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REVIEW

Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis

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Background: The role of platinum-based neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) patients is highly controversial and it is not endorsed by current guidelines. Our meta-analysis aimed to better elucidate its activity, efficacy and safety.

Material and methods: A systematic search of Medline, Web of Science and conferences proceedings up to 30 October 2017 was carried out to identify randomized controlled trials (RCTs) investigating platinum-based versus platinum-free neoadjuvant chemotherapy in TNBC patients. Using the fixed and random effects models, pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CI) were calculated for pathological complete response (pCR, defined as ypT0/is pN0), event-free survival (EFS), overall survival (OS) and grade 3 and 4 adverse events (AEs: neutropenia, anemia, thrombocytopenia and neuropathy).

Results: Nine RCTs ($N = 2109$) were included. Overall, platinum-based neoadjuvant chemotherapy significantly increased pCR rate from 37.0% to 52.1% (OR 1.96, 95% CI 1.46–2.62, $P < 0.001$). Platinum-based neoadjuvant chemotherapy remained significantly associated with increased pCR rate also after restricting the analysis to the three RCTs ($N = 611$) that used the same standard regimen in both groups of weekly paclitaxel (with or without carboplatin) followed by anthracycline and cyclophosphamide (OR 2.53, 95% CI 1.37–4.66, $P = 0.003$). Conversely, among the 96 *BRCA*-mutated patients included in two RCTs, the addition of carboplatin was not associated with significantly increased pCR rate (OR 1.17, 95% CI 0.51–2.67, $P = 0.711$). Two RCTs ($N = 748$) reported survival outcomes: no significant difference in EFS (HR 0.72, 95% CI 0.49–1.06, $P = 0.094$) and OS (HR 0.86, 95% CI 0.46–1.63, $P = 0.651$) was observed.
A significant higher risk of grade 3 and 4 hematological AEs, with no increased risk of grade 3 and 4 neuropathy was observed with platinum-based neoadjuvant chemotherapy.

Conclusion: In TNBC patients, platinum-based neoadjuvant chemotherapy is associated with significantly increased pCR rates at the cost of worse hematological toxicities. Platinum-based neoadjuvant chemotherapy may be considered an option in TNBC patients.

PROSPERO registration number: CRD42018080042.

Key words: neoadjuvant chemotherapy, triple-negative breast cancer, platinum agents, *BRCA*

Introduction

Triple-negative breast cancer (TNBC) accounts for ~10%–20% of all breast tumors [1]. Although TNBC is characterized by aggressive behavior, it is particularly sensitive to cytotoxic chemotherapy (the so-called 'triple negative paradox') [2]. In the neoadjuvant setting, TNBC patients have higher response rates to standard chemotherapy when compared with women affected by hormone receptor-positive breast cancer. Approximately 30%–40% of TNBC patients achieve a pathological complete response (pCR) after standard anthracycline plus cyclophosphamide- and taxane-based neoadjuvant chemotherapy [3]. The achievement of pCR in TNBC patients has a strong prognostic value, larger than in other breast cancer subtypes [4, 5]. Therefore, neoadjuvant chemotherapy is currently considered the preferred approach for the majority of TNBC patients with early-stage disease [6].

Platinum agents (i.e. carboplatin and cisplatin) are cytotoxic DNA damaging compounds leading to DNA strand breaks and possible consequent cell apoptosis; this peculiar mechanism of action makes them specially active in cancer cells with DNA repair deficiency such as those harbouring deleterious mutations in the *BRCA* genes [7]. Based on the biological rationale for a heightened susceptibility of TNBC to DNA-damaging compounds [8], several trials have investigated the possible role of platinum agents as a treatment option in TNBC patients. Although some of these studies have suggested a possible benefit for platinum-based neoadjuvant chemotherapy in TNBC patients, available results are mixed and controversial. Therefore, according to current breast cancer guidelines, the addition of a platinum agent to standard neoadjuvant chemotherapy in unselected TNBC patients is not recommended while its use may be considered in breast cancer patients with deleterious germline *BRCA* mutations [9–12].

To provide up to date evidence on this important controversial topic, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) aiming to better elucidate the role of platinum-based neoadjuvant chemotherapy in TNBC patients.

Methods

This was a quantitative synthesis of available RCTs evaluating the activity, efficacy and safety of platinum-based (experimental arm) versus platinum-free (control arm) neoadjuvant chemotherapy in TNBC patients.

Search strategy and study identification

Eligible studies were identified by a systematic literature search of the Medline and Web of Science databases, with no language or date restriction up to 30 October 2017. The search strategy was carried out using the following keywords: 'breast cancer', 'platinum', 'carboplatin', 'cisplatin', 'neoadjuvant' and 'chemotherapy'. Specific keywords and free text terms were combined with Boolean operators. A review of conference proceedings from the European Society for Medical Oncology (ESMO) congress, the American Society of Clinical Oncology (ASCO) annual meeting, and the San Antonio Breast Cancer Symposium (SABCS) was also conducted to identify relevant unpublished studies. Relevant articles were cross-referenced to confirm that all possible pertinent records were identified.

The systematic literature search was carried out independently by two authors (FP and ML) and any discrepancies were solved by discussion with a third author (EdA).

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

This study is registered with the PROSPERO registration number CRD42018080042; the full protocol is freely available in the PROPSPERO website.

Selection criteria and data extraction

To be included in the present meta-analysis, eligible studies had to satisfy all the following inclusion criteria: (i) phase II or III RCTs; (ii) RCTs including TNBC patients who received platinum-based neoadjuvant chemotherapy in the experimental arm and platinum-free neoadjuvant chemotherapy in the control arm (for RCTs including patients with breast cancer subtypes other than TNBC, only those with available results in the TNBC cohort were included); (iii) studies with available information on pCR rates in the experimental and control arms to estimate the odds ratio (OR) and 95% confidence intervals (CI).

Exclusion criteria were: (i) non-RCTs conducted to evaluate the role of platinum-based neoadjuvant chemotherapy in TNBC patients; (ii) RCTs investigating platinum-based neoadjuvant chemotherapy in patients with breast cancer subtypes other than TNBC; (iii) ongoing studies with results not presented or published at the time of the literature search.

The following variables were extracted from all the included RCTs, if available: name of the trial, year of publication, study design, number of randomized patients, germline *BRCA* mutational status, type and dose of chemotherapy administered, number of patients with pCR, objective response rate (ORR), event-free survival (EFS) and overall survival (OS) and grade 3 and 4 adverse events (AEs: neutropenia, anemia, thrombocytopenia and neuropathy) in the platinum-based and platinum-free neoadjuvant chemotherapy arms.

Study objectives

The primary objective of this meta-analysis was to compare the activity of platinum-based versus platinum-free neoadjuvant chemotherapy in TNBC patients, in terms of pCR (defined as no residual invasive tumor in both the breast and the axilla, i.e. ypT0/is pN0). Four main analyses were conducted including: (i) all RCTs irrespective of the chemotherapy backbone; (ii) only RCTs in which anthracycline- and taxane-based neoadjuvant chemotherapy was used in both treatment arms; (iii) only RCTs in which the same neoadjuvant chemotherapy backbone (with or without a platinum agent) was administered in both treatment arms; (iv) only RCTs that used the same standard neoadjuvant chemotherapy regimen of weekly paclitaxel (with or without a platinum agent) followed by anthracycline plus cyclophosphamide in both treatment arms. In addition, a further analysis was conducted to assess the benefit of platinum-based neoadjuvant chemotherapy according to germline *BRCA* mutational status.

