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Annals of Oncology 29: 661–668, 2018
doi:10.1093/annonc/mdx772
Published online 8 December 2017

ORIGINAL ARTICLE

A randomized phase II study evaluating different maintenance schedules of nab-paclitaxel in the first-line treatment of metastatic breast cancer: final results of the IBCSG 42-12/BIG 2-12 SNAP trial

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[‡]The investigators in the SNAP trial and the leadership and staff of the International Breast Cancer Study Group are listed in the supplementary Appendix, available at *Annals of Oncology* online.

Note: This study was previously presented at the 2016 San Antonio Breast Cancer Symposium.

Background: The phase II SNAP trial was designed to evaluate the efficacy of alternative chemotherapy schedules for prolonged administration in HER2-negative metastatic breast cancer (MBC), after a short induction at conventional doses.

Patients and methods: Between April 2013 and August 2015, 258 women untreated with chemotherapy for MBC were randomly assigned to receive three different maintenance chemotherapy schedules after three cycles of identical induction chemotherapy: arm A, nab-paclitaxel 150 mg/m^2 days 1 and 15 Q28; arm B, nab-paclitaxel 100 mg/m^2 days 1, 8 and 15 Q28; arm C, nab-paclitaxel 75 mg/m^2 days 1, 8, 15 and 22 Q28. Induction was three cycles nab-paclitaxel 150/125 mg/m^2, days 1, 8 and 15 Q28. The primary objective was to evaluate the efficacy of each maintenance schedule, in terms of progression-free survival (PFS), as compared with the historical reference of 7-month median PFS reported by previous studies with first-line docetaxel. One-sample, one-sided log-rank tests were utilized. Quality-of-life (QoL) evaluation was carried out, and the global indicator for physical well-being was defined as the primary QoL end point; completion rates of QoL forms were >90%.

Results: In total, 255 patients were assessable for the primary end point. After 18.2-month median follow-up, 182 PFS events were observed. Median PFS was 7.9 months [90% confidence interval CI 6.8–8.4] in arm A, 9.0 months (90% CI 8.1–10.9) in arm B and 8.5 months (90% CI 6.7–9.5) in arm C. PFS in arm B was significantly longer than the historical reference of first-line docetaxel ($P = 0.03$). Grade ≥2 sensory neuropathy was reported in 37.9%, 36.1% and 31.2% of the patients in arm A, B and C, respectively (Grade ≥3 in 9.1%, 5.6% and 6.6% of the patients, respectively). Noteworthy, the QoL scores for sensory neuropathy did not worsen with prolonged nab-paclitaxel administration in any of the maintenance arms.

Conclusion: The SNAP trial demonstrated that alternative nab-paclitaxel maintenance schedules with reduced dosages after a short induction at conventional doses are feasible and active in the first-line treatment of MBC.
Registration: ClinicalTrials.gov NCT01746225

Key words: metastatic breast cancer, maintenance chemotherapy, alternative treatment schedules

Introduction

Metastatic breast cancer (MBC) can be successfully managed for years [1–4] with appropriate treatments, aimed at prolonging survival with good quality-of-life (QoL) and symptom palliation. Virtually all MBC patients are candidates to chemotherapy, either upfront or after failure of multiple lines of endocrine therapy. Whereas the selection of the most appropriate chemotherapy regimen is influenced by patient and disease-related factors as well as by patient/physician preferences, controversy remains about how long chemotherapy should be continued in the absence of disease progression, due to its long-term impact on patient QoL.

In the past, several randomized clinical trials have addressed the issue of prolonged chemotherapy administration in MBC [5–16], comparing shorter with longer durations as first-line treatment. Most studies indicated that longer treatment results in an improved time to progression, but failed to consistently show a survival benefit. A systematic review including 11 of these trials showed that prolonged chemotherapy was associated with a clinically meaningful and statistically significant improvement in progression-free survival (PFS) and a moderate, but significant, improvement in overall survival (OS) [17]. On the basis of these results, prolonged chemotherapy administration may now be justified, in light of an appreciable survival benefit for some patients [18]. However, in all trials, maintenance schedules were based on full therapeutic drug dosages, with a potential impact on QoL due to the prolonged chemotherapy exposure. In this perspective, the SNAP trial was designed to improve the efficacy and tolerability of prolonged chemotherapy administration by studying alternative maintenance schedules while preserving and possibly improving treatment efficacy in this disease setting. The availability of a new nanoparticle albumin-bound taxane, nab-paclitaxel, represented an opportunity to test this hypothesis, as this agent has been shown to reduce the toxicity associated with standard taxane administration, while increasing antitumor efficacy [19, 20].

