



Timing of nivolumab with neoadjuvant carboplatin and paclitaxel for early triple-negative breast cancer (BCT1902/IBCSG 61-20; Neo-N): a non-comparative, open-label, randomised, phase 2 trial

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Summary

Background The optimal scheduling of PD-1 inhibitors with neoadjuvant chemotherapy in patients with early triple-negative breast cancer is unknown. We aimed to investigate the activity of two differing schedules of neoadjuvant nivolumab initiation with 12 weeks of carboplatin and paclitaxel for this patient population.

Methods Neo-N is an investigator-initiated, non-comparative, open-label, randomised, phase 2 trial conducted at 12 hospitals in Australia, one in New Zealand, and one in Italy. Participants had to be aged 18 years or older; have an Eastern Cooperative Oncology Group performance status of 0–1, clinical stage I (cT1cN0) or II (cT1cN1, cT2cN0–1, or cT3cN0), oestrogen receptor expression of less than 1%, and progesterone receptor expression of less than 10%; had to be HER2 negative; and have previously untreated operable breast cancer with adequate organ function. Participants were stratified according to age and randomly assigned (1:1) centrally using a computer-generated sequence with a minimisation algorithm to either nivolumab 240 mg then 2 weeks later nivolumab 360 mg and carboplatin AUC5 every 3 weeks with concurrent paclitaxel 80 mg/m² once per week for 12 weeks (lead-in group) or concurrent nivolumab 360 mg and carboplatin AUC5 every 3 weeks with once per week paclitaxel 80 mg/m² for 12 weeks then 240 mg nivolumab 2 weeks later (concurrent group). Data were collected from registration until the 100-day safety follow-up visit, and survival follow-up continues. The primary endpoint was pathological complete response (ypT0/Tis ypN0) at the time of surgery, analysed in each group separately and in all patients who received at least one dose of all three study treatment (modified intention-to-treat population). The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12619001308189, and EudraCT, 2019-003465-18, and is ongoing.

Findings Between July 6, 2020, and April 1, 2022, 124 participants were enrolled and 14 were ineligible. 110 participants were randomly assigned and 108 were included in the modified intention-to-treat analysis (53 in the lead-in group and 55 in the concurrent group). Median follow-up was 12 months (IQR 7–18). All patients were female with a median age of 49 years (IQR 43–60). 18 (17%) patients had clinically node-positive disease; 37 (34%) had clinical stage I, 70 (65%) had stage II, and one (1%) had stage III disease. The pathological complete response rate was observed in 27 (51% [39–63]) of 53 patients in the nivolumab lead-in group and in 30 (55% [43–66]) of 55 in the concurrent group. Treatment-related grade 3–4 adverse events occurred in 70 (65%; 32 [60%] of 53 in the lead-in group and 38 [69%] of 55 in the concurrent group) of 108 patients, with the most common being decreased neutrophil count (25 [47%] of 53 in the lead-in group vs 28 [53%] of 55 in the concurrent group), anaemia (six [11%] vs ten [19%]), and increased alanine aminotransferase (three [6%] vs three [6%]). Serious adverse events were reported in 16 (30%) patients in the lead-in group and 26 (47%) in the concurrent group. Treatment-related serious adverse events occurred in seven (13%) patients in the lead-in group and 20 (36%) in the concurrent group. No treatment-related deaths occurred during the study.

Interpretation While this study did not support the hypothesis that lead-in nivolumab before chemotherapy was associated with a pathological complete response advantage, high pathological complete response rates were reached supporting shorter duration, non-anthracycline regimens in patients with newly diagnosed triple-negative breast cancer. Future trials are warranted to compare this regimen with the current standards of care.

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Introduction

Triple-negative breast cancer is associated with a worse prognosis, and has fewer treatment options, than

oestrogen receptor-positive or HER2 (also known as ERBB2)-positive breast cancer.¹ The prognosis for patients with early stage triple-negative breast cancer

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See [Comment](#) page 273

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Research in context

Evidence before this study

We searched PubMed for studies published in English from database inception to May 31, 2019, with a manual search of reference lists, using the terms “neoadjuvant”, “breast cancer”, AND “PD-(L)1”, identified phase 1 and 2 trial data supporting efficacy of checkpoint inhibition in triple negative breast cancer using atezolizumab, pembrolizumab, and durvalumab.

Evidence quality was low. Clinical uncertainty remains regarding the ideal sequencing strategy of PD-1 inhibitors with chemotherapy and whether shorter duration of non-anthracycline based chemotherapy when combined with immunotherapy can be effective in biomarker-selected populations.

Added value of this study

Since August, 2011, neoadjuvant immunotherapy (PD-1 inhibitor) in addition to chemotherapy is the standard of care in the management of patients with early-stage triple negative breast cancer. The Neo-N trial evaluated a 12-week non-anthracycline containing neoadjuvant chemotherapy regimen (the current standard is a 24-week regimen) and

two sequencing strategies of nivolumab (monotherapy then combination chemotherapy or concurrently with chemotherapy). Sequencing of nivolumab did not result in a meaningful difference in pathological complete response rates. However, we found that pathological complete response rates were high with this 12-week regimen.

Implications of all the available evidence

While long-term outcomes of this trial are still not mature, pathological complete response rates have become clinically meaningful in the setting of neoadjuvant immunochemotherapy for patients with early-stage triple negative breast cancer. Our study showed pathological complete response rates similar to other similar studies (NeoPACT; NCI10013), which suggests that shorter duration neoadjuvant chemotherapy with PD-1 inhibition could be efficacious and associated with less toxic effects than the current 24 week standard of care, particularly in biomarker selected populations independent of nivolumab sequencing. This finding remains to be evaluated in future clinical studies.

varies widely and the risk of distant recurrence rises with increasing stage.² However, even patients with lower stage resectable clinical T category (cT1b cN0) who typically receive chemotherapy can have excess breast cancer mortality, suggesting that this patient population requires novel approaches.³ Triple-negative breast cancers have been observed in the past 20 years to have a greater immune infiltrate relative to other breast cancer subtypes.⁴ Immune checkpoint inhibition in combination with chemotherapy has the potential to overcome therapeutic resistance associated with intratumoral heterogeneity and genomic instability.⁵ Hence, investigation of the potential benefit of checkpoint inhibition has been of high interest in this breast cancer subtype.

Neoadjuvant chemotherapy and PD-1 targeting immunotherapy became standard of care in 2021 for patients with stage 2 or stage 3 triple-negative breast cancer due to improved pathological complete response rates and event-free survival in the KEYNOTE-522 trial.⁶ KEYNOTE-522 used a 24-week regimen of paclitaxel, carboplatin, doxorubicin–epirubicin, cyclophosphamide, and pembrolizumab. Current guidelines recommend considering a neoadjuvant approach for cT1c cN0 and higher stages using anthracycline and taxane, with pembrolizumab included for cT2 or higher stage.⁷ 20% patients with cT1c cN0 triple-negative breast cancer have nodal metastases identified with upfront surgery and can be downstaged to ypN0 after neoadjuvant therapy.⁸ However, many patients with clinical stage I disease, and some with stage II disease, might not require intensive systemic therapy regimens to reach long-term survival, and cytotoxic treatment de-escalation could potentially be

reached without sacrificing efficacy in the setting of PD-1 immunotherapy.¹ Further rationale for an anthracycline-free chemotherapy regimen and shorter duration of treatment is to reduce the risk of long-term side-effects, such as cardiac dysfunction, secondary leukaemia, sustained peripheral lymphopenia, and poorer quality of life.^{9,10}

Pathological complete response is associated with an excellent prognosis after neoadjuvant systemic therapy in patients with triple-negative breast cancer, and pathological complete responses reached in the setting of neoadjuvant PD-1 targeted therapy have become clinically meaningful. The poorer prognosis in patients with early stage triple-negative breast cancer without a pathological complete response can be improved by postsurgical adjuvant therapies, such as capecitabine or olaparib, in patients with pathogenic germline variants in *BRCA1* or *BRCA2*.^{11,12} Higher expression of PD-L1 correlates with improved outcomes with checkpoint inhibitor therapy for patients with metastatic triple-negative breast cancer.¹³ Although PD-L1 positivity is not a prerequisite for this treatment strategy in the neoadjuvant setting, pathological complete response rates are higher in this subpopulation regardless of the use of immunotherapy.⁶ The presence of stromal tumour-infiltrating lymphocytes also suggests a more immune sensitive environment associated with a higher rate of pathological complete response and improved prognosis.^{14,15} These biomarkers, the pathological complete response endpoint and the possibility of further adjuvant therapy can allow us to individualise, optimise, and shorten neoadjuvant treatment for some patients without sacrificing outcomes.

Exploratory data from the GeparNuevo trial suggested that scheduling the checkpoint inhibitor before commencing chemotherapy might augment efficacy.^{16,17} There are potential biological advantages to an immunotherapy monotherapy lead-in window, such as optimal facilitation of expansion and proliferation of pre-existing intratumoural T cells, before the myelosuppression and immunosuppression associated with intensive cytotoxic chemotherapy and concomitant corticosteroids.^{9,18} Contrary to this theory, some cytotoxic chemotherapy agents have been shown to induce immunogenic cancer cell death, which might augment the effectiveness of immunotherapy, remove regulatory T cells, and as a result, create a less hostile microenvironment for cytotoxic tumour specific T cells.¹⁹ Taxane and carboplatin have a favourable efficacy and toxicity profile, showing pathological complete response rates in patients with stage I–III triple-negative breast cancer between 45–55% without an anthracycline.^{20,21} Nivolumab is a monoclonal antibody against PD-1 that was chosen for evaluation in this study due to efficacy data and regulatory approval in several solid organ malignancies.²² This finding and efficacy in metastatic breast cancer,^{13,23} made nivolumab a rational choice for evaluation in patients with early breast cancer.

In this study, we aimed to investigate the activity of two differing schedules of neoadjuvant nivolumab initiation (lead-in and concurrent), with 12 weeks of carboplatin and paclitaxel, for patients with stage I or II newly diagnosed triple-negative breast cancer. We further hypothesised that the addition of nivolumab in immune biomarker selected patient subgroups could reach high pathological complete response rates despite an anthracycline-free 12-week chemotherapy regimen.

Methods

Study design and participants

Neo-N is an investigator-initiated, non-comparative, open-label, randomised, phase 2 trial conducted at 12 hospitals in Australia, one in New Zealand, and one in Italy (appendix p 20). The protocol, patient information and consent forms and associated documentation were approved by each institutions' human research ethics committee (reference HREC/58087/PMCC-2019). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline. Written, informed consent was obtained from participants before any study procedures. Patient representatives were involved in the design, conduct, and interpretation of this trial and in the writing of the manuscript. The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12619001308189, and EudraCT, 2019-003465-18, and is ongoing.

Participants were recruited from investigators' clinical practices and had to be aged 18 years or older; have an

Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, clinical stage I (cT1cN0) or II (cT1cN1, cT2cN0–1, or cT3cN0) according to the American Joint Committee on Cancer (version 8), oestrogen receptor expression of less than 1%, and progesterone receptor expression of less than 10%; had to be HER2 negative (as per American Society of Oncology–College of American Pathologists);²⁴ and have previously untreated operable breast cancer with adequate organ function (assessed clinically and by haematology [electrolytes, liver function tests, and creatinine]). Low progesterone expression was allowed based on data indicating that these tumours exhibit similar treatment responses to triple-negative breast cancer.²⁵ All histological types were permitted and there was no molecular subtype restriction. Patients were excluded if the cancer was inoperable, was diagnosed as stage III or IV, or multifocal or multicentric; or in the presence of substantial comorbidities (cardiovascular, pulmonary, autoimmune, or infectious); or if they had contraindications to study treatment.

Randomisation and masking

Participants were stratified according to age (<40 or ≥40 years) and randomly assigned (1:1) centrally using a computer-generated sequence with a minimisation algorithm developed by Breast Cancer Trials (BCT) to nivolumab given as a single lead-in monotherapy dose 2 weeks before starting concurrent chemotherapy (lead-in group) or nivolumab given concurrently with chemotherapy then as a single lead-out monotherapy dose (concurrent group). Participants were enrolled by site investigators, assigned to treatment by site clinical trial coordinators. These personnel remained involved in the trial. There was no masking in this open-label study.

Procedures

Participants received either nivolumab 240 mg then 2 weeks later received nivolumab 360 mg and carboplatin AUC5 every 3 weeks with concurrent paclitaxel 80 mg/m² once per week for 12 weeks (lead-in group) or concurrent nivolumab 360 mg and carboplatin AUC5 every 3 weeks with once per week paclitaxel 80 mg/m² for 12 weeks then 240 mg nivolumab 2 weeks later (concurrent group). All agents were given intravenously. Short-acting granulocyte colony stimulating factor was permitted, and paclitaxel plus carboplatin were permitted when the neutrophil count was 800 cells per mm³ or higher and platelets 75 000 cells per mm³ or higher. Dose reduction of chemotherapy was permitted for protocol-defined toxicity. Dose reduction of nivolumab was not permitted. Prechemotherapy corticosteroids were administered according to institutional protocols. A tumour biopsy was taken at week 2 for translational research in this trial. Sentinel lymph node biopsy was permitted in patients who were clinically node negative prechemotherapy or

See Online for appendix

those with conversion from clinically node positive to clinically node negative status. In those with conversion, when fewer than three sentinel lymph nodes were removed, the tumour was considered as non-pathological complete response due to the potential for a false negative result, regardless of whether a clipped node was removed. Adjuvant nivolumab was not used and any adjuvant therapy was at investigator discretion. Doxorubicin and cyclophosphamide were recommended postoperatively, before capecitabine, if the surgical specimen had a substantial burden of residual cancer. Adjuvant olaparib was not available during the study period.

Study visits occurred once every 3 weeks during treatment. Visits included clinically directed physical examination to exclude progression during treatment and recording concomitant medications for adverse events related to study treatment, ECOG performance status, haematology or biochemistry, confirmation of negative serum or urine pregnancy test for women of child-bearing potential, and adverse events (as per Common Terminology Criteria for Adverse Events; version 5). Participants had mammography and breast ultrasound at baseline, with CT and bone scan as clinically indicated. Sex and indigenous status were self-reported. Ethnicity data were not recorded. At the presurgical visit (within 21 days before surgery), information was collected on clinically directed physical examination to exclude progression during treatment,

ECOG performance status, adverse events, laboratory assessments, breast ultrasound, and surgical assessment. At the safety follow-up visit 100 days after the last dose of nivolumab, data on non-serious and serious adverse events were collected. Participant withdrawal from the study could occur at their own request or at the request of the investigator, with no further follow-up. If study treatment was ceased early, follow-up continued up to 3 years. Data were collected from registration until the 100-day safety follow-up visit. Survival follow-up is still ongoing and will continue every 6 months up to 3 years after randomisation collecting data associated with medication for immune endocrinopathies (eg, thyroid, pituitary, adrenal, and diabetes), immune-related adverse events or serious adverse events, invasive breast cancer events, and anticancer treatments after surgery (including systemic therapy and radiotherapy). Central determination of stromal tumour-infiltrating lymphocyte quantity was assessed on the baseline pretreatment tumour core biopsy according to previously described criteria by a single pathologist.¹⁵ The pathologist was masked to clinical outcomes. Central PD-L1 testing was performed using the SP142 immunohistochemistry assay (Ventana, F Hoffmann-La Roche, Rotkreuz, Switzerland), with positivity defined as at least 1% of positive immune cells. When this trial protocol was finalised in October, 2019, SP-142 antibody was chosen because it was a validated PD-L1 assay in breast cancer at that time. Pathological complete response was determined locally. Residual cancer burden was reported using the classification of Symmans and colleagues.²⁶

Outcomes

The primary endpoint was pathological complete response (defined as the absence of invasive disease in the breast and axilla, with or without ductal carcinoma in situ [ypT0/Tis ypN0]) at the time of surgery, analysed in each group separately and, as a post-hoc analysis, combined. Secondary endpoints were pathological complete response in the breast (ypT0/Tis), residual cancer burden, change in Ki-67, tumour clinical response rate by WHO criteria, event-free survival (time from randomisation until progression of disease, breast cancer recurrence or death), overall survival (time from randomisation until death from any cause), and safety. 3-year event free survival and overall survival will be reported after all patients have completed 3 years of follow-up. Ki-67 at surgery was recorded as zero in patients with a pathological complete response. Additional secondary endpoints were to estimate pathological complete response rates according to the stromal tumour-infiltrating lymphocytes ($\geq 30\%$ vs $< 30\%$; performed using standard criteria¹⁵) and PD-L1 expression ($\geq 1\%$ vs $< 1\%$). The 30% stromal tumour-infiltrating lymphocyte cutoff was based on the good

