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ORIGINAL RESEARCH

Long-term outcomes of a randomized, open-label, phase II study comparing cabazitaxel versus paclitaxel as neoadjuvant treatment in patients with triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE)

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Background: The GENEVIEVE study, comparing neoadjuvant cabazitaxel versus paclitaxel in triple-negative breast cancer (TNBC) and luminal B/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC), previously reported significant differences in pathological complete response (pCR) rates. Effects on long-term outcome are unknown.

Patients and methods: GENEVIEVE randomized patients with cT2-3, any cN or cT1, cN+/pN_{SLN}+, centrally confirmed TNBC or luminal B/HER2-negative BC (latter defined as estrogen/progesterone receptor-positive and >14% Ki-67-stained cells) to receive either cabazitaxel 25 mg/m^2 q3w for four cycles or paclitaxel 80 mg/m^2 weekly for 12 weeks. Anthracycline-containing chemotherapy was allowed in case of histologically proven invasive residuals as neoadjuvant treatment or after surgery as adjuvant treatment. Here we report the secondary endpoints invasive disease-free survival (iDFS), distant disease-free survival (DDFS), and overall survival (OS).

Results: Of the 333 patients randomized, 74.7% and 83.2% completed treatment in the cabazitaxel and paclitaxel arms, respectively. After a median follow-up of 89.3 months (interquartile range 68.8-97.3 months), 80 iDFS events (43 after cabazitaxel and 37 after paclitaxel) and 47 deaths (23 after cabazitaxel and 24 after paclitaxel) were reported. IDFS rates were not significantly different between the cabazitaxel and paclitaxel arms after a 3-year (83.6% versus 85.0%) and 5-year follow-up (76.2% versus 78.3%) [hazard ratio (HR) = 1.27, 95% confidence interval 0.82-1.96, $P = 0.294$], respectively. DDFS rates at 3 years (88.6% versus 87.8%) and 5 years (82.1% versus 82.8%) for cabazitaxel and paclitaxel were comparable (HR = 1.15, $P = 0.573$). Similarly, OS rates at 3 years (91.6% versus 91.8%) and 5 years (89.2% versus 86.8%) showed no significant differences (HR = 1.05, $P = 0.872$). Subgroup analysis for TNBC and luminal B/HER2-negative BCs indicated no significant variations in 3- or 5-year iDFS, DDFS, or OS.

Conclusions: The significant differences in pCR rates observed in both treatment arms did not significantly impact long-term outcomes for patients treated with cabazitaxel versus paclitaxel in the GENEVIEVE trial.

Key words: breast cancer, HER2-negative, cabazitaxel, paclitaxel, survival

INTRODUCTION

Neoadjuvant treatment of breast cancer (BC) has become an established therapeutic approach, especially for aggressive subtypes, such as triple-negative BC (TNBC), human epidermal growth factor receptor 2 (HER2)-positive BC, or locally advanced cases. In the era of individualized therapy,

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the preoperative phase is increasingly being used to de-escalate surgical interventions and provide prognostic information for tailoring further systemic therapy.[1,2] Pathological complete response (pCR) is one of the factors that strongly influences long-term outcomes. Several meta-analyses have shown that achieving pCR following neoadjuvant therapy correlates with patient outcomes, such as improved event-free and overall survival (OS) rates.[3-7]

In addition to anthracyclines, taxanes are established as a standard component of the (neo)adjuvant chemotherapy regimen for BC. Sequential protocols of anthracycline plus cyclophosphamide followed by weekly paclitaxel are comparably effective as the reverse sequence starting with taxane, followed by an anthracycline-containing regimen.[8-11] Moreover, the GeparSepto trial demonstrated that nab-paclitaxel, a solvent-free formulation, significantly increased the proportion of patients achieving a pCR and improved disease-free survival (DFS) compared to solvent-based paclitaxel followed by anthracycline-based chemotherapy.[12,13]

Drug resistance compromises the antitumor efficacy of paclitaxel and docetaxel formulations. As a second-generation taxane, cabazitaxel has shown *in vitro* and *in vivo* activity in cell lines and tumors that are resistant to docetaxel and paclitaxel.[14] Owing to its structure, cabazitaxel has a low affinity for the P-glycoprotein efflux pump, and, as a consequence, has the potential to overcome taxane resistance.[15,16]

