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REVIEW

Targeted therapy in triple-negative metastatic breast cancer: a systematic review and meta-analysis

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Objective: To perform a systematic review and meta-analysis of randomized controlled trials that compared the efficacy of targeted therapy to conventional chemotherapy (CT) in patients with metastatic triple-negative breast cancer (TNBC).

Methods: Several databases were searched, including Medline, Embase, LILACS, and CENTRAL. The primary end point was progression-free survival (PFS). We performed a meta-analysis of the published data. The results are expressed as hazard ratio (HR) or risk ratio, with their corresponding 95% confidence intervals (95% CIs).

Results: The final analysis included twelve trials comprising 2,054 patients with TNBC, which compared conventional CT alone against CT combined with targeted therapy (bevacizumab [Bev], sorafenib [Sor], cetuximab, lapatinib, and iniparib). PFS was superior in previously untreated patients with TNBC who received Bev plus CT compared to CT alone (fixed effect, HR 0.62, 95% CI 0.51–0.75; $P<0.00001$). Also, PFS was higher in one study that tested Bev plus CT combination in previously treated patients (HR 0.49, 95% CI 0.33–0.74; $P=0.0006$). Sor plus CT was also tested as first-line and second-line treatments. The pooled data of PFS favored the combination CT plus Sor (fixed effect, HR 0.69, 95% CI 0.49–0.98; $P=0.04$). Comparisons of iniparib plus CT also had a better PFS than CT alone (fixed effect, HR 0.75, 95% CI 0.62–0.90; $P=0.002$).

Conclusion: Targeted therapy, when associated with conventional CT, demonstrated gains in the PFS of patients with TNBC.

Keywords: triple-negative, chemotherapy, breast cancer, systematic review

Core evidence clinical impact summary for targeted therapy in triple-negative metastatic breast cancer

Outcome measure	Evidence	Implications
Disease-oriented evidence	Iniparib or cetuximab when associated with the conventional chemotherapy, demonstrated gains in the response rate.	The overall response rate was higher in patients who received the combination of chemotherapy plus iniparib or cetuximab.
Patient-oriented evidence	Bevacizumab, sorafenib and iniparib plus conventional chemotherapy, showed superiority in the progression-free survival of patients with triple-negative breast cancer.	A significant benefit was found in the progression-free survival using conventional chemotherapy associated with targeted therapy (bevacizumab, or sorafenib and iniparib).
Economic evidence	Neither a cost effectiveness nor a budgetary impact analysis were performed	Neither a cost effectiveness nor a budgetary impact analysis were performed

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Introduction

Metastatic breast cancer is generally considered an incurable malignancy.[1] The primary goals of treatment have been palliation and disease control, with some therapies providing a limited survival benefit.[1]

Around 10%–17% of breast cancers are defined as triple-negative (TN), ie, absence of estrogen receptor, progesterone receptor, and of overexpression and/or amplification of the *HER2/NEU* gene.[2–8] These tumors have some similarities with those known as basal-like tumors, since both affect young patients (<50 years old) and have a higher prevalence in women of African descent, besides being significantly more aggressive, with higher risk of systemic recurrence and death than other breast tumors.[3,4,9,10] The peak risk of recurrence of these tumors happens between the first and third years after diagnosis, and most deaths occur within the first 5 years after therapy starts.[3,8,11]

The finding that *BRCA1* mutations are present in a substantial proportion (25%) of patients with TN breast cancer (TNBC) and the similarities of these tumors with the basal-like subtype suggest that the therapeutic approach can be shared between these tumors.[4,12,13] Preclinical studies have shown that these tumors are sensitive to alkylating agents, such as mitomycin C and platinum analogues (cisplatin and carboplatin).[14,15]

Currently, cytotoxic chemotherapy (CT) is the only option of treatment for metastatic TNBC. Women with TNBC do not seem to benefit from endocrine therapy or trastuzumab.[14] Some molecular-targeted therapies have demonstrated efficacy in this subgroup of patients.[16,17] Bevacizumab (Bev), a monoclonal antibody against vascular endothelial growth factor, used in association with conventional CT was evaluated in randomized studies that included TNBC patients. Results for this subgroup showed a benefit for this medication.[16,17] Other examples of drugs with potential benefit for TNBC are cetuximab (epidermal growth-factor receptor inhibition)[18] and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition.[19]

Due to the lack of specific information, there are no published evidence-based clinical guidelines with explicit recommendations about which systemic treatment scheme is more appropriate for these patients with advanced TNBC.[9,11] The clinical impact of molecular-targeted therapy in the TN population is still not clear.[20] Most information about TN patients comes from subgroup analyses of larger trials, and to our knowledge no systematic synthesis of the studies has been performed so far.

