# Efficacy and safety of first-line carboplatin-paclitaxel and carboplatin-gemcitabine in patients with advanced triple-negative breast cancer: a monocentric, retrospective comparison

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# Abstract

**Background:** Platinum-based chemotherapy is widely used in patients with advanced triple-negative breast cancer (TNBC). However, the most effective platinum-based chemotherapy combination in the first-line treatment setting remains unclear.

**Methods:** We evaluated the efficacy of first-line carboplatin-paclitaxel (CP) or carboplatin-gemcitabine (CG) combinations in advanced TNBC patients treated at “Fondazione IRCCS Istituto Nazionale dei Tumori” between April 2007 and April 2021. CP and CG were compared in terms of progression-free survival (PFS), overall survival (OS) and incidence of adverse events (AEs). Multivariable Cox Models were used to adjust the efficacy of CP *vs.* CG for clinically relevant covariates.

**Results:** Of 418 consecutive advanced breast cancer patients receiving carboplatin-based doublet chemotherapy, 88 patients had advanced TNBC and were treated in the first-line setting. Of these, 56 (63.6%) and 32 (36.4%) patients received CP and CG, respectively. Clinically relevant variables were well-balanced in the two treatment cohorts, except for a higher percentage of patients with shorter disease-free interval in the CG group (59.4% *vs.* 44.6%; p value 0.038). After adjusting for clinically relevant variables, patients receiving CG had significantly better PFS when compared to CP-treated patients [aHR: 0.49 (95%CI: 0.27-0.87), p value 0.014]. Of note, CG was associated with better PFS only among patients previously treated with taxanes in the (neo)adjuvant setting (aHR: 0.39; 95%CI: 0.21-0.75), but not in patients not exposed to taxanes (aHR: 1.20; 95%CI: 0.37-3.88). CG was also independently associated with better OS when compared to CP [aHR: 0.31 (95%CI: 0.15-0.64), p value 0.002]. Overall, grade 3-4 AEs were more common in patients treated with CG than in patients treated with CP (68.8% *vs.* 21.4%, p value 0.009).

**Conclusions:** CG and CP are effective and well tolerated first-line platinum doublets in advanced TNBC patients. CG could be more effective than CP in patients previous exposed to taxanes despite worse toxicity profile.


# Introduction

Breast cancer (BC) is the primary cause of cancer-related death in women, with 684,996 deaths in 2020 worldwide [1]. Approximately 15–20% of all BCs are classified as triple-negative BC (TNBC), as defined by absent or minimal (< 1%) expression of estrogen receptor and progesterone receptor by immunohistochemistry (IHC) analysis, and by absence of Human Epidermal growth factor Receptor 2 (HER2) overexpression by IHC and/or *HER2* gene amplification by *in situ* hybridization (ISH). TNBC is the most clinically aggressive and deadly BC subtype, and its clinical course is characterized by a higher risk of distant metastases after curative surgery and by shorter survival in patients with advanced disease [2–4]. Indeed, median overall survival (OS) in the advanced stage does not go beyond two years even with the most effective systemic treatments [5–8].

Recently, the advent of new biomarkers and pharmacological targets has remarkably expanded the therapeutic options for patients with advanced TNBC [9–10]. In particular, PolyAdenosine diphosphate-Ribose Polymerase inhibitors (PARPi) in patients harboring germline *BRCA*1/2 mutations, or first-line chemo-immunotherapy combinations in patients with programmed death-ligand 1 (PD-L1)-positive neoplasms, have significantly prolonged patient progression free survival (PFS) and/or OS [6, 11, 12]. Despite these progresses, chemotherapy remains the mainstay of treatment for advanced TNBC patients. Several chemotherapeutical agents, such as taxanes (paclitaxel, nab-paclitaxel, docetaxel), anthracyclines (doxorubicin, liposomal doxorubicin), anti-metabolites (capecitabine, gemcitabine), microtubule inhibitors (eribulin, vinorelbine) and platinum agents (carboplatin, cisplatin), are potentially effective anti-TNBC treatments. Unfortunately, the duration of tumor control with these agents, used either alone or in combination, is sub-optimal in the majority of patients, and advanced TNBC cells becomes progressively more chemo-resistant during the course of subsequent lines of therapy. Therefore, using the most effective therapies in the first- or second-line treatment settings is a clinical priority, potentially impacting on long-term clinical outcomes.

Different studies support the use of platinum-based combinations in advanced TNBC patients. In a retrospective analysis including 379 metastatic TNBC patients, platinum-based chemotherapy was associated with longer PFS compared to non-platinum-based chemotherapy (7.8 *vs.* 4.9 months respectively), without statistically significant OS differences in the two patient cohorts [13]. TNBCs arising in patients harboring germline *BRCA*1/2 gene mutations are exquisitely sensitive to platinum compounds, which induce the formation of DNA inter-stand and DNA-protein crosslinks [14–16]. In the phase III, randomized trial TNT, carboplatin monotherapy was associated with higher tumor overall response rates (ORR) when compared with docetaxel monotherapy in advanced TNBC patients bearing germline *BRCA1/2* mutations; on the other hand, in the whole patient cohort carboplatin and docetaxel showed similar antitumor activity/efficacy, with carboplatin being associated with a better safety profile [17]. To date, different platinum-based doublets, including gemcitabine-, vinorelbine-, paclitaxel- and nab-paclitaxel-based combinations, have been evaluated in prospective studies, and higher response rates have been reported with chemotherapy doublets (ranging between 28% and 69.2%) as compared to single-agent chemotherapy [7, 18–27]. However, the long-term benefit associated with platinum doublets, as well as the most effective chemotherapy partner to be used in combination with platinum salts, remain unclear.

On these grounds, we conducted a retrospective analysis to evaluate the efficacy and the safety profiles of first-line carboplatin-gemcitabine (CG) and carboplatin-paclitaxel (CP) combinations in advanced TNBC patients treated in our Institution between 2007 and 2021.

# Methods

# Study setting and inclusion criteria

This is a retrospective, monocentric study that included advanced TNBC patients treated with first-line platinum-based chemotherapy at Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) between April 2007 and April 2021. Inclusion criteria were: (a) women with pathologically/cytologically confirmed diagnosis of TNBC, as defined as estrogen receptor (ER) and progesterone receptor (PgR) expression in less than 1% of cancer cells by IHC analysis, and an IHC score for HER2 expression of 0/1+, or an IHC score of 2 + in the absence of *HER2* gene amplification by ISH analysis. For the definition of TNBC, the most recently collected tumor specimen (i.e., surgical tumor specimen for patients not undergoing tumor re-biopsy for metastatic disease, or biopsy of a metastatic lesion for patients undergoing tumor re-biopsy at disease relapse after surgery) was used; (b) advanced disease, as defined as the presence of distant metastases or locally advanced, inoperable disease; (c) age ≥ 18 years; (d) treatment with at least one cycle of one of the following first-line regimens: CG (carboplatin at an area under the curve (AUC) of 2 plus gemcitabine 800 mg/m$^2$, both administered i.v. on days 1 and 8 every 3 weeks; or carboplatin at an AUC of 5 on day 1 every 3 weeks plus gemcitabine 800 mg/m$^2$ on days 1 and 8 every 3 weeks), or CP (carboplatin AUC 2 plus paclitaxel 80 mg/m$^2$, both administered i.v. on days 1 and 8 every 3 weeks); (e) availability of data regarding clinical outcomes, including patient PFS and OS; (f) available data about previous therapies received (i.e., surgery, radiotherapy and (neo)adjuvant therapy); (g) available data about number and sites of metastatic lesions; (h) available data about treatment-related adverse events (AEs).