Cabazitaxel is approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients with progressive disease during or after docetaxel-based therapy[17] and sequential therapy with cabazitaxel significantly improves OS in that situation.[18] In metastatic BC, two phase II trials demonstrated promising results, in terms of response rates and safety, for the use of cabazitaxel in patients previously treated with taxanes, especially those with taxane resistance.[19,20] However, an open-label phase II/III trial with 3-weekly cabazitaxel versus weekly paclitaxel in patients with HER2-negative metastatic BC revealed comparable progression-free survival (PFS) and OS between both arms.[21]

Before the GENEVIEVE phase II trial started, no data for cabazitaxel in the neoadjuvant treatment of patients with operable TNBC or luminal B/HER2-negative BC were published. Results of the primary endpoint analysis were published previously and showed a significantly lower pCR rate (1.2% versus 10.8%; $P = 0.001$) and significantly more hematological and non-hematological toxicities in the cabazitaxel arm compared to the paclitaxel arm, although there were no differences in drug exposure and patient compliance.[22] The follow-up of survival parameters is important to rule out the potential detrimental effects of cabazitaxel.

In the present analysis, we report the secondary endpoints of invasive DFS (iDFS), distant DFS (DDFS), OS, and locoregional recurrence-free interval (LRRFI) in the GENEVIEVE trial.

PATIENTS AND METHODS

The GENEVIEVE trial (NCT01779479) is a prospective, multicenter, randomized, open-label, phase II study that assessed the efficacy and safety of 3-weekly cabazitaxel versus weekly paclitaxel administered as neoadjuvant treatment in primary invasive HER2-negative BC. Patients with stage cT2-3, any cN or cT1cN+/pN_{SLN}+, and centrally confirmed TNBC or luminal B/HER2-negative BC (the latter defined as estrogen receptor and/or progesterone receptor-positive and $>$ 14% Ki-67-stained cells) before enrollment were included in the study. The details of the trial design have been previously published.[22]

Patients were randomly assigned 1 : 1 using the Pocock minimization method and a computerized system to receive either cabazitaxel 25 mg/m^2 on day 1 every 3 weeks for a total of four cycles or paclitaxel 80 mg/m^2 weekly for 12 weeks as study treatment followed by surgery and adjuvant epirubicin and cyclophosphamide (EC) as per the investigator's decision (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103009). After an amendment, patients received anthracycline-containing chemotherapy as additional neoadjuvant treatment before surgery, if a core biopsy detected invasive tumor residuals after the end of the study treatment. In case of a negative core biopsy result, surgery was carried out to obtain histological confirmation, and EC was given after surgery when indicated (Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2024.103009). Treatment with cabazitaxel or paclitaxel was continued until proof of non-pCR by core biopsy, surgery, disease progression, unacceptable toxicity, or patients' withdrawal of consent. The trial was conducted in 44 sites in Germany and completed its planned duration.

The trial protocol was reviewed and approved by all independent ethics committees and authorities. Written informed consent was obtained from all patients. Stratification was carried out according to the nodal stage status [cN0 versus c(p)N+] and BC subtype (TNBC versus luminal B/HER-negative BC).

The primary endpoint analysis of the pCR rate, defined as the complete absence of invasive carcinoma on histological examination of the breast, was recently published.[22] The pCR rate was independent of lymph node involvement (ypT0/is ypN0/+) at the time of the final surgery and was confirmed by an independent, blinded, centralized review of the histology report.

Secondary endpoints included in the final analysis were iDFS, DDFS, OS, and LRRFI, and they were defined as the time between randomization and the first event.

Sample size was estimated assuming a pCR rate of 15%, in controls (GBG database) and targeting a clinical improvement of 10% (i.e. pCR = 25% in the experimental arm); a total of 326 patients (163 per arm) were required for the one-sided Fisher's exact test ($\alpha = 0.1$). Accounting for 2% of patients randomized but not treated, a total of 332 randomized patients were needed.

All patients who started therapy after randomization were included in the modified intent-to-treat (ITT) population. Analyses of the time-to-event endpoints were planned with a mature follow-up of at least 5 years with a completion rate of at least 70%. Differences in iDFS, DDFS, and OS between

the treatment arms were analyzed using the log-rank test and were visualized using Kaplan—Meier curves. The Cox proportional hazard model was used to estimate the hazard ratio (HR) of cabazitaxel to paclitaxel with a 95% confidence interval (CI). The significance level for the secondary endpoints was set to a two-sided $\alpha = 0.05$.