Methods

Study design and patients

Trial IBCSG 42-12/BIG 2-12, SNAP (Schedules of nab-Paclitaxel), was a multicenter, randomized, phase II clinical trial assessing three alternative maintenance chemotherapy regimens using nab-paclitaxel as first-line treatment in MBC. The IBCSG Ethics Committee and ethics committees at each participating institution and relevant health authorities approved the study protocol; all patients provided written informed consent. The IBCSG Data and Safety Monitoring Committee reviewed the trial twice-yearly. Eligible women were ≥18 years, with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1 and life expectancy >3 months. Patients had stage IV MBC that was HER2-negative estrogen receptor (ER)–negative or endocrine-resistant ER-positive (defined as having failed at least one prior endocrine therapy or candidate for first-line chemotherapy), and measurable or non-measurable according to RECIST 1.1 criteria. Prior adjuvant chemotherapy was allowed, provided it stopped ≥12 months before enrollment.

Randomization procedures

Eligible women were randomly assigned (1 : 1 : 1) to three alternative schedules of nab-paclitaxel (Abraxane®; Celgene, Boudry, Switzerland) (Figure 1). Each treatment arm included an induction phase consisting of three nab-paclitaxel cycles at conventional dosages and a maintenance phase as follows: arm A, nab-Paclitaxel 150 mg/m^2 days 1 and 15 Q28; arm B, nab-paclitaxel 100 mg/m^2 days 1, 8 and 15 Q28; arm C, 75 mg/m^2 days 1, 8, 15 and 22 Q28. In the original study design, the induction phase consisted of nab-paclitaxel 150 mg/m^2 days 1, 8 and 15 Q28, but was modified to 125 mg/m^2 days 1, 8 and 15 Q28 following a safety review of the first 48 treated patients. Treatment was administered until progressive disease, unacceptable toxicity or patient refusal.

Study procedures

Patients were monitored with physical examination, biochemistry and hematology, and evaluated for disease response according to RECIST version 1.1 at baseline and every 12 weeks until documented progression, even after treatment discontinuation for reasons other than progression. Targeted adverse events were reported for each cycle and graded according to CTCAE v4.0.

End points

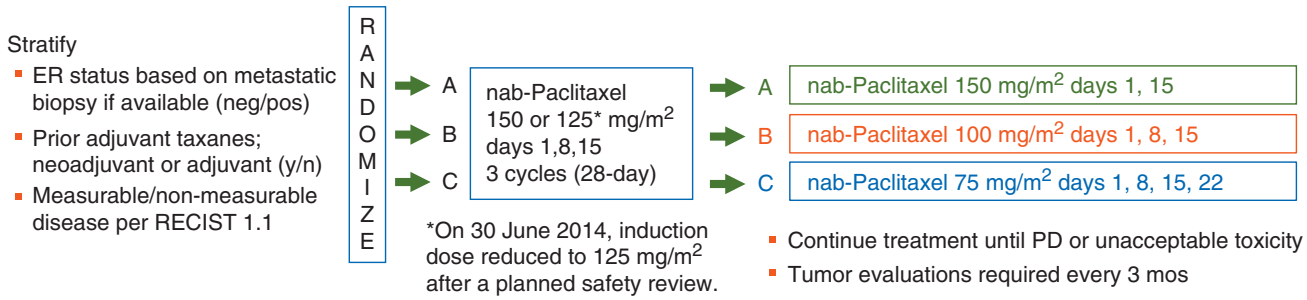
The primary end point was PFS, defined as time from randomization to disease progression or death from any cause, provided death occurred within 12 weeks following the last disease assessment; otherwise the end point was censored at date of last progression-free assessment. Secondary end points included tolerability (adverse events), feasibility (completion of treatment per protocol for ≥24 weeks), best overall response according to RECIST 1.1, OS (time from randomization to death from any cause; otherwise censored at date last known alive) and QoL.

Statistical considerations

PFS distributions were estimated by Kaplan–Meier method and two-sided 90% confidence interval (CI) for the median PFS was provided based on complementary log-log transformation. PFS of each treatment arm was compared with an historical control PFS of first-line docetaxel using a one-sample, one-sided ($\alpha = 0.05$) log-rank test without adjustment for multiple tests. An historical reference of 7-month median PFS was selected based on the most recent trial with a docetaxel control arm [19]. Seventy-six patients (63 PFS events) per arm, and accrual of 8 patients per month over 30 months plus 12 months additional follow-up, provided 88% power to detect an improvement in median PFS from 7 to 10 months. The final sample size was 86 patients per arm, assuming 12% drop out without documented PFS event. Secondary end points were summarized descriptively.

Quality of life

Patients completed a paper-based QoL assessment at baseline (before randomization), and day 1 of each of the first 12 cycles, unless treatment



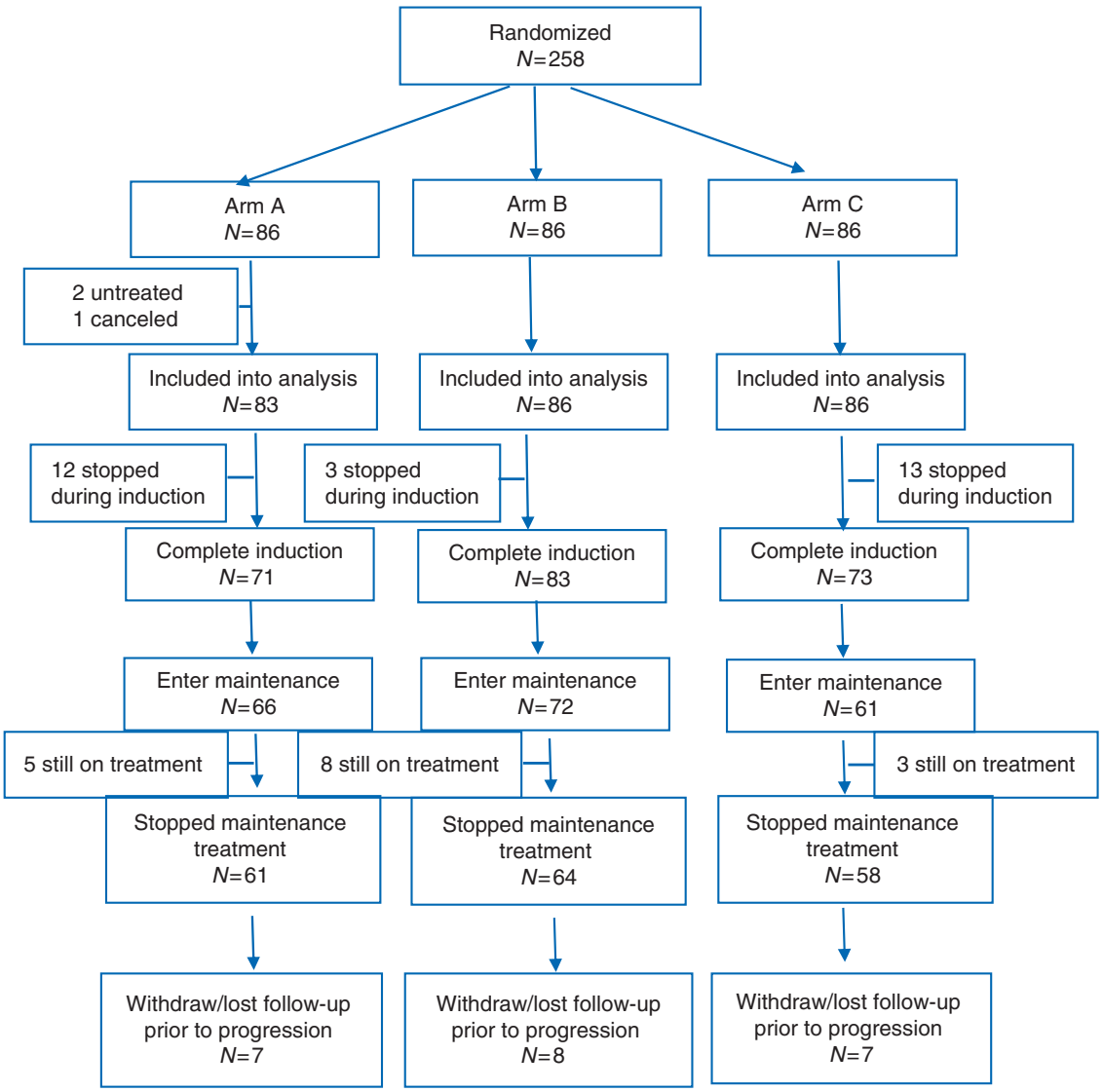


Figure 1. IBCSG 42-12/BIG 2-12 SNAP (Schedules of nab-paclitaxel) schema and CONSORT flow diagram.

was discontinued earlier. Forms were completed before any diagnostic procedures (exception: baseline) or treatment administration. The assessment consisted of global indicators for physical well-being, which was defined as the primary QoL end point, mood, coping effort, overall treatment burden and symptom-specific indicators for appetite, tiredness, hair loss and feeling sick (nausea/vomiting) based on the GLQ-8. All indicators were in linear analogue self-assessment format ranging 0–100. A clinically significant change was conservatively defined as at least ±8 points. Sensory neuropathy was assessed by 4-item subscale of the FACT/GOG-Ntx with a 5-point response format ('not at all' to 'very much', score ranging 0–16). Scores of all indicators were linearly transformed to range from 0 to 100 with higher numbers reflecting a better condition.

The changes in QoL scores from baseline to day 1 of cycle 4 (after the three induction cycles), and from day 1 of cycle 4 to day 1 of cycle 12 were summarized descriptively. Treatment effects on changes in QoL score during maintenance therapy were analyzed by repeated-measures modeling, including timepoint (cycle), induction dose, age and treatment arm as covariates.

Results

The SNAP trial enrolled 258 patients in 35 centers in six countries from April 2013 to August 2015; 255 patients initiated treatment and were considered assessable (Figure 1).

Patient and disease characteristics were balanced between the three groups (Table 1). The median age at randomization was 58 years (range 27–85). ECOG PS was 0 in 63.9% of patients. Approximately three-quarters of the patients had ER-positive tumors (82.4%), 210 (82.4%) had measurable disease and 184 (72.2%) had visceral involvement. Prior adjuvant taxane was administered in 80 patients (31.4%).

Efficacy

After median follow-up of 18.2 months (range <1–36 months), 182 PFS events were documented. The median PFS was 7.9 months (90% CI 6.8–8.4) in arm A, 9.0 months (90% CI 8.1–10.9) in arm B and 8.5 months (90% CI 6.7–9.5) in arm C (Figure 2). PFS observed in arm B was significantly longer than the historical reference of median 7 months reported with first-line docetaxel (one-sided log-rank $P = 0.03$). Eighty-five patients died. The median OS was 25.8 months (90% CI 16.9 to infinity) in arm A, 26.2 months (90% CI 21.0 to infinity) in arm B and 25.5 months (90% CI 22.7 to infinity) in arm C (supplementary Figure S1, available at *Annals of Oncology* online).

Complete response occurred in 15 patients: 5 (6.0%), 6 (7.0%) and 4 (4.7%) in arms A, B and C, respectively; and partial response in 110 patients: 34 (41.0%), 41 (47.7%) and 35 (40.7%) in arms A, B and C, respectively. Stable disease was observed in 103 patients: 39 (47.0%), 33 (38.4%) and 31 (36%) in arms A, B and C, respectively. Clinical benefit, defined as duration of stable disease ≥24 weeks or partial or complete response, were observed in 165 patients: 54 (65.1%), 59 (68.6%), and 52 (60.5%) in arms A, B and C, respectively.

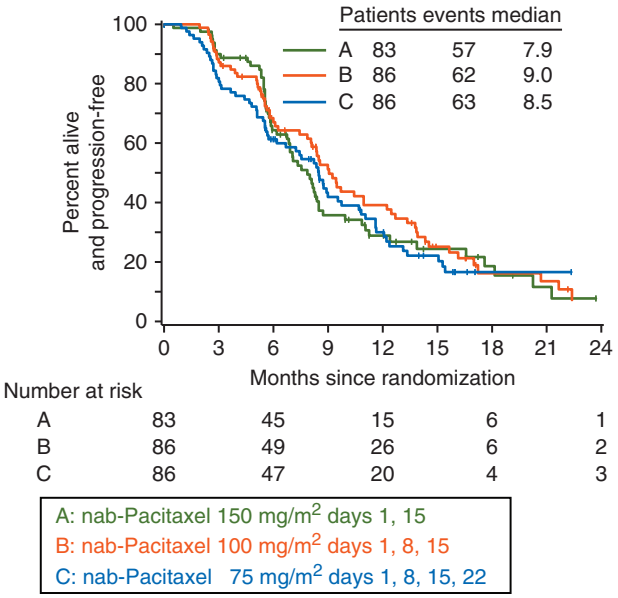


Figure 2. Kaplan–Meier estimates of progression-free survival according to treatment arm.

Feasibility and adverse events

Feasibility, defined as completing induction and maintenance treatment according to protocol for ≥24 weeks, was 48.2% (90%

Table 1. Patient, disease and prior treatment characteristics of 255 patients in the SNAP trial

	Arm A ($N = 83$)	Arm B ($N = 86$)	Arm C ($N = 86$)	Total ($N = 255$)
Age (years), median (range)	58 (35–85)	56 (27–83)	60 (38–83)	58 (27–85)
<70 years	74 (89.2 %)	74 (86.0%)	72 (83.7%)	220 (86.3%)
≥70 years	9 (10.8%)	12 (14.0%)	14 (16.3%)	35 (13.7%)
Body mass index (kg/m^2)				
<25	41 (49.4%)	43 (50.0%)	33 (38.4%)	117 (45.9%)
≥25 and <30	18 (21.7%)	22 (25.6%)	31 (36.0%)	71 (27.8%)
≥30	24 (28.9%)	21 (24.4%)	22 (25.6%)	67 (26.3%)
ECOG PS 0 (cycle 1 day 1)	49 (59.0%)	59 (68.6%)	55 (64.0%)	163 (63.9%)
De novo stage IV MBC	27 (32.5%)	17 (19.8%)	24 (27.9%)	68 (26.7%)
ER positive[a]	72 (86.7%)	69 (80.2%)	69 (80.2%)	210 (82.4%)
PgR positive[a]	56 (67.5%)	62 (72.1%)	62 (72.1%)	180 (70.6%)
Measurable disease	68 (81.9%)	73 (84.9%)	69 (80.2%)	210 (82.4%)
Dominant metastatic site viscera	53 (63.9%)	66 (76.7%)	65 (75.6%)	184 (72.2%)
Number of metastatic sites				
≤3	74 (89.2%)	71 (82.6%)	70 (81.4%)	215 (84.3%)
>3	9 (10.8%)	15 (17.4%)	16 (18.6%)	40 (15.7%)
Prior adjuvant chemotherapy	44 (53.0%)	53 (61.6%)	41 (47.7%)	138 (54.1%)
Prior adjuvant taxane	26 (31.3%)	28 (32.6%)	26 (30.2%)	80 (31.4%)
Prior adjuvant endocrine therapy	42 (50.6%)	56 (65.1%)	54 (62.8%)	152 (59.6%)
Prior endocrine therapy for metastatic disease	30 (36.1%)	30 (34.9%)	33 (38.4%)	93 (36.5%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; MBC, metastatic breast cancer; PgR, progesterone receptor.
[a]On the basis of metastasis, if available, otherwise primary tumor.

CI 38.7% to 57.8%), 50.0% (90% CI 40.7% to 59.3%) and 51.2% (90% CI 41.8% to 60.5%) for arms A, B and C, respectively.

In the induction phase, 122 and 133 patients received nab-paclitaxel at the starting dose of 150 and 125 mg/m^2, respectively. Overall, 227 of the 255 (89%) patients completed three cycles of induction treatment: their median relative dose intensity was 86.1% with the nab-paclitaxel 150 mg/m^2 and 93.3% with the 125 mg/m^2 dose. At least one adverse event occurred in 244 of the 255 patients (95.7%; Table 2): 120 of 122 (98.4%) at the nab-paclitaxel 150 mg/m^2 and 124 of 133 (93.2%) at the 125 mg/m^2 dose. Grade ≥2 peripheral sensory neuropathy was reported in 14.8% (90% CI 9.8% to 21.1%) of patients treated with the 150 mg/m^2 dose and 7.5% (90% CI 4.1% to 12.4%) with 125 mg/m^2. Grade ≥3 peripheral sensory neuropathy occurred in 2.5% (90% CI 0.7% to 6.2%) and in 0% (90% CI 0% to 2.2%) of patients, respectively.

One hundred ninety-nine patients started maintenance treatment. Grade ≥2 peripheral sensory neuropathy was reported in 37.9% (90% CI 27.9% to 48.7%) of patients in arm A, 36.1% (90% CI 26.7% to 46.4%) in arm B and 31.2% (90% CI 21.5% to 42.3%) in arm C. Grade ≥3 was reported for 9.1% (90% CI 4.0% to 17.2%), 5.6% (90% CI 1.9% to 12.3%) and 6.6% (90% CI 2.3% to 14.4%) of patients, respectively (supplementary Figure S2, available at *Annals of Oncology* online). Dose reductions/delays due to peripheral sensory neuropathy occurred in 21.2%, 11.1% and 11.4% of patients in arms A, B and C, respectively.

Quality of life

Completion rates of QoL forms were >90% through the cycle 12 assessment and were similar between treatment arms. At baseline, patients reported low scores for tiredness (mean ± SD in arm A 56.6 ± 28.6; arm B 57.0 ± 29.7; arm C 53.8 ± 29.7), physical well-being (arm A 66.3 ± 27.5; arm B 69.0 ± 29.1; arm C 63.3 ± 27.7), mood (arm A 64.0 ± 27.3; arm B 64.4 ± 27.1; arm C 53.4 ± 28.4) and coping effort (arm A 56.7 ± 31.8; arm B 61.7 ± 29.0; arm C 44.3 ± 31.8) indicating impaired QoL before starting treatment (supplementary Table S1, available at *Annals of Oncology* online). During the induction phase (baseline to day 1 of cycle 4), hair loss (mean ± SD of change in arm A -70.2 ± 41.9; arm B -77.3 ± 34.5; arm C -72.6 ± 32.8) and sensory neuropathy (arm A -19.0 ± 25.2; arm B -20.6 ± 22.7; arm C -18.8 ± 23.8) showed the most pronounced worsening in symptoms and treatment burden was substantially impaired (supplementary Table S1, available at *Annals of Oncology* online).

Figure 3 summarizes changes in QoL scores during the maintenance phase. Hair loss significantly improved during maintenance therapy, with patients in arms B (mean difference 18.6; 95% CI 7.5–29.6; $P = 0.001$) and C (mean difference 10.9; 95% CI 0.4–21.5; $P = 0.04$) reporting a greater improvement compared with those in arm A. Noteworthy, the scores for sensory neuropathy did not worsen with prolonged nab-paclitaxel administration in any of the maintenance arms. There were also no significant differences in changes for the other symptoms. Patients in arm C reported a significantly greater improvement in mood compared with arm A (mean difference 13.3; 95% CI 6.1–20.6; $P < 0.001$) and arm B (mean difference 9.6; 95% CI 2.8–16.4; $P = 0.01$). There were no significant differences in changes for the other global indicators.

Discussion

The SNAP trial shows that in the first-line treatment of MBC, a chemotherapy maintenance schedule with single-agent nab-paclitaxel at reduced doses, after a short-term induction at

Table 2. Adverse events (maximum grade) reported among 255 patients initiating the induction phase and 199 patients who initiated the maintenance phase of the SNAP trial

Adverse event (CTCAE v4.0)	Induction phase All Arms (*N* = 255)				Maintenance phase											
					Arm A (*N* = 66)				Arm B (*N* = 72)				Arm C (*N* = 61)			
	Grade				Grade											
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Peripheral sensory neuropathy	40.8	9.8	1.2	0	39.4	28.8	9.1	0	37.5	30.6	5.6	0	45.9	24.6	6.6	0
Neutropenia	6.7	32.5	19.2	3.9	12.1	15.2	4.5	1.5	11.1	23.6	8.3	0	16.4	21.3	6.6	0
Decreased platelets	7.1	0	0	0.4	3.0	0	0	0	2.8	1.4	0	0	3.3	0	0	0
Febrile neutropenia	–	–	1.2	0	–	–	0	0	–	–	1.4	0	–	–	0	0
Anemia	33.3	23.9	2.0	0	45.5	9.1	0	0	44.4	18.1	2.8	0	49.2	9.8	0	0
Nausea	27.1	5.9	0.8	–	21.2	4.5	1.5	–	18.1	2.8	0	–	26.2	3.3	1.6	–
Vomiting	7.8	1.6	1.2	0	7.6	0	1.5	0	6.9	2.8	0	0	13.1	1.6	1.6	0
Diarrhea	20.0	4.3	3.5	0	10.6	0	3.0	0	12.5	2.8	1.4	0	13.1	6.6	0	0
Allergic reaction	4.3	0.8	0	0	6.1	0	0	0	1.4	1.4	0	0	3.3	0	0	0
Pneumonitis	0.4	1.2	0	0	0	0	0	0	1.4	1.4	0	0	0	4.9	0	0
Total patients with ≥1 AE[a]	95.7				95.5				95.8				96.7			

Data are percentage of patients. Dash (–) indicates the grade is not relevant for the AE.
[a]Includes reports of other grades 3–5 AEs (data not shown).

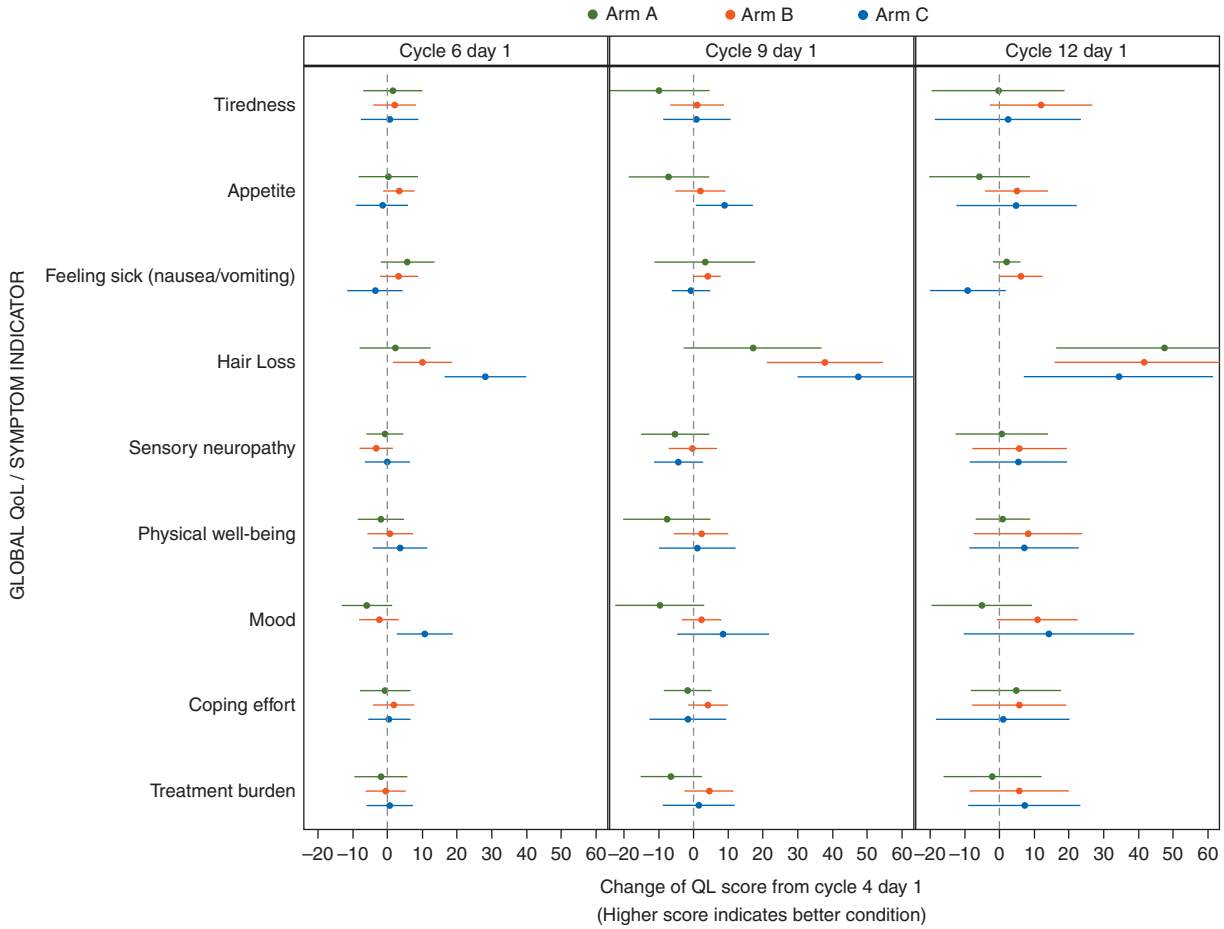


Figure 3. Changes in quality-of-life scores from day 1 of cycle 4 (after completion of three induction treatment cycles, before initiating maintenance phase) according to the maintenance schedule of nab-Paclitaxel administration for cycles 6, 9 and 12. Data are summarized as mean with 95% confidence interval.

conventional doses, is feasible and more active than the historical data available with single-agent docetaxel. In particular, median PFS in arm B, with a dose de-escalation from 150/125 to 100 mg/m^2 days 1, 8 and 15 Q28, was significantly longer than the historical PFS of docetaxel (PFS 9.0 versus 7.0 months, $P = 0.03$). This result needs to be interpreted with caution, due to the lack of a prospective comparison with a docetaxel single-agent control arm. However, these data must be weighted taking into account that all major guidelines recommend to prolong chemotherapy until disease progression [1, 18], with a non-negligible impact on patient tolerability in the setting of incurable disease. This recommendation is based on the results of clinical trials comparing different chemotherapy durations at full therapeutic doses. In this perspective, the results of the SNAP trial indicate that prolonged administration of nab-paclitaxel at reduced doses may represent an innovative treatment strategy to improve the outcome of MBC patients, while preserving patients' QoL.

As expected, neurotoxicity was the most frequent adverse event, reported in about one-third of the patients during the maintenance phase. Indeed, in the Gradishar et al. study [19], comparing three different nab-paclitaxel schedules with docetaxel in MBC, the incidence of sensory neuropathy was similar, with a shorter time to recovery (from grade 3 to grade $\leq$2) in the nab-paclitaxel arm. Noteworthy, in the SNAP QoL study, after the substantial and expected deterioration in neurotoxicity during induction, there was a marginal change with prolonged chemotherapy administration. Furthermore, patients reported improvements in their perception of hair loss and in mood during maintenance therapy, particularly in arms B and C. For some of the other QoL domains a similar tendency was seen. These data further support the concept that prolonged chemotherapy administration in responding patients is not associated with a deterioration in QoL, thus confirming the QoL data already reported by two of the published studies on maintenance chemotherapy [5, 21, 22]. The QoL analysis of the SNAP trial, together with the PFS data obtained in arm B, support the use of reduced nab-paclitaxel doses during the maintenance phase, considering its favorable impact on QoL and the palliative intent in this advanced disease stage.

A limitation of our trial is the absence of a direct comparison with a standard dose prolonged chemotherapy arm, as patient selection may have led to a longer PFS than the historical control, but is mitigated by having three investigational arms. A trial design to include a fourth control arm for direct comparison would have required about 150 patients per arm, accrual to which would be very difficult in view of emerging results with new biological compounds.

In conclusion, the SNAP trial was the first trial of prolonged chemotherapy administration that evaluated de-escalation of a chemotherapeutic agent, nab-paclitaxel as maintenance treatment in HER2-negative MBC patients. Its results indicate that an alternative maintenance nab-paclitaxel schedule, with reduced doses after a short-term induction chemotherapy at conventional doses, is feasible and resulted in a median PFS significantly greater than the historical reference of 7.0 months achieved with conventional docetaxel. The QoL analysis of the SNAP trial, together with the PFS data, supports the use of nab-paclitaxel at reduced doses (100 mg/m^2 days 1, 8 and 15 Q28) as maintenance following a short induction at full therapeutic dosages.

Acknowledgements

The authors thank the patients, physicians, nurses, trial coordinators and pathologists who participated in the SNAP clinical trial. The International Breast Cancer Study Group (IBCSG) coordinated the trial and is responsible for the study design, random assignment, collection and management of data, medical review, data analysis and reporting, in collaboration with the Breast International Group (BIG), Cancer Trials Ireland and the SOLTI Group.

Funding

Celgene and International Breast Cancer Study Group (no grant numbers apply). SNAP received financial support for trial conduct from Celgene and the International Breast Cancer Study Group (IBCSG) (no grant number applies). Celgene provided drug supply. Celgene had no role in the reporting or interpretation of the trial, other than a minority representation on the Steering Committee. Support for the coordinating group was provided by IBCSG: Frontier Science and Technology Research Foundation (FSTRF; no grant number applies), Swiss Group for Clinical Cancer Research (SAKK; no grant number applies), Cancer Research Switzerland/Oncosuisse/Cancer League Switzerland (no grant number applies) and the Foundation for Clinical Cancer Research of Eastern Switzerland (OSKK; no grant number applies).

Disclosure

AG has disclosed being been paid honoraria by Celgene, Eisai and Teva (individual); consulting/advisory fees by Celgene, Eisai and Teva (individual); speakers' bureau by Celgene, Eisai, Teva and Pierre Fabre (individual). UH-S has disclosed being paid consulting/advisory fees by AstraZeneca (individual) and travel expenses by Pfizer (individual). MC has disclosed being paid honoraria by Novartis (individual); consulting/advisory role by Pierre Fabre, Pfizer, OBI Pharma, Puma Biotechnology, Celldex and AstraZeneca (individual). MJK has disclosed being paid consulting/advisory fees by Roche, Novartis and Genomic Health (individual); travel expenses by Roche (individual). RvM has disclosed being paid honoraria by AmGen, Bayer and Roche (individual); consulting/advisory fees by AmGen, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck and Novartis (institution); research funding by Bayer and Merck (institution). JC has disclosed being paid honoraria by Roche, Novartis, Eisai, Celgene and Pfizer (institution); consulting/advisory fees by Roche, Celgene, AstraZeneca, Cellestia Biotech AG and Biothera Pharmaceuticals (individual). JW has disclosed being paid honoraria and consulting/advisory fees by Roche and Pfizer (individual); speakers' bureau by Pfizer; travel expenses by Roche (individual). OP has disclosed being paid consulting/advisory fees by Roche, Pfizer and Novartis (individual); travel expenses by Roche (individual). MMR disclosed being paid consulting/advisory fees by Merck (individual) and Ipsen (institution); research funding by Veridex, OncoGenex, Pfizer, Ipsen, Novartis, Merck, Ferring, Celgene, AstraZeneca and Pierre Fabre (institution). GJ disclosed being paid honoraria by Novartis, Roche, Lilly and Pfizer (individual); consulting/advisory fees by Novartis, Celenge, Roche, Amgen, Pfizer, Bristol-Myers Squibb, Lilly and Puma Biotechnology (individual); research funding by Novartis and Roche (individual); travel expenses by Novartis, Roche, Pfizer and Lilly (individual). All remaining authors have declared no conflicts of interest.

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