# Objectives of the study

The objectives of this study were to compare the antitumor efficacy, activity and safety profiles of CG and CP as a first-line treatment in patients with advanced TNBC. The primary study endpoint was PFS, as defined as the time between treatment initiation and disease progression or patient death from any cause, whichever occurred first. OS, ORR, disease control rate (DCR) and duration of response (DOR) were secondary activity/efficacy endpoints. ORR was defined as the percentage of patients achieving partial response (PR) or complete response (CR) as their best response. DCR was defined as the percentage of patients achieving PR, CR, or stable disease (SD) as their best response. OS was defined as the time between chemotherapy initiation and patient death from any cause. Disease-free interval (DFI) was defined as the time between surgical resection of the primary tumor and the detection of disease recurrence. The DOR was defined as the time between the first documentation of PR or CR and disease progression or patient death from any cause. Patients who had not undergone disease progression or death at the time of data cut-off and analysis were censored at the time of their last disease evaluation.

# Exploratory evaluations

We performed an exploratory evaluation to study the potential impact of previous exposure to taxanes on the efficacy (in terms of PFS or OS) of CG *vs.* CP. For this evaluation, we analyzed the interaction between previous exposure to taxanes (yes *vs.* no) and the efficacy of CG *vs.* CP (see *Statistical analyses* below). In addition, since 1st line platinum chemotherapy has been shown to be superior to taxane-based chemotherapy in advanced TNBC patients who are carries of pathogenic *BRCA1* or *BRCA2* mutations, we also performed an exploratory analysis to evaluate the potential impact of germline *BRCA1* or *BRCA2*

mutations on the PFS of patients included in this study (regardless of the treatment cohort) [17]. For this analysis, patients were divided in three different cohorts: a) patients undergoing genetic evaluations and found to be carriers of pathogenetic germline *BRCA1* or *BRCA2* alterations; b) patients undergoing genetic testing and not found to be carries of pathogenetic germline *BRCA1* or *BRCA2* alterations; c) patients not undergoing genetic testing. We reported results of PFS evaluations in these three cohorts.

# Sensitivity analysis excluding patients with de novo metastatic disease

In addition to including the presence of *de novo* metastatic disease as a covariate in all multivariable analyses performed in this study, we also performed a sensitivity analysis in which we evaluated the impact of CG and CP on patient PFS and OS after removing patients diagnosed with *de novo* metastatic disease. In these multivariable Cox models, we included the same covariates included in the main models (see *Statistical analyses* below), with the only exception of presence/absence of *de novo* metastatic disease.

# Assessment of treatment efficacy and safety

Tumor response was assessed every three chemotherapy cycles (~ every 2 months) through computed tomography (CT) or magnetic resonance imaging (MRI) using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Tumor radiological assessment was performed by central review by a radiologist. Data were collected at the time of patient enrollment. AEs were classified according to common terminology criteria for adverse events (CTCAE) version 4.03 of June 14, 2010 of National Institutes of Health, National Cancer Institute. Hematological toxicities were collected from computerized blood sample data. Non-hematological toxicities were retrieved from medical records, where they had been regularly annotated during patient visits.

# Statistical analyses

The $\chi 2$ test was used to study the distribution of dichotomous patient- or tumor-related variables in CG *vs.* CP groups, whereas the Welch Two Sample t test was used to compare the distribution of continuous variables in the two patient groups. Median follow-up was calculated using reverse Kaplan Meier method. The impact of the type of platinum doublet (CG *vs.* CP) on PFS and OS was evaluated through Cox proportional hazard models. Clinically relevant variables previously associated with clinical outcomes in advanced TNBC patients, namely age, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), body mass index (BMI), previous taxane exposure, previous anthracycline exposure, DFI, *de novo* metastatic (stage IV) disease, number of metastatic sites, presence of lung, liver, brain or bone metastases at treatment initiation, were included in multivariable models [6, 7, 19, 27]. To avoid the exclusion of patients for whom data on specific covariates were not available, missing data were imputed, and Cox models for the main study analyses were fitted by including imputed data. Single imputation technique using mean value of the available data was performed [28]. Results of the main analyses were confirmed in Cox models in which we only included original data (i.e., without imputation). Adjusted PFS and OS estimates based on multivariable Cox proportional hazard regression models were

calculated by using the “conditional method”, and represented as adjusted survival curves [29, 30]. Bootstrap resampling method (1000 times) provided robust estimates of adjusted median PFS/OS and 95% confidence intervals (CI), as well as estimates of the median differences between the two treatment groups with the corresponding 95% CIs [31]. To test the impact of the interaction between type of treatment (CG *vs.* CP) and previous taxane exposure, we also fitted multivariable Cox models in which we included a product term accounting for the interaction between these variables. A threshold of significance (p value) of 0.10 was set for the interaction term analyses, while other statistical evaluations were considered as statistically significant if the p value was lower than 0.05. All statistical analyses were performed using the software R (version 4.0.2 (2020-06-22)).

# Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

# Results

*Patient population*

We evaluated 418 advanced BC patients treated with platinum-based doublets in our Institution between April 2007 and April 2021 (Additional file 1: **Figure S1)**. Of these, 88 patients had advanced TNBC and received carboplatin-based combinations as a first-line treatment for advanced disease; therefore, they were selected for the current study. Patient and tumor characteristics are reported in **Table 1**. Median patient age in the whole patient cohort was 55.9 years (range 34-80). Of 88 patients included, 56 (63.6%) were treated with CP, while 32 (36.4%) received CG. The majority of patients had previously received taxane- and anthracycline-based chemotherapy in the (neo)adjuvant setting (n = 62, 70.5% and n = 66, 75.0%, respectively), while only three patients (3.4%) had previously received (neo)adjuvant carboplatin. Nine patients were diagnosed with *de novo* metastatic disease (n = 3 in the CP subgroup and n = 6 in the CG subgroup, p-value = 0.103). The majority of patients had visceral involvement (n = 56, 63.6%) and an ECOG PS of 0 (n = 55, 62.5%). Baseline characteristics were well balanced in the two treatment groups, with the exception of a higher proportion of patients with shorter DFI in the CG group when compared to the CP group (59.4% *vs.* 44.6%; $\chi 2$ test p value = 0.038). Out of the 88 patients included in the study, 79 patients were diagnosed with limited-stage disease and had undergone basal evaluation of ER/PgR/HER2 status. Of these 79 patients, 60 (75.9%) had a diagnosis of TNBC from the beginning of their clinical history (i.e., on the basis of basal ER/PgR/HER2 status evaluation in the primary tumor), while 16 (20.3%) and 2 (2.5%) patients were initially diagnosed with HR+HER2- BC and HER2+ BC, respectively, and their tumors underwent biological switch to TNBC upon disease recurrence and biological tumor re-characterization of disease recurrence (Additional file 1: **Table S1**). The proportion of patients undergoing a HR+HER2- BC/HER2+ BC to TNBC conversion was numerically lower in the CG group as compared to the CP group (Additional file 1: **Table S1**).