Secondary objectives were to evaluate the activity, efficacy and safety of platinum-based versus platinum-free neoadjuvant

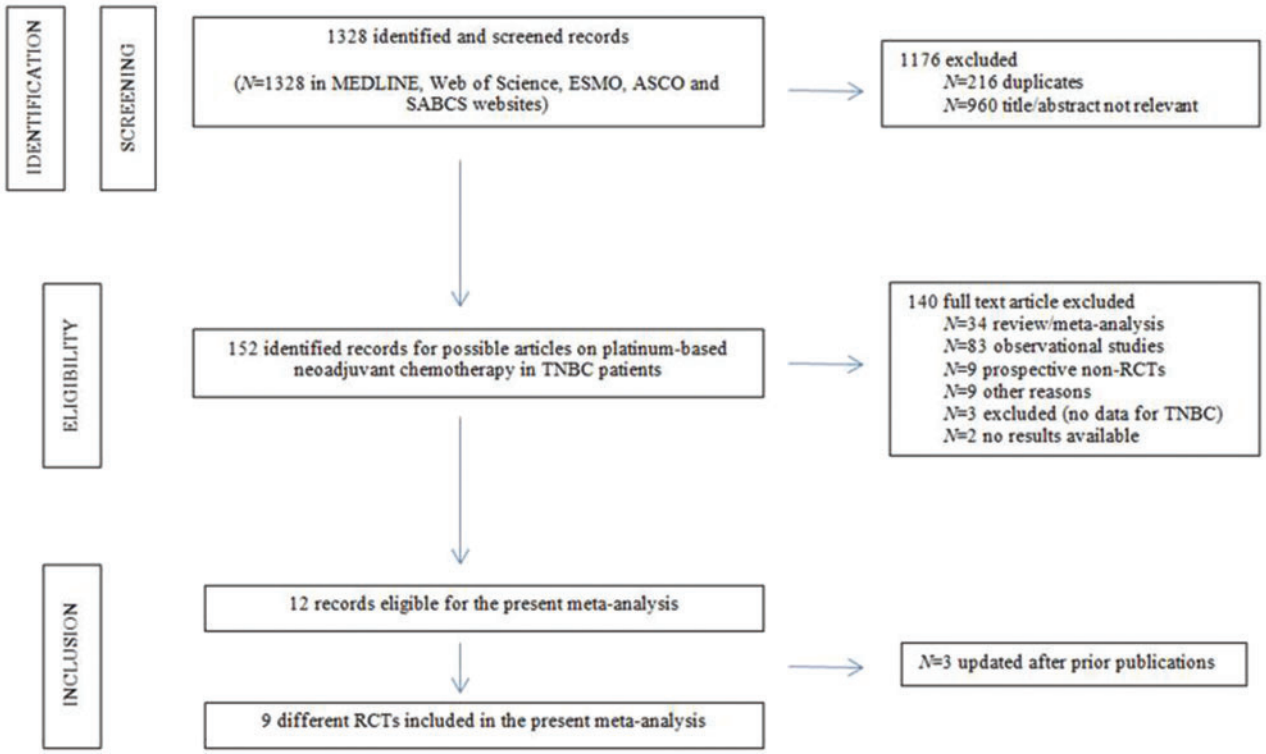

Figure 1. The PRISMA flow chart summarizing the process for the identification of eligible randomized controlled trials. ESMO, European Society for Medical Oncology; ASCO, American Society of Clinical Oncology; SABCS, San Antonio Breast Cancer Symposium; TNBC, triple-negative breast cancer; RCTs, randomized controlled trials.

chemotherapy in TNBC patients in terms of: (i) ORR; (ii) EFS and OS; (iii) grade 3 and 4 AEs (neutropenia, anemia, thrombocytopenia and neuropathy).

Statistical analysis

ORs and 95% CI were calculated for the effect of platinum-based versus platinum-free neoadjuvant chemotherapy for pCR, ORR, grade 3 and 4 AEs. An OR >1 indicates higher pCR, ORR and grade 3 and 4 AEs rates in the platinum-based neoadjuvant chemotherapy group. An OR <1 indicates lower pCR, ORR and grade 3 and 4 AEs rates in the platinum-based neoadjuvant chemotherapy group. Hazard ratios (HRs) and 95% CI were calculated for the effect of platinum-based versus platinum-free neoadjuvant chemotherapy in terms of EFS and OS. HR <1 indicates improved EFS and OS with platinum-based neoadjuvant chemotherapy. HR >1 indicates reduced EFS and OS with platinum-based neoadjuvant chemotherapy.

The Mantel–Haenzel method was used to obtain fixed effects model of the pooled ORs [14], and standard checks of the homogeneity assumption was performed [15]. In the presence of significant heterogeneity among the trials, the more appropriate method of DerSimonian and Laird was computed for the pooled estimate of the ORs using the random effects model [16]. To obtain a quantitative measure of the degree of inconsistency in the results of the studies, the Higgins I^2 index was computed [17]. The likelihood of publication bias was assessed by visual inspection of funnel plot for study size against treatment effect [18] and with Harbords' asymmetry test [19].

The pooled ORs and HRs were considered statistically significant if the 95% CI did not include 1.0, with a P value of <0.05 (two-sided).

Sensitivity analyses (aiming to define whether the pooled OR and HR estimates were stable or they mainly depended on one single or a few of the included RCTs) were conducted by recalculating the pooled OR and HR estimates after exclusion of each individual study.

The STATA software version 13.1 (StataCorp LP, College Station, TX) was used for all statistical analyses and for the generation of the forest plots.

Results

The systematic literature search returned 1328 records (Figure 1). After the exclusion of 1316 non-relevant records, 12 potentially eligible RCTs were considered [20–31]. Among them, two were updates of prior published studies [27, 29] and one was a secondary analysis of an already included RCT [28]. Hence, nine different RCTs were included in the current meta-analysis (Figure 1).

Two RCTs were published only in abstract form [24, 26]. The two RCTs conducted by the German Breast Group included both TNBC and HER2-positive breast cancer patients [21, 26], and the UMIN000003355 RCT included also hormone receptor-positive/HER2-negative breast cancer patients [23]: for the purpose of the present meta-analysis, only data pertaining to TNBC patients participating in these RCTs were considered.

A total of 2109 TNBC patients were included in the present meta-analysis, of whom 1046 (49.6%) received platinum-based and 1063 (50.4%) platinum-free chemotherapy.

Table 1. Main characteristics of the randomized controlled trials included in the present meta-analysis

Study	Study design	Primary end point	Secondary end points	Treatment arms	TNBC patients, *n*
GEICAM/2006-03 [20]	Phase II	ypT0/is	ypT0/is pN0, clinical response rate, safety,	EC—DCb	47
				EC—D	46
GeparSixto GBG66 [21]	Phase II	ypT0 pN0	ypT0/is pN0, clinical response rate, safety, efficacy	P+Dox+Bev+Cb	158
				P+Dox+Bev	157
CALGB 40603 Alliance [22]	Phase II	ypT0/is	ypT0/is pN0, safety, RFS and OS	P+Cb±Bev → ddAC	221
				P±Bev → ddAC	212
UMIN000003355 [23]	Phase II	ypT0/is pN0	Clinical response rate, safety, DFS	PCb → CEF	37
				P → CEF	38
Aguilar Martinez et al. [24]	Phase II	ypT0/is pN0	Clinical response rate, safety	Cis+P → Cis+Dox	30
				P → FAC	31
NCT01276769 [25]	Phase II	ypT0/is pN0	ORR, safety, RFS, OS	PCb	44
				EP	43
GeparOcto GBG84 [26]	Phase III	ypT0/is pN0	Toxicity, DFS, OS	PDoxCb	203
				DdEPC	200
WSG-ADAPT [30]	Phase II	ypT0/is pN0	Toxicity, EFS, OS	Nab-P+Cb	146
				Nab-P+Gem	178
BrighTNess [31]	Phase III	ypT0/is pN0	Clinical response rate, toxicity, EFS, OS	P+Cb → AC	160
				P → AC	158