The objective of this study was to perform a systematic review of the literature, with a meta-analysis of randomized studies that evaluated the targeted therapies with conventional CT versus conventional CT alone in patients with TNBC (or basal-like tumor).

Methods

Study-selection criteria

Types of studies

Randomized prospective studies that compared targeted therapy combined with conventional CT versus conventional CT alone in patients with TNBC (or basal-like tumor) were included. We included studies that specifically evaluated this population or those in which a separate analysis for the TNBC patients was performed.

Types of participants

The selected studies included patients with metastatic TNBC.

Search strategy for identification of studies

A broad search on the main computerized databases was conducted, including Embase, LILACS, Medline, Science Citation Index (SCI), CENTRAL, the National Cancer Institute Clinical Trials Service, and the Clinical Trials Register. In addition, the annual meeting proceedings of the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium, the American Association for Cancer Research, and the European Society for Medical Oncology were searched. The manufacturer of Bev in Brazil (Roche) was consulted about ongoing studies that had not yet been published or identified.

The search-strategy methodology for randomized controlled trials[21] recommended by the Cochrane Collaboration[22] was used for Medline. We used an adaptation of this same strategy[21] for Embase, and for LILACS we applied the search-strategy methodology reported by Castro et al.[23] An additional search was performed on the SCI database looking for articles that were cited in the included studies. We added the specific terms pertinent to this review to the overall search-strategy methodology for each database.

The overall search strategy was: 1) "breast neoplasms," 2) "triple negative," 3) "chemotherapy," and 4) randomized controlled trial. Searches in electronic databases combined terms 1–4.

If the data regarding the TN population were not available in the original report, we searched many secondary sources and tried to contact the authors of those studies in order to obtain the information.

Critical evaluation of the selected studies

All references retrieved by the search strategies had their title and abstract evaluated by two of the researchers. Every reference with the least indication of fulfilling the inclusion criteria

was listed as preselected. We retrieved the complete articles of all preselected references. They were analyzed by two different researchers and included or excluded according to the previously reported criteria. Excluded trials and the reason for their exclusion were listed and checked by a third reviewer. Two reviewers read the included studies, and all data of interest were extracted using a standard formulary. If the TNBC analysis was not reported in the original paper, we looked for it in many different sources, such as secondary publications, meeting publications, and direct contact with authors, among others.

Details regarding the main methodology characteristics empirically linked to bias[24] were extracted, and the methodological validity of each selected trial was assessed by two reviewers (TEAB and OC). Particular attention was given to some items: the generation and concealment of the sequence of randomization; blinding; application of intention-to-treat analysis; sample size predefinition; adverse-event reports; if the trial was multicentric or unicentric; and the sponsorship.

Data extraction

Two independent reviewers extracted the data. The name of the first author and the year of publication were used to identify the study. All data were extracted directly from the text or calculated from the available information when necessary. The data on all trials were based on the intention-to-treat principle, so they compared all patients allocated to one treatment with all those allocated to the other.

The primary end point was progression-free survival (PFS). Progression was defined as development of new lesions or "unequivocal progression" of existing lesions, as defined by the original researchers. Secondary end points included objective response rate, overall survival (OS), and adverse events (grade $\geq$3).

Adverse events analyzed were: neutropenia, thrombocytopenia, anemia, febrile neutropenia (hematological); and fatigue, nausea, thromboembolic events, vomiting, rash, left ventricular dysfunction, hand/foot skin reaction, allergic reaction, proteinuria, hypertension, mucositis, neuropathy, headache, bleeding events, and gastrointestinal perforation (nonhematological).

Analysis and presentation of results

The data were analyzed using the Review Manager 5.0.24 statistical package (Cochrane Collaboration, Oxford, UK).[25] Dichotomous clinical outcomes are reported as risk ratios (RRs) and survival data as hazard ratios (HRs).[26] The corresponding 95% confidence intervals (95% CIs) were calculated, and a significant *P*-value was considered to be less than 5% ($P<0.05$). Statistical heterogeneity was calculated through the I^2 method (25% was considered low-level heterogeneity, 25%–50% moderate-level heterogeneity, and >50% high-level heterogeneity).[27,28]

If time-to-event data were not available in the study's reports, they were then indirectly estimated, using the methods described by Parmar et al.[26] A pooled estimate of the HR was computed by a fixed-effect model according to the inverse-variance method.[29] Thus, for effectiveness or side effects, an HR or RR greater than 1 favors the standard arm (conventional CT), whereas an HR or RR less than 1 favors the experimental treatment (targeted therapy with CT).

