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Annals of Oncology 30: 109–114, 2019
doi:10.1093/annonc/mdy475
Published online 24 October 2018

ORIGINAL ARTICLE

Dose tailoring of adjuvant chemotherapy for breast cancer based on hematologic toxicities: further results from the prospective PANTHER study with focus on obese patients

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Note: An earlier version of this study was presented at the 2018 ASCO meeting.

Background: Adjuvant chemotherapy (ACT) for breast cancer improves relapse-free survival (BCRFS) and overall survival. Differences in terms of efficacy and toxicity could partly be explained by the significant interpatient variability in pharmacokinetics which cannot be captured by dosing according to body surface area. Consequently, tailored dosing was prospectively evaluated in the PANTHER trial.

Patients and methods: PANTHER is a multicenter, open-label, randomized phase III trial which compared tailored, dose-dense (DD) epirubicin/cyclophosphamide (E/C) and tailored docetaxel (D) (tDD) with standard interval 5-fluorouracil/E/C and D. The primary end point was BCRFS and the primary efficacy analysis has been previously published. In this secondary analysis, we aimed to retrospectively explore the concept of dose tailoring. Our two hypotheses were that BCRFS would not vary depending on the cumulative administered epirubicin dose; and that dose tailoring would lead to appropriate dosing and improved outcomes for obese patients, who are known to have worse prognosis and increased toxicity after DD ACT.

Results: Patients treated with tDD had similar BCRFS regardless of the cumulative epirubicin dose ($P = 0.495$), while obese patients in this group [body mass index (BMI) $\geq$30] had improved BCRFS compared with nonobese ones (BMI <30) [hazard ratio (HR) = 0.51, 95% confidence interval (CI) 0.30–0.89, $P = 0.02$]. Moreover, tDD was associated with improved BCRFS compared with standard treatment only in obese patients (HR = 0.49, 95% CI 0.26–0.90, $P = 0.022$) but not in nonobese ones (HR = 0.79, 95% CI 0.60–1.04, $P = 0.089$). The differences were not formally statistically significant (P for interaction 0.175). There were no differences in terms of toxicity across the epirubicin dose levels or the BMI groups.

Conclusions: Dose tailoring is a feasible strategy that can potentially improve outcomes in obese patients without increasing toxicity and should be pursued in further clinical studies.

ClinicalTrials.gov identifier: NCT00798070.

Key words: adjuvant chemotherapy, breast cancer, dose dense, obese, dose tailoring

Introduction

A large body of literature, culminating in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 100 000 randomized patients, has definitively demonstrated that administration of adjuvant polychemotherapy (ACT) following resection of early breast cancer (BC) improves patient outcomes, while there is a significant trend for better efficacy in terms of long-term survival with higher cumulative anthracycline doses [1]. Moreover, the dose-dense (DD) administration (i.e. every 2 weeks) of ACT has been shown to further improve outcomes compared with standard schedules (i.e. every 3 weeks) with an absolute 10-year gain in terms of BC mortality of 2.9% [95% confidence interval (CI) 1.2–4.6, $P = 0.0003$] [2]. However, even though the relative magnitude of benefit derived from ACT is the same regardless of clinicopathologic factors such as estrogen receptor (ER) status and age, patient prognosis is affected by a large number of tumor- and host-related factors.

Among those factors, obesity has consistently been shown to negatively affect patient survival, conferring an increased risk for relapse or death by approximately one-third [3]. Although open for speculation, a possible reason that could partly explain this phenomenon could be inadequate chemotherapy dosing. On the other hand, the tolerability and frequency and severity of adverse events following ACT vary greatly between patients. Differences in terms of efficacy and toxicity can be explained by the significant interpatient variability in terms of the pharmacokinetic properties of ACT, which cannot be captured by a rudimentary marker such as the body surface area (BSA). Supporting this hypothesis, simply administering higher doses of DD ACT to obese patients by using the real, unadjusted BSA—as supported by contemporary guidelines [4]—leads to increased toxicity without improving outcomes [5].

In light of retrospective data supporting the concept of dose tailoring according to the hematologic nadirs and a feasibility randomized phase II trial [6–11], the confirmatory phase III PANTHER trial was conducted in Austria, Germany and Sweden [12]. In total, 2017 patients were enrolled and randomized to receive either tailored, DD (tDD) therapy (group A) or standard ACT (group B). After a median follow-up of 5.3 years, the hazard ratios (HRs) of both the primary end point [BC relapse-free survival (BCRFS) HR = 0.79, 95% CI 0.61–1.01, $P = 0.06$] and the secondary end points [event-free survival (EFS), overall survival (OS), distant disease-free survival (DDFS)] all favored the experimental treatment, although only the difference in EFS was statistically significant (HR = 0.79; 95% CI 0.63–0.99; $P = 0.04$). Following these results, with this secondary analysis of the PANTHER trial we aimed to further explore the concept of dose tailoring, by focusing both on the efficacy per epirubicin dose level and on the treatment effects in obese patients.

Patients and methods

Study design

PANTHER is a prospective, randomized, open-label, multicenter phase III trial, which was conducted in 86 centers in Sweden, Germany and Austria by the Swedish Breast Cancer Group, the German Breast Group, and the Austrian Breast & Colorectal Cancer Study Group. The trial protocol was approved by ethics review boards at the participating sites and health authorities in all countries. All patients provided written informed consent before inclusion. The study was conducted according to the Declaration of Helsinki and the principles of good clinical practice and was registered at the ClinicalTrials.gov website, identifier NCT00798070.

Patients, administered treatment and outcomes

Details regarding the trial design and study population have been previously presented [12]. In brief, eligible patients had early resected BC, either node-positive or high-risk node-negative disease (defined as patient age <35 years or ER-negative disease, grade 3 and larger than 2 cm in diameter) and an Eastern Cooperative Oncology Group Performance Status score of 0 or 1. Patients were randomized 1 : 1 to receive either tailored according to hematologic toxicity epirubicin (E) and cyclophosphamide (C) every 2 weeks for four cycles, followed by tailored docetaxel (D) every 2 weeks for four cycles (group A); or standard therapy with three cycles of 5-fluorouracil/E/C ($FE_{100}C$) every 3 weeks, followed by three cycles of D_{100} every 3 weeks (group B). The primary end point of the study was BCRFS, defined as the time to BC relapse or death due to BC. Key secondary end points included OS (time to death by any cause); EFS (time to BC relapse, contralateral BC, any malignancy or death by any cause); DDFS (time to distant metastases or death due to BC); and toxicity according to version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.

Statistical analysis

Within the scope of this retrospective, exploratory secondary analysis, we aimed to test two hypotheses: primarily, that the efficacy of tailored DD ACT would be the same regardless of the cumulative anthracycline dose; and secondly, that dose tailoring would overcome the negative prognostic effect of obesity. For the former, patients that received tDD were divided into three groups according to the cumulative epirubicin dose (<360, 361–420 and >420 mg/m^2) and were compared in terms of BCRFS. For the latter, the entire patient population was divided into two groups, according to the body mass index (BMI; <30 and ≥30 kg/m^2 based on a previous report [5]). BCRFS was compared according to BMI and received treatment.

Time for event-free patients in all survival analyses was calculated from the date of randomization to the date of last clinical visit. The Kaplan–Meier method was used to estimate survival, with the graphs representing the complement to these estimates (time to failure). Proportional hazards regression models were used to estimate the effect of treatment, BMI and the interaction between treatment and BMI on time to failure. Results from the models are presented as HRs together with 95% CI. Reported P values refer to the Wald test. The interaction between treatment and BMI was tested both by using BMI as a dichotomized (BMI <30, BMI >30), and as a continuous variable. Test for differences in baseline clinical and demographic factors and cumulative epirubicin and BMI group were carried out by using the Fishers exact test for categorical variables, and by using linear regression for continuous variables.

Results

Patient characteristics

The baseline characteristics of the entire patient population have been previously described [12]. In total, 135 patients received <360 mg/m^2 epirubicin (dose level 1), compared with 482 and 384 who received 361–420 mg/m^2 (dose level 2) and over 420 mg/m^2 (dose level 3), respectively. In Table 1, the baseline clinical and

Table 1. Baseline clinical and demographic characteristics, per cumulative epirubicin dose at the experimental arm

Dose level (mg/m^2)	≤360	361–420	>420	*P* value
Number of patients	135	482	384	
Median age (range)	51 (27–69)	53 (23–70)	50 (28–68)	0.001
Type of surgery				
Mastectomy	60 (44%)	219 (45%)	181 (47%)	0.822
BCS	75 (56%)	263 (55%)	203 (53%)	
Tumor size (cm)				
≤2	47 (35%)	205 (43%)	161 (42%)	
2–5	75 (56%)	239 (50%)	193 (51%)	0.519
>5	13 (10%)	36 (8%)	27 (7%)	
Positive nodes				
0	4 (3%)	15 (3%)	12 (3%)	
1–3	70 (52%)	290 (60%)	231 (60%)	0.660
4–9	42 (31%)	120 (25%)	101 (26%)	
>9	19 (14%)	57 (12%)	40 (10%)	
Tumor grade				
1	6 (5%)	28 (6%)	25 (7%)	
2	74 (55%)	231 (48%)	179 (47%)	
3	54 (40%)	220 (46%)	179 (47%)	0.532
ER/PR status				
ER or PR+	108 (80%)	389 (81%)	308 (80%)	0.958
ER and PR−	27 (20%)	92 (19%)	76 (20%)	
HER2 status				
Positive	17 (13%)	61 (13%)	81 (21%)	0.002
Negative	118 (87%)	420 (87%)	303 (79%)	

BCS, breast conserving surgery; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Baseline clinical and demographic characteristics, per body mass index group, both treatment groups

BMI	<30	≥30	*P* value
Number of patients	1398	444	
Median age (range)	50 (21–70)	53 (28–68)	<0.001
Type of surgery			
Mastectomy	675 (48%)	201 (45%)	
BCS	723 (52%)	243 (55%)	0.276
Tumor size (cm)			
≤2	616 (44%)	157 (35%)	
2–5	688 (49%)	245 (55%)	
>5	89 (7%)	42 (10%)	0.001
Positive nodes			
0	45 (3%)	12 (3%)	
1–3	810 (58%)	249 (56%)	
4–9	382 (27%)	125 (28%)	0.748
>9	161 (12%)	58 (13%)	
Tumor grade			
1	82 (6%)	23 (5%)	
2	674 (58%)	231 (52%)	
3	638 (46%)	189 (43%)	0.377
ER/PR status			
ER or PR +	1112 (80%)	353 (80%)	
ER and PR−	285 (20%)	90 (20%)	1.000
HER status			
Positive	229 (16%)	80 (18%)	0.423
Negative	1169 (84%)	364 (82%)	
Menopausal status			
Premenopausal	779 (56%)	188 (42%)	
Postmenopausal	561 (40%)	235 (53%)	<0.001
Unknown	58 (4%)	21 (5%)	
Allocated to treatment			
Standard	703 (50%)	224 (51%)	0.957
Experimental	695 (50%)	220 (49%)	
Endocrine treatment			
Aromatase Inhibitor	455 (32%)	187 (42%)	<0.001
Tamoxifen	544 (38%)	125 (28%)	
Goserelin	109 (8%)	22 (5%)	0.099
No endocrine	326 (23%)	105 (23%)	0.371
Unknown	71 (5%)	30 (6%)	

BCS, breast conserving surgery; ER, estrogen receptor; PR, progesterone receptor.

demographic characteristics of patients grouped per dose level are presented. In addition, in the entire population and in the tDD group, 444 and 224 patients, respectively, had a BMI of over 30 kg/m^2, while 1398 and 703, respectively, had a BMI under 30 kg/m^2. The baseline characteristics per BMI group in the entire study population are presented in Table 2. As shown in Tables 1 and 2, the baseline characteristics were balanced between the dose level and BMI subgroups, with the exception of a slightly higher number of HER2-positive tumors among patients receiving the highest cumulative epirubicin dose and a small difference in tumor size between the BMI groups. More patients in the BMI ≥30 group were postmenopausal; however, menopausal status did not have an effect on patient outcomes (supplementary Figure S1, available at *Annals of Oncology* online).

Treatment efficacy and toxicity per dose level

Among patients treated with tDD, the cumulative epirubicin dose was not statistically significantly associated with BCRFS ($P = 0.495$). Specifically, using the lowest dose level (1) as a comparator, there were nonstatistically significant trends for worse prognosis for patients receiving cumulative epirubicin at dose level 2 (HR = 1.45, 95% CI 0.76–2.76) and dose level 3 (HR = 1.29, 95% CI 0.66–2.49) (Figure 1). Expectedly, due to the nature of dose tailoring, the frequency of hematologic toxicities between the three dose levels did not differ; interestingly, neither did the rates of nonhematologic toxicities (supplementary Table S1, available at *Annals of Oncology* online).

Treatment efficacy and toxicity according to BMI

Among patients treated with tDD, obese ones (BMI ≥30) had improved BCRFS compared with nonobese ones (BMI <30) (HR = 0.51, 95% CI 0.30–0.89, $P = 0.02$). In contrast, treatment outcomes for patients treated with standard therapy did not differ between the BMI groups (HR = 0.82, 95% CI 0.55–1.22, $P = 0.32$) (Figure 2). Moreover, tDD was associated with improved BCRFS compared with standard treatment only in

obese patients (HR = 0.49, 95% CI 0.26–0.90, $P = 0.02$) but not in nonobese ones (HR = 0.79, 95% CI 0.60–1.04, $P = 0.08$) (Figures 2 and 3 and supplementary Table S2, available at *Annals of Oncology* online). In line with these observations, using BMI as a linear variable, the improvement in terms of BCRFS with the experimental treatment compared with the standard one was greater with increasing BMI values (Figure 3). Nevertheless, the test for interaction between treatment and BMI as a dichotomized variable and as a linear one revealed *P* values of 0.175 and 0.225, respectively, suggesting that the differences were not formally statistically significant. In supplementary Table S3, available at *Annals of Oncology* online, the most common grade 3 and 4 hematologic and nonhematologic adverse events are presented, per treatment and BMI group. No significant differences were noted according to BMI within the experimental or standard therapy groups.

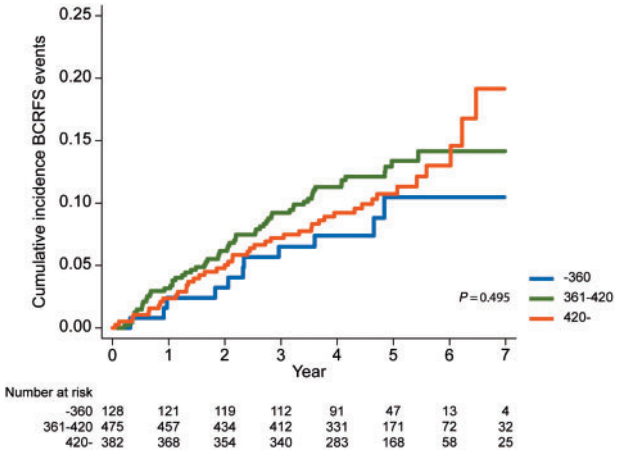

Figure 1. Cumulative incidence curve for the endpoint of breast cancer relapse-free survival per cumulative epirubicin dose, ≤360, 361–420 and >420 mg/m^2. BCRFS, breast cancer relapse-free survival.

Discussion

In this secondary analysis of a randomized phase III clinical trial, we aimed to investigate in depth two core concepts of dose tailoring: that certain patients might currently be overtreated and that de-escalation could be considered without compromising outcomes; and that dosing according to BSA may lead to inappropriate dosing and suboptimal outcomes for some patients, particularly obese ones.

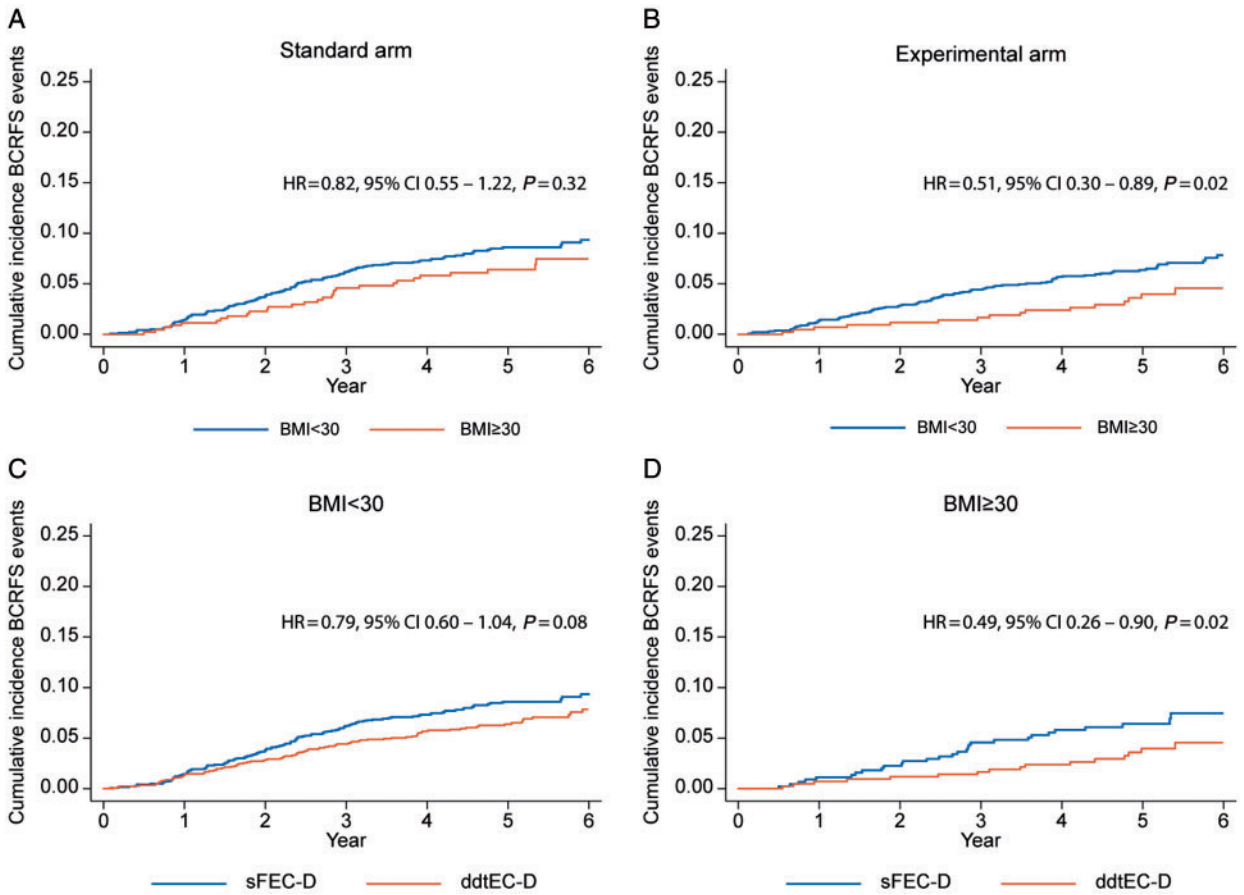

Figure 2. Cumulative incidence curves for the endpoint of BCRFS per treatment group (standard, A or tailored dosed, B); and per body mass index group (<30, C or ≥30, D). BCRFS, breast cancer relapse-free survival; BMI, body mass index; ddtEC-D, dose-dense tailored epirubicin, cyclophosphamide–docetaxel; sFEC-D, standard fluorouracil, epirubicin, cyclophosphamide–docetaxel; HR, hazard ratio; 95% CI, 95% confidence interval.

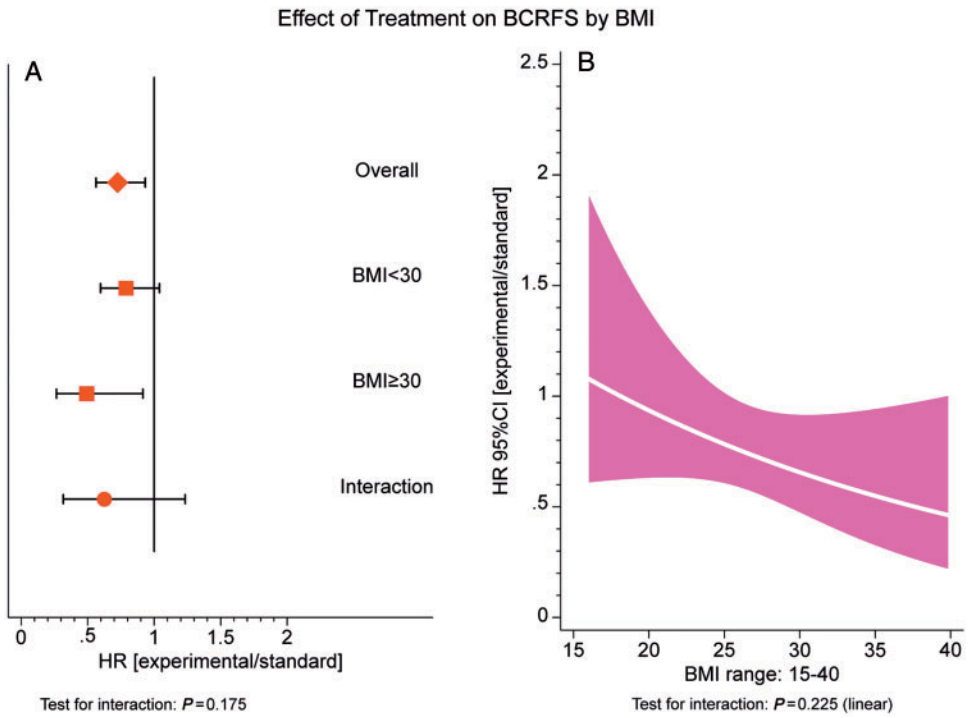

Figure 3. Effect of treatment by body mass index as a dichotomous (A) and as a linear variable (B). BCRFS, breast cancer relapse-free survival; BMI, body mass index; HR, hazard ratio.

Indeed, our findings support both of these hypotheses. Despite the lower cumulative epirubicin dose, BCRFS did not differ between the three dose level groups that received tailored ACT. This finding is phenomenally in contrast with the findings of the EBCTCG meta-analysis, in which better outcomes were achieved with higher anthracycline doses [1]. However, increasing the dose beyond a certain threshold seems to not confer further improvement in terms of survival [13]. Moreover, older studies simply comparing a higher to a lower dose are not comparable to one based on tailoring, thus on the administration of biologically equivalent doses. As a result, one could postulate that these observations are explained not by an underlying dose-dependent effect, but rather by avoiding undertreating patients, using in this case a readily available biomarker such as the hematologic nadirs. Supporting the hypothesis of a biologically equivalent dose was the absence of significant differences in terms of toxicity according to the cumulative epirubicin dose.

Furthermore, obesity has been repeatedly correlated with worse outcomes of early BC according to retrospective analyses of prospective studies using various combinations of anthracyclines with or without taxanes and variable BSA cut-offs. This association seems to be consistent in ER-positive disease, although some [14–16], but not all studies [17, 18] report a similar association regarding ER-negative BC as well. A number of biologic reasons have been proposed as causes for this observation [3]. In addition to those, the use of BSA as the basis of ACT dosing could be partly to blame, since using an upper limit of 2 m^2 leads to unnecessary undertreatment, supported by the lower pathologic complete remission rates in the neoadjuvant setting of BC [15]. Moreover, using an unadjusted BSA as recommended by guidelines has been shown to expose obese patients receiving DD ACT (which, as previously mentioned, improves patient survival compared with standard ACT and should be regarded as the standard of care [2]) to excess toxicity without improving outcomes [5]. In the PANTHER trial, consistent trends suggested improved outcomes for obese patients treated with tailored, but not standard therapy, and for better efficacy of tailored compared with standard dosing in obese, but not nonobese patients. Although not formally statistically significant, these results are in line with our hypothesis that tailoring can circumvent the inferior prognosis conferred by obesity, possibly due to appropriate chemotherapy dosing. This hypothesis is further supported by the observation that, contrary to previously published experience with DD ACT [5], the frequency of serious adverse events was not higher among obese patients, underscoring the feasibility of appropriate individualized dosing thanks to tailoring.

On the other hand, this study suffers from some limitations that should be acknowledged. These exploratory findings should be regarded more as supportive of the concept of dose tailoring, rather than as evidence for it or as practice changing. In addition, lack of statistical power could have masked any existing association and led to inconclusive results, although in our comparisons, the HRs were always in favor of our hypotheses. However, the results of the primary analysis of the PANTHER trial, although formally statistically negative, revealed strong trends in favor of the experimental therapy [12]. Taking into account the prolonged natural history of BC, with longer follow-up a formal association may become apparent. Until then, tailored DD ACT should only be pursued within the context of a clinical trial.

In conclusion, dose tailoring potentially avoids overdosing without compromising outcomes and may improve long-term survival in obese patients, who currently fare worse than

nonobese ones. Although exploratory, these results highlight the feasibility and value of tDD ACT and underscore the need for validation in future studies.

Funding

This study was supported by grants from the Swedish Cancer Society to the Karolinska Institutet (grant numbers CAN 2016/791 and CAN 2017/1043), from the Swedish Breast Cancer Association (BRO), from the research funds at Radiumhemmet (grant number 164003), and from Amgen, Roche, and Sanofi-Aventis to the Swedish Breast Cancer Group (SweBCG) at Karolinska University Hospital, the German Breast Group (GBG), and the Austrian Breast & Colorectal Cancer Study Group (ABCSG). Grant numbers not applicable, unless stated.

Disclosure

TF: institutional grants from Roche and Pfizer and personal fees from Novartis, Pfizer, Roche and UpToDate; VM: personal fees from Amgen, Celgene, Roche and AstraZeneca; RG: honoraria from Amgen, Roche, AstraZeneca and MSD; consulting role in Celgene, Roche, BMS and AstraZeneca; travel fees from Roche, Amgen, AstraZeneca, Janssen; research funding from Celgene, Roche, BMS and AstraZeneca. GS: personal fees and nonfinancial support from Amgen; MG: employment in Sandoz; honoraria from Amgen, Astra Zeneca, Celgene, Eli Lilly, Novartis, NanoString Technologies and Roche; consulting role in Accelsoirs; research funding from Astra Zeneca, Novartis, Pfizer and Roche; travel fees from Amgen, Astra Zeneca, Celgene, Eli Lilly, Ipsen, Novartis and Pfizer; SL: honoraria to institution from AstraZeneca, Amgen, Novartis, Pfizer, Roche, Puma; consulting role in AstraZeneca, Amgen, Novartis, Pfizer, Roche, Puma; research funding to institution from Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva, Vifor. JB: Jonas Bergh's research group receives research fundings from Merck paid to Karolinska Institutet and from Amgen, Bayer, Pfizer, Roche and Sanofi-Aventis paid to Karolinska University Hospital; no personal payments; payment from UpToDate for a chapter in breast cancer prediction paid to Asklepios Medicine HB. AM, N-OB, MU, HJ, MH and PM have declared no conflicts of interest.

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