*Treatment efficacy and antitumor activity*

At data cut-off and analysis (April 1, 2021), median patient follow-up was 41.19 months (IQR 28.73 – 54.05). With a total number of 83 progression events and 68 death events, median PFS and OS in the whole patient population were 6.49 months (95% CI: 5.26 – 8.94) and 18.0 months (95% CI: 15.5 – 27.6), respectively. At multivariable analysis, CG was independently associated with significantly better PFS when compared to CP [Hazard Ratio (HR): 0.49; 95% CI: 0.27-0.87; p value 0.014], while not being diagnosed with *ab initio* metastatic disease (no *vs.* yes) and a higher number of metastatic sites (>3 *vs.* 1-3) were associated with worse PFS (HR: 3.93; 95% CI: 1.18-13.11; p value = 0.026 and HR: 2.70; 95% CI: 1.09-6.66; p value = 0.032, respectively) (**Table 2)**. After adjustment for the same covariates, CG was also associated with significantly better patient OS (HR: 0.31; 95% CI: 0.15-0.64; p value = 0.002), along with longer DFI after surgery, here evaluated as a continuous variable (HR: 0.99; 95% CI: 0.986-0.999; p value = 0.028). By contrast, factors associated with worse OS were: not being diagnosed with metastatic disease *ab initio* (HR: 6.33; 95% CI: 1.20-33.42; p value = 0.030), worse ECOG PS (HR: 5.11; 95% CI: 2.34-11.18; p value < 0.001), presence of lung metastases (HR: 2.05; 95% CI: 1.07-3.92; p value = 0.031), presence of liver metastases (HR: 2.37; 95% CI: 1.20-4.68; p value = 0.013) (**Table 3)**. PFS and OS estimates in the two treatment groups, adjusted for the covariates included in the Cox multivariable models, are shown as adjusted survival curves in **Figure 1A** and **1B**, respectively. Patients treated with CG had longer adjusted PFS and OS when compared to patients treated with CP combination (8.98 *vs.* 5.36 months for adjusted PFS and 31.59 *vs.* 15.68 months for adjusted OS). These results were confirmed by bootstrap analyses performed on adjusted survival curves, which showed statistically significant survival advantage in patients treated with CG *vs.* CP in terms of both PFS [median PFS: 9.01 months (95% CI: 6.35 – 10.59) *vs.* 5.29 months (95% CI: 4.47 – 6.71), absolute PFS difference: 3.45 months (95% CI: 0.07 – 5.53)] and OS [median OS: 30.05 months (95% CI: 18.21 – 48.33) *vs.* 15.48 months (95% CI: 12.30 – 20.35), absolute OS difference: 14.17 months (95% CI: 2.30 – 32.65)].

Of note, CG treatment maintained an independent association with significantly better patient PFS and OS when multivariable analysis was repeated by using original data (i.e., without imputation of missing data) (Additional file 1: **Table S2** and **Table S3**, respectively), and also at a sensitivity multivariable analysis that excluded patients with *de novo* metastatic disease [HR of 0.37 (95% CI: 0.20-0.72) and 0.33 (95% CI: 0.16-0.69) for PFS and OS] (Additional file 1: **Table S4** and **Table S5**, respectively).

Tumor response was evaluated in 87 patients according to RECIST 1.1 criteria. Overall, we detected 9 CR (10.3%), 41 PR (47.1%), 18 SD (20.7%) and 19 disease progression (PD) (21.8%) as best tumor responses, resulting in an ORR of 57.5% (95% CI: 46.4 – 68.0) and in a DCR of 78.2% (95% CI: 68.0 – 86.3). We found no statistically significant ORR differences between patients treated with CG or CP [58.9% (95% CI: 45.0-71.9) *vs*. 54.8% (95% CI: 36.0-72.7), respectively; p-value = 0.70]. The DCR was also similar in the two treatment groups [83.3% for CG (95% CI: 65.3-94.4) *vs.* 75.4% (95% CI: 62.2-85.9) for CP, p value = 0.53]. Although DOR was numerically higher in patients treated with CG as compared to patients receiving CP, this difference did not reach statistical significance (Additional file 1: **Table S6**).

*Impact of previous taxane exposure on treatment efficacy*

To investigate if worse PFS in CP-treated patients could be in part justified by the fact that some patients had previously received taxane-based (neo)adjuvant therapy, possibly resulting in more taxane-resistant disease at the time of first-line treatment initiation, we performed an exploratory analysis to investigate the potential impact of the interaction between previous taxane exposure (yes *vs.* no) and the type of platinum doublet (CG *vs.* CP) on patient PFS. In a multivariable model that also included a product term accounting for the interaction between these two variables, CG was associated with significantly better PFS (HR of 0.39; 95% CI: 0.21 – 0.75) in patients previously exposed to taxanes, but not in patients not pre-treated with taxanes (HR: 1.20; 95% CI: 0.37-3.88) (**Table 4**). Not being diagnosed with *de novo* metastatic disease and a higher number of metastatic sites maintained their significant association with worse PFS [HR 4.86 (95% CI: 1.48-15.98; p value = 0.009) and HR 2.90 (95% CI: 1.18-7.15; p value = 0.021)]. Results of this exploratory analysis suggest that the observed association between CP and worse PFS might be driven by the subset of patients previously exposed to taxane-based chemotherapy in the (neo)adjuvant setting. Adjusted PFS curves stratified on the basis of previous taxane exposure and type of platinum-based doublet are shown in **Figure 2A**. By contrast, CG was associated with better OS regardless of previous exposure to taxanes (p value of interaction term: 0.772) (**Table 5**). In this model, higher ECOG PS scores retained a strong association with worse OS (HR 4.95; 95% CI: 2.20 – 11.12; p value <0.001). Adjusted OS curves stratified on previous taxane exposure in CP and CG subgroups are shown in **Figure 2B.**

*Impact of germline BRCA1/BRCA2 status on the efficacy of CG/CP doublets*

The presence of germline *BRCA1* or *BRCA2* mutations has been associated with an increased sensitivity to platinum-based chemotherapy in advanced TNBC patients [17]. In our patient cohort, 30 patients (34.1%) underwent genetic testing for the evaluation of germinal *BRCA1* and *BRCA2* status. Of these patients, 13 (43.3%) were found to be carries of pathologic germline *BRCA1/BRCA2* mutations, while 17 patients (56.7%) had wild type *BRCA1/BRCA2* genes. Germline *BRCA1/BRCA2* mutation carriers were equally distributed in the CG and CP groups (Additional file 1: **Table S7**). Although median PFS was numerically longer in *BRCA1/2* mutation carries as compared to patients with wild type *BRCA1/2* status or patients not evaluated for the presence of germline *BRCA1/2* mutations (8.98 vs. 6.36 vs. 6.4 months, respectively), this difference did not reach statistically significant differences, likely due to the low number of patients included in these sub-cohorts (Additional file 1: **Figure S2**).

*Treatment Safety and Tolerability*

Treatment-related AEs are described in **Table 6**. The incidence of any grade AEs was 85.7% in CP subgroup and 100% in CG subgroup (p value = 0.063). Hematologic AEs were the most common any-grade AEs in patients treated with CG, and we found a statistically higher incidence of neutropenia (90.6% *vs.* 66.1%, p value = 0.021) and thrombocytopenia (59.4% *vs.* 14.3%, p value < 0.001) in CG vs. CP groups. Other AEs more commonly occurring in patients treated with CG than in patients treated with CP were any grade fatigue (59.4% *vs.* 32.1%, p value = 0.024) and increased blood ALT levels (56.2% *vs.* 19.6%, p-value

= 0.001). On the other hand, CP was associated with significantly higher rates of peripheral neuropathy (26.8% *vs.* 3.1%, p value = 0.013). Considering the whole patient population, 34 out of 88 patients (38.6%) experienced AEs graded as 3 or 4. Overall, CG was associated with higher rates of G3-G4 AEs as compared to CP [22 out of 32 patients (68.8%) *vs.* 12 out of 56 patients (21.4%), p-value = 0.009). In the whole patient cohort, the most common G3-G4 AE was neutropenia, and it occurred significantly more frequently in patients treated with CG (59.4% *vs.* 12.5%, p-value < 0.001). Moreover, 6 patients in the CG subgroup experienced G3-G4 thrombocytopenia compared to one thrombocytopenia event in the CP subgroup (18.7% *vs.* 1.8%, p value = 0.016). While the median number of doublet chemotherapy cycles and the proportion of patients switching to single-agent chemotherapy was not statistically significantly different in the CG *vs.* CP cohorts, a higher proportion of patients in the CG arm underwent dose reduction or omission of one or more treatment administrations as compared to the CP arm. In addition, the absolute number and proportion of chemotherapy cycles that were omitted (over the total number of cycles) was significantly higher in the cohort of patients treated with CG (Additional file 1: **Table S8**).