EC-DCb: epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 for four cycles followed by docetaxel 75 mg/m^2 plus carboplatin area under curve (AUC) 6 for four cycles; EC-D: epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 for four cycles followed by docetaxel 100 mg/m^2; P + Dox + Bev + Cb: paclitaxel 80 mg/m^2 plus nonpegylated liposomal doxorubicin 20 mg/m^2, both once a week for 18 weeks plus bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously plus carboplatin at a dose of 2.0 AUC, once every week for 18 weeks; P + Dox + Bev: paclitaxel 80 mg/m^2 plus nonpegylated liposomal doxorubicin 20 mg/m^2, both once a week for 18 weeks plus bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously with all cycles; P + Cb ± Bev → ddAC: paclitaxel 80 mg/m^2 once per week for 12 weeks concurrent carboplatin AUC 6 once every 3 weeks for four cycles, followed by doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 once every 2 weeks for four cycles, and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles; P± Bev → ddAC: paclitaxel 80 mg/m^2 once per week for 12 weeks followed by doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 once every 2 weeks for four cycles, and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles; PCb → CEF: four cycles of carboplatin AUC 5 every 3 weeks concurrent weekly paclitaxel (days 1, 8, 15) followed by four cycles of cyclophosphamide 500 mg/m^2/plus epirubicin 100 mg/m^2 plus 5′-fluorouracile 500 mg/m^2 every 3 weeks; P → CEF: weekly paclitaxel (days 1, 8, 15) followed by four cycles of cyclophosphamide 500 mg/m^2/plus epirubicin 100 mg/m^2 plus 5′-fluorouracile 500 mg/m^2 every 3 weeks; Cis + P → Cis + Dox: cisplatin 30 mg/m^2 plus weekly paclitaxel 80 mg/m^2 for 12 weeks, followed to cisplatin 75 mg/m^2 plus doxorubicin 50 mg/m^2 every 3 weeks for four cycles; P → FAC: weekly paclitaxel 80 mg/m^2 for 12 weeks followed by 5′-fluorouracile 500 mg/m^2 plus doxorubicin 50 mg/m^2 plus cyclophosphamide 500 mg/m^2 every 3 weeks for four cycles; PCb: paclitaxel 175 mg/m^2 on day 1 plus carboplatin AUC 5 on day 2, every 3 weeks for four to six cycles; EP: epirubicin 75 mg/m^2 on day 1 and paclitaxel 175 mg/m^2 on day 2 every 3 weeks for four to six cycles; PDoxCb: paclitaxel 80 mg/m^2 weekly simultaneously with nonpegylated liposomal doxorubicin 20 mg/m^2 simultaneously with carboplatin AUC 1.5 weekly for 18 weeks; ddEPC: epirubicin 150 mg/m^2 every 2 weeks for three cycles followed by paclitaxel 225 mg/m^2 every 2 weeks for three cycles followed by cyclophosphamide 2000 mg/m^2 every 2 weeks for three cycles; Nab-P + Cb: nab-paclitaxel 125 mg/m^2 plus carboplatin AUC 2 day 1, 8 every 3 weeks for 12 weeks; Nab-P+ Gem: nab-paclitaxel 125 mg/m^2 plus gemcitabine 1000 mg/m^2 day 1, 8 every 3 weeks for 12 weeks; P + Cb →AC: paclitaxel 80 mg/m^2 weekly + Cb AUC 6 every 3 weeks for 12 weeks followed by doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 2 or 3 weeks; P→AC: paclitaxel 80 mg/m^2 weekly followed by doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 2 or 3 weeks; TNBC, triple-negative breast cancer; RFS, relapse-free survival; DFS, disease-free survival; EFS, event-free survival; OS, overall survival; ORR, objective response rate.

Main characteristics of the included RCTs are reported in Table 1. All but one [24] RCTs used carboplatin as platinum agent. In seven RCTs ($N = 1698$ patients), anthracycline- and taxane-based neoadjuvant chemotherapy was used in both groups [20–24, 26, 31]. The same chemotherapy backbone (with or without carboplatin) was used in five of the included RCTs ($N = 1234$ patients) [20–23, 31]. The same standard chemotherapy regimen of weekly paclitaxel (with or without carboplatin) followed by anthracycline plus cyclophosphamide in both groups was used in three of the included RCTs ($N = 611$patients) [22, 23, 31].

All TNBC patients included in the GeparSixto GBG66 study [21] and half of those enrolled in the CALGB study [22] received also bevacizumab in both the platinum-based and platinum-free chemotherapy arms. Two out of the three arms of the BrighTNess trial were considered for the purpose of the present meta-analysis: arm B [weekly paclitaxel plus carboplatin plus veliparib placebo (i.e. platinum-based neoadjuvant chemotherapy arm)] and arm C [weekly paclitaxel plus carboplatin placebo plus veliparib placebo (i.e. platinum-free neoadjuvant chemotherapy arm)] [31].

Germline *BRCA* mutational status was available for 609 patients in two RCTs [28, 31]. A total of 96 *BRCA*-mutated patients were included, 50 of the 291 patients (17.2%) included in the GeparSixto GBG66 study and 46 of the 318 patients (14.5%) randomized in the BrighTNess trial.

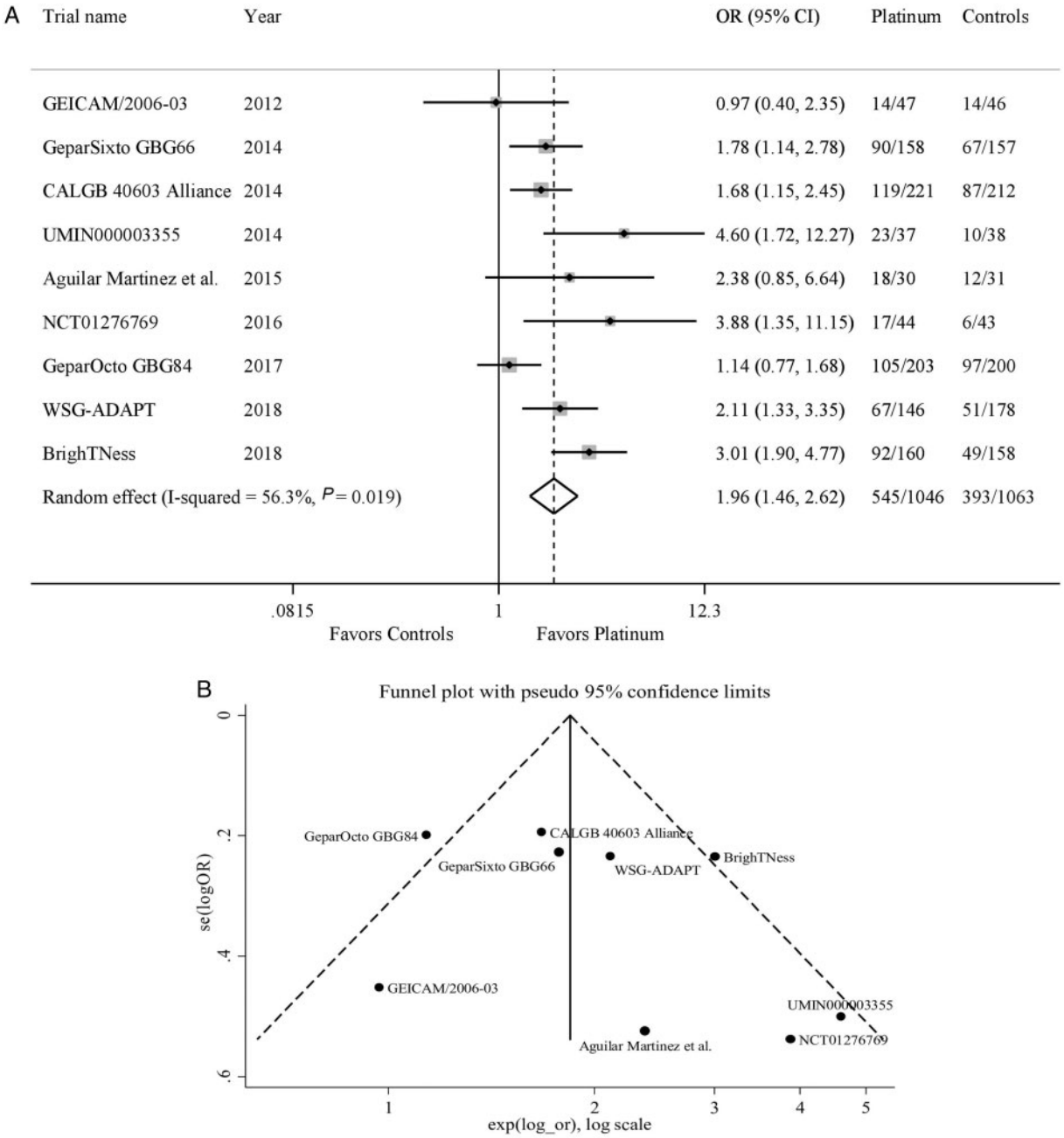

Figure 2. (A) Odds ratio for pathological complete response of platinum-based (Platinum) versus platinum-free (Controls) neoadjuvant chemotherapy in all included randomized controlled trials (the size of the squares is proportional to the weight of each study). (B) Funnel plot with pseudo 95% confidence limits for the effect of platinum-based neoadjuvant chemotherapy estimated from individual studies (horizontal axis) against the study size (vertical axis): publication bias is unlikely as suggested by the symmetric inverted funnel shape. OR, odds ratio; CI, confidence intervals.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 or 4.0 was used to classify the observed AEs in the included RCTs; two RCTs did not report the specific rates of grade 3 and 4 AEs in the two treatment arms [24, 26].