RESULTS

After a median follow-up of 89.3 months (interquartile range 68.8-97.3 months), 80 iDFS events (43 after cabazitaxel and 37 after paclitaxel) and 11 deaths without previous event (7 after cabazitaxel and 4 after paclitaxel) were reported in 333 patients. Invasive locoregional relapse occurred in 15 patients treated with cabazitaxel and 13 patients treated with paclitaxel. Secondary malignancies were observed in 10 cases (5 after cabazitaxel and 5 after paclitaxel). In total, 47 deaths (23 after cabazitaxel and 24 after paclitaxel) were reported. The types of recurrence as the first invasive disease event are shown in Table 1. Baseline characteristics of patients have been reported previously[22] and are shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103009.

No significant difference was observed in the 3-year (83.6% cabazitaxel versus 85.0% paclitaxel) and 5-year (76.2% cabazitaxel versus 78.3% paclitaxel) iDFS rates between the treatment arms (HR = 1.27, 95% CI 0.82-1.96, $P = 0.294$) (Figure 1). Similarly, the 3-year (88.6% cabazitaxel versus 87.8% paclitaxel) and 5-year (82.1% cabazitaxel versus 82.8% paclitaxel) DDFS rates (HR = 1.15, 95% CI 0.71-1.86, $P = 0.573$) (Figure 2) and LRRFI (HR = 1.124, 95% CI 0.54-2.33, $P = 0.753$) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103009) were comparable between the two arms. In concordance with these findings, no significant differences were reported in the 3-year (91.6% cabazitaxel versus 91.8% paclitaxel) and 5-year (89.2% cabazitaxel versus 86.8% paclitaxel) OS rates between the treatment arms (HR = 1.05, 95% CI 0.59-1.86, $P = 0.872$) (Figure 3).

As shown in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.103009, in the cabazitaxel arm, 83 patients (50%) underwent surgery immediately after cabazitaxel while 78 patients (47%) received additional EC as neoadjuvant chemotherapy due to the detection of invasive tumor residuals after the end of the study treatment. In the paclitaxel arm, 88 patients (53%) underwent surgery after paclitaxel and 77 patients (46%) received additional EC as neoadjuvant chemotherapy. Of those who underwent surgery directly, more patients in the paclitaxel arm achieved a pCR in comparison to patients in the cabazitaxel arm [17/88 patients (19.3%) versus 2/83 patients (2.4%), respectively]. Most patients who did not achieve pCR following immediate surgery received adjuvant EC in both arms [59/81 (73%) in the cabazitaxel arm and 56/71 (79%) in the paclitaxel arm].

Patients who received additional neoadjuvant EC before surgery achieved virtually no pCR (0% in the cabazitaxel arm and 1% in the paclitaxel arm). Most of these patients went on to receive non-EC adjuvant therapy (77% in the cabazitaxel arm and 73% in the paclitaxel arm) as opposed to EC adjuvant therapy (19% in the cabazitaxel arm and 27% in the paclitaxel arm). The types of additional neoadjuvant and adjuvant chemotherapy received by patients in both arms are summarized in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103009.

Table 1. First event details

First event of the patient	Cabazitaxel, $N = 166$ *n* (%)	Paclitaxel, $N = 167$ *n* (%)	Overall, $N = 333$ *n* (%)
Patient with no events	123 (74.1)	130 (77.8)	253 (76.0)
Site of first invasive disease event	43 (25.9)	37 (22.2)	80 (24.0)
- Distant relapse	14 (8.4)	14 (8.4)	28 (8.4)
- Invasive locoregional relapse	15 (9.0)	13 (7.8)	28 (8.4)
- Invasive contralateral breast cancer	2 (1.2)	1 (0.6)	3 (0.9)
- Secondary malignancy	5 (3.0)	5 (3.0)	10 (3.0)
- Death without previous event	7 (4.2)	4 (2.4)	11 (3.3)

Explorative landmark analyses stratified by pCR showed no significant differences in iDFS, DDFS, and OS, neither overall nor in the TNBC and luminal subgroup analyses. In the overall population of patients receiving additional EC before surgery, iDFS was significantly higher in the paclitaxel arm (HR 2.296, $P = 0.020$), and a similar trend was observed for DDFS (overall: HR = 1.93, $P = 0.1$; subgroup TNBC: HR = 6.239, $P = 0.087$) Moreover, iDFS was significantly higher in the paclitaxel arm (HR = 11.75, $P = 0.018$) for patients with TNBC who received additional neoadjuvant EC compared to paclitaxel.