# Discussion

The use of platinum-based chemotherapy combinations as a standard first-line treatment for advanced TNBC patients is a debated topic. On the one hand, single-agent carboplatin has demonstrated similar antitumor activity when compared to single-agent docetaxel as a first-line therapy for advanced TNBC, and it is more active than docetaxel in the subset of advanced TNBC patients bearing germline *BRCA1* or *BRCA2* mutations [17]. On the other hand, combination chemotherapy, including platinum-based doublets, has not demonstrated to improve patient OS when compared to single-agent chemotherapy despite longer PFS and higher ORRs, and it also results in higher toxicity rates [32,33]. In addition, the increasing use of carboplatin as part of standard neoadjuvant chemotherapy regimens might contribute to the relatively low use of platinum doublets as first-line treatments in advanced TNBC patients [34,35]. Even when platinum-based doublets are considered for advanced TNBC treatment, the most effective drug to be combined with carboplatin/cisplatin is still unclear.

Here, we found that CG, when a first-line chemotherapy combination in advanced TNBC patients, is independently associated with significantly better PFS and OS when compared to CP. These results are especially relevant if we take into account that CG-treated patients: a) had significantly shorter DFI, which is indicative of more aggressive and/or chemo-resistant disease; b) more frequently underwent treatment dose reduction/omissions when compared to patients treated with CP. To explain the observed superiority of CG over CP, we reasoned that previous tumor exposure to taxanes, which are part of the standard-of-care therapy in the (neo)adjuvant setting, might determine a more taxane-resistant disease, thus resulting in shorter PFS in patients treated with CP when compared to patients treated with CG. Consistent with this hypothesis, CG was associated with better PFS (when compared to CP) only in patients previously exposed to taxanes, while CG and CP were similarly effective in patients who had not received prior taxane-based therapy. Although these findings are of potential clinical interest, they should be interpreted with caution due to the limited number of patients included in the taxane-pre-treated or taxane-not-pretreated CG or CP cohorts. Future prospective trials including a larger number of patients are needed to

investigate if carboplatin-gemcitabine might be a more effective 1$^{st}$ line treatment option as compared to CP in taxane-pretreated, advanced TNBC patients.

In addition to prior patient exposure to taxanes, the following two factors could contribute to explain the more favorable clinical outcomes observed in the CG cohort as compared to the CP cohort: 1) while most of patients had previously received taxanes as a (neo)adjuvant therapy, only 3 of them had previously received carboplatin, and none of them had been exposed to gemcitabine; therefore, patients receiving CG in our clinical cohort were exposed concomitantly to two new chemotherapeutical agents that they had never received during their clinical course, thus potentially resulting in higher tumor sensitivity to the treatment and better PFS; 2) gemcitabine modulates antitumor immunity, and in particular it reduces myeloid-derived suppressive cells, regulatory T cells (Tregs) and B-cells, while concomitantly enhancing T-cell mediated anti-tumor immune effects [36,37]. In this regard, the recently published phase III trial Keynote-355, which showed that the addition of pembrolizumab to platinum-based doublets (carboplatin-nab-paclitaxel, carboplatin-paclitaxel or carboplatin-gemcitabine) prolongs patient PFS especially in the case of tumors expressing PD-L1 and with high combined positive score (CPS), failed to reveal a positive impact of pembrolizumab in the subset of patients receiving carboplatin-gemcitabine [27]. These results could reflect the fact that gemcitabine is sufficiently potent to modulate systemic immunity, thus reducing the therapeutic impact of adding pembrolizumab to platinum-gemcitabine doublets. An ongoing phase III study, namely the IMpassion132 trial, is evaluating the combination of atezolizumab with capecitabine or carboplatin plus gemcitabine in patients with advanced TNBC recurring ≤ 12 months after completing standard (neo)adjuvant anthracycline and taxane chemotherapy. The primary endpoint of this study is OS, and this trial may provide further evidence on the efficacy of combining immune-checkpoint inhibitors with platinum-gemcitabine doublets [38]. In the recently published phase II trial TnAcity, first-line carboplatin-nab-paclitaxel resulted in longer PFS when compared to nab-paclitaxel-gemcitabine (8.3 *vs.* 5.5 months, respectively) or carboplatin-gemcitabine (8.3 *vs.* 6.0 months, respectively) combinations, thus suggesting that nab-paclitaxel could be the best partner to combine with carboplatin in this setting [7]. The main limitations of TnAcity consist in the relatively low number of patients included, and in the fact that nab-paclitaxel is not approved as a first-line therapy for TNBC treatment in Europe; therefore, since the TnAcity study did not compare the efficacy of CG and CP, the conclusions of this trial are poorly applicable to the clinical practice in Europe and Italy. In a Chinese, phase III trial that randomized 240 advanced TNBC patients to gemcitabine plus either cisplatin or paclitaxel, the cisplatin-gemcitabine combination was associated with significantly better PFS when compared to the paclitaxel-gemcitabine combination (HR for PFS 0.69; 95% CI: 0.523-0.915) [24]. However, in this study the absence of a cisplatin-paclitaxel arm prevents any evaluation on the most effective platinum-based combination (i.e. cisplatin-gemcitabine or cisplatin-paclitaxel).

Several variables, including previous exposure to carboplatin and taxanes, or the presence of *BRCA1/2* mutations, could affect the clinical efficacy of different first-line platinum-based combinations. For instance, in the recently published phase III, randomized BROCADE3 trial, carboplatin-paclitaxel, alone or combined with the PARP inhibitor veliparib, was associated with excellent PFS (median PFS of 12.6

and 14.5 months in the carboplatin-paclitaxel and carboplatin-paclitaxel-veliparib, respectively) in advanced TNBC patients bearing germline *BRCA1/2* mutations [39]. In our study, although PFS was numerically longer in patients carrying germline *BRCA1/BRCA2* mutations, these differences did not reach statistical significance, likely due to the low number of patients included. Future prospective studies are needed to investigate if platinum-based doublets are more effective in *BRCA1/BRCA2* mutations carries than in *BRCA1/BRCA2* wt patients, as well as to determine the most effective platinum doublets in advanced TNBC patients carrying pathogenic *BRCA1/BRCA2* mutations.

The main limitations of our study consist in its retrospective design and in the relatively low number of patients included. Strengths of the study consist in: 1) the homogeneity of the clinical cohort, which included advanced TNBC patients treated with first-line platinum-based doublets; 2) its monocentric nature, which guarantees reproducible collection of data, tumor response assessment and homogeneous patient management; 3) finally, tumor ORR, median PFS and median OS in the whole patient cohort were in line with data previously reported in the literature, thus indicating that our study cohort is representative of the population of advanced TNBC patients receiving first-line chemotherapy.

# Conclusions

To the best of our knowledge, this is the first study to compare the efficacy and safety of two commonly used platinum doublets, namely CG and CP, as first-line chemotherapy options in advanced TNBC patients. Although our findings need prospective validation in larger patient cohorts, they suggest that CG and CP are valuable treatment options in this poor-prognosis patient population, with an acceptable toxicity profile. In particular, future prospective studies should investigate if CG might be a preferred treatment option for patients previously exposed to taxanes in the (neo)adjuvant treatment setting.