Pathological complete response rates

Overall, including all the nine RCTs, 938 of 2109 (44.5%) patients achieved a pCR after neoadjuvant treatment, 545 of 1046 (52.1%) in the platinum-based chemotherapy group and 393 of 1063 (37.0%) in the platinum-free chemotherapy group (OR 1.96, 95% CI 1.46–2.62, $P < 0.001$; $I^2 = 56.3\%$, $P = 0.019$) (Figure 2A). The sensitivity analysis showed a stability of the pooled OR estimates with only marginal fluctuations by excluding each study at a time (supplementary Table S1, available at *Annals of Oncology* online). The funnel plot (Figure 2B) and the Harbords asymmetry test ($P = 0.282$) showed no evidence of publication bias.

In the seven RCTs that used anthracycline- and taxane-based chemotherapy in both arms [20–24, 26, 31], 797 of 1698 (46.9%)

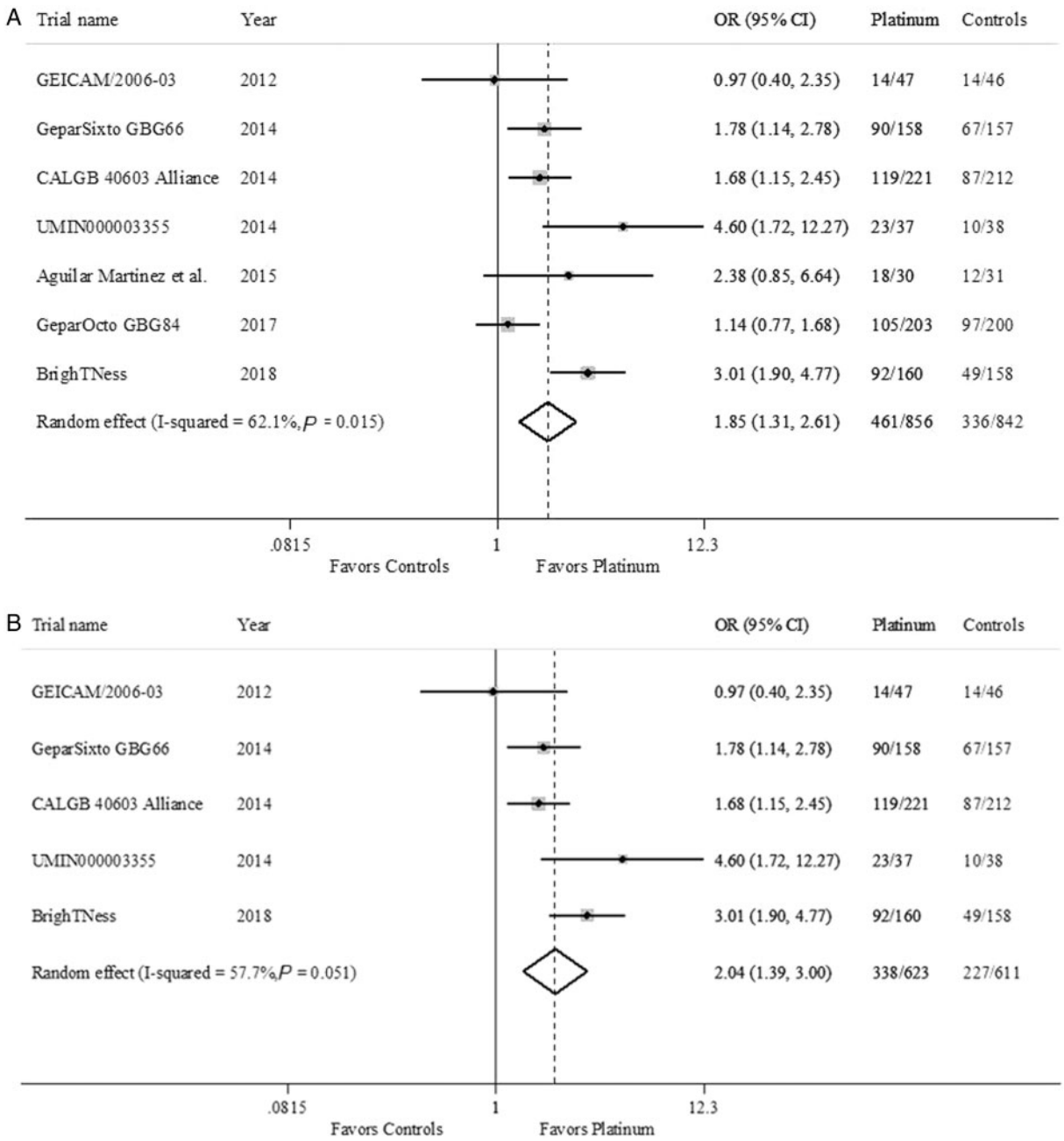

Figure 3. Odds ratios for pathological complete response of platinum-based (Platinum) versus platinum-free (Controls) neoadjuvant chemotherapy in the randomized controlled trials using: (A) anthracycline- and taxane-based chemotherapy in both treatment arms; (B) the same chemotherapy backbone in both treatment arms; (C) the same standard neoadjuvant chemotherapy regimen in both treatment arms. The size of the squares is proportional to the weight of each study. OR, odds ratio; CI, confidence intervals.

patients achieved a pCR after neoadjuvant treatment, 461 of 856 (53.9%) in the platinum-based chemotherapy group and 336 of 842 (39.9%) in the platinum-free chemotherapy group (OR 1.85, 95% CI 1.31–2.61, $P < 0.001$; $I^2 = 62.1\%$, $P = 0.015$) (Figure 3A). Supplementary Table S2, available at *Annals of Oncology* online displays the sensitivity analysis.

In the five RCTs with the same chemotherapy backbone (with or without carboplatin) in both groups [20–23, 31], 565 of 1234 (45.8%) patients achieved a pCR after neoadjuvant treatment, 338 of 623 (54.2%) in the platinum-based chemotherapy group, and 227 of 611 (37.1%) in the platinum-free chemotherapy group (OR 2.04, 95% CI 1.39–3.00, $P < 0.001$; $I^2 = 57.7\%$, $P = 0.051$) (Figure 3B). Supplementary Table S3, available at *Annals of Oncology* online displays the sensitivity analysis.