In contrast, landmark analyses for patients who underwent surgery immediately after study medication showed significantly better iDFS and OS in the cabazitaxel group (HR = 0.311, $P = 0.04$, and HR = 0.122, $P = 0.045$, respectively), and a trend was observed for DDFS in the luminal subgroup (HR = 0.169, $P = 0.1$). Moreover, iDFS was significantly higher in the cabazitaxel arm (HR = 0.118, $P = 0.044$) for the luminal subgroup. The addition of adjuvant chemotherapy showed no significant differences in survival outcomes between the overall population and the TNBC and luminal BC subgroups.

Subgroup analysis for TNBC and luminal B/HER2-negative BCs did not show any significant differences in the 3- or 5-year iDFS, DDFS, or OS. Despite the lack of a significant difference in iDFS in the TNBC subgroup, a higher number of iDFS events was observed in the cabazitaxel arm compared to the paclitaxel arm in this subgroup (20 versus 12 events, respectively, $P = 0.097$) (Figure 4).

Regarding the effect of covariates, as expected, nodal status at baseline [27.5% cN0 versus 72.5% c(p)N+), 95% CI 1.13-3.02, $P = 0.014$] and clinical tumor stage (93.8% cT1-2 versus 6.3% cT3, 95% CI 1.33-8.22, $P = 0.010$) were significant prognostic factors for iDFS (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103009). DDFS was significantly affected by tumor stage (92.4% cT1-2 versus 7.6% cT3, 95% CI 1.63-10.22, $P = 0.003$),

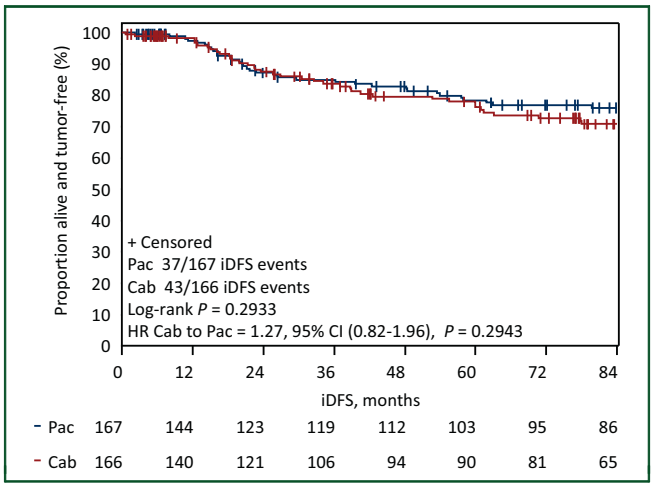

Figure 1. Kaplan–Meier curves comparing both treatment groups for iDFS. Cab, cabazitaxel; HR, hazard ratio; iDFS, invasive disease-free survival; Pac, paclitaxel.

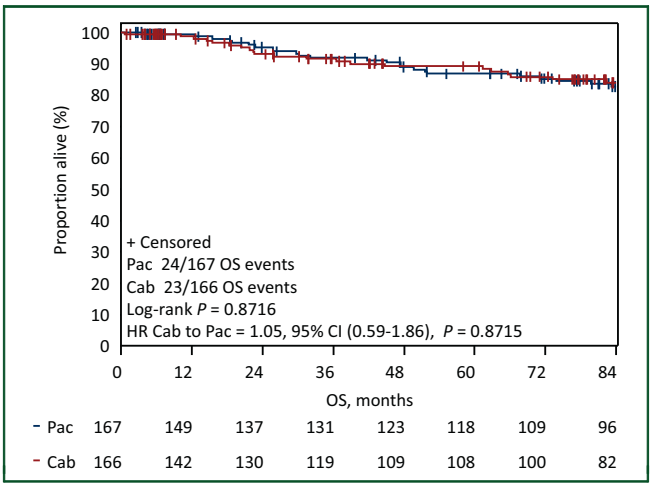

Figure 3. Kaplan–Meier curves comparing both treatment groups for OS. Cab, cabazitaxel; HR, hazard ratio; OS, overall survival; Pac, paclitaxel.

