Original Research

Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto—GBG 84): A randomised phase III trial☆

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Abstract **Background:** GeparOcto compared efficacy and safety of two chemotherapy regimens in high-risk early breast cancer (BC): sequential treatment with intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddEPC) and weekly treatment with paclitaxel plus non-pegylated liposomal doxorubicin (M, Myocet®) with additional carboplatin (PM(Cb)) in triple-negative BC (TNBC).

Patients and methods: Patients with cT1c-cT4a-d and centrally assessed human epidermal growth factor receptor (HER)2-positive BC or TNBC were eligible, irrespective of nodal status, luminal B-like tumours only if pN+.

Patients were randomised (stratified by BC subtype, Ki67, lymphocyte-predominant BC) to receive 18 weeks of E (150 mg/m^2) followed by P (225 mg/m^2) followed by C (2000 mg/m^2), each q2w for 3 cycles or weekly P (80 mg/m^2) plus M (20 mg/m^2) plus, in TNBC, Cb (area under curve (AUC) 1.5). HER2-positive BC patients additionally received trastuzumab (6 [loading dose 8]mg/kg q3w) and pertuzumab (420 [840]mg q3w) with all P and C cycles. Primary end-point was pathological complete response (pCR, ypT0/is ypN0), secondary end-points included other pCR definitions, pCR in stratified subpopulations, tolerability and compliance. This trial is registered with ClinicalTrials.gov number NCT02125344.

Results: 945/961 randomised patients started treatment. The median age was 48 years; 7.6% had cT3-4, 46% cN+, 66% G3, 40% HER2-positive, 43% TNBC. pCR rate with iddEPC was 48.3%, with PM(Cb) 48.0%, respectively (PM(Cb) versus iddEPC odds ratio 0.99; 95% confidence interval 0.77—1.28, $P = 0.979$) with no significant differences observed in TNBC, HER2-positive, luminal B-like subtypes. 16.4% with iddEPC and 34.1% with PM(Cb) discontinued treatment ($P < 0.001$), mainly due to adverse events; two patients on PM(Cb) died.

Conclusions: In high-risk early BC there is no difference in pCR rates following neoadjuvant treatment with iddEPC or weekly PM(Cb), respectively. iddEPC is one of the effective dose-dense regimens feasible in daily practice.

1. Introduction

In patients with primary operable breast cancer (BC), adjuvant and neoadjuvant chemotherapy (NACT) are accepted as equally effective [1,2], but NACT is the clinically preferred option to improve breast conserving surgery rate and gain information on pathologic complete response (pCR) which is associated with long-term outcome [3—5].

In node-positive BC patients, the dose-dense application of sequential doxorubicin (A), paclitaxel (P) and cyclophosphamide (C) significantly prolonged overall survival (OS) compared to conventionally scheduled APC every 3 weeks [6]. Similarly, intense dose-dense (idd) sequential epirubicin, paclitaxel and cyclophosphamide (iddEPC) yielded significantly higher 5-year OS rates compared with conventionally scheduled chemotherapy in high-risk BC [7]. This effect is irrespective of oestrogen receptor (ER) status even with longer follow-up reaching 10 years [8]. In contrast, the 10-year follow-up data of the E1199/Intergroup trial showed no longer any superiority for ER+/ human epidermal growth factor receptor (HER)2-negative patients [9]. Although a direct head-to-head comparison is missing, iddEPC has become a preferred adjuvant regimen for patients with more than three positive nodes considering an absolute 10% OS benefit after 10 years follow-up [7]. Likewise, a recent meta-analysis showed that dose-dense and/or sequential administration of chemotherapy consistently improved recurrence-free, BC-specific and OS over conventionally scheduled regimens [10]. In HER2-positive disease, trastuzumab in combination with chemotherapy has been established as standard of care [11,12], and more recently, dual

blockade with pertuzumab in high-risk HER2-positive disease has shown a further improvement in pCR rates and invasive disease-free survival (DFS) [13–15]. In triple-negative breast cancer (TNBC), addition of carboplatin to anthracycline- and taxane-containing NACT also increased pCR rates [16–18]. Importantly, the higher pCR rate observed with the addition of weekly carboplatin to weekly paclitaxel and non-pegylated liposomal doxorubicin (PM(Cb)) in the GeparSixto trial (53.2% versus 36.9%; odds ratio [OR] 1.94; *P* = 0.005) translated into a significantly improved 3-year DFS [19,20]. Thus, iddEPC (concomitantly with dual blockade in HER2-positive disease) and weekly PM (plus dual blockade in HER2-positive or carboplatin in TNBC (PM(Cb)) are currently two treatment options with highest efficacy in high-risk early-stage BC. The phase III GeparOcto study compared these two regimens to define the optimal systemic treatment strategy for patients with high-risk early BC including node-positive luminal B-like disease.

2. Patients and methods

2.1. Patient selection and study design

Following written informed consent, patients with previously untreated, unilateral or bilateral, non-metastatic invasive BC were enrolled. Patients aged ≥18 years and a Karnofsky index of ≥90% were eligible, if they had clinical stage T1c-T4a-d tumours and central pathology assessment of ER, progesterone receptor (PgR), HER2 status, Ki67 and lymphocyte-predominant breast cancer (LPBC) on pretreatment core biopsy. Hormone receptor (HR)-negativity was defined as <1% stained cells and HER2-positivity as immunohistochemical staining of 3+ or in case of 2+ by a HER2 to chromosome 17 (HER2:-CEP17) ratio ≥2.0 analysed by dual-probe in-situ hybridisation. Patients with HER2-positive or TNBC were eligible irrespective of nodal status, while patients with luminal B-like tumours (defined as ER and/or PgR ≥1%, HER2-negative, Ki67 > 20%) were eligible only in case of histologically verified involved lymph nodes.

Further eligibility criteria and randomisation details are provided in Supplementary Appendix. The study protocol was approved by the responsible ethics committee and the relevant competent authority.

Patients were randomised centrally at the German Breast Group headquarters in a 1:1 ratio to receive either iddEPC or weekly paclitaxel in combination with non-pegylated liposomal doxorubicin with additional carboplatin in TNBC (PM(Cb)). The randomisation was stratified based on central testing by BC subtype (HER2-/HR+ versus HER2-/HR-versus HER2+), Ki67 (≤20% versus >20%) and LPBC (no [<60% stromal tumour infiltrating lymphocytes {sTIL}] versus yes [≥60% sTIL]) at baseline.

2.2. Treatment

Patients in the iddEPC arm received epirubicin 150 mg/m^2 every 2 weeks (q2w) for three cycles followed by paclitaxel 225 mg/m^2 q2w for three cycles followed by cyclophosphamide 2000 mg/m^2 q2w for three cycles. In the PM(Cb) arm, patients received paclitaxel 80 mg/m^2 weekly in combination with non-pegylated liposomal doxorubicin (M) 20 mg/m^2 weekly and, in case of TNBC, additional carboplatin AUC 1.5 weekly for 18 weeks. Patients with HER2-positive disease received trastuzumab 6 (loading dose [LD] 8) mg/kg every 3 weeks (q3w) and pertuzumab 420 (LD 840) mg q3w simultaneously to all chemotherapy cycles other than E in the iddEPC arm (Supplementary Figure S1).

Treatment continued until surgery, disease progression, unacceptable toxicity or withdrawal of consent.

2.3. Study assessments

The primary efficacy end-point was pCR defined as no residual invasive tumour cells in any resected specimens of the breast and axillary nodes (ypT0/is ypN0).

Secondary short-term efficacy end-points included other pCR definitions (ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT[any] ypN0); pCR rates in stratified subpopulations; clinical response (complete versus partial versus no change); breast conservation rate; tolerability and treatment adherence including frequency of dose delays and reductions. Long-term efficacy end-points will be reported later with sufficient follow-up.

Detailed definitions of response end-points are provided in Supplementary Appendix. Toxicity reported as adverse events (AEs) was based on NCI-CTCAE v4.0.

2.4. Statistical analysis

Sample size calculations assumed a pCR rate of 50% for iddEPC and an increase to 60% for PM(Cb), requiring 463 patients to start therapy in each arm for a continuity corrected χ2-test to show the superiority of PM(Cb) with 85% power and a two-sided α of 0.05. It was planned to recruit 950 patients (including 2.5% randomised patients expected not to start treatment and not to be included in the intent-to-treat population) with an intended equal proportion of patients with HER2-positive, triple-negative and luminal B-like tumours. Two-sided 95% confidence intervals (CIs) were calculated for the efficacy end-points according to Pearson and Clopper [21]. The difference in pCR was evaluated as rate difference (PM(Cb) arm minus iddEPC arm) with 95% CI. Additionally, an OR with 95% CI was provided. A non-inferiority test was planned if the superiority test failed to detect a significant difference. The non-inferiority margin for difference in pCR was set to 5% with non-inferiority to be claimed if the lower limit

of the two-sided 95% CI for difference in pCR was greater than −5%.

There was no adjustment for multiple comparisons in the analyses of stratified subpopulations. A Breslow–Day interaction test was performed to assess interaction between treatment arm and binary subgroup; for the BC subtype, a logistic regression with an interaction term was performed to assess interaction. Univariate and multivariate logistic regressions were performed for pCR to report OR with 95% CI and to adjust for treatment group, age, tumour size, nodal status, grade, histological type, hormone receptors and LPBC.

Secondary efficacy end-points were reported in a similar way. The proportion of patients with AEs or treatment modifications was compared using Fisher's exact test. Reasons for treatment modifications, apart from discontinuations, were not mutually exclusive. Relative total dose intensity (RTDI) was defined as the dose intensity achieved by a patient relative to intended dose intensity based on the planned schedule of chemotherapy.

Details on statistical analysis and used software are provided in Supplementary Appendix. The trial is registered with ClinicalTrials.gov number NCT02125344.

3. Results

3.1. Baseline

Between 12/2014 and 06/2016, 1204 patients were screened for eligibility, of whom 961 patients were randomised at 57 sites, and 945 started treatment. Treatment was completed by 393/470 (83.6%) patients in the iddEPC and 313/475 (65.9%) in the PM(Cb) arm ($P < 0.001$) (Fig. 1).

Median age at study entry was 48.0 (21–76) years. 382 (40.4%) patients had HER2-positive tumours, 403 (42.6%) TNBC and 160 (16.9%) high-risk luminal B/HER2-negative tumours. Baseline patient and tumour characteristics were balanced between the arms (Table 1). Additional baseline patient and tumour characteristics according to biological subtype are presented in Supplementary Table S1ABC.

3.2. Efficacy

Overall, 938 (99.3%) patients underwent surgery, and 227/470 patients who started iddEPC (48.3% [95%CI 43.7–52.9%]) achieved a pCR (ypT0/is ypN0) compared with 228/475 who started PM(Cb) (48.0% [95%CI 43.4–52.6%]; continuity corrected χ^2-test $P = 0.979$) corresponding to an OR of 0.99 (95%CI 0.77–1.28). Non-inferiority of PM(Cb) could not be claimed. There were no differences between treatment groups in pCR rates according to other definitions or other secondary efficacy end-points (Table 2).

In most of the stratified and prospectively defined subgroups, the pCR (ypT0/is ypN0) rates were not significantly different between treatment arms (Supplementary Table S2). Logistic regression analysis, however, showed a significantly higher pCR rate only in the LPBC subgroup for patients treated with iddEPC compared with PM(Cb) (OR PM(Cb) versus iddEPC 0.43; 95%CI 0.20–0.95, $P = 0.036$). The test for interaction of the treatment effect in patients with LPBC versus no LPBC on the pCR rate was significant ($P = 0.027$) (Fig. 2). Multivariable logistic regression analysis confirmed that treatment with PM(Cb) did not predict for achievement of pCR after adjustment for baseline and stratification factors (OR 0.99; 95%CI, 0.75–1.31; $P = 0.931$). Among the stratification factors, biological subtype (TNBC OR 5.39; 3.20–9.07, $P < 0.001$; HER2+ OR 9.78; 5.80–16.5, $P < 0.001$ compared to HER2-/HR+) and LPBC (OR 2.28; 1.48–3.52, $P < 0.001$ compared to no LPBC) were independent predictors for achievement of pCR. Also, age ($P = 0.022$) and grade ($P < 0.001$) were independent predictors of pCR (Supplementary Table S3A). Results on multivariable logistic regression analyses per biological subtype are presented in Supplementary Table S3BCD.

3.3. Adherence to treatment

Across all biological subgroups, treatment discontinuations were less common in patients treated with iddEPC compared with the PM(Cb) group (HER2-/HR+ 14.1% versus 30.5%, $P = 0.014$; HER2-/HR- 16.5% versus 34.5%, $P < 0.001$; HER2+ 17.2% versus 35.3%, $P < 0.001$).

The chemotherapy dose was delayed in 351 patients (74.7%) in the iddEPC arm and 420 (88.4%) patients in the PM(Cb) arm, respectively ($P < 0.001$). These delays were due to haematological toxicity in 23.2% and 31.6% ($P = 0.004$) and due to non-haematological toxicities in 26.8% and 53.7% ($P < 0.001$), respectively. The chemotherapy dose had to be reduced in 216 (46.0%) patients in the iddEPC (Supplementary Figure S2A) compared with 271 (57.1%) in the PM(Cb) arm (Supplementary Figure S2B) ($P < 0.001$), which was due to haematological toxicity in 24.3% versus 13.3% ($P < 0.001$) and due to non-haematological toxicities in 27.7% versus 43.4% ($P < 0.001$), respectively.

The described dose modifications led to the median RTDI of 94.7% in the iddEPC compared with 78.8% in PM(Cb) arm ($P < 0.001$).

3.4. Safety

Grade 3–4 haematological AEs were more frequent with iddEPC compared with PM(Cb) (423 (90.0%) versus 137 (28.8%) ($P < 0.001$)). Overall, the rates of toxic treatment effects such as anaemia, leukopenia, neutropenia, febrile neutropenia, thrombocytopaenia
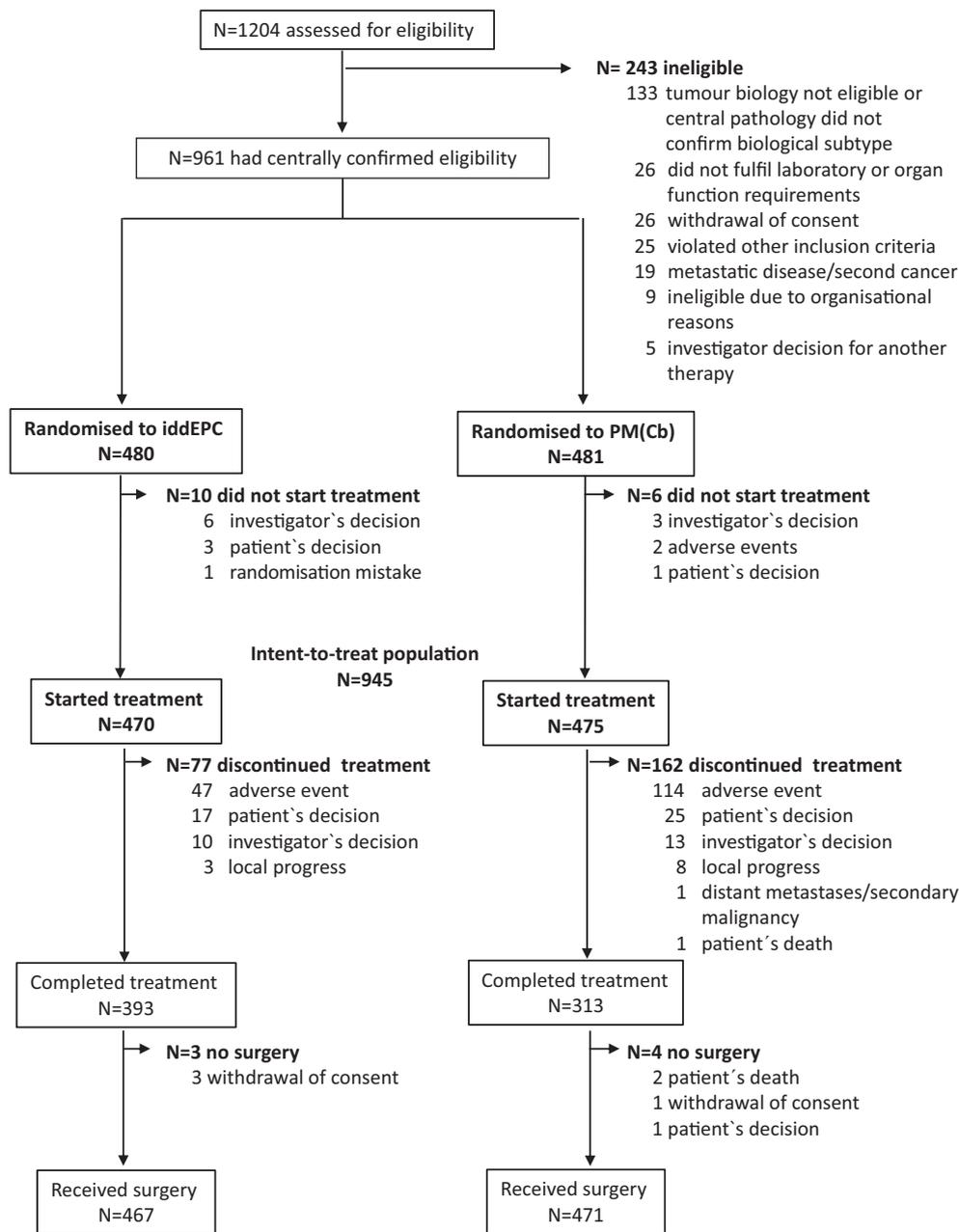
Fig. 1. Trial profile. iddEPC, intense dose-dense epirubicin, paclitaxel, and cyclophosphamide; PM(Cb), paclitaxel plus non-pegylated liposomal doxorubicin with additional carboplatin in triple-negative breast cancer.

and increased values of liver enzymes and creatinine were all higher with iddEPC. At least one non-haematological AE any grade was reported for all patients in both treatment arms. Non-haematological grade ≥ 3 AEs were higher in the PM(Cb) arm: 203 (43.2%) versus 247 (52.0%), respectively ($P = 0.008$). Among the high-grade AEs, pneumonia was reported in four (0.9%) patients in the iddEPC and 31 (6.5%) in the PM(Cb) arm ($P < 0.001$) and pneumonitis, which was a predefined AE of special interest (AESI), in 0 (0%) and 12 (2.5%), respectively ($P < 0.001$) (Table 3). Toxicity data

according to use of carboplatin or not in the PM(Cb) arm are presented in Supplementary Table S4.

Overall, 345 (36.5%) patients reported at least one serious AE, 174 (37.0%) in the iddEPC and 171 (36.0%) in the PM(Cb) arm ($P = 0.787$), and 41 (4.3%) at least one AESI, 12 (2.6%) in the iddEPC and 29 (6.1%) in the PM(Cb) arm ($P = 0.010$), which were treatment-related in 11 (2.3%) and 28 (5.9%) patients, respectively ($P = 0.008$). Two deaths under therapy occurred in the PM(Cb) arm due to pneumonia and multiple septic cerebral embolism.

Table 1
Patient and tumour characteristics at baseline.

Parameter	Category	iddEPC ($N = 470$)	PM(Cb) ($N = 475$)	Overall ($N = 945$)
Age, years	<30	12 (2.6)	17 (3.6)	29 (3.1)
	30-<40	88 (18.7)	100 (21.1)	188 (19.9)
	40-<50	158 (33.6)	154 (32.4)	312 (33.0)
	50-<60	142 (30.2)	133 (28.0)	275 (29.1)
	60-<70	60 (12.8)	63 (13.3)	123 (13.0)
	≥70	10 (2.1)	8 (1.7)	18 (1.9)
	Median (years) (range)	48.0 (23.0−76.0)	48.0 (21.0−76.0)	48.0 (21.0−76.0)
Menopausal status	Premenopausal	288 (61.3)	290 (61.1)	578 (61.2)
	Postmenopausal	182 (38.7)	185 (38.9)	367 (38.8)
Tumour stage by palpation	cT1	155 (37.9)	172 (41.1)	327 (39.5)
	cT2	202 (49.4)	196 (46.9)	398 (48.1)
	cT3	35 (8.6)	31 (7.4)	66 (8.0)
	cT4a-c	8 (2.0)	5 (1.2)	13 (1.6)
	cT4d	9 (2.2)	14 (3.3)	23 (2.8)
	Missing	61	57	118
	Median tumour size (mm) (range)	30.0 (3.0−150.0)	25.0 (1.0−150.0)	30.0 (1.0−150.0)
Tumour stage by sonography	cT1	177 (38.3)	180 (38.5)	357 (38.4)
	cT2	251 (54.3)	251 (53.6)	502 (54.0)
	cT3	17 (3.7)	18 (3.8)	35 (3.8)
	cT4a-c	8 (1.7)	5 (1.1)	13 (1.4)
	cT4d	9 (1.9)	14 (3.0)	23 (2.5)
	Missing	8	7	15
	Median tumour size (mm) (range)	24.0 (8.0−147.0)	23.0 (7.0−150.0)	23.0 (7.0−150.0)
Nodal stage by palpation	cN0	293 (63.3)	287 (62.3)	580 (62.8)
	cN1	145 (31.3)	151 (32.8)	296 (32.0)
	cN2	15 (3.2)	13 (2.8)	28 (3.0)
	cN3	10 (2.2)	10 (2.2)	20 (2.2)
	Missing	7	14	21
Nodal stage by sonography	cN0	249 (54.4)	249 (53.9)	498 (54.1)
	cN1	167 (36.5)	179 (38.7)	346 (37.6)
	cN2	20 (4.4)	18 (3.9)	38 (4.1)
	cN3	22 (4.8)	16 (3.5)	38 (4.1)
	Missing	12	13	25
Sentinel node biopsy	None	217 (46.2)	196 (41.3)	413 (43.7)
	Negative	166 (35.3)	176 (37.1)	342 (36.2)
	Positive	86 (18.3)	101 (21.3)	187 (19.8)
	None detected	1 (0.2)	2 (0.4)	3 (0.3)
Histological tumour type	Ductal or ductal-lobular invasive	382 (81.3)	392 (82.5)	774 (81.9)
	Lobular invasive	0 (0.0)	0 (0.0)	0 (0.0)
	Other	88 (18.7)	83 (17.5)	171 (18.1)
Tumour grading	G1	8 (1.7)	10 (2.1)	18 (1.9)
	G2	158 (33.6)	144 (30.3)	302 (32.0)
	G3	304 (64.7)	321 (67.6)	625 (66.1)
ER/PgR, central pathology	Both ER, PgR negative	263 (56.0)	256 (53.9)	519 (54.9)
	ER and/or PgR positive	207 (44.0)	219 (46.1)	426 (45.1)
HER2, central pathology	Negative	278 (59.1)	285 (60.0)	563 (59.6)
	Positive	192 (40.9)	190 (40.0)	382 (40.4)
Breast cancer subtype (stratification)	HER2-/HR+	78 (16.6)	82 (17.3)	160 (16.9)
	HER2-/HR-	200 (42.6)	203 (42.7)	403 (42.6)
	HER2+	192 (40.9)	190 (40.0)	382 (40.4)
Ki67, central pathology (stratification)	≤20%	29 (6.2)	31 (6.5)	60 (6.3)
	>20%	441 (93.8)	444 (93.5)	885 (93.7)
LPBC (stratification)	No	410 (87.2)	412 (86.7)	822 (87.0)
	Yes	60 (12.8)	63 (13.3)	123 (13.0)

ER, oestrogen receptor; HR, hormone receptor; PgR, progesterone receptor; HER, human epidermal growth factor receptor; LPBC, lymphocyte-predominant breast cancer; iddEPC, intense dose-dense epirubicin, paclitaxel, and cyclophosphamide; PM(Cb), paclitaxel plus non-pegylated liposomal doxorubicin with additional carboplatin in triple-negative breast cancer.
Data are N (valid %) unless otherwise stated.

Table 2
Comparison of treatment efficacy for the primary end-point (ypT0/is ypN0) and different secondary end-points.

Parameter	Category	iddEPC (N = 470)	PM(Cb) (N = 475)	PM(Cb) versus iddEPC OR (95% CI)	Unadjusted P-value[a]
ypT0/is ypN0	No	243 (51.7)	247 (52.0)		
	Yes	227 (48.3, 43.7 −52.9)	228 (48.0, 43.4 −52.6)	0.99 (0.77−1.28)	0.927
	Difference, 95% CI[b]	−0.3% (−6.7%, 6.1%)			
ypT0 ypN0	No	275 (58.5)	269 (56.6)		
	Yes	195 (41.5, 37.0 −46.1)	206 (43.4, 38.9 −48.0)	1.08 (0.83−1.40)	0.559
ypT0 ypN0/+	No	254 (54.0)	244 (51.4)		
	Yes	216 (46.0, 41.4 −50.6)	231 (48.6, 44. −53.2)	1.11 (0.86−1.44)	0.411
ypT0/is ypN0/+	No	216 (46.0)	217 (45.7)		
	Yes	254 (54.0, 49.4 −58.6)	258 (54.3, 49.7 −58.9)	1.01 (0.78−1.31)	0.933
ypTany ypN0	No	116 (24.7)	129 (27.2)		
	Yes	354 (75.3, 71.2 −79.2)	346 (72.8, 68.6 −76.8)	0.88 (0.66−1.18)	0.385
Breast conserving surgery	No	146 (31.3)	148 (31.4)		
	Yes	321 (68.7, 64.3 −72.9)	323 (68.6, 64.2 −72.7)	0.99 (0.75−1.31)	0.958
	No surgery	3	4		
Clinical response	Overall response	421 (89.6, 86.5 −92.2)	419 (88.2, 85.0 −91.0)	0.87 (0.58−1.31)	0.505
	Complete response	143 (30.4)	155 (32.6)		
	Partial response	278 (59.1)	264 (55.6)		
	No change	36 (7.7)	41 (8.6)		
	Progressive disease	8 (1.7)	14 (2.9)		
	Missing	5 (1.1)	1 (0.2)		
Axilla conserving surgery (SNB)	No	247 (52.9)	234 (49.5)		
	Yes	220 (47.1, 42.5 −41.7)	239 (50.5, 45.9 −55.1)	1.15 (0.89−1.48)	0.295
	No surgery	3	2		

iddEPC, intense dose-dense epirubicin, paclitaxel, and cyclophosphamide; PM(Cb), paclitaxel plus non-pegylated liposomal doxorubicin with additional carboplatin in triple-negative breast cancer; OR, odds ratio; CI, confidence interval; pCR, pathological complete response.
Data are N (%) or N (%, 95% CI) or OR (95% CI).
[a] P-value for response yes versus no.
[b] Non-inferiority for PM(Cb) cannot be claimed because the lower limit of the 2-sided 95% interval for pCR rate difference (PM(Cb) minus iddEPC) is not greater than −5% (predefined non-inferiority margin).
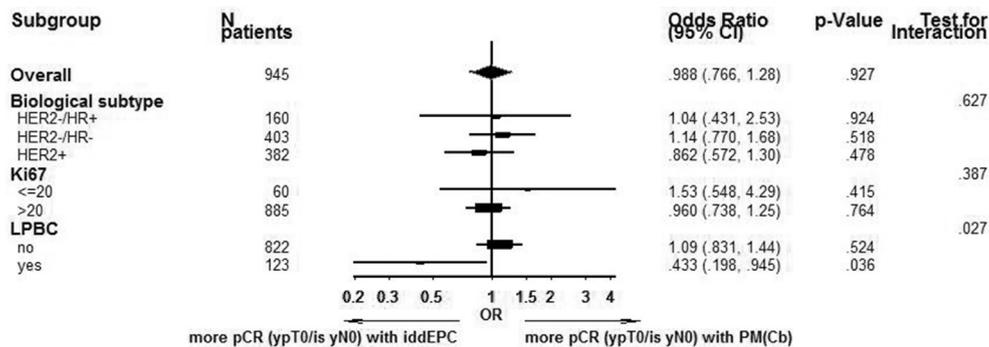

Fig. 2. Forest plot for pCR (ypT0/is ypN0) in predefined subgroups. pCR, pathological complete response; CI, confidence interval; HER, human epidermal growth factor receptor; HR, hormone receptor; LPBC, lymphocyte-predominant breast cancer; iddEPC, intense dose-dense epirubicin, paclitaxel, and cyclophosphamide; OR, odds ratio; PM(Cb), paclitaxel plus non-pegylated liposomal doxorubicin with additional carboplatin in triple-negative breast cancer.

Table 3
Haematologic and non-haematologic toxicities.

Adverse event	Grade	iddEPC ($N = 470$)	PM(Cb) ($N = 475$)	Overall ($N = 945$)	P-value
Anaemia	Any	466 (99.1)	437 (92.0)	903 (95.6)	<0.001
	3−4	36 (7.7)	20 (4.2)	56 (5.9)	0.027
Leukopenia	Any	450 (95.7)	401 (84.4)	851 (90.1)	<0.001
	3−4	404 (86.0)	48 (10.1)	452 (47.8)	<0.001
Neutropenia	Any	422 (89.8)	305 (64.2)	727 (76.9)	<0.001
	3−4	392 (83.4)	112 (23.6)	504 (53.3)	<0.001
Febrile neutropenia	Any	60 (12.8)	16 (3.4)	76 (8.0)	<0.001
Thrombocytopaenia	Any	367 (78.1)	145 (30.5)	512 (54.2)	<0.001
	3−4	44 (9.4)	15 (3.2)	59 (6.2)	<0.001
Increased bilirubin	Any	32 (6.8)	20 (4.2)	52 (5.5)	0.088
	3−4	0 (0.0)	1 (0.2)	1 (0.1)	1.000
Increased AP	Any	300 (64.9)	182 (39.3)	482 (52.1)	<0.001
	3−4	2 (0.4)	0 (0.0)	2 (0.2)	0.249
Increased ASAT	Any	208 (44.3)	134 (28.3)	342 (36.2)	<0.001
	3−4	4 (0.9)	2 (0.4)	6 (0.6)	0.450
Increased ALAT	Any	346 (73.6)	234 (49.4)	580 (61.4)	<0.001
	3−4	24 (5.1)	8 (1.7)	32 (3.4)	0.004
Increased creatinine	Any	57 (12.1)	28 (5.9)	85 (9.0)	<0.001
	3−4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Fatigue and asthenia	Any	372 (79.1)	342 (72.0)	714 (75.6)	0.012
	3−4	60 (12.8)	41 (8.6)	101 (10.7)	0.045
Headache	Any	152 (32.3)	117 (24.6)	269 (28.5)	0.009
	3−4	4 (0.9)	2 (0.4)	6 (0.6)	0.449
Nausea	Any	316 (67.2)	236 (49.7)	552 (58.4)	<0.001
	3−4	17 (3.6)	6 (1.3)	23 (2.4)	0.020
Vomiting	Any	103 (21.9)	67 (14.1)	170 (18.0)	0.002
	3−4	12 (2.6)	2 (0.4)	14 (1.5)	0.007
Mucositis	Any	270 (57.4)	312 (65.7)	582 (61.6)	0.011
	3−4	28 (6.0)	36 (7.6)	64 (6.8)	0.365
Stomatitis	Any	156 (33.2)	174 (36.6)	330 (34.9)	0.276
	3−4	14 (3.0)	26 (5.5)	40 (4.2)	0.074
Diarrhoea	Any	191 (40.6)	262 (55.2)	453 (47.9)	<0.001
	3−4	12 (2.6)	32 (6.7)	44 (4.7)	0.003
Anorexia	Any	117 (24.9)	88 (18.5)	205 (21.7)	0.018
	3−4	8 (1.7)	6 (1.3)	14 (1.5)	0.603
Thromboembolic event	Any	28 (6.0)	55 (11.6)	83 (8.8)	0.003
	3−4	9 (1.9)	16 (3.4)	25 (2.6)	0.223
Alopecia	Any	412 (87.7)	421 (88.6)	833 (88.1)	0.688
Skin reactions	Any	252 (53.6)	364 (76.6)	616 (65.2)	<0.001
	3−4	11 (2.3)	57 (12.0)	68 (7.2)	<0.001
Allergic reactions	Any	88 (18.7)	57 (12.0)	145 (15.3)	0.005
	3−4	7 (1.5)	4 (0.8)	11 (1.2)	0.383
Peripheral sensory neuropathy	Any	392 (83.4)	345 (72.6)	737 (78.0)	<0.001
	3−4	34 (7.2)	26 (5.5)	60 (6.3)	0.288
Arthralgia	Any	207 (44.0)	103 (21.7)	310 (32.8)	<0.001
	3−4	18 (3.8)	4 (0.8)	22 (2.3)	0.002
Myalgia	Any	175 (37.2)	97 (20.4)	272 (28.8)	<0.001
	3−4	16 (3.4)	6 (1.3)	22 (2.3)	0.032
Epistaxis	Any	59 (12.6)	132 (27.8)	191 (20.2)	<0.001
	3−4	0 (0.0)	3 (0.6)	3 (0.3)	0.249
Dyspnoea	Any	93 (19.8)	87 (18.3)	180 (19.0)	0.619
	3−4	6 (1.3)	5 (1.1)	11 (1.2)	0.772
Fever without neutropenia	Any	107 (22.8)	146 (30.7)	253 (26.8)	0.007
	3−4	7 (1.5)	17 (3.6)	24 (2.5)	0.061
Pneumonia	Any	5 (1.1)	46 (9.7)	51 (5.4)	<0.001
	3−4	4 (0.9)	31 (6.5)	35 (3.7)	<0.001
Infection other than pneumonia	Any	205 (43.6)	252 (53.1)	457 (48.4)	0.004
	3−4	30 (6.4)	32 (6.7)	62 (6.6)	0.896
LVEF≥10% decrease from baseline and <50%[a]	Any	5 (1.1)	5 (1.1)	10 (1.1)	1.000
Pneumonitis[b]	Any	3 (0.6)	21 (4.4)	24 (2.5)	<0.001

Table 3 (*continued*)

Adverse event	Grade	iddEPC (*N* = 470)	PM(Cb) (*N* = 475)	Overall (*N* = 945)	*P*-value
	3−4	0 (0.0)	12 (2.5)	12 (1.3)	<0.001
Heart failure, according to NYHA[c]	Any	4 (0.9)	1 (0.2)	5 (0.5)	0.215
	3−4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.

Data are *N* (valid %) unless otherwise stated.

All AESIs were treatment related except for one case of pneumonitis (any grade) in the PM(Cb) arm and one case of heart failure (any grade) in the iddEPC arm.

AESI, AE of special interest; AP, alkaline phosphatase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; iddEPC, intense dose-dense epirubicin, paclitaxel, and cyclophosphamide; PM(Cb), paclitaxel plus non-pegylated liposomal doxorubicin with additional carboplatin in triple-negative breast cancer.

[a] Adverse event (AE) of special interest.
[b] AE of special interest, if grade 2 or higher.
[c] AE of special interest, if NYHA class 3 or 4.

4. Discussion

The National Comprehensive Cancer Network (NCCN) guidelines recommend dose-dense chemotherapy as a standard of care, if an indication for chemotherapy is given [22]. Several adjuvant randomised trials and the recent meta-analysis of the Early Breast Cancer Trialists' Collaborative Group have shown that dose-dense or dose-intensified chemotherapy resulted in superior OS as compared with conventionally dosed chemotherapy [6,7,9,23,24]. The iddEPC regimen, in particular, yielded impressing results with persistently higher OS rates compared with conventionally scheduled chemotherapy (absolute OS benefit of 10% after 10 years irrespective of ER status) and manageable toxicity [6,7] and was therefore recommended as a standard of care by German guidelines [25,26]. However, direct comparisons of different dose-dense regimens are rare [27,28] and have been exclusively performed in the adjuvant setting. Most importantly, iddEPC has never been compared to one of the (neo)adjuvant dose-dense standard regimen ACdd (or ECdd) x4 q2w followed by 12x P q1w.

The GeparOcto study compared the efficacy, treatment adherence and toxicity of the two most potent dose-dense regimens in the neoadjuvant setting by randomising the iddEPC regimen against experimental PM(Cb). In contrast to our initial hypothesis, PM(Cb) did not result in higher pCR rates compared with iddEPC but led to more treatment discontinuations and was associated with significantly higher rates of non-haematological, especially pulmonal, toxicity. The observed pCR rates of 14.4% for HR-positive/HER2-negative, 60.2% for HER2-positive and 50.1% for TNBC, respectively, are in line with pCR rates reported from other randomised trials evaluating dual-blockade in high-risk early-stage HER2-positive disease and carboplatin in TNBC, respectively [4,13,15,29]. In triple-negative patients, the iddEPC regimen including high-dose cyclophosphamide was equally effective to PM(Cb) with conventionally dosed carboplatin.

Randomised data on dose-dense neoadjuvant therapy, however, are limited, and design-specific limitations make interpretation difficult [30,31]. In the AGO-1 trial [29], preoperative idd chemotherapy significantly improved both the pCR rate (18% versus 10%) and OS compared with conventionally scheduled chemotherapy.

The dose-dense weekly regimen of PM(Cb) was first investigated in GeparSixto and showed significantly higher pCR rates and improved DFS in TNBC when weekly carboplatin was added to paclitaxel and non-pegylated liposomal doxorubicin. It was therefore chosen for further evaluation [15,18] and direct comparison to the well characterised iddEPC regimen.

In GeparOcto, treatment with PM(Cb) did not predict for higher pCR after adjustment for baseline and stratification factors. However, in addition to age and grading, the stratification factors biological subtype and LPBC were independent predictors for achievement of pCR, which is also described in the literature [4,23]. Recently, sTILs have been shown to be independently predictive for sensitivity to chemotherapy irrespective of BC subtype [32]. In GeparOcto, patients with LPBC had a significant, 19% higher pCR rate when treated with iddEPC compared with PM(Cb) with a significant test for interaction, likely due to the higher dose-intensity of iddEPC as compared with PM(Cb) with significantly more dose delays, dose reductions and complete treatment discontinuations observed in the latter group. Main reason for differences in treatment modification in the iddEPC and PM(Cb) arm were non-haematological toxicities causing dose delays in 25.7% versus 52.8% (*P* < 0.001) and dose reductions in 27.2% versus 42.3% (*P* < 0.001) of patients, respectively. These numbers are in line with earlier reports from the phase III AGO-ETC and phase II GeparSixto trials [6,15].

Overall, more patients in the PM(Cb) arm discontinued treatment (16.4% versus 34.1%; *P* < 0.001), mainly due to AEs. As expected, haematological AEs were more frequent in the iddEPC arm, but rates of any non-haematological grade ≥3 AEs were again higher in the PM(Cb) arm (43.2% versus 52.0%; *P* = 0.008). Particularly, among the high-grade AEs, pneumonia was reported in four (0.9%) patients in the iddEPC and 31 (6.5%) in the PM(Cb) arm (*P* < 0.001) and pneumonitis, which was a predefined AESI, in 0 (0%) and 12 (2.5%), respectively (*P* < 0.001). In addition, two deaths during

treatment occurred in the PM(Cb) group, one due to pneumonia and the second due to multiple septic cerebral embolisms concomitant with pneumonia, an extent not observed within GeparSixto [15]. There are several recent case reports about a rare association of treatment with pegylated liposomal doxorubicin and pneumonitis [33,34]. The reason of this association is unclear and reports of an association with non-pegylated liposomal doxorubin besides GeparSixto are lacking. Nevertheless, GeparOcto confirmed our GeparSixto experience that severe and even life-threatening pneumonitis may occur in 2–3% of patients treated with PM(Cb). Therefore, specifically in this high-risk adjuvant setting, PM(Cb) should not be offered.

Despite a pronounced and significantly higher incidence of haematological toxicity, iddEPC is a more feasible regimen with better treatment adherence due to the lower rate of non-haematological toxicities. Overall, 2618 patients have been treated with iddEPC in the AGO-ETC [6], GAIN-1 [26] and GeparOcto trial and only three treatment-related deaths have been reported, corresponding to a mortality rate of 0.1%, which is lower in comparison to conventionally dosed chemotherapy. Long-term toxicity data need to be awaited. Previously, nine cases (1.4%) of secondary leukaemia/myelodysplastic syndromes were reported in the iddEPC arm after 10-year follow-up [7] which was consistent with data of the Canadian MA5 trial [35].

In summary, in high-risk early-stage BC patients, non-inferiority of weekly PM(Cb) in comparison with iddEPC could not be shown. Interestingly, patients with LPBC achieved a significantly higher pCR rate with iddEPC than with PM(Cb). Especially non-haematological toxicity was more pronounced with weekly PM(Cb), whereas the elevated haematological toxicity of iddEPC had no negative clinical impact. iddEPC appeared to be more feasible than PM(Cb) in high-risk early BC patients and should be considered as one of the effective dose-dense regimens either in the adjuvant or neoadjuvant setting.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.015.

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