Three RCTs investigated the addition of platinum agents to the same standard neoadjuvant chemotherapy regimen of weekly paclitaxel (with or without carboplatin) followed by anthracycline plus cyclophosphamide [22, 23, 31]. For the purpose of this analysis, only patients included in the two arms without bevacizumab of the CALGB study were included. In these three RCTs,

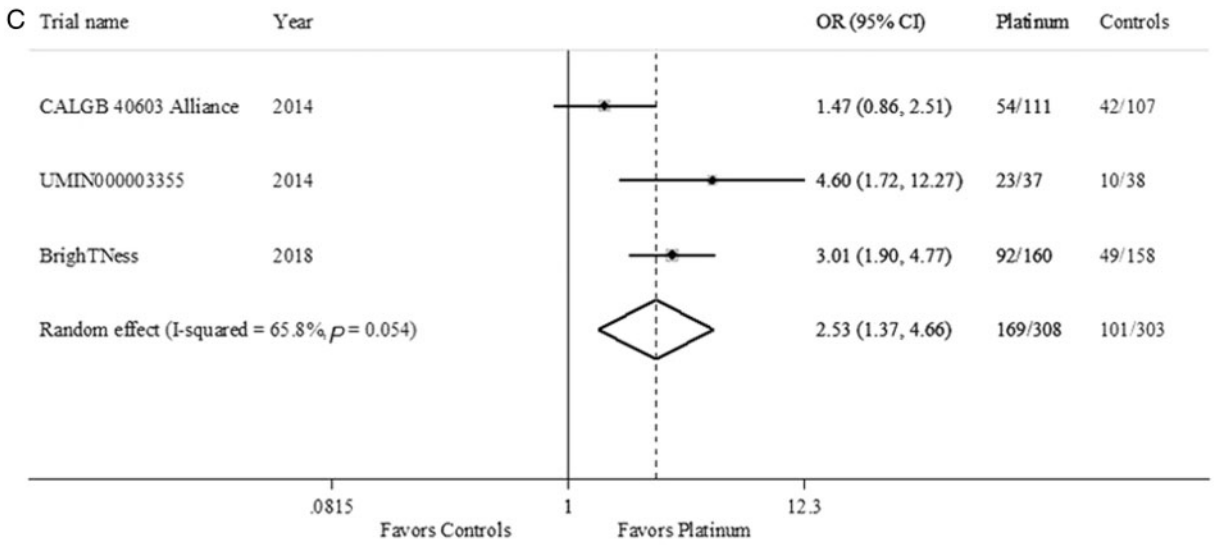

Figure 3. Continued.

270 of 611 (44.2%) patients achieved a pCR after neoadjuvant therapy, of whom 169 of 308 (54.9%) in the platinum-based chemotherapy group and 101 of 303 (33.3%) in the platinum-free chemotherapy group (OR 2.53, 95% CI 1.37–4.66, $P = 0.003$; $I^2 = 65.8\%$, $P = 0.054$) (Figure 3C). Supplementary Table S4, available at *Annals of Oncology* online displays the sensitivity analysis.

Two RCTs reported pCR rates according to germline *BRCA* mutational status [28, 31]: a total of 96 *BRCA*-mutated patients and 513 patients without *BRCA* mutations were included in these analyses.

Among *BRCA*-mutated patients, 54 of 96 (56.2%) achieved a pCR, 29 of 50 (58.0%) in the platinum-based chemotherapy group and 25 of 46 (54.3%) in the platinum-free chemotherapy group (OR 1.17, 95% CI 0.51–2.67, $P = 0.711$; $I^2 = 0.0\%$, $P = 0.615$) (Figure 4A).

Among patients without *BRCA* mutations, 230 of 513 (44.8%) achieved a pCR, of whom 146 of 256 (57.0%) in the platinum-based chemotherapy group and 84 of 257 (32.7%) in the platinum-free chemotherapy group (OR 2.72, 95% CI 1.71–4.32, $P < 0.001$; $I^2 = 39.3\%$, $P = 0.199$) (Figure 4B).

Objective response rate

Five RCTs reported the ORR at the end of neoadjuvant chemotherapy [20, 21, 23, 25, 31]; the methods of assessment used in these RCTs are reported in the supplementary Table S5, available at *Annals of Oncology* online.

Overall, the ORR after neoadjuvant therapy was 81.2% (1031 of 1269 patients), 86.3% (550 of 637) in the platinum-based chemotherapy group and 76.1% (481 of 632) in the platinum-free chemotherapy group (OR 1.97, 95% CI 1.11–3.49, $P < 0.001$; $I^2 = 68.8\%$, $P = 0.012$) (supplementary Figure S1, available at *Annals of Oncology* online). Supplementary Table S6, available at *Annals of Oncology* online displays the sensitivity analysis.

EFS and OS

Two RCTs reported the survival outcomes [27, 29]. Median follow-up was 39 months in the CALGB study [27] and 47.3 months in the GeparSixto GBG66 study [29].

No significant differences in EFS (HR 0.72, 95% CI 0.49–1.06, $P = 0.094$; $I^2 = 33.0\%$, $P = 0.222$) (Figure 5A) nor in OS (HR 0.86, 95% CI 0.46–1.63, $P = 0.651$; $I^2 = 63.9\%$, $P = 0.096$) (Figure 5B) were observed.

Grade 3 and 4 adverse events

The Geparsixto GBG66 and UMIN000003355 RCTs did not report the specific rates of AEs in the subgroup of TNBC patients [21, 23]. However, the results of these two RCTs were included in the present safety analysis, under the assumption that the risk of presenting AEs should not have been influenced by hormone receptor status. Figure 6 displays the safety profile overview for grade 3 and 4 AEs in the platinum-based versus platinum-free chemotherapy group.

Neutropenia. Seven RCTs reported the rates of grade 3 and 4 neutropenia [20–23, 25, 30, 31]. Overall, 772 of 2030 (37.8%) patients developed grade 3 and 4 neutropenia after neoadjuvant treatment, 535 of 1007 (53.1%) in the platinum-based chemotherapy group and 237 of 1023 (23.2%) in the platinum-free chemotherapy group (OR 3.19, 95% CI 1.55–6.54, $P = 0.002$; $I^2 = 90.0\%$, $P = 0.000$) (supplementary Figure S2 and Table S7, available at *Annals of Oncology* online).

Anemia. Six RCTs reported the rates of grade 3 and 4 anemia [20–23, 30, 31]. Overall, 108 of 1939 (5.6%) patients developed grade 3 and 4 anemia after neoadjuvant treatment, 104 of 960 (10.8%) in the platinum-based chemotherapy group and 4 of 979 (0.4%) in the platinum-free chemotherapy group (OR 15.01, 95% CI 4.86–46.30, $P < 0.001$; $I^2 = 29.6\%$, $P = 0.213$) (supplementary Figure S3 and Table S8, available at *Annals of Oncology* online).

Thrombocytopenia. Seven RCTs reported the rates of grade 3 and 4 thrombocytopenia [20–23, 25, 30, 31]. Overall, 121 of 2030 (6.0%) patients developed grade 3 and 4 thrombocytopenia after neoadjuvant treatment, 111 of 1007 (11.0%) in the platinum-based chemotherapy group and 10 of 1023 (1.0%) in the platinum-free chemotherapy group (OR 8.32, 95% CI 2.88–23.98, $P < 0.001$; $I^2 = 35.5\%$, $P = 0.158$) (supplementary Figure S4 and Table S9, available at *Annals of Oncology* online).

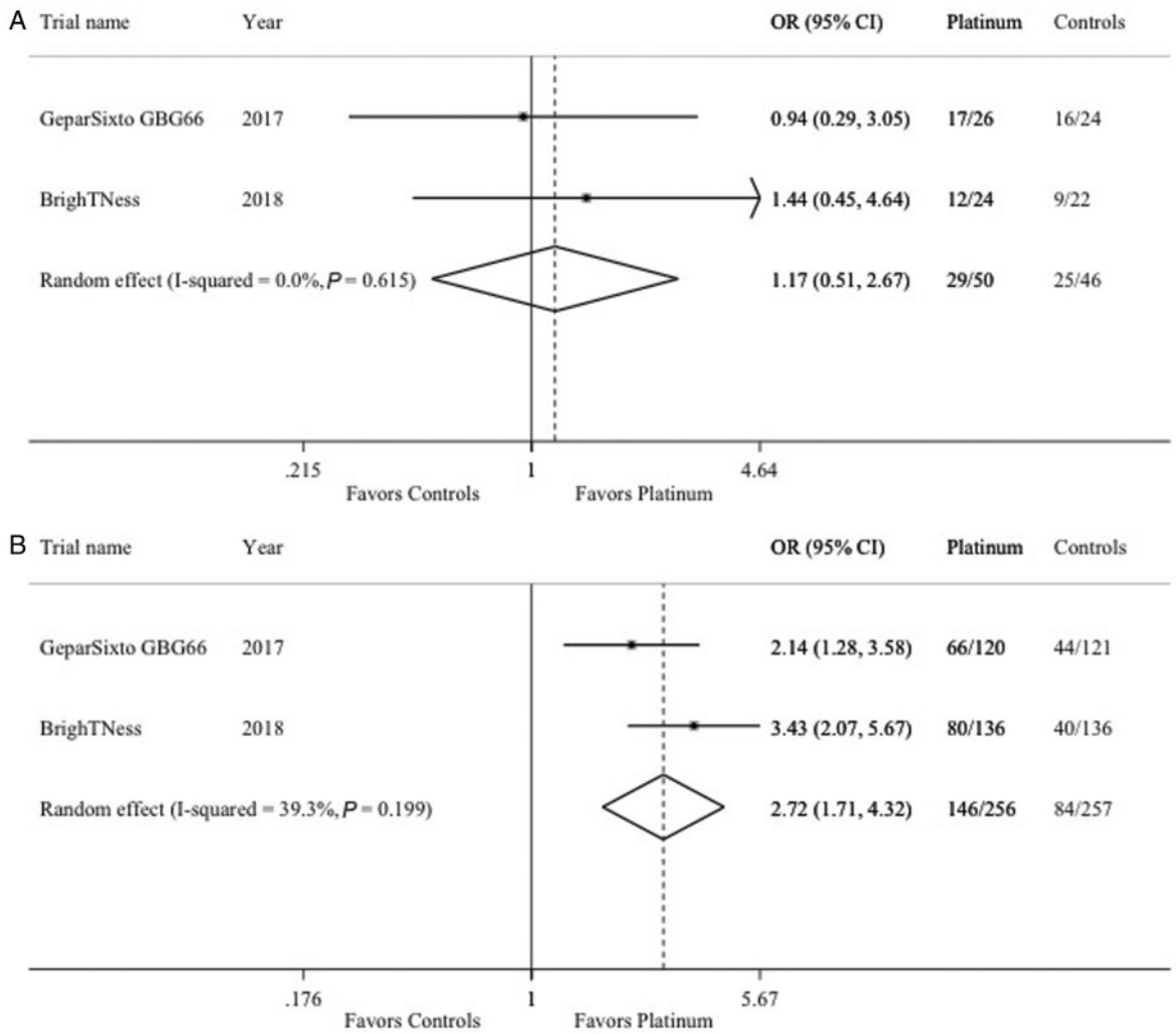

Figure 4. Odds ratios for pathological complete response of platinum-based (Platinum) versus platinum-free (Controls) neoadjuvant chemotherapy in: (A) *BRCA*-mutated breast cancer patients; (B) breast cancer patients without *BRCA* mutations. The size of the square is proportional to the weight of each study. OR, odds ratio; CI, confidence intervals.

Neuropathy. Six RCTs reported the rates of grade 3 and 4 neuropathy [21–23, 25, 30, 31]. Overall, 70 of 1937 (3.6%) patients developed grade 3 and 4 neuropathy after neoadjuvant treatment, 35 of 960 (3.6%) in the platinum-based chemotherapy group and 35 of 977 (3.6%) in the platinum-free chemotherapy group (OR 1.05, 95% CI 0.64–1.71, $P = 0.854$; $I^2 = 0.0\%$, $P = 0.565$) (supplementary Figure S5 and Table S10, available at *Annals of Oncology* online).

Discussion

This is the largest and most up to date meta-analysis assessing the activity, efficacy and safety of platinum-based chemotherapy as neoadjuvant treatment in TNBC patients. We observed that platinum-based neoadjuvant chemotherapy is associated with significant higher pCR rates at the cost of greater risk of hematological toxicities. In the two RCTs reporting survival outcomes, no significant difference was observed in EFS and OS. Notably, *BRCA*-mutated patients experienced overall high pCR rates without significant further effect observed with the addition of carboplatin.

In a prior meta-analysis including five RCTs ($N = 745$) using different chemotherapy regimens, platinum-based neoadjuvant chemotherapy was associated with higher pCR rates in TNBC patients [risk ratio (RR) 1.45, 95% CI 1.25–1.68, $P < 0.0001$]. However, no clear indication on the added role of platinum agents in patients receiving standard anthracycline- and taxane-based neoadjuvant chemotherapy could be obtained from this meta-analysis and no data on survival outcomes or germline *BRCA* mutational status were reported. Moreover, following this meta-analysis, additional RCTs investigated the role of platinum-based neoadjuvant chemotherapy in TNBC patients. Nevertheless, available results from single studies have been considered insufficient to recommend the use of a platinum agent as standard component of the neoadjuvant chemotherapy backbone in unselected TNBC patients [9–12].

The present meta-analysis including nine RCTs ($N = 2109$) provides updated evidence on the debated role of platinum-based neoadjuvant chemotherapy in TNBC patients. A significant

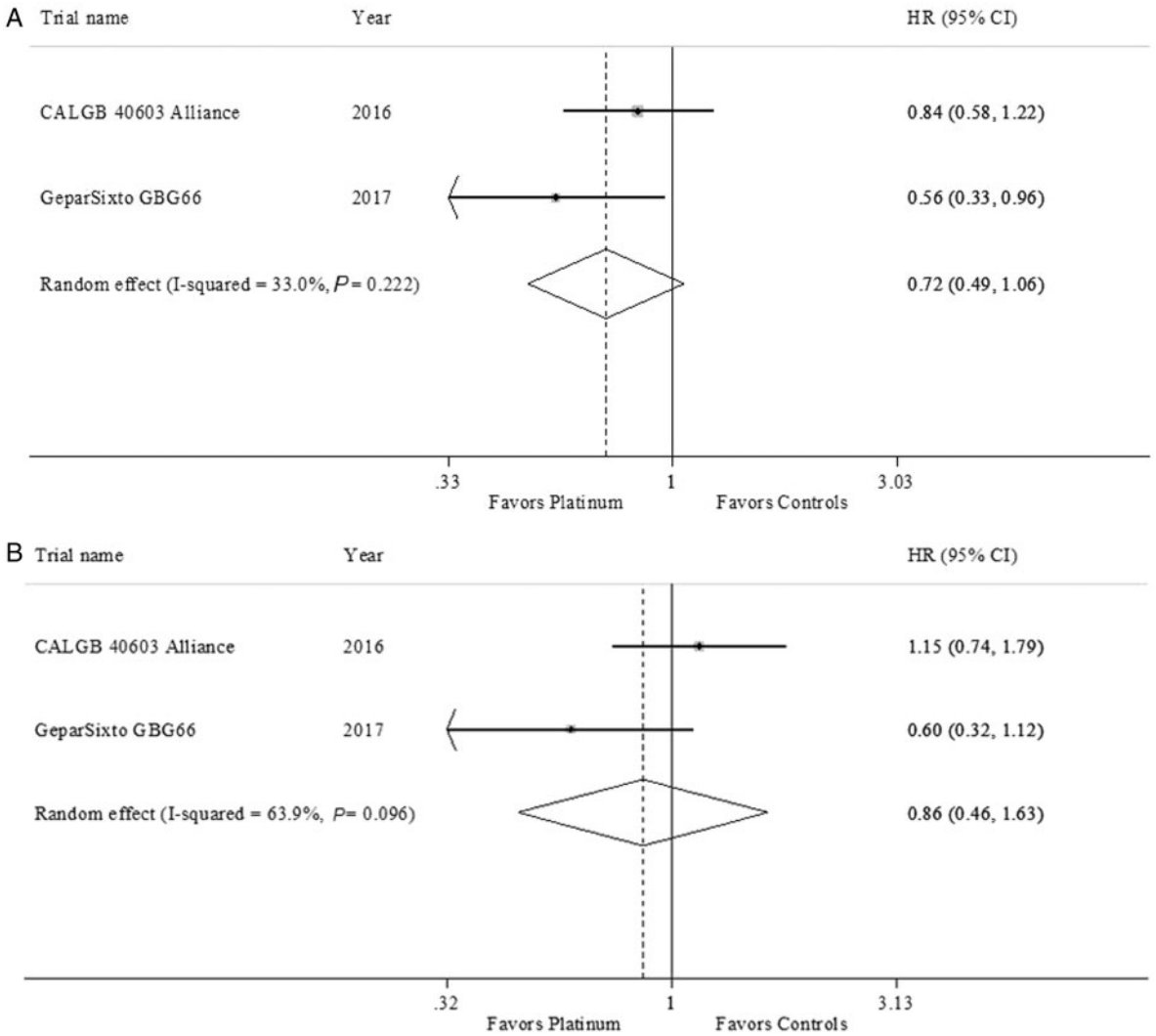

Figure 5. Hazard ratios for event-free survival (A) and overall survival (B) of platinum-based (Platinum) versus platinum-free (Controls) neoadjuvant chemotherapy. The size of the squares is proportional to the weight of each study. HR, hazard ratio; CI, confidence intervals.