If a high level of statistical heterogeneity was found in the meta-analysis, an additional analysis was performed using the random-effects model described by DerSimonian and Laird,[30] which provides a more conservative analysis.

To assess the possibility of publication bias, the funnel-plot test described by Egger et al was performed.[31] When the pooled results were significant, the number of patients needed to treat to benefit one (NNT) was calculated by pooling absolute-risk differences in the trials included in this meta-analysis.[32–34] For all analysis, a forest plot was generated to display results.

Results

Figure 1 represents the flow of identification and inclusion of trials, as recommended by the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement.[35] In the first search, 215 articles were obtained. Thirty-two studies were selected and retrieved for full-text analysis. Of these studies, 20 were excluded for various reasons, described in Table 1.

The final analysis included twelve trials comprising 2,048 patients. The targeted therapies studied were Bev, sorafenib (Sor), cetuximab, lapatinib, and PARP inhibitors. Some of the included studies[18,36,37] did not report the TNBC subgroup analysis in the original article, and this information was obtained at conference presentations and/or other subsequent publications (Table 2). A quality assessment of the included studies is shown in Table 3. According to the funnel-plot[31] analysis, the possibility of publication bias was low for all end points.

Chemotherapy with bevacizumab

Four studies evaluated Bev plus CT versus CT alone: three in first-line[16,17,38–40] and one in second-line therapy.[41–42] Most of the studies used a dose of Bev of 15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks, depending on the chemotherapy regimen. One three-arm study (AVADO)[16] evaluated Bev at two different doses: one group received Bev 7.5 mg/kg and another 15 mg/kg. We used the 15 mg/kg results to perform this meta-analysis.

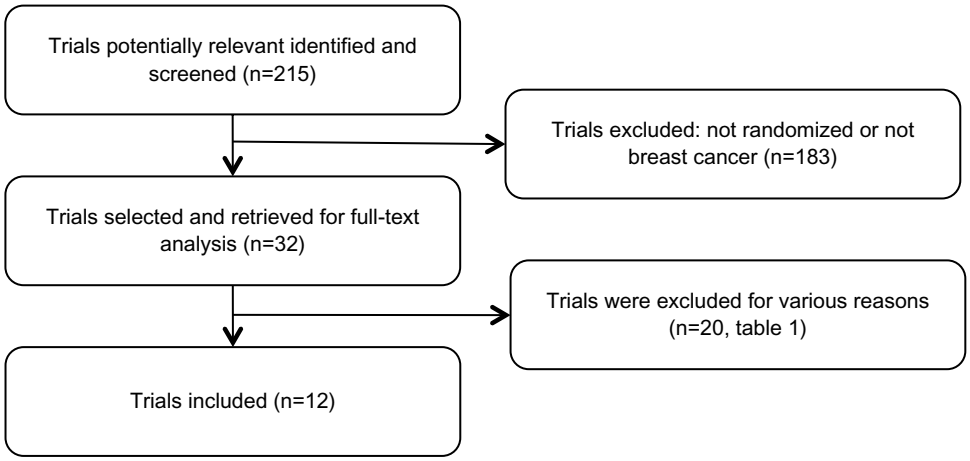

Figure 1 Trial-selection flow.

Bev was combined with many different CT regimens (paclitaxel, docetaxel, capecitabine, anthracyclines, gemcitabine, and vinorelbine). The results showed a superior PFS in patients who received Bev plus CT compared to CT alone in previously untreated TNBC (fixed effect, HR =0.62; 95% CI 0.51–0.75; $P<0.00001$; NNT =2) with no significant heterogeneity ($\chi^2=4.01$, degrees of freedom (*df*)=3; $P=0.26$; $I^2=25\%$) (Figure 2). These studies did not report either the response-rate data or the OS for the TN subgroup.