histological tumor type (89.4% other versus 10.6% lobular invasive, 95% CI 1.01-4.83, $P = 0.049$), and Ki-67 (%) (3.0% $\leq$ 14% versus 97.0% >14%, 95% CI 0.05-0.85, $P = 0.028$) (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103009). For OS, a significant influence was observed for the covariates tumor stage (91.5% cT1-2 versus 8.5% cT3, 95% CI 1.72-13.5, $P = 0.003$) and Ki-67 (%) (4.3% $\leq$ 14% versus 95.7% >14%, 95% CI 0.04-0.63, $P = 0.009$) (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.103009).

DISCUSSION

The GENEVIEVE study (NCT01779479) was the first randomized controlled phase II trial to compare neoadjuvant treatment efficacy of 3-weekly cabazitaxel to weekly paclitaxel for patients with operable TNBC or luminal B/HER2-negative BC. Despite the statistically and clinically significant pCR difference between the two treatment arms, which favors standard paclitaxel over cabazitaxel (10.8% versus 1.2%; $P = 0.001$), our results demonstrated no significant difference in clinical outcome in 3-year and 5-year iDFS (HR = 1.27, 95% CI 0.82-1.96, $P = 0.294$) as well as OS (HR = 1.05, 95% CI 0.59-1.86, $P = 0.872$) between the two treatment arms.

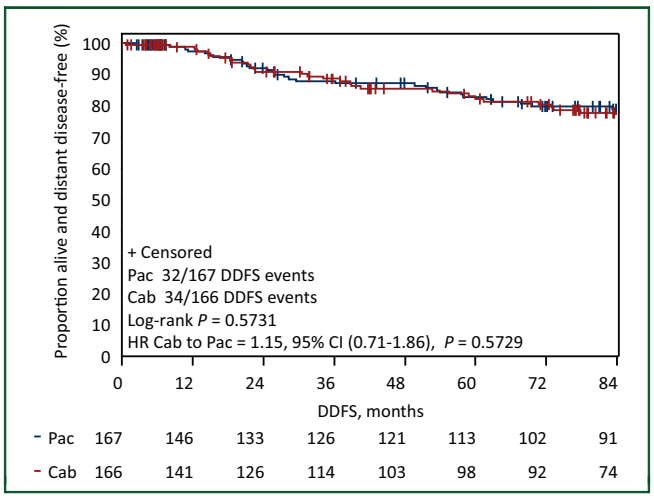

Figure 2. Kaplan–Meier curves comparing both treatment groups for DDFS. Cab, cabazitaxel; DDFS, distant disease-free survival; HR, hazard ratio; Pac, paclitaxel.

Previous data have shown that pCR after neoadjuvant chemotherapy significantly correlates with improved event-free survival and OS, especially in TNBC and HER2-positive BC.[1,23,24] As the survival rates in the GENEVIEVE trial were not affected by the significantly lower pCR rate in patients treated with cabazitaxel, the reliability of pCR as a surrogate marker for clinical outcomes remains conflicting, even though influence from adjuvant chemotherapy in non-pCR cases can be suspected. The interpretation of the analysis is difficult as 47% of patients received EC as part of the neoadjuvant therapy. Even after the amendment that allowed presurgical treatment with EC, if a core biopsy after study treatment and before scheduled surgery demonstrated residual disease, at least half of the patients in both arms still received taxane-only as neoadjuvant treatment for 12 weeks (50% with cabazitaxel and 53% with paclitaxel; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.103009). The low percentage of additional EC in the neoadjuvant treatment might explain the overall low pCR rates. Nevertheless, out of 153 patients where prolonged neoadjuvant treatment with EC was selected, only 1 patient achieved a pCR. However, the pCR difference is not affected by the fairly equally distributed number of patients treated with each taxane.