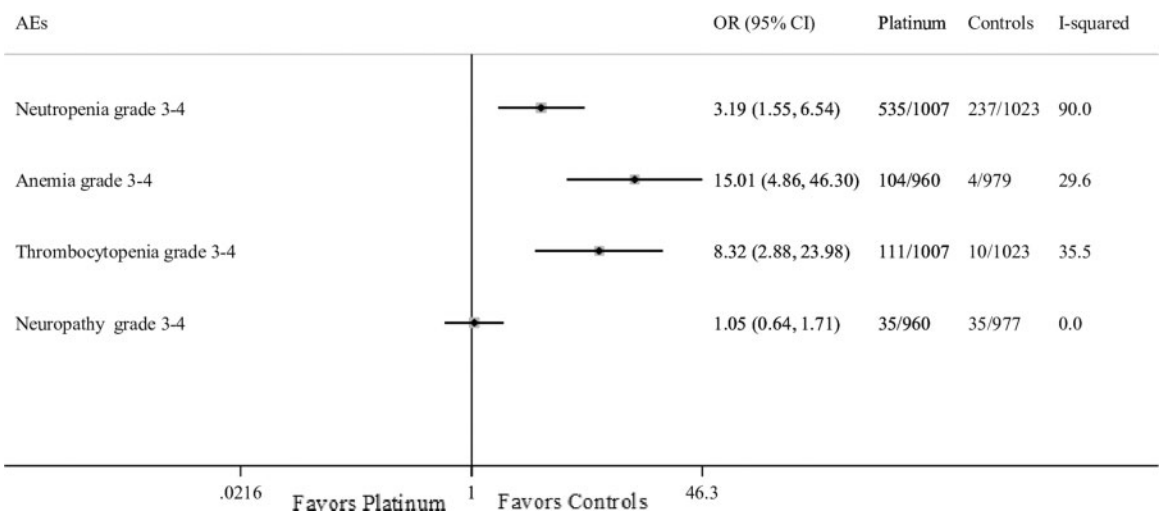

Figure 6. Safety profile overview. Odds ratios for grade 3 and 4 neutropenia, grade 3 and 4 anemia, grade 3 and 4 thrombocytopenia and grade 3 and 4 neuropathy in the platinum-based (Platinum) versus platinum-free (Controls) neoadjuvant chemotherapy. OR, odds ratio; CI, confidence intervals.

absolute 15.1% increased pCR rate was observed with the use of platinum-based neoadjuvant chemotherapy (OR 1.96, 95% CI 1.46–2.62, $P < 0.001$). Even when considering only the five RCTs in which the same anthracycline-and taxane-based chemotherapy backbone was used in both groups, the addition of carboplatin continued to provide a significant added benefit (absolute 17.1% increased pCR rate; OR 2.04, 95% CI 1.39–3.00, $P < 0.001$). Importantly, the beneficial effect of adding carboplatin did not change and was even more important when the analysis was restricted to the three RCTs in which patients received the current standard neoadjuvant chemotherapy with weekly paclitaxel followed by anthracycline and cyclophosphamide (absolute 21.6% increased pCR rate; OR 2.53, 95% CI 1.37–4.66, $P = 0.003$).

A rather high heterogeneity was observed in the pCR analyses. However, a positive effect for platinum-based neoadjuvant chemotherapy was shown in most of the included trials with the exception particularly of the GEICAM/2006-03 study [20]. Of note, in this study, only basal-like TNBC (defined as hormonal receptor-negative/HER2-negative and cytokeratin 5/6 or EGFR-positive) patients were included, and a lower dose of taxane (docetaxel, 75 mg/m^2) was administered in the platinum-based chemotherapy arm when compared with the platinum-free chemotherapy arm (docetaxel, 100 mg/m^2). Moreover, unlike all the other trials included in the present meta-analysis, patients enrolled in the GEICAM/2006-03 study received the alkylating agent cyclophosphamide before platinum-based chemotherapy. Hence, it is not possible to exclude that a prior treatment with DNA damaging agents may reduce the likelihood of benefitting from the addition of a platinum agent to standard neoadjuvant chemotherapy.

Although the achievement of pCR after neoadjuvant chemotherapy has a strong positive prognostic value in TNBC [4, 5], it is still unclear whether an increase in pCR rates translates into improved survival outcomes. Obtaining data on these crucial clinical end points remains critical. Only two RCTs ($N = 748$ patients) reported survival outcomes [27, 29]; although both studies were underpowered to detect a potential survival benefit, significantly improved survival outcomes were observed with the addition of carboplatin in patients without germline *BRCA* mutations in the GeparSixto GBG66 study [28]. Nevertheless, the pooled results showed no significant difference in both EFS (HR 0.72, 95% CI 0.49–1.06, $P = 0.094$) and OS (HR 0.86, 95% CI 0.46–1.63, $P = 0.651$). Survival outcomes from the other RCTs and particularly from the BrighTNess trial (one of the largest RCT in this setting that reported a nearly doubling in pCR rates with the addition of carboplatin to standard neoadjuvant chemotherapy and with available information on *BRCA* mutational status) are awaited to better assess the potential long-term benefit of this treatment strategy [31].

Our meta-analysis showed a significant higher incidence of grade 3 and 4 hematological AEs using platinum-based neoadjuvant chemotherapy. Hence, breast cancer patients treated with platinum-based therapy may experience a possible greater incidence of treatment discontinuations and dose reductions [21, 22]. For these reasons, optimal patient's selection, a proper counselling on the pros and contras of adding a platinum agent to standard neoadjuvant chemotherapy as well as close clinical follow-up during treatment are crucial on this regard. The WSG-ADAPT trial has recently reported evidence on the occurrence of few dose reductions and manageable toxicity using an alternative weekly schedule [30]. Specifically, in this trial, carboplatin was administered with an area under the curve (AUC) of 2 together with nanoparticle albumin-bound paclitaxel with the schedule 2 weeks on 1 week off. Based also on data coming from the treatment of other cancers types [32], a weekly regimen may be the best compromise to escalate treatment activity while maintaining a more tolerable hematological toxicity profile.

Up to 15% of TNBC patients are found to carry a deleterious germline *BRCA* mutation [33]. Therefore, germline *BRCA* testing is recommended in all TNBC patients diagnosed up to 60 years of age [34]. As the *BRCA* genes are critical regulators of the DNA repair machinery for the maintenance of genomic stability, the loss of *BRCA* function may render these tumors particularly sensitive to DNA damaging agents, including platinum agents [35]. Based on this strong biologic rationale, several studies have investigated the possible role of platinum agents in the treatment of *BRCA*-mutated breast cancer patients in both the metastatic and neoadjuvant settings. The Triple Negative Trial (TNT) showed that carboplatin has similar performance than docetaxel as first-line therapy in unselected metastatic TNBC patients but led to a doubling in both ORR (68% versus 33.3%, $P = 0.03$) and progression-free survival (6.8 versus 4.4 months, $P = 0.002$) in *BRCA*-mutated patients [36]. Taking into account these results, current guidelines endorse the use of platinum-based chemotherapy as the preferred option in patients with *BRCA*-associated metastatic TNBC previously exposed to anthracyclines and taxanes [37]. In the neoadjuvant setting, several non-RCTs showed that single-agent platinum-based therapy is an active regimen in a high proportion of *BRCA*-mutated breast cancer patients, especially in those with TNBC [38, 39]. However, available data on the benefit of adding a platinum agent in *BRCA*-mutated patients receiving standard neoadjuvant chemotherapy are more limited and controversial. So far, only two RCTs reported pCR results according to germline *BRCA* mutational status [28, 31]. Pooled results from these RCTs showed that the addition of carboplatin to paclitaxel followed by anthracycline plus cyclophosphamide was not associated with a significant increased pCR rate in *BRCA*-mutated breast cancer patients (OR 1.17, 95% CI 0.51–2.67, $P = 0.711$) while the benefit was present in patients without *BRCA* mutations (OR 2.72, 95% CI 1.71–4.32, $P < 0.001$). However, no solid conclusions can be drawn on this regard considering the limited number of *BRCA*-mutated patients ($N = 96$) included in the analysis. Notably, an overall higher pCR rate was observed for the platinum-free regimen in this patient population (54.3%) when compared with the pCR rate in patients without *BRCA* mutations (32.7%). These findings may suggest an increased vulnerability of these tumors (characterized by limited DNA repair capacities) to anthracycline-induced single-stranded and double-stranded DNA breaks [28]. Further research efforts are warranted to define the best chemotherapy regimen for *BRCA*-mutated breast cancer patients in the early setting.