Table 1 Characteristics of the excluded studies

Study	Reasons for exclusion
Chia[54]	Metastatic TN subgroup but not randomized
Curigliano et al[55]	Sunitinib versus QT in one arm
Berry et al[56]	Stratified patients only by hormone receptor
Gluz et al[57]	CT in high doses
Rodenhuis et al[58]	CT in high doses
Silver et al[59]	Neoadjuvant TN subgroup and nonrandomized
Bonnefoi et al[60]	Stratified patients only by hormone receptor
Leone et al[61]	Neoadjuvant CT and nonrandomized
Torrisi et al[62]	Neoadjuvant CT and nonrandomized
Ryan et al[63]	Neoadjuvant CT and nonrandomized
Frasci et al[64]	Neoadjuvant CT and nonrandomized
Finn et al[65]	Metastatic TN subgroup and nonrandomized
Wang et al[66]	Metastatic TN subgroup and nonrandomized
Citron et al[67]	Stratified patients only by hormone receptor
Garber et al[68]	Neoadjuvant CT and nonrandomized
Byrski et al[69]	Neoadjuvant CT and nonrandomized
von Minckwitz et al[70]	Stratified patients only by hormone receptor
Carey et al[71]	Cetuximab in both groups
Bhattacharrya et al[72]	Not targeted therapy
Rugo[73]	Not targeted therapy

Abbreviations: TN, triple negative; CT, chemotherapy.

In the study that evaluated Bev plus CT in second-line therapy, PFS was also superior in the group that received Bev (HR =0.49, 95% CI 0.33–0.74; $P=0.0006$).[41,42] A nonsignificant, higher OS was seen for the TNBC patients that received Bev (HR =0.624, 95% CI 0.39–1.007) (Table 2). The proportion of hematologic toxicities was similar between the group that received Bev plus CT compared to the one that received CT alone. Some nonhematologic toxicities reported were more frequent in patients who received Bev plus CT: proteinuria (fixed effect, RR =11.87, 95% CI 3.41–41.32; $P=0.0001$), hypertension (fixed effect, RR =13.72, 95% CI 6.93–27.15; $P<0.00001$), neuropathy (fixed effect, RR =1.40, 95% CI 1.09–1.79; $P=0.008$), and bleeding events (fixed effect, RR =5.81, 95% CI 1.87–18.01; $P=0.002$). The other nonhematologic toxicities were similar between the groups.

Chemotherapy with sorafenib

One study compared Sor plus CT versus CT in first-line treatment,[37,43] and two in second-line treatment.[1,36,44,45] In first-line treatment, Sor (400 mg, orally, twice daily) was associated with paclitaxel, and in second-line treatment Sor was associated with gemcitabine or with capecitabine (Table 2). The response rate was not reported for the TNBC subgroup.

PFS was superior for the group treated with Sor in second-line therapy (fixed effect, HR =0.58, 95% CI 0.36–0.93; $P=0.02$; NNT =2). In the pooled overall analysis, PFS remained superior in the group that received Sor versus CT alone (fixed effect, HR =0.69, 95% CI 0.49–0.98; $P=0.04$), regardless of the treatment line (Figure 3). There was no heterogeneity in this analysis ($\chi^2=1.15$, *df*=2; $P=0.56$; $I^2=0\%$). One study reported the OS data, and there was no difference between the groups.[1,44,45]

Table 2 Characteristics of the randomized studies that evaluated different schemes of chemotherapy only in the advanced TNBC (or "basal like" tumor) subgroup

