Article type: Original article

Title: 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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Running Head: Maintenance chemotherapy schedules for metastatic breast cancer

Key message: The SNAP trial shows alternative maintenance chemotherapy schedules with single-agent nab-Paclitaxel at reduced doses after a short-term induction at conventional doses are feasible and active in first-line treatment of metastatic breast cancer. Quality-of-life scores for neuropathy showed minimal further decline during maintenance after the substantial and expected decline during induction therapy.

ABSTRACT

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.

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 1,15 Q28; Arm B, nab-Paclitaxel 100 mg/m^2 days 1,8,15 Q28; Arm C, nab-Paclitaxel 75 mg/m^2 days 1,8,15,22 Q28. Induction was three cycles nab-Paclitaxel 150/125 mg/m^2, days 1,8,15 Q28. The primary objective was to evaluate the efficacy of each maintenance schedule, in terms of progression-free survival (PFS), as compared to the historical reference of 7-month median PFS reported by previous studies with first-line docetaxel.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 evaluation was performed, global indicator for physical well-being was defined as the primary endpoint; completion rates of quality-of-life forms were >90%.

Results: 255 patients were evaluable for the primary endpoint. After 18.2 months median follow-up, 182 PFS events were observed. 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(90%CI 8.1-10.9) in Arm B and 8.5 months (90%CI 6.7-9.5) in Arm C. PFS in Arm B was significantly longer than the historical reference of first-line docetaxel (*P*=0.03).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 patients in Arm A, Arm B and Arm C, respectively (Grade≥3 in 9.1%, 5.6% and 6.6% of patients, respectively). Noteworthy, the quality-of-life 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.

Keywords: Metastatic breast cancer, maintenance chemotherapy, alternative treatment schedules
Registration: ClinicalTrials.gov NCT01746225

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 candidate 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 quality-of-life.

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 and a moderate, but significant improvement in overall survival [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 quality-of-life 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 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) (**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 1,15 Q28; Arm B, nab-Paclitaxel 100 mg/m^2 days 1,8,15 Q28; Arm C, 75 mg/m^2 days 1,8,15,22, Q28. In the original study design, the induction phase consisted of nab-Paclitaxel 150 mg/m^2 days 1,8,15 Q28, but was modified to 125 mg/m^2 days 1,8,15 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 exam, 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 reason other than progression. Targeted adverse events were reported for each cycle and graded according to CTCAE v4.0.

Endpoints

The primary endpoint was progression-free survival (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 endpoint was censored at date of last progression-free assessment. Secondary endpoints included tolerability (adverse events), feasibility (completion of treatment per protocol for ≥24 weeks), best overall response according to RECIST 1.1, overall survival (OS; time 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 to an historical-control PFS of first-line docetaxel using a one-sample, one-sided (α=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 endpoints were summarized descriptively.

Quality of Life (QoL)

Patients completed a paper-based QoL assessment at baseline (prior to randomization), and day 1 of each of the first 12 cycles, unless treatment 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 endpoint, 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 (LASA) 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 0-100 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 evaluable **(Figure 1).** Patient and disease characteristics were balanced between the three groups (**Table 1**). The median age at randomization was 58 years (range, 27 to 85). ECOG PS was 0 in 63.5% of patients. Approximately three-quarters of the patients had ER-positive tumors (82.9%), 210 (82.4%) had measurable disease and 184 patients (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-infinity) in Arm A, 26.2 months (90%CI 21.0-infinity) in Arm B and 25.5 months (90%CI 22.7-infinity) in Arm C ***(*Figure S1*).***

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. Stable disease was observed in 103 patients; 39 (47.0%) in Arm A, 33 (38.4%) in Arm B and 31 (36%) in Arm C. 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%) for Arms A, B, C respectively.

Feasibility and Adverse Events

Feasibility, defined as completing induction and maintenance treatment according to protocol for ≥24 weeks, was 48.2% (90%CI 38.7-57.8%), 50.0% (90%CI 40.7-59.3%), and 51.2% (90%CI 41.8-60.5%) for Arms A, B, C respectively.

In the induction phase, 122 and 133 patients received nab-Paclitaxel at the starting dose of 150 mg/m² and 125 mg/m^2, respectively. Overall, 227/255 (89%) patients completed 3 cycles of induction treatment: their median relative dose-intensity was 86.1% with the nab-Paclitaxel 150 mg/m² and 93.3% with the 125 mg/m² dose. At least one AE occurred in 244/255 patients (95.7%; **Table 2**): 120/122 (98.4%) at the nab-Paclitaxel 150 mg/m² and 124/133 (93.2%) at the 125 mg/m² dose**.** Grade ≥2 peripheral sensory neuropathy was reported in 14.8% (90%CI 9.8-21.1%) of patients treated with the 150 mg/m² dose and 7.5% (90%CI 4.1-12.4%) with 125 mg/m². Grade ≥3 peripheral sensory neuropathy occurred in 2.5% (90%CI 0.7-6.2%) and in 0% (90% CI 0-2.2%) of patients, respectively.