Taken together, the findings of our meta-analysis question the current recommendation to possibly consider the use of platinum-based neoadjuvant chemotherapy only in *BRCA*-mutated patients. On this regard, prospective validation of biomarkers predicting sensitivity to platinum agents is required to better identify the group of TNBC patients with an increased likelihood of deriving benefit from the use of platinum-based neoadjuvant chemotherapy [40–42].

Some limitations of the present analysis should be considered in the interpretation of our findings. This is a meta-analysis based

on abstracted data: thus, without individual patient data, the association between treatment benefit and toxicity with other important factors (including patient's age, dose and length of chemotherapy) was not possible to be evaluated. Moreover, results of two included RCTs are currently available only in abstract form. Finally, data on survival outcomes as well as treatment effect according to germline *BRCA* mutational status have been reported so far by only two RCTs. Nevertheless, these limitations should not influence the overall interpretation of our results that provide valuable information on the debated role of the addition of platinum agents to standard neoadjuvant chemotherapy in TNBC patients. Specifically, these findings give updated point estimates on the benefits and risks of including a platinum agent as part of neoadjuvant systemic therapy that may help physicians and patients during treatment decision-making.

In conclusion, our meta-analysis showed that platinum-based neoadjuvant chemotherapy was associated with significant increased pCR rates in TNBC patients at the cost of worse hematological toxicities. These findings suggest that the addition of a platinum agent to standard neoadjuvant anthracycline- and taxane-based chemotherapy may be considered an option in TNBC patients. Long-term follow-up analysis from all the RCTs and additional subgroup analyses according to germline *BRCA* mutational status are awaited to further clarify the role of platinum-based chemotherapy as neoadjuvant treatment of TNBC patients.

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References

1. Gluz O, Liedtke C, Gottschalk N et al. Triple-negative breast cancer–current status and future directions. Ann Oncol 2009; 20(12): 1913–1927.
2. Carey LA, Dees EC, Sawyer L et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 2007; 13(8): 2329–2334.
3. Liedtke C, Mazouni C, Hess KR et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26(8): 1275–1281.
4. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384(9938): 164–172.
5. von Minckwitz G, Untch M, Blohmer J-U et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30(15): 1796–1804.
6. Harbeck N, Gluz O. Neoadjuvant therapy for triple negative and HER2-positive early breast cancer. Breast 2017; 34(Suppl 1): S99–S103.
7. Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 2007; 7(8): 573–584.
8. Lehmann BD, Bauer JA, Chen X et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011; 121(7): 2750–2767.
9. Gradishar WJ, Anderson BO, Balassanian R et al. NCCN Guidelines Insights: breast Cancer, Version 1.2017. J Natl Compr Canc Netw 2017; 15(4): 433–451.
10. Curigliano G, Burstein HJP, Winer E et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol 2017; 28(8): 1700–1712.
11. Senkus E, Kyriakides S, Ohno S et al. Primary breast cancer: eSMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5): v8–30.
12. Paluch-Shimon S, Pagani O, Partridge AH et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast 2017; 35: 203–217.
13. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
14. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22(4): 719–748.
15. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy 2002; 7(1): 51–61.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3): 177–188.
17. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11): 1539–1558.
18. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006; 25(20): 3443–3457.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109): 629–634.
20. Alba E, Chacon JI, Lluch A et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012; 136(2): 487–493.
21. von Minckwitz G, Schneeweiss A, Loibl S et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014; 15(7): 747–756.
22. Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: cALGB 40603 (Alliance). J Clin Oncol 2015; 33(1): 13–21.
23. Ando M, Yamauchi H, Aogi K et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat 2014; 145(2): 401–409.
24. Martinez MCA, Arce-Salinas C, Alvarado-Miranda A et al. Randomized phase II trial to evaluate the safety and efficacy of neoadjuvant cisplatin in combination with taxanes-anthracyclines vs taxanes-anthracyclines

alone in locally advanced triple negative breast cancer. J Clin Oncol 2015; 33(Suppl 15): e12024–e12024.
25. Zhang P, Yin Y, Mo H et al. Better pathologic complete response and relapse-free survival after carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for locally advanced triple-negative breast cancer: a randomized phase 2 trial. Oncotarget 2016; 7(37): 60647–60656.
26. Schneeweiss A, Moebus V, Tesch H et al. A randomised phase III trial comparing two dose-dense, dose-intensified approaches (EPC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto). J Clin Oncol 2017; 35(Suppl 15): 518–518.
27. Sikov WM, Berry DA, Perou CM et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance). Cancer Res 2016; 76(Suppl 4): S2-05.
28. Hahnen E, Lederer B, Hauke J et al. Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol 2017; 3(10): 1378–1385.
29. Untch M, Schneeweiss A, Salat C et al. Long-term survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative (TNBC) and HER2-positive early breast cancer (GeparSixto). Ann Oncol 2017; 28(Suppl 5): mdx362.014.
30. Gluz O, Nitz U, Liedtke C et al. Comparison of neoadjuvant Nab-Paclitaxel+Carboplatin vs Nab-Paclitaxel+Gemcitabine in triple-negative breast cancer: randomized WSG-ADAPT-TN Trial Results. J Natl Cancer Inst 2017; doi:10.1093/jnci/djx258.
31. Loibl S, O'Shaughnessy J, Untch M et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018; 19(4): 497–509.
32. Pignata S, Scambia G, Katsaros D et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014; 15(4): 396–405.
33. Sharma P, Klemp JR, Kimler BF et al. Germline BRCA mutation evaluation in a prospective triple-negative breast cancer registry: implications for hereditary breast and/or ovarian cancer syndrome testing. Breast Cancer Res Treat 2014; 145(3): 707–714.
34. Daly MB, Pilarski R, Berry M et al. NCCN Guidelines Insights: genetic/Familial High-Risk Assessment: breast and Ovarian, Version 2.2017. J Natl Compr Canc Netw 2017; 15(1): 9–20.
35. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001; 411(6835): 366–374.
36. Tutt A, Tovey H, Cheang MCU et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med 2018; 24(5): 628–637.
37. Cardoso F, Costa A, Senkus E et al. 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol 2017; 28(12): 3111–3111.
38. Byrski T, Gronwald J, Huzarski T et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 2010; 28(3): 375–379.
39. Byrski T, Huzarski T, Dent R et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2014; 147(2): 401–405.
40. Telli ML, Timms KM, Reid J et al. Homologous Recombination Deficiency (HRD) Score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res 2016; 22(15): 3764–3773.
41. Turner NC. Signatures of DNA-repair deficiencies in breast cancer. N Engl J Med 2017; 377(25): 2490–2492.
42. Birkbak N, Li Y, Pathania S et al. Overexpression of BLM promotes DNA damage and increased sensitivity to platinum salts in triple negative breast and serous ovarian cancers. Ann Oncol 2018; 29(4): 903–909.