Study	Treatment	N (TN)	Response rate	Progression-free survival (months)	Overall survival	Source of data for the TNBC analysis
Bevacizumabe ± CT						
Miles et al[16]/Miller et al[17]/O'Shaughnessy et al[18,38]/Robert[39,40]	1st line CT	232	NR	*E2100*: 5.3 vs 10.6 months HR =0.49 (0.34–0.70)	NR	SABC, O'Shaughnessy et al[38]
	CT + Bev	163		*AVADO*: $Bev_{7,5}$: 5.4 vs 6.2 months HR 0.69 (0.44–1.08) Bev_{15}: 5.4 vs 8.2 months HR 0.53 (0.34–0.84)		
		279		*RIBBON*-1 (BEV_{15}): Cape: 4.2 vs 6.1 months HR: 0.72 (0.49–1.06) AT: 6.2 vs 6.5 months HR 0.78 (0.53–1.15)		
Brufsky et al[41,42]	2nd line	159	18%	$Bev_{10\ or\ 15}$:		Subgroup analysis, Brufsky et al[42]
	CT		41%	2.7 months	12.6 months	
	CT + Bev			6.0 months HR: 0.494 (0.33–0.74)	17.9 months HR: 0.624 (0.39–1.007)	
Sorafenibe ± QT						
Hudis et al[36]	≤2nd line	50	NR	2.6 months	NR	Gelmon et al[74]
	CT			3.1 months		
	CT + Sor			HR: 0.57 (0.30–1.09)		
Baselga et al[1,44]/Gomez et al[45]	≤2nd line	53	NR	2.5 months	16.1 months	Subgroup analysis[1]
	QT			4.3 months	17.5 months	
	QT + Sor			HR: 0.596 (0.3–1.1)	HR: 0.98 (0.5–1.89)	
Gradishar[37]	1st line	94	NR	5.5 months	NR	Rodler et al[75]
	CT			5.6 months		
	CT + Sor			HR: 0.856 (0.504–1.454)		
Cetuximab ± CT						
O'Shaughnessy et al[18]	≤2nd line	72		5.1 months	12.3 months	O'Shaughnessy et al[18]
	CT		30%	4.7 months	15.5 months	
	CT + cetuximab		49%	NS	NS	
Baselga et al[46]	≥1st line	173	10%	1.5 months	9.4 months	SABC, Baselga et al[46]
	CT		20%	3.7 months	12.9 months	
	CT + cetuximab		*P*=0.11	HR: 0.67 (0.47–0.97)	HR: 0.82 (0.56–1.2)	
Lapatinib ± CT						
Finn et al[47]	1st line	131	NR	4.8 months	NR	Subgroup analysis, Finn et al[47]
	CT			4.6 months		
	CT + lapatinib			HR: 1.25 (0.85–1.83)		
PARP inhibitors						
O'Shaughnessy et al[19]	≤2nd line	519	30%	4.1 months	11.1 months	ASCO, O'Shaughnessy et al[19]
	CT		34%	5.1 months	11.8 months	
	CT + iniparib			HR: 0.79 (0.646–0.976)	HR: 0.87 (0.687–1.116)	
O'Shaughnessy et al[48,49]	≤2nd line	123	32%	3.3 months	7.7 months	O'Shaughnessy et al[48]
	CT		52%	5.9 months	2.3 months	
	CT + iniparib		*P*=0.02	HR: 0.59 (0.39–0.90)	HR: 0.57 (0.36–0.9)	

Abbreviations: CT, chemotherapy; PARP, poly(ADP-ribose) polymerase; Bev, bevacizumabe; Cape, capecitabina; AT, antracycline and taxane; HR, hazard ratio; SABC, San Antonio Breast Cancer Symposium; ASCO, American Society of Clinical Oncology; TN, triple negative; NS, not significant; BC, breast cancer; NR, not reported.

The proportion of hematologic toxicities was similar between the group that received Sor plus CT compared to the one that received CT alone. Hand/foot skin reaction and mucositis were more frequent in patients treated with Sor plus CT (hand/foot skin reaction fixed effect, RR =5.00, 95% CI =3.30–7.58, $P<0.00001$; mucositis fixed effect, RR =2.79, 95% CI 1.01–7.72, $P=0.05$). The other nonhematologic toxicities were similar between the groups.

Chemotherapy with cetuximab

Cetuximab plus CT was studied in patients previously treated for metastatic disease in two randomized studies. Cetuximab

Table 3 Methodological characteristics and definition of PFS of original trials

Reference	Randomization described	Allocation concealment adequate?	ITT	Sample size calculation showed	Multicentric?	Independent/ blinded evaluation	Sponsor	Definition of PFS	OBS
Miller et al[17]	Y	Y	Y	Y	Y	N	Mixed	Time from randomization to disease progression or death from any cause	
Miles et al[16]	Y	Y	Y	Y	Y	N	Mixed	Time from randomization to disease progression or death from any cause	
Robert et al[39,40]	Y	Y	Y	Y	Y	N	Mixed	Time from randomization to disease progression or death from any cause	
Brufsky et al[41,42]	Y	Y	Y	Y	Y	Y	Industry	Time from randomization to disease progression or death from any cause	
Hudis et al[36]	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Abstract data only
Baselga et al[1,44] Gomez et al[45]	Y	Y	Y	Y	Y	N	Industry	Measured from the date of randomization to the date of first documented disease progression	
Gradishar[37] Gradishar et al[43]	Y	Y	Y	N	Y	Y	Industry	N/A	
O'Shaughnessy et al[18]	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Abstract data only
Baselga et al[46]	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Abstract data only
Finn et al[47]	y	Y	Y	Y	Y	Y	Industry	Time from random assignment until disease progression or death because of disease under study	
O'Shaughnessy et al[18,48,49]	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Abstract data only
O'Shaughnessy et al[18,48,49]	Y	Y	N	Y	Y	N	Industry	Time from randomization to confirmation of disease progression or death	

Abbreviations: Y, yes; N, no; N/A, not available; PFS, progression-free survival; ITT, intention to treat; OBS, observation.