One hundred ninety-nine patients started maintenance treatment. Grade ≥2 peripheral sensory neuropathy was reported in 37.9% (90%CI 27.9-48.7%) of patients in Arm A, 36.1% (90%CI 26.7-46.4%) in Arm B and 31.2% (90%CI 21.5-42.3%) in Arm C. Grade ≥3 was reported for 9.1% (90%CI 4.0-17.2%), 5.6% (90%CI 1.9-12.3%) and 6.6% (90%CI

2.3-14.4%) of patients, respectively (**Figure S2**). Dose reductions/delays due to peripheral sensory neuropathy occurred in 21.2%, 11.1% and 11.4% of patients, respectively, in Arms A, B and C.

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 **(Table S1)**. 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 **(Table S2)**.

Figure 3 summarizes changes in QoL scores during the maintenance phase. Hair loss significantly improved during maintenance therapy, with patients in Arms B (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 to 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 to 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 conventional doses, is feasible and more active than the historical data available with docetaxel single-agent. In particular, median PFS in Arm B, with a dose de-escalation from 150/125 to 100 mg/m² days 1,8,15 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 and confirm 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 vey 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, support the use of nab-Paclitaxel at reduced doses (100 mg/m^2 days 1,8,15 Q28) as maintenance following a short induction at full therapeutic dosages.

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DISCLOSURES

Dr. Gennari has disclosed being been paid honoraria by Celgene, Eisai, Teva (individual); consulting/advisory fees by Celgene, Eisai, Teva (individual); speakers' bureau by Celgene, Eisai, Teva, Pierre Fabre (individual). Dr. Hasler-Strub has disclosed being paid consulting/advisory fees by AstraZeneca (individual) and travel expenses by Pfizer (individual). Dr. Colleoni has disclosed being paid honoraria by Novartis (individual); consulting/advisory role by Pierre Fabre, Pfizer, OBI Pharma, Puma Biotechnology, Celldex, AstraZeneca (individual). Dr. Kennedy has disclosed being paid

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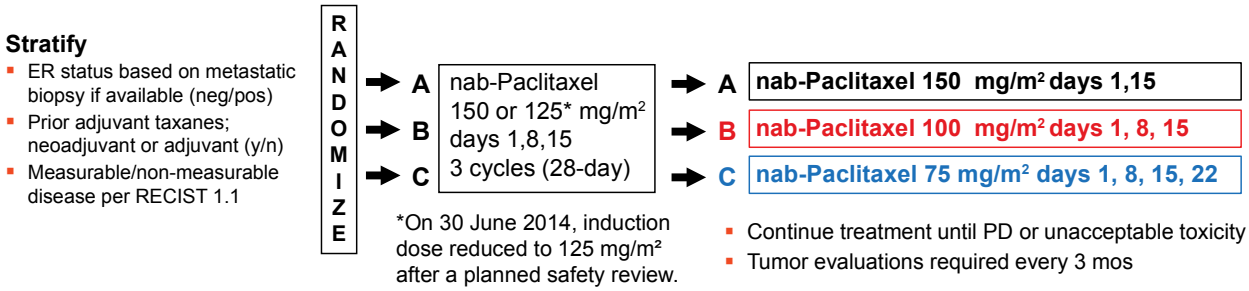
FIGURE LEGENDS

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

Figure 2. Kaplan-Meier estimates of progression-free survival (PFS) according to treatment arm.

Figure 3. Changes in quality-of-life scores from day 1 of cycle 4 (after completion of 3 induction treatment cycles, prior to 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% CI.

Figure 1.