# Abbreviations

AEs: Adverse Events

AUC: Area Under the Curve

BC: Breast Cancer

BMI: Body Mass Index

CG: Carboplatin plus Gemcitabine

CI: Confidence Interval

CP: Carboplatin plus Paclitaxel

CR: Complete Response

DCR: Disease Control Rate

DFI: Disease-Free Interval

DOR: Duration Of Response

ECOG: Eastern Cooperative Oncology Group

ER: Estrogen Receptor

HER2: Human Epidermal Growth Factor Receptor 2

HR: Hazard Ratio

i.v.: Intravenous

IHC: ImmunoHistoChemistry

ISH: In Situ Hybridization

ORR: Overall Response Rate

OS: Overall Survival

PARPi: Polyadenosine Diphosphate-Ribose Polymerase Inhibitors

PD-L1: Programmed Death-Ligand 1

PFS: Progression Free Survival

PgR: Progesterone Receptor

PR: Partial Response

PS: Performance Status

SD: Stable Disease

TNBC: Triple Negative Breast Cancer

# Declarations

### Authors' contributions

Conceptualization: CV and RL. Data curation: RL, LM, GP, AR and SM. Formal analysis: LM, RL and CV. Software: LM. Investigation: RL, CV, LM, GP, FL, GF, AR, EZ, RLe, BC, CD, AV, SM, GS, GVB, GC, GP and FdB.

Validation: RLe. Writing – original draft: RL and CV. Writing – review & editing: LM, GP, FL, GF, AR, EZ, RLe, BC, CD, AV, SM, GS, GVB, GC, GP and FdB. Supervision: CV, GS, GVB, GC, GP and FdB.


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### Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The study protocol was approved by the Internal Review Board (IRB) and the Local Ethics Committee of the “Fondazione IRCCS Istituto Nazionale dei Tumori” (INT 79/17). Patient data were collected according to the ethical principles for medical research involving human subjects adopted in the Declaration of Helsinki. Patients who were alive at the time of data collection and/or analyses signed an informed consent for the use of their data for research purposes.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no conflicts of interest related to this work

## References


1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021;71(3):209–249.
2. Malorni L, Shetty PB, De Angelis C, Hilsenbeck S, Rimawi MF, Elledge R, et al. Clinical and biologic features of triple-negative breast cancers in a large cohort of patients with long-term follow-up. Breast Cancer Res Treat. 2012;136(3):795–804.

3. Murthy RK, Song J, Raghavendra AS, Li Y, Hsu L, Hess KR, et al. Incorporation of clinical and biological factors improves prognostication and reflects contemporary clinical practice. npj Breast Cancer. 2020;6(1):11.
4. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429–34.
5. Den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK, Lohrisch CA. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat. 2017;161(3):549–56.
6. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine. 2018;379(22):2108–21.
7. Yardley DA, Coleman R, Conte P, Cortes J, Brufsky A, Shtivelband M, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol. 2018;29(8):1763–70.
8. Gobbini E, Ezzalfani M, Dieras V, Bachelot T, Brain E, Debled M, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer. 2018;96:17–24.
9. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750–67.
10. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World J Clin Oncol. 2014;5(3):412–24.
11. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. New England Journal of Medicine. 2017;377(6):523–33.
12. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. New England Journal of Medicine. 2018;379(8):753–63.
13. Zhang J, Fan M, Xie J, Wang Z, Wang B, Zhang S, et al. Chemotherapy of metastatic triple negative breast cancer: Experience of using platinum-based chemotherapy. Oncotarget. 2015;6(40):43135–43.
14. Chválová K, Brabec V, Kaspárková J. Mechanism of the formation of DNA-protein cross-links by antitumor cisplatin. Nucleic Acids Res. 2007;35(6):1812–21.
15. Deans AJ, West SC. DNA interstrand crosslink repair and cancer. Nat Rev Cancer. 2011;11(7):467–80.
16. Byrski T, Dent R, Blecharz P, Foszczynska-Kloda M, Gronwald J, Huzarski T, et al. Results of a phase II open-label, non-randomized trial of cisplatin chemotherapy in patients with BRCA1-positive metastatic breast cancer. Breast Cancer Res. 2012;14(4):R110.

17. Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med. 2018;24(5):628–37.
18. Vernieri C, Prisciandaro M, Milano M, Cona MS, Maggi C, Brambilla M, et al. Single-Agent Gemcitabine vs. Carboplatin-Gemcitabine in Advanced Breast Cancer: A Retrospective Comparison of Efficacy and Safety Profiles. Clin Breast Cancer. 2019;19(2):e306-e18.
19. Vernieri C, Milano M, Mennitto A, Maggi C, Ferrari B, Rinaldi L, et al. Antitumor activity and safety profile of weekly carboplatin plus paclitaxel in metastatic breast cancer: a ten-year, monocentric, retrospective study. Breast Cancer Res Treat. 2017;165(2):365–73.
20. Saloustros E, Nikolaou M, Kalbakis K, Polyzos A, Christofillakis C, Kentepozidis N, et al. Weekly Paclitaxel and Carboplatin Plus Bevacizumab as First-Line Treatment of Metastatic Triple-Negative Breast Cancer. A Multicenter Phase II Trial by the Hellenic Oncology Research Group. Clin Breast Cancer. 2018;18(1):88–94.
21. Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, Welch R, et al. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. Clin Breast Cancer. 2013;13(6):416–20.
22. Chew HK, Doroshow JH, Frankel P, Margolin KA, Somlo G, Lenz HJ, et al. Phase II studies of gemcitabine and cisplatin in heavily and minimally pretreated metastatic breast cancer. J Clin Oncol. 2009;27(13):2163–9.
23. Xu B, Jiang Z, Kim SB, Yu S, Feng J, Malzyner A, et al. Biweekly gemcitabine-paclitaxel, gemcitabine-carboplatin, or gemcitabine-cisplatin as first-line treatment in metastatic breast cancer after anthracycline failure: a phase II randomized selection trial. Breast Cancer. 2011;18(3):203–12.
24. Hu XC, Zhang J, Xu BH, Cai L, Ragaz J, Wang ZH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2015;16(4):436–46.
25. Vassilomanolakis M, Koumakis G, Barbounis V, Demiri M, Pateras H, Efremidis AP. Vinorelbine and cisplatin in metastatic breast cancer patients previously treated with anthracyclines. Ann Oncol. 2000;11(9):1155–60.
26. O'Shaughnessy J, Schwartzberg L, Danso MA, Miller KD, Rugo HS, Neubauer M, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. J Clin Oncol. 2014;32(34):3840–7.
27. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020;396(10265):1817–28.
28. Zhang Z. Missing data imputation: focusing on single imputation. Ann Transl Med. 2016;4(1):9.
29. Nieto FJ, Coresh J. Adjusting survival curves for confounders: a review and a new method. Am J Epidemiol. 1996;143(10):1059–68.

30. Therneau TM, Crowson CS, Atkinson EJ. Adjusted Survival Curves. 2015.
31. Heller G, Venkatraman ES. Resampling Procedures to Compare Two Survival Distributions in the Presence of Right-Censored Data. Biometrics. 1996;52(4):1204–13.
32. Egger SJ, Chan MMK, Luo Q, Wilcken N. Platinum-containing regimens for triple-negative metastatic breast cancer. Cochrane Database Syst Rev. 2020;10:CD013750.
33. Pandy JGP, Balolong-Garcia JC, Cruz-Ordinario MVB, Que FVF. Triple negative breast cancer and platinum-based systemic treatment: a meta-analysis and systematic review. BMC Cancer. 2019;19(1):1065.
34. Poggio F, Bruzzone M, Ceppi M, Pondé NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29(7):1497–508.
35. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, 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.
36. Vernieri C, Mennitto A, Prisciandaro M, Huber V, Milano M, Rinaldi L, et al. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict efficacy of platinum-based chemotherapy in patients with metastatic triple negative breast cancer. Sci Rep. 2018;8(1):8703.
37. Suzuki E, Sun J, Kapoor V, Jassar AS, Albelda SM. Gemcitabine has significant immunomodulatory activity in murine tumor models independent of its cytotoxic effects. Cancer Biol Ther. 2007;6(6):880–5.
38. Cortés J, André F, Gonçalves A, Kümmel S, Martín M, Schmid P, et al. IMpassion132 Phase III trial: atezolizumab and chemotherapy in early relapsing metastatic triple-negative breast cancer. Future Oncol. 2019;15(17):1951–61.
39. Diéras V, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(10):1269–82.