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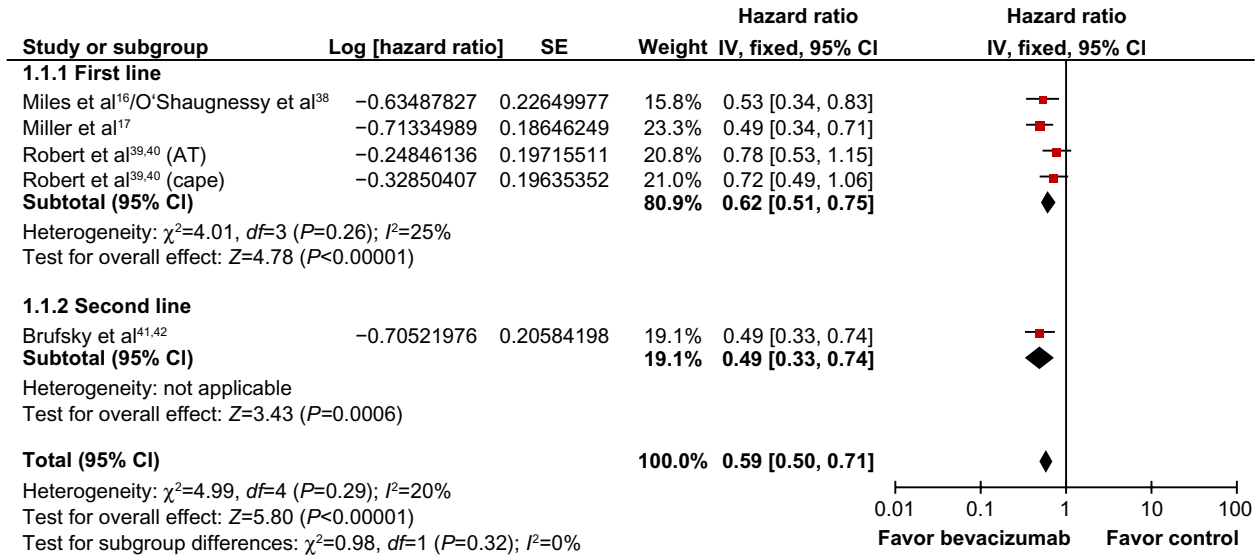

Figure 2 Comparative effect on progression-free survival of chemotherapy plus bevacizumab versus chemotherapy alone (fixed-effect model analysis).
Abbreviations: SE, standard error; IV, inverse variance; cape, capecetabin; CI, confidence interval; AT, antracycline and taxane; *df*, degrees of freedom.

(400 mg/m^2 initial dose followed by 250 mg/m^2 weekly) was combined with irinotecan and carboplatin in one study[18] and with cisplatin in another study[46] (Table 2).

The meta-analysis showed a higher response rate for the CT with cetuximab group versus CT alone (fixed effect, RR =0.85, 95% CI 0.74–0.97; *P*=0.02). There was no heterogeneity in this analysis (χ^2=1.11, *df*=1; *P*=0.29; I^2=10%). Only one study[46] reported complete PFS and OS data for cetuximab. In this study, PFS was higher for the group of patients treated with cetuximab plus CT versus CT alone (HR =0.67, 95% CI 0.47–0.97); OS was similar between the groups (HR =0.82, 95% CI 0.56–1.2). The other study[18] was presented in a conference and did not report PFS or OS data. We contacted the author about these data, but received no answer. The available conference presentation reported medians and stated that there was no statistically significant difference between the groups in either the median PFS (5.1 months versus 4.7 months) or in the median OS (12.3 months versus 15.5 months).

Neutropenia and rash were more frequent in patients who received cetuximab plus CT compared to those that received CT alone (neutropenia fixed effect, RR =1.85, 95% CI 1.36–2.52, *P*<0.0001; rash fixed effect, RR =16.64, 95% CI 1.02–272.53, *P*=0.05). The other toxicities were similar between the groups.

Chemotherapy with lapatinib

We found only one study evaluating CT plus lapatinib (1,500 mg orally daily)[47] versus conventional CT (paclitaxel)

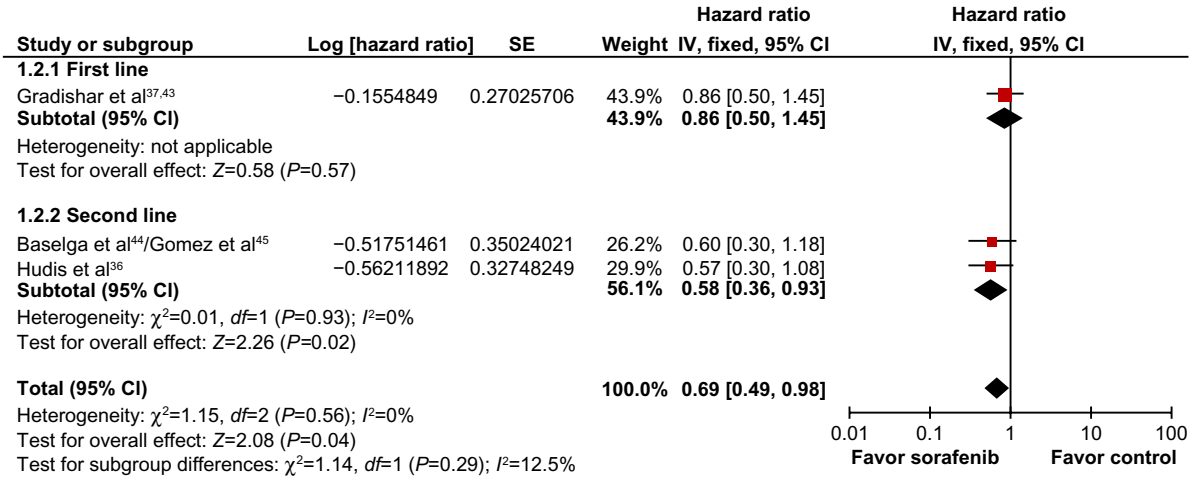

Figure 3 Comparative effect on progression-free survival of chemotherapy plus sorafenib versus chemotherapy alone (fixed-effect model analysis).
Abbreviations: SE, standard error; IV, inverse variance; CI, confidence interval; *df*, degrees of freedom.

in patients without previous treatment. PFS was similar between the groups (HR =1.25, 95% CI 0.85–1.83).

Chemotherapy with PARP inhibitor (iniparib)

Two studies evaluated CT with PARP inhibitors (iniparib 5.6 mg/kg; intravenous on days 1, 4, 8, and 11 every 21 days) in patients previously treated[19,48,49] (Table 2). A pooled analysis of the studies showed a higher response rate favoring the iniparib plus CT group (fixed effect, RR =0.90, 95% CI 0.80–0.10; P=0.05) with significant heterogeneity (χ^2=2.94, df=1; P=0.09; I^2=66%). As planned, a random-effects model analysis was performed to better explore this heterogeneity: in this analysis, the response rate did not reach a statistically significant level (random effects, RR =0.84, 95% CI 0.64–1.11; P=0.23).

PFS was higher in the group that received iniparib plus CT (fixed effect, HR =0.75, 95% CI 0.62–0.90; P=0.002; NNT =3). There was moderate heterogeneity (χ^2=1.54, df=1; P=0.21; I^2=35%) (Figure 4). A random-effects model analysis was performed, and PFS remained favorable to the CT plus iniparib group (random effects, HR =0.72, 95% CI 0.56–0.94; P=0.02).

The meta-analysis of OS data favored the group that received iniparib plus CT (fixed effect, HR =0.80, 95% CI 0.65–0.98; P=0.03) but with significant heterogeneity (χ^2=2.57, df=1; P=0.11; I^2=61%) (Figure 5). The random-effects model analysis for this end point did not reach a significant difference (random effects, HR =0.74, 95% CI 0.49–1.11; P=0.14). Hematologic and nonhematologic toxicities were similar between the groups.

Discussion

As a group, patients with TN tumors have a relatively poor outcome and cannot be treated with endocrine therapy or therapies targeted to human epidermal growth factor receptor type 2.[50] Indeed, this group remains a poorly studied one: there are only a few studies designed specifically to evaluate the effect of CT in TNBC.

This systematic review aimed to evaluate the efficacy of different targeted therapies in TNBC. The results of the meta-analysis showed that these patients might benefit from some of these new therapies: there were significant benefits in PFS associated with Bev, Sor, and iniparib, regardless of the line of treatment; however, cetuximab results are inconclusive so far.

A possible effect of targeted therapies on OS could not be drawn from the published literature, as this end point was not consistently reported in most of the original trials for the TNBC population. The only feasible OS meta-analysis was the one derived from the studies that tested iniparib, in which results were heterogeneous and did not reach statistical significance in a random-effects model analysis.[30] Historically, clinical studies in the advanced breast cancer setting have used PFS as the primary end point,[51] but there is still controversy concerning whether it correlates with OS.[52,53]

In general, the toxicity reported in the studies was expected and not limiting.[16,17,38–40] Bev plus CT was associated with higher rates of proteinuria, hypertension, neuropathy, and bleeding events; hand/foot skin reaction and mucositis were more common in patients who received Sor plus CT; neutropenia and rash were more frequent in patients who received cetuximab plus CT.

Despite these encouraging results, many unsolved questions remain regarding targeted therapies combined with CT in TNBC patients. There are still no answers for some important points: which is the most suitable chemotherapy scheme for the association, which are the best molecular-targeted therapies, how to determine the ideal treatment sequence, and the real impact of using targeted therapy combined with CT in overall survival.

An important drawback of this study is that most of the data used in the meta-analysis came from subgroups that were not reported in the original publication and were obtained from secondary sources. Also limiting is the lack of important data from many of the included trials. Ideally, new trials should be performed in this specific population, and trials performed with the general breast cancer population should plan and report separately the results for TNBC patients.

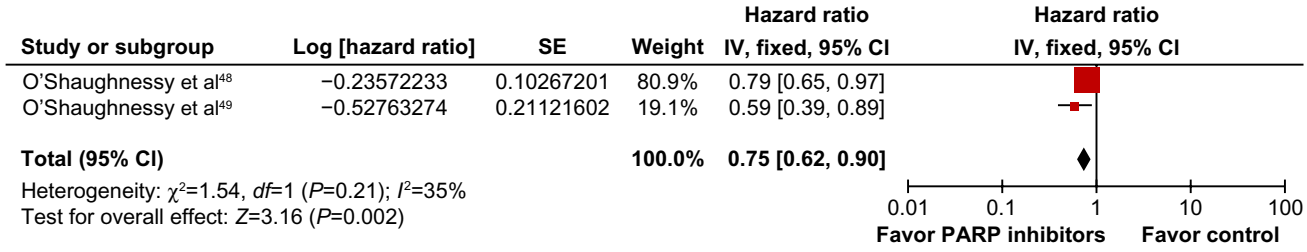

Figure 4 Comparative effect on progression-free survival of chemotherapy plus iniparib versus chemotherapy alone (fixed-effect model analysis).
Abbreviations: SE, standard error; IV, inverse variance; CI, confidence interval; *df*, degrees of freedom; PARP, poly(adenosine diphosphate-ribose) polymerase.

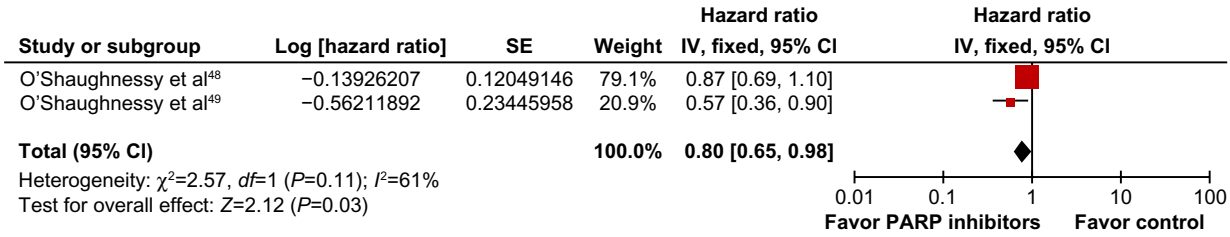

Figure 5 Comparative effect on overall survival of chemotherapy plus iniparib versus chemotherapy alone (fixed-effect model analysis).
Abbreviations: SE, standard error; IV, inverse variance; CI, confidence interval; *df*, degrees of freedom; PARP, poly(adenosine diphosphate-ribose) polymerase.

Studies already published could also make a significant contribution to the understanding of this subject if an analysis was published with data from this subgroup.

Conclusion

Targeted therapy, when associated with conventional CT, demonstrated gain in PFS in patients with TNBC. The results concerning OS are still uncertain.

Author contributions

All authors of this research paper directly participated in the planning, execution, or analysis of the study. OC and LP conceived of the study, participated in its design and coordination, and helped to draft the manuscript. OC and TEAB carried out the data selection. All authors participated in the analysis. Also, all authors of this paper read and approved the final version submitted.

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Disclosure

The authors report no conflicts of interest in this work.

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