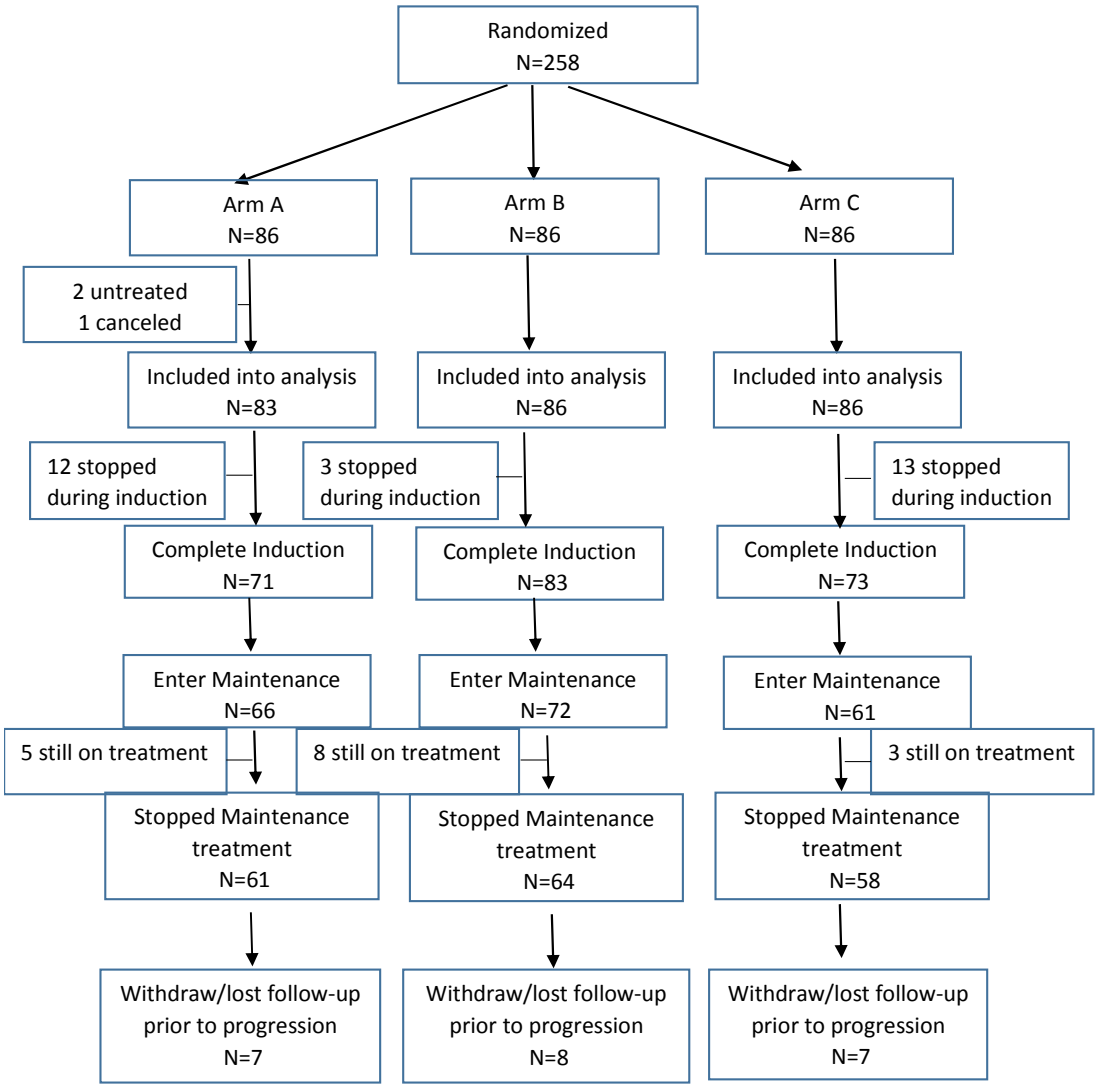


Fig. 2

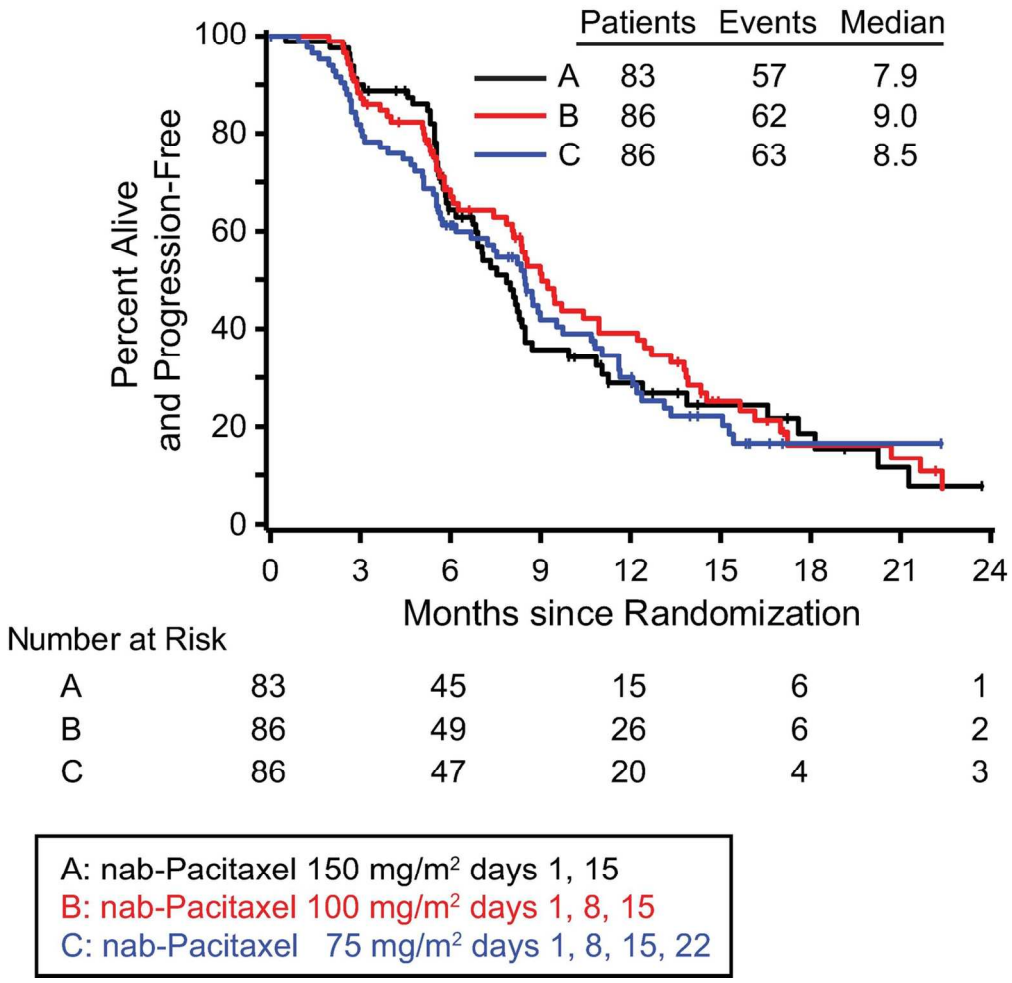


Figure 2. Kaplan-Meier estimates of progression-free survival (PFS) according to treatment arm

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Fig 3

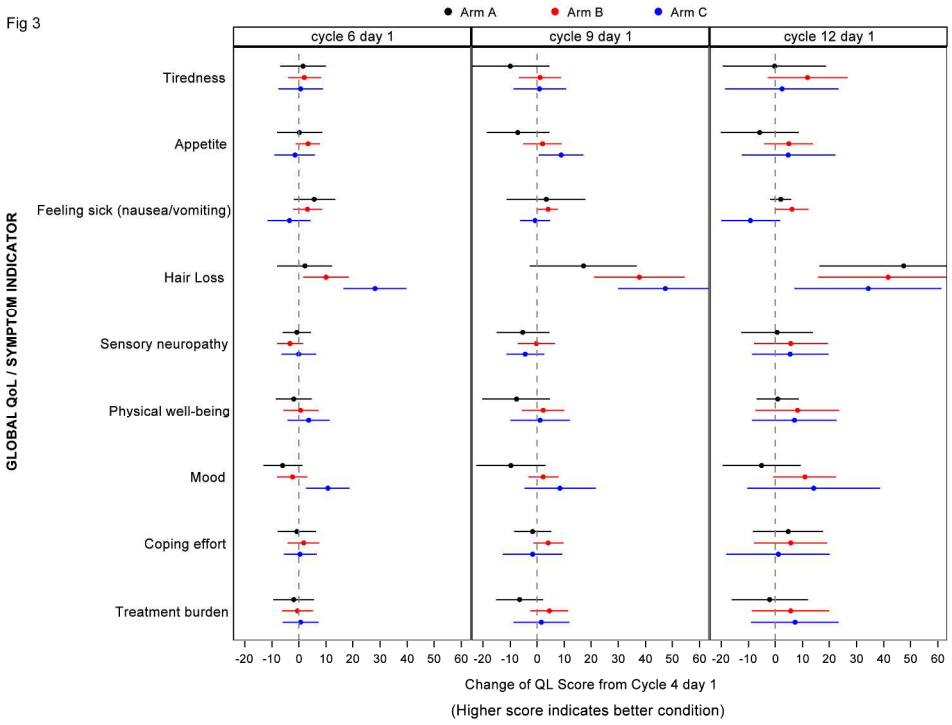

Figure 3. Changes in quality-of-life scores from day 1 of cycle 4 (after completion of 3 induction treatment cycles, prior to initiating maintenance phase) according to the maintenance schedule of nab-Paclitaxel administration for cycles 6, 9, and 12. Data are summarized as mean with 95% CI

273x203mm (300 x 300 DPI)

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 (yrs), 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*	72 (86.7%)	69 (80.2%)	69 (80.2%)	210 (82.4%)
PgR positive*	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%)

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ER=estrogen receptor; MBC=metastatic breast cancer; PgR=progesterone receptor

* On basis of metastatsis, if available, otherwise primary tumor

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. Data are % of patients.

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*	95.7					95.5				95.8				96.7			

Dash (-) indicates the grade is not relevant for the AE

* Includes reports of other grade 3-5 AEs (data not shown)