# Tables

**Table 1**. Patient and disease characteristics

| | Overall | CP | CG | *P* value |
|---|---|---|---|---|
| | N= 88 | N= 56 | N= 32 | |
| **Age, median (range)** | 55.9 (34-80) | 56.5 (34-79) | 55.0 (39-80) | 0.792 |
| **ECOG PS** | | | | |
| 0 | 55 (62.5) | 35 (62.5) | 20 (62.5) | 0.246 |
| 1 | 18 (20.5) | 8 (14.3) | 10 (31.2) | |
| NA | 15 (17.0) | 13 (23.2) | 2 (6.3) | |
| **BMI (Kg/m$^2$)** | | | | |
| < 25 | 41 (46.6) | 25 (44.6) | 16 (50.0) | 0.793 |
| ≥ 25 | 47 (53.4) | 31 (55.4) | 16 (50.0) | |
| **DFI (years)** | | | | |
| < 3 | 44 (50.0) | 25 (44.6) | 19 (59.4) | **0.038** |
| ≥ 3 | 33 (37.5) | 27 (48.3) | 6 (18.7) | |
| NA | 11 (12.5) | 4 (7.1) | 7 (21.9) | |
| **Previous Taxanes** | | | | |
| No | 26 (29.5) | 18 (32.1) | 8 (25.0) | 0.643 |
| Yes | 62 (70.5) | 38 (67.9) | 24 (75.0) | |
| **Previous Anthracyclines** | | | | |
| No | 22 (25.0) | 11 (19.6) | 11 (34.4) | 0.201 |
| Yes | 66 (75.0) | 45 (80.4) | 21 (65.6) | |
| **Previous Carboplatin** | | | | 0.617 |
| No | 85 (96.6) | 55 (98.2) | 30 (93.7) | |
| Yes | 3 (3.4) | 1 (1.8) | 2 (6.3) | |
| ***De novo* metastatic disease** | | | | |
| No | 79 (89.8) | 53 (94.6) | 26 (81.3) | 0.103 |
| Yes | 9 (10.2) | 3 (5.4) | 6 (18.7) | |
| **N. metastatic sites** | | | | 0.720 |
| 1-3 | 74 (84.1) | 46 (82.1) | 28 (87.5) | |
| >3 | 14 (15.9) | 10 (17.9) | 4 (12.5) | |
| **Visceral disease** | | | | |

| | | | | |
|---|---|---|---|---|
| No | 32 (36.4) | 20 (35.7) | 12 (37.5) | 1.000 |
| Yes | 56 (63.6) | 36 (64.3) | 20 (62.5) | |
| **Liver metastasis** | | | | |
| No | 66 (75.0) | 44 (78.6) | 22 (68.8) | 0.443 |
| Yes | 22 (25.0) | 12 (21.4) | 10 (31.2) | |
| **Lung metastasis** | | | | |
| No | 43 (48.9) | 25 (44.6) | 18 (56.2) | 0.409 |
| Yes | 45 (51.1) | 31 (55.4) | 14 (43.8) | |
| **Bone metastasis** | | | | |
| No | 42 (47.7) | 25 (44.6) | 17 (53.1) | 0.586 |
| Yes | 46 (52.3) | 31 (55.4) | 15 (46.9) | |
| **Brain metastasis** | | | | |
| No | 80 (90.9) | 51 (91.1) | 29 (90.6) | 1.000 |
| Yes | 8 (9.1) | 5 (8.9) | 3 (9.4) | |

Data are presented as n (%) except where otherwise specified. The p value of the unpaired t-test (age) or $\chi 2$ test (other variables) is indicated in bold numbers when statistically significant. In case of not available (NA) information for specific variables, the p value refers to the $\chi 2$ test performed after excluding patients with NA data.

Abbreviations: BMI: body mass index; CG: Carboplatin plus Gemcitabine; CP: Carboplatin plus Paclitaxel; DFI: Disease Free Interval; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status.

**Table 2**. Multivariable analysis for PFS.

| Variables | HR | 95% CI | *P* value |
|---|---|---|---|
| Type of treatment<br>CG *vs.* CP | 0.49 | 0.27 – 0.87 | 0.014 |
| Age (years)<br>≤ 65 *vs.* > 65 | 1.20 | 0.58 – 0.87 | 0.624 |
| ECOG PS* | 1.36 | 0.72 – 2.51 | 0.342 |
| BMI ($kg/m^2$)<br>≥ 25 *vs.* < 25 | 0.60 | 0.34 – 1.07 | 0.083 |
| Previous taxanes<br>Yes *vs.* No | 1.99 | 0.92 – 4.31 | 0.079 |
| Previous anthracyclines<br>Yes *vs.* No | 0.51 | 0.25 – 1.04 | 0.064 |
| DFI (years)* | 0.99 | 0.98 – 1.00 | 0.073 |
| *De novo* metastatic disease<br>No *vs.* Yes | 3.93 | 1.18 – 13.11 | 0.026 |
| N° of metastatic sites<br>> 3 *vs.* ≤ 3 | 2.70 | 1.09 – 6.66 | 0.032 |
| Lung metastasis<br>Yes *vs.* No | 0.78 | 0.45 – 1.36 | 0.380 |
| Liver metastasis<br>Yes *vs.* No | 1.57 | 0.85 – 2.90 | 0.147 |
| Brain metastasis<br>Yes *vs.* No | 1.46 | 0.62 – 3.46 | 0.391 |
| Bone metastasis<br>Yes *vs.* No | 0.86 | 0.52 – 1.44 | 0.564 |

*Covariates with imputed data are evaluated as continuous variables. The p value is indicated in bold numbers when statistically significant.

Abbreviations: BMI: Body Mass Index; CG: Carboplatin plus Gemcitabine; CI: Confidence Interval; CP: Carboplatin plus Paclitaxel; DFI: Disease Free Interval; ECOG PS: Eastern Cooperative Oncology Group

Performance Status; HR: Hazard Ratio.

**Table 3**. Multivariable analysis for OS.

| Variables | HR | 95% CI | *P* value |
|---|---|---|---|
| Type of treatment<br>CG *vs.* CP | 0.31 | 0.15 – 0.64 | 0.002 |
| Age (years)<br>≤ 65 *vs.* > 65 | 1.63 | 0.68 – 3.91 | 0.270 |
| ECOG PS* | 5.11 | 2.34 – 11.18 | <0.001 |
| BMI (kg/m$^2$)<br>≥ 25 *vs.* < 25 | 0.72 | 0.37 – 1.39 | 0.324 |
| Previous taxanes<br>Yes *vs.* No | 2.07 | 0.93 – 4.62 | 0.075 |
| Previous anthracyclines<br>Yes *vs.* No | 0.67 | 0.30 – 1.48 | 0.319 |
| DFI (years)* | 0.99 | 0.98 – 0.99 | 0.028 |
| *De novo* metastatic disease<br>No *vs* Yes | 6.33 | 1.20 – 33.42 | 0.030 |
| N° of metastatic sites<br>> 3 *vs.* ≤ 3 | 0.80 | 0.31 – 2.07 | 0.641 |
| Lung metastasis<br>Yes *vs.* No | 2.05 | 1.07 – 3.92 | 0.031 |
| Liver metastasis<br>Yes *vs.* No | 2.37 | 1.20 – 4.68 | 0.013 |
| Brain metastasis<br>Yes *vs.* No | 1.61 | 0.60 – 4.31 | 0.344 |
| Bone metastasis<br>Yes *vs.* No | 1.40 | 0.79 – 2.50 | 0.249 |

*Covariates with imputed data are evaluated as continuous variables. The p value is indicated in bold numbers when statistically significant.