Subgroup analysis for TNBC and luminal B/HER2-negative tumors did not reveal any significant differences in survival outcomes between the taxanes, but a trend for better iDFS was observed in favor of the paclitaxel group in the TNBC subgroup ($P = 0.097$). The explorative landmark analyses after surgery showed no clear results and must be interpreted carefully, since, depending on the choice of subgroup, paclitaxel or cabazitaxel seemed to be at an advantage. Caution must be exercised given the small number of cases. In contrast, the GeparTRIO study could not

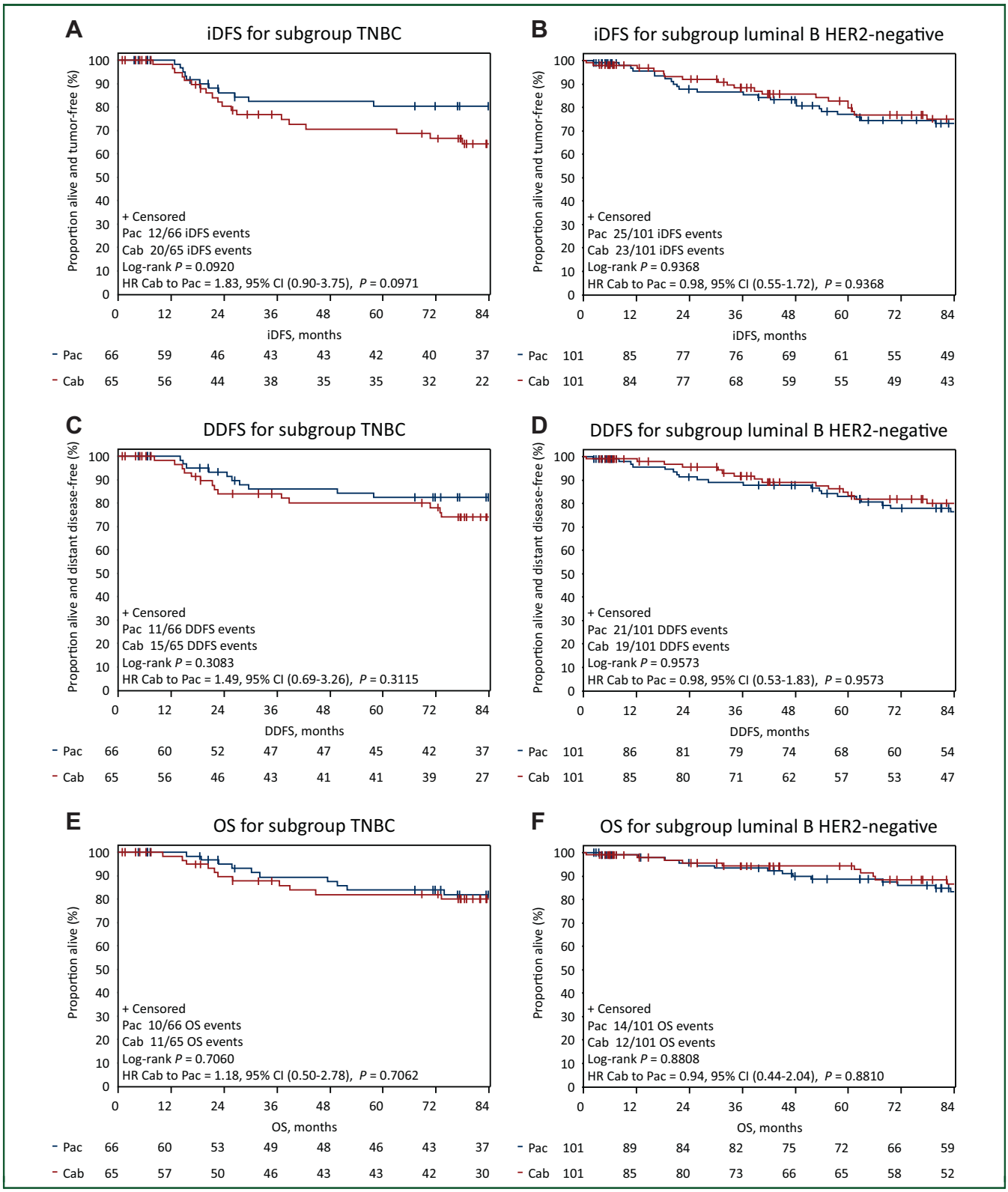

Figure 4. Survival curves for subgroups TNBC and luminal B/HER2-negative.
Cab, cabazitaxel; DDFS, distant disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival; OS, overall survival; Pac, paclitaxel; TNBC, triple-negative breast cancer.

demonstrate an increase in pCR or an improvement in long-term outcomes following a change in treatment for patients who did not respond to treatment after two cycles of TAC (docetaxel, doxorubicin, cyclophosphamide).[25] Furthermore, the Adapt TN trial with 336 patients could not demonstrate that additional post-neoadjuvant EC therapy improves survival in the TNBC subgroup.[26] It is thus difficult to put the results of the GENEVIEVE study into perspective,

as data for cabazitaxel in breast cancer are rare, and long-term efficacy of neoadjuvant therapy in patients with TNBC or luminal B/HER2-negative BC has not been reported.

In addition, the survival data for cabazitaxel in metastatic BC are limited. In a recently published open-label phase II/III study, patients ($N = 158$) were treated with six cycles of 3-weekly cabazitaxel (25 mg/m^2) or weekly paclitaxel (80 mg/m^2) over 18 weeks.[21] The PFS for patients with HER2-negative metastatic BC treated with 3-weekly cabazitaxel was comparable to that for patients receiving weekly paclitaxel (6.7 versus 5.8 months, HR = 0.87; 80% CI 0.70-1.08, $P = 0.40$). Similarly, there was no difference in the median OS (HR = 1.00, 95% CI 0.69-1.45, $P = 0.99$), although patients receiving cabazitaxel had a lower risk of peripheral neuropathy and better patient-reported quality-of-life outcomes. In the HeCOG trial, 3-weekly cabazitaxel was administered as second-line treatment in 48 patients with HER2-negative metastatic BC previously treated with taxanes. In this phase II single-arm study, the overall response rates were 22.6% in the ITT population, 23.3% in taxane-resistant cases, and 20.5% in taxane-non-resistant cases. At a median follow-up of 39.6 months, the median PFS and OS were 3.7 months (95% CI 2.2-4.4 months) and 15.2 months (95% CI 11.3-19.4 months), respectively.[20] Comparable with cabazitaxel in metastatic BC, a randomized phase III study of second-line paclitaxel as monotherapy as well as a real-world efficacy analysis of nab-paclitaxel showed PFS of 3.6 months and 4.0 months, respectively.[27,28]

The United States Food and Drug Administration and the European Medicines Agency have proposed that the results of neoadjuvant trials in high-risk populations (i.e. HER2-positive and TNBC) could contribute to accelerated drug approval. A meta-analysis of dose-dense treatments revealed an increase in pCR rates with better long-term outcomes.[29] In our study, a 3-weekly dosing schedule was chosen, which does not represent a dose-dense therapy. One hypothesis suggests that a weekly low-dose protocol could lead to a higher dose intensity and greater drug efficacy than a 3-weekly protocol. The ConCab trial in mCRPC compared a 3-weekly versus weekly dose regimen of cabazitaxel to evaluate PFS and OS. This study showed similar OS rates between the treatment arms (14.6 months versus 15.6 months, 95% CI 0.58-1.58 months, $P = 0.85$), respectively.[30]

Another factor that may influence the treatment response is the correct dosing regimen. However, it is challenging to identify the most effective dose, as the latest results of the FIRSTANA trial in mCRPC patients showed that neither 20 mg/m^2 nor 25 mg/m^2 of cabazitaxel were superior to docetaxel in terms of OS (for cabazitaxel 20 mg/m^2 HR = 1.01, 95% CI 0.85-1.20, $P = 0.997$; and for cabazitaxel 25 mg/m^2 HR = 0.97, 95% CI 0.82-1.16, $P = 0.757$).[31] Cabazitaxel-based drug delivery systems and further development of nanoformulations are promising for the treatment of cancer in preclinical and clinical settings in the future.[15]

The strength of this study lies in its randomized design and long-term follow-up, yet the study is limited by virtue of the small number of patients in the treatment arms. Additionally, the fact that a high albeit comparable proportion of patients in both treatment arms received only the study medication in the neoadjuvant setting compromises the pCR rates and the interpretation of their prognostic impact on outcome. Even though prolongation of neoadjuvant treatment with EC in case of residual disease had little to no effect at all for achieving a pCR, potential impact of further EC irrespective if applied adjuvantly or neoadjuvanly in case of non-pCR is to be considered.

In conclusion, the GENEVIEVE study, with a median follow-up of 89 months, demonstrated comparable long-term survival outcomes in patients with TNBC or luminal B/HER2-negative primary BC treated with cabazitaxel versus paclitaxel as neoadjuvant therapy which were not affected by the significantly lower pCR rate in the cabazitaxel arm. In view of a less favorable toxicity profile, cabazitaxel is not a convincing alternative to standard paclitaxel in this treatment setting.

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DISCLOSURE

MU declares honoraria from AstraZeneca, Art tempi, Amgen, Daiji Sankyo, Lilly, Roche, Pfizer, MSD Oncology, Pierre Fabre, Sanofi-Aventis, Myriad, Seagen, Gilead, Novartis, Stemline and to operate in a consulting or advisory role for Amgen, Lilly, Roche, Pfizer, Lilly, Pierre Fabre, Novartis, MSD Oncology, Roche, Agendia, Seagen, Gilead, Lily, Stemline, Genzyme and Onkowissen.de. All honoraria and fees are paid to the employer/institution. TL has received honoraria from Amgen, Roche, MSD, Novartis, Pfizer, Lilly, GSK, Gilead, AstraZeneca, Daiichi-Sankyo and non-financial support from Pfizer, AstraZeneca, Gilead, Daiichi-Sankyo and Stemline. TL participates in advisory boards from MSD, Roche, Pfizer, Lilly, Myriad, Esai, GSK, Gilead, Daiichi-Sankyo and Roche. CH reports honoraria as speaker/advisory board member from Roche, Novartis, AstraZeneca and Aristo Pharma. NF and VN declare to be GBG Forschungs GmbH employee. GBG Forschungs GmbH received funding for research grants from AbbVie, Amgen, AstraZeneca, BMS, Daiichi-Sankyo, Gilead, Molecular Health, Novartis, Pfizer and Roche (paid to the institution); other (non-financial/medical writing) from Daiichi-Sankyo, Gilead, Novartis, Pfizer, Roche and Seagen (paid to the institution). GBG Forschungs GmbH has licensing fees from VMscope GmbH. In addition, GBG Forschungs GmbH has a patent EP21152186.9 pending, a patent EP19808852.8 pending, and a patent EP14153692.0

pending. JH reports personal fees and non-financial support from Daiichi-Sankyo, non-financial support from Hologic, personal fees from MSD Oncology, personal fees from Novartis, personal fees from Palleos Health Care, personal fees from Pfizer, personal fees from Roche Pharma, personal fees from Seagen, outside the submitted work; he also declares to be GBG Forschungs GmbH employee. GBG Forschungs GmbH received funding for research grants from AbbVie, AstraZeneca, BMS, Daiichi-Sankyo, Gilead, Novartis, Pfizer and Roche (paid to the institution); other (non-financial/medical writing) from Daiichi-Sankyo, Gilead, Novartis, Pfizer, Roche and Seagen (paid to the institution). GBG Forschungs GmbH has following royalties/patents: EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8 and VM Scope GmbH. SL declares to be GBG Forschungs GmbH employee (CEO); receives grants from AbbVie, AstraZeneca, Celgene, Daiichi-Sankyo, Immunomedics/Gilead, Molecular Health, Novartis, Pfizer and Roche; honoraria for advisory board from AbbVie, Amgen, AstraZeneca, BMS, Celgene, DSI, EirGenix, Gilead, GSK, Lilly, Merck, Novartis, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Roche, Sanofi and Seagen; honoraria as invented speaker from AstraZeneca, DSI, Gilead, Novartis, Pfizer, Roche, Seage and Medscape. SL reports non-financial interest as advisory role in AGO Kommission Mamma, as principal investigator (Aphinity), as member in AGO, ASCO, DKG, ESMO and other non-financial interest from AstraZeneca, Daiichi-Sankyo, immunomedica/Gilead, Novartis, Pfizer, Roche and Seagen. GBG Forschungs GmbH has following royalties/patents: EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8 and VM Scope GmbH. All other authors have declared no conflicts of interest.

DATA SHARING

All relevant data are within the paper and its supporting information files. The data underlying the results presented in the study are available from GBG. Some restrictions apply due to confidentiality of patient data. Since these data are derived from a prospective clinical trial with ongoing follow-up collection, there are legal and ethical restrictions to sharing sensitive patient-related data publicly. Interested groups may request the 'Cooperation Proposal Form' from trafo@gbg.de.

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