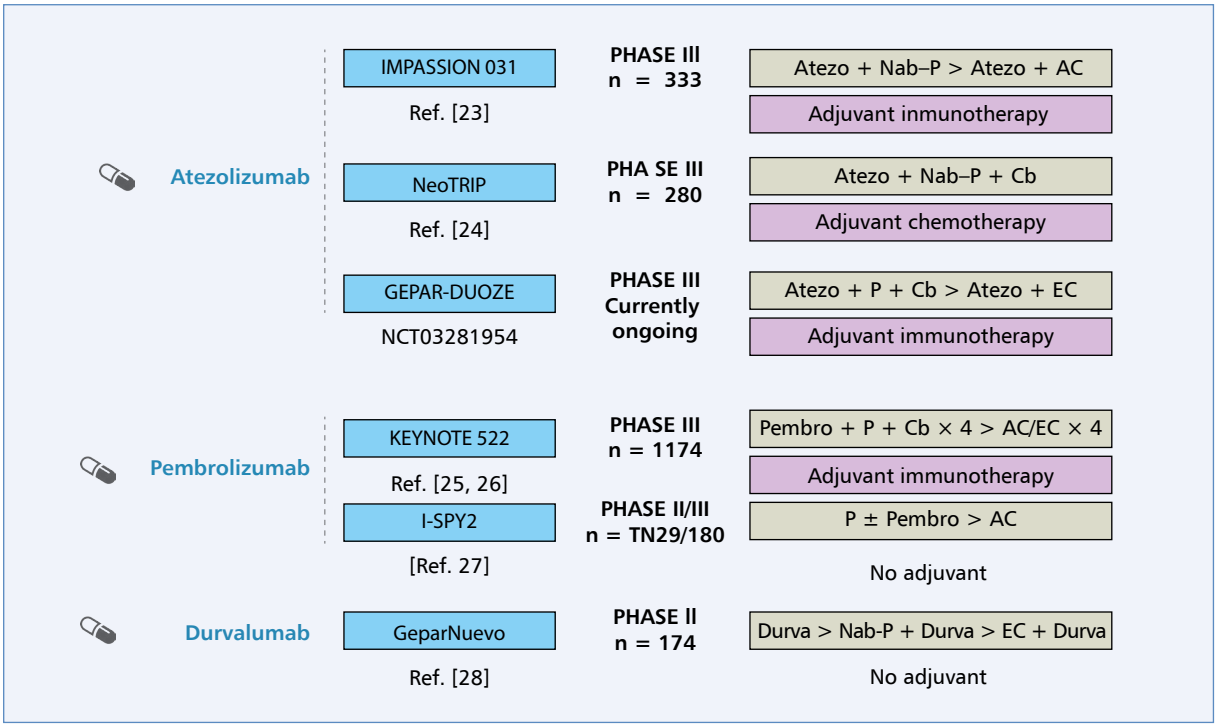

Figure 1. Overview of the main clinical trials on the use of IT in the neoadjuvant treatment of early-stage triple-negative breast cancer [Based on: slide Nº37 SEOM VIRTUAL 2020 "CM TN: Immunotherapy is here to stay" Dr. Elena García-Martínez. Morales Meseguer University Hospital. Murcia]; > — followed by; A — doxorubicin; Atezo — atezolizumab; C — cyclophosphamide; Cb — carboplatin; Durva — durvalumab; E — epirubicin; P — paclitaxel; Pembro — pembrolizumab; T — docetaxel

pCR, regardless of how they achieve it, maintain high DFS 36 months, around 93% (DFS 36 months pCR IT arm 94.4%, DFS 36 months pCR QT arm 92.5%, with no significant difference HR = 0.73; 95% CI 0.39–1.36). However, for those who do not achieve pCR, there is a clear benefit in favor of the use of pembrolizumab (at 36 months, DFS IT *vs.* QT arm 67.4% *vs.* 56.8%; HR = 0.70 95% CI 0.52–0.95). Despite this, it is noteworthy that there continues to be a difference of around 30% in DFS at 36 months between those patients who receive IT and achieve pCR and those who do not. This concept will be important in thinking about the question of adjuvant [26, 27].

The KEYNOTE 522 trial reported no significant difference in terms of OS at 36 months (89.7% *vs.* 86.9%; HR = 0.72; 95% CI 0.51–1.02) [26, 27].

The phase II/III I-SPY2 trial is still ongoing. It has an adaptive design that allows the inclusion of new research arms that are compared in parallel. It is designed for high-risk stage II/III breast tumors, with an interim analysis published on the use of pembrolizumab. Data on 250 patients were analyzed, of which 69 were included in the pembrolizumab arm, with only 20 TNBC. In patients with TNBC, there was a significant increase in the pCR rate (60% *vs.* 12%) in favor of pembrolizumab. Consistent with the results of the KEYNOTE 522 trial, in those patients who did not obtain pCR, the fact of having received pembrolizumab in neoadjuvant therapy improved their DFS with respect to the control [28].

In phase II GeparNuevo trial, which evaluated the combination of durvalumab with QT, was negative in terms of its primary end-point pCR (53.4% *vs.* 44.2%; p = 0.28). However, it is striking that the reported results regarding 3-year survival parameters were all significantly favorable to the durvalumab arm [iDFS 77.2% *vs.* 85.6% (HR = 0.48; 95% CI 0.27–1.09), DDFS 78.4% *vs.* 91.7% (HR = 0.31; 95% CI 0.13–0.74) OS 83.5% *vs.* 95.2% (HR = 0.24; 95% CI 0.08–0.72)] [29].

Issues and challenges in sequential adjuvant

cT2 and/or ≥cN1: the question of adjuvant after neoadjuvant

Figure 2 [26, 27, 30, 31] summarizes adjuvant options after neoadjuvant and surgery in early-stage TNBC.

In patients who achieve pCR

A good starting point to address the question of adjuvant after neoadjuvant treatment in TNBC is to return

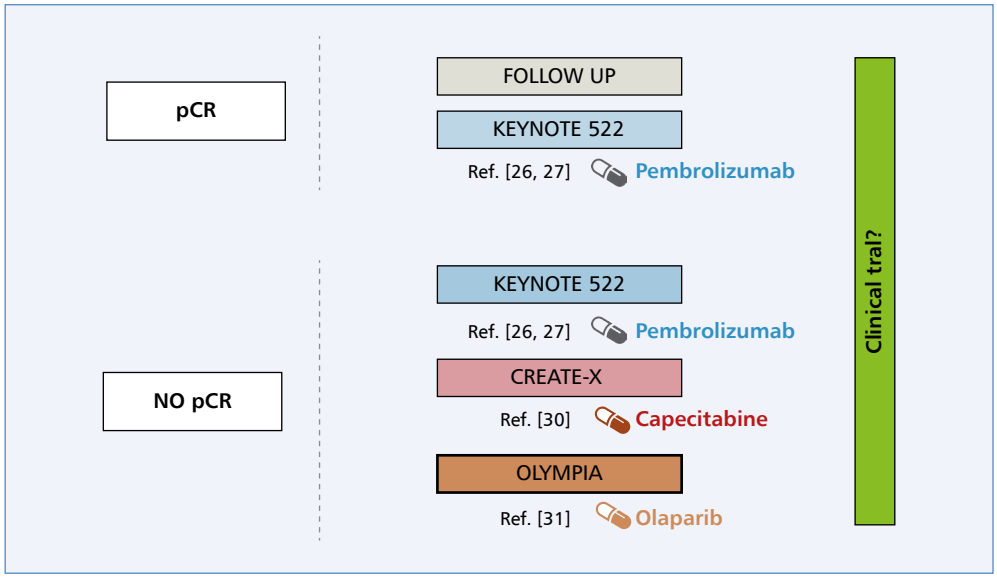

Figure 2. Overview of adjuvant options after neoadjuvant and surgery in early-stage triple-negative breast cancer; pCR — pathological complete response

to the results in pCR-stratified DFS of the KEYNOTE 522 trial, which reinforced the favorable prognosis of patients who achieve pCR, regardless of the treatment with which they achieve it [26, 27].

Within this subgroup of patients, there is the possibility of continuing with pembrolizumab in adjuvant (after performing neoadjuvant with pembrolizumab) based on the KEYNOTE 522 scheme [26, 27].

However, the results of stratification of survival curves by pCR suggest that de-escalation approaches could be explored with a clear clinical impact in terms of toxicity [32, 33]. The OptimICE-PCR trial is designed to randomize patients with TNBC and pCR after neoadjuvant chemoimmunotherapy to adjuvant pembrolizumab for 27 weeks or observation. There are no published results yet [34].

In patients who do not achieve pCR

Given the significant benefit in DFS relative to the use of IT with pembrolizumab according to the KEYNOTE 522 scheme, in those patients who do not achieve pCR it could be concluded that, without a doubt, this subgroup of patients who receive IT in neoadjuvant therapy should continue with pembrolizumab in adjuvant therapy [26, 27]. However, there are several caveats to this categorical statement.

First, the KEYNOTE 522 trial confronted pembrolizumab versus placebo in adjuvant, without including capecitabine in adjuvant as a control group. This is because recruitment for this study began before this drug was positioned in adjuvant as standard of care, following the results of the CREATE-X trial [32, 33]. In the phase III CREATE-X trial capecitabine demonstrated benefit in DFS and OS at 5 years versus placebo (DFS 74.1% *vs.* 67.7%; HR = 0.7; p = 0.005; OS 89.2% *vs.* 83.9%; p < 0.01) [30].

Second, despite continuing with pembrolizumab, DFS remains approximately 30% lower relative to those patients achieving pCR. Bonadio et al. [33] reflected on this point in their article on management of TNBC patients after neoadjuvant pembrolizumab. They pointed out the importance of exploring escalation strategies, such as the possibility of administering concomitant pembrolizumab + capecitabine or designing adjuvant strategies with sequence therapy [33].

In addition, among patients who do not achieve pCR, there is a subgroup with a worse prognosis. Within KEYNOTE 522, a subanalysis of outcomes stratified by residual cancer burden (RCB) was performed. It was observed that patients with higher residual disease burden (defined as RCB-3) had worse survival rates, and it was striking that this subgroup of patients had worse DFS at 3 years in the IT arm compared to the control (DFS 26.2% pembrolizumab; 95% CI 13.5–41 *vs.* 34.6% control; 95% CI 17.5–52.5). In this subgroup, it is urgent to explore escalation strategies [33]. In our center, we tried to include these patients with particularly poor prognoses in a clinical trial.

Third, at the San Antonio Breast Cancer Symposium 2022, a post-hoc analysis exploring the role of adjuvant radiotherapy in the results of the KEYNOTE-522 trial was published as a poster. They classified patients according to whether or not they had received adjuvant radiotherapy and, in those who had received it, distinguished according to whether it was administered concurrently or sequentially. The pCR rate was determined

as the primary endpoint and survival and toxicity data as secondary endpoints. In this post-hoc analysis, the administration of adjuvant RT and how it was administered did not influence the results with respect to pCR and DFS [35].

Fourth, targeted therapy with PARP inhibitors is another possibility in the adjuvant treatment of patients with TNBC and mutated *BRCA*. This mutation is present in about 10–15% of TNBC patients [33]. The phase III OlympiA clinical trial led to the approval of olaparib in an adjuvant setting. They included patients with germline *BRCA1/2* mutation who had received prior perioperative chemotherapy with anthracycline (and/or taxane) based regimens and stratified them into two subgroups: patients with TN tumors on the one hand and patients with HER2-positive/hormone receptor-positive tumors on the other. Within both groups, patients were randomized to receive olaparib versus placebo. The primary endpoint was iDFS, with a statistically significant difference in favor of olaparib at 36 months (85.9% *vs.* 77.1%; HR = 0.58; 95% CI 0.41–0.82), with benefit maintained in all subgroups. It also concluded in favor of olaparib in terms of DDFS at 36 months (87.5% *vs.* 80.4%; HR = 0.57; 95% CI 0.39–0.83). However, no significant difference was found in OS (92% *vs.* 88.3%; HR = 0.68; 95% CI 0.44–1.05) [31].

Bonadio et al. [33] recommend prioritizing olaparib as adjuvant therapy for BRCA-mutated tumors. They point out that, although there are no studies directly comparing olaparib with capecitabine or pembrolizumab, in the case of ovarian cancer (in which the prevalence of *BRCA1/2* germline mutations and homologous recombination deficiency are higher), clinical trials have shown little activity of immunotherapy in monotherapy. By extrapolation, given the pathophysiologic similarity, these authors are betting on olaparib in this particular clinical scenario [33].

Fifth, we should not forget the possibility of including our patients in clinical trials, especially if we can predict, based on the available evidence, a worse prognosis with the treatments approved to date.

Within the broad landscape of clinical trials, the ongoing phase III SASCIA trial is noteworthy. It is designed to compare adjuvant sacitumumab-govitecan *versus* the treating physician's adjuvant treatment of choice. Although they support other patient profiles, patients with TNBC who have not achieved pCR after 16 weeks of neoadjuvant taxane-based QT can be included in this trial [36].

Conclusions

The search for pCR in neoadjuvant therapy and the issues and challenges in sequential adjuvant therapy in localized stages of TNBC are currently two hot topics.

In neoadjuvant, efforts have been directed to optimize the chemotherapy schedule, with the role of platinum-based drugs gaining relevance and the role of anthracyclines being increasingly questioned in relation to their inherent toxicity. The combination with immunotherapy (pembrolizumab) has revolutionized the therapeutic landscape and is currently considered the new standard of care for high-risk patients.

Research on adjuvant therapy after neoadjuvant therapy is at its peak, with numerous investigations open in this field. Although we have tools such as capecitabine, pembrolizumab (in the case of having received neoadjuvant therapy with IT), or olaparib (in the case of germline BRCA-mutated tumors), there is an urgent need to design escalation strategies and investigate new drugs that improve DFS in those patients who do not achieve pCR after neoadjuvant therapy.

Author contributions

I.S.L.: conceptualization, visualization, methodology, project management, writing: proofreading and editing.

J.A.G.M.: proofreading and editing.

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Conflict of interest

The authors declare no conflicts of interest.

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