Abbreviations: BMI: Body Mass Index; CG: Carboplatin plus Gemcitabine; CI: Confidence Interval; CP: Carboplatin plus Paclitaxel; DFI: Disease Free Interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard Ratio.

**Table 4**. Multivariable model for PFS including the interaction between previous taxane exposure and type of platinum doublet

| Variables | HR | 95% CI | *P* value |
|---|---|---|---|
| Type of treatment x Previous taxanes | | | 0.091[#] |
| CG *vs.* CP | | | |
| - Previous taxanes | 0.39 | 0.21 – 0.75 | |
| - No previous taxanes | 1.20 | 0.37 - 3.88 | |
| Age (years) | 1.21 | 0.58 – 2.52 | 0.615 |
| ≤ 65 *vs.* > 65 | | | |
| ECOG PS* | 1.70 | 0.85 – 3.40 | 0.132 |
| BMI (kg/m$^2$) | 0.59 | 0.33 – 1.05 | 0.073 |
| ≥ 25 *vs.* < 25 | | | |
| Previous anthracyclines | 0.56 | 0.27 – 1.16 | 0.119 |
| Yes *vs.* No | | | |
| DFI (years)* | 0.99 | 0.99 – 1.00 | 0.110 |
| *De novo* metastatic disease | 4.86 | 1.48 – 15.98 | 0.009 |
| No *vs* Yes | | | |
| N° of metastatic sites | 2.90 | 1.18 – 7.15 | 0.021 |
| > 3 *vs.* ≤ 3 | | | |
| Lung metastasis | 0.80 | 0.46 – 1.40 | 0.438 |
| Yes *vs.* No | | | |
| Liver metastasis | 1.67 | 0.90 – 3.09 | 0.101 |
| Yes *vs.* No | | | |
| Brain metastasis | 1.42 | 0.60 – 3.36 | 0.421 |
| Yes *vs.* No | | | |
| Bone metastasis | 0.81 | 0.48 – 1.37 | 0.433 |
| Yes *vs.* No | | | |

*Covariates with imputed data are evaluated as continuous variables. [#]A threshold of significance of 0.1 was set for the interaction test. The p value is indicated in bold numbers when statistically significant.

Abbreviations: BMI: Body Mass Index; CG: Carboplatin plus Gemcitabine; CI: Confidence Interval; CP: Carboplatin plus Paclitaxel; DFI: Disease Free Interval; ECOG PS: Eastern Cooperative Oncology Group

Performance Status; HR: Hazard Ratio.

**Table 5**. Multivariable model for OS analyzing the interaction between previous taxane exposure and type of platinum doublet

| Variables | HR | 95% CI | *P* value |
|---|---|---|---|
| Type of treatment x Previous taxanes | | | 0.772[#] |
| CG *vs.* CP | | | |
| - Previous taxanes | 0.32 | 0.15 – 0.69 | |
| - No previous taxanes | 0.22 | 0.02 – 2.05 | |
| Age (years) | 1.61 | 0.67 – 3.88 | 0.286 |
| ≤ 65 *vs.* > 65 | | | |
| ECOG PS* | 4.95 | 2.20 – 11.12 | <0.001 |
| BMI (kg/m$^2$) | 0.73 | 0.37 – 1.42 | 0.349 |
| ≥ 25 *vs.* < 25 | | | |
| Previous anthracyclines | 0.65 | 0.29 – 1.46 | 0.300 |
| Yes *vs.* No | | | |
| DFI (years)* | 0.99 | 0.98 – 0.99 | 0.028 |
| *De novo* metastatic disease | 6.25 | 1.17 – 33.33 | 0.032 |
| No *vs* Yes | | | |
| N° of metastatic sites | 0.80 | 0.31 – 2.06 | 0.639 |
| > 3 *vs.* ≤ 3 | | | |
| Lung metastasis | 2.01 | 1.04 – 3.89 | 0.040 |
| Yes *vs.* No | | | |
| Liver metastasis | 2.35 | 1.19 – 4.65 | 0.014 |
| Yes *vs.* No | | | |
| Brain metastasis | 1.60 | 0.60 – 4.29 | 0.350 |
| Yes *vs.* No | | | |
| Bone metastasis | 1.41 | 0.79 – 2.52 | 0.244 |
| Yes *vs.* No | | | |

*Covariates with imputed data are evaluated as continuous variables. #A threshold of significance of 0.1 was set for the interaction test. The p value is indicated in bold numbers when statistically significant.

Abbreviations: BMI: Body Mass Index; CG: Carboplatin plus Gemcitabine; CI: Confidence Interval; CP: Carboplatin plus Paclitaxel; DFI: Disease Free Interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard Ratio.

**Table 6**. Treatment-related adverse events in the CG and CP cohorts.

| AEs | Any Grade | | *P* value | Grade ≥ 3 | | *P* value |
|---|---|---|---|---|---|---|
| | CP | CG | | CP | CG | |
| | N= 56 | N= 32 | | N= 56 | N= 32 | |
| **Anemia** | | | 0.345 | | | |
| No | 13 (23.2) | 4 (12.5) | | 51 (91.1) | 30 (93.8) | 0.970 |
| Yes | 43 (76.8) | 28 (87.5) | | 5 (8.9) | 2 (6.2) | |
| **Neutropenia** | | | **0.021** | | | |
| No | 19 (33.9) | 3 (9.4) | | 49 (87.5) | 13 (40.6) | **<0.001** |
| Yes | 37 (66.1) | 29 (90.6) | | 7 (12.5) | 19 (59.4) | |
| **Thrombocytopenia** | | | **<0.001** | | | |
| No | 48 (85.7) | 13 (40.6) | | 55 (98.2) | 26 (81.3) | **0.016** |
| Yes | 8 (14.3) | 19 (59.4) | | 1 (1.8) | 6 (18.7) | |
| **Peripheral neuropathy** | | | **0.013** | | | |
| No | 41 (73.2) | 31 (96.9) | | - | - | - |
| Yes | 15 (26.8) | 1 (3.1) | | | | |
| **Diarrhea** | | | 0.970 | | | |
| No | 51 (91.1) | 30 (93.8) | | - | - | - |
| Yes | 5 (8.9) | 2 (6.2) | | | | |
| **Constipation** | | | 0.970 | | | |
| No | 51 (91.1) | 30 (93.8) | | - | - | - |
| Yes | 5 (8.9) | 2 (6.2) | | | | |
| **Nausea** | | | 0.270 | | | |
| No | 41 (73.2) | 19 (59.4) | | - | - | - |
| Yes | 15 (26.8) | 13 (40.6) | | | | |
| **Vomiting** | | | 0.868 | | | |
| No | 51 (91.1) | 28 (87.5) | | - | - | - |
| Yes | 5 (8.9) | 4 (12.5) | | | | |
| **Mucositis** | | | 0.617 | | | |
| No | 55 (98.2) | 30 (93.8) | | - | - | - |
| Yes | 1 (1.8) | 2 (6.2) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Fatigue** | | | **0.024** | | | |
| No | 38 (67.9) | 13 (40.6) | | 55 (98.2) | 31 (96.9) | 1.000 |
| Yes | 18 (32.1) | 19 (59.4) | | 1 (1.8) | 1 (3.1) | |
| **AST increase** | | | 0.073 | | | |
| No | 46 (82.1) | 20 (62.5) | | - | - | - |
| Yes | 10 (17.9) | 12 (37.5) | | | | |
| **ALT increase** | | | **0.001** | | | |
| No | 45 (80.4) | 14 (43.8) | | 56 (100) | 30 (93.8) | 0.251 |
| Yes | 11 (19.6) | 18 (56.2) | | 0 (0) | 2 (6.2) | |
| **Infusion-related reaction** | | | - | | | |
| No | - | - | | 55 (98.2) | 32 (100) | 1.000 |
| Yes | | | | 1 (1.8) | 0 (0) | |

Data are presented as n (%) except where otherwise specified. The p value of the χ2 test assessing the association between each AE and the type of treatment received is indicated in the right column of the table. The p value is indicated in bold numbers when statistically significant.

Abbreviations: AE: Adverse Event; CG: Carboplatin plus Gemcitabine; CP: Carboplatin plus Paclitaxel.

# Figures

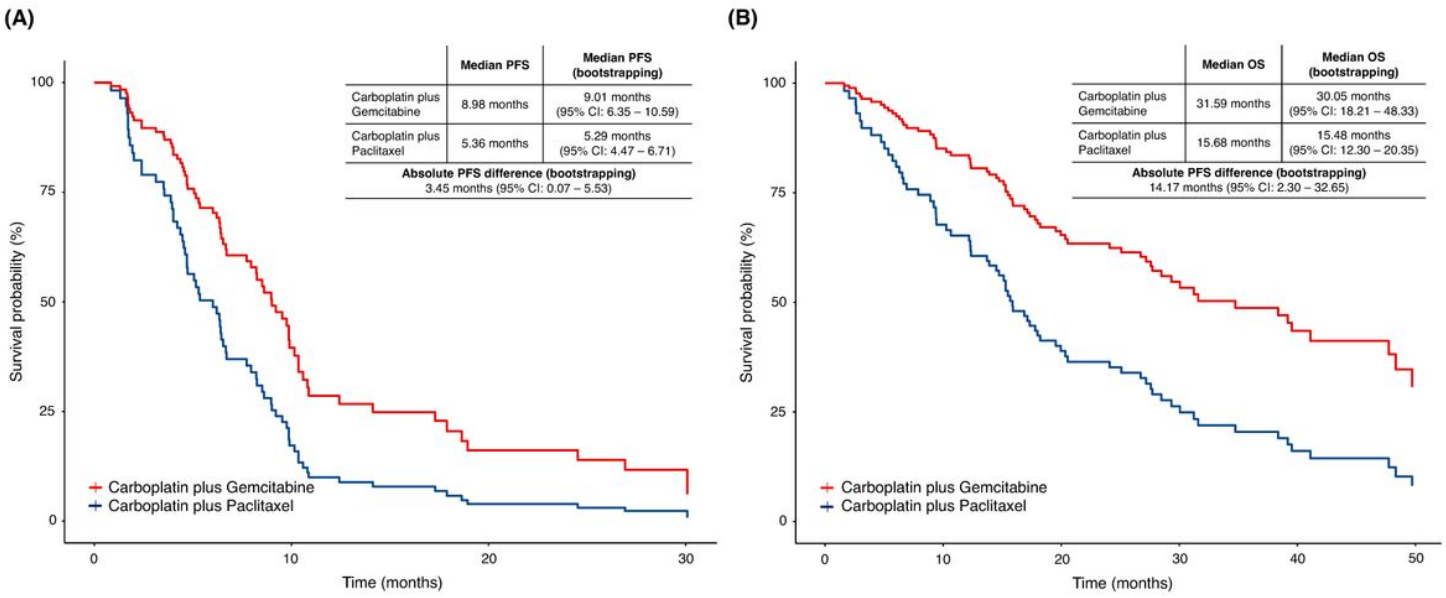


**Figure 1**

Progression free survival (PFS) and overall survival (OS) curves according to first line chemotherapy (Carboplatin plus Paclitaxel *vs.* Carboplatin plus Gemcitabine) and adjusted for multivariable Cox model.

**A:** Adjusted PFS curves; **B:** Adjusted OS curves.

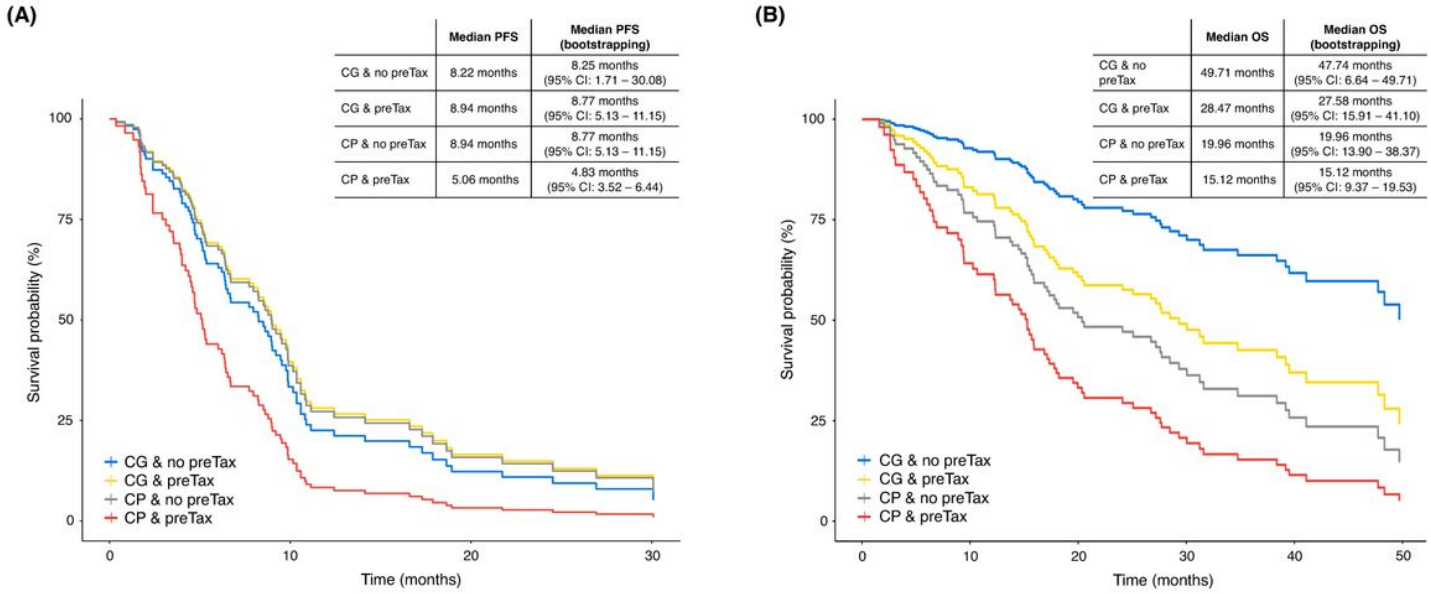


**Figure 2**

Progression free survival (PFS) and overall survival (OS) curves adjusted for multivariable Cox model, stratified on type of first line platinum-based chemotherapy (Carboplatin plus Paclitaxel (CP) *vs.* Carboplatin plus Gemcitabine (CG)) and previous taxane exposure (preTax *vs.* no preTax).

**A:** Adjusted PFS curves; **B:** Adjusted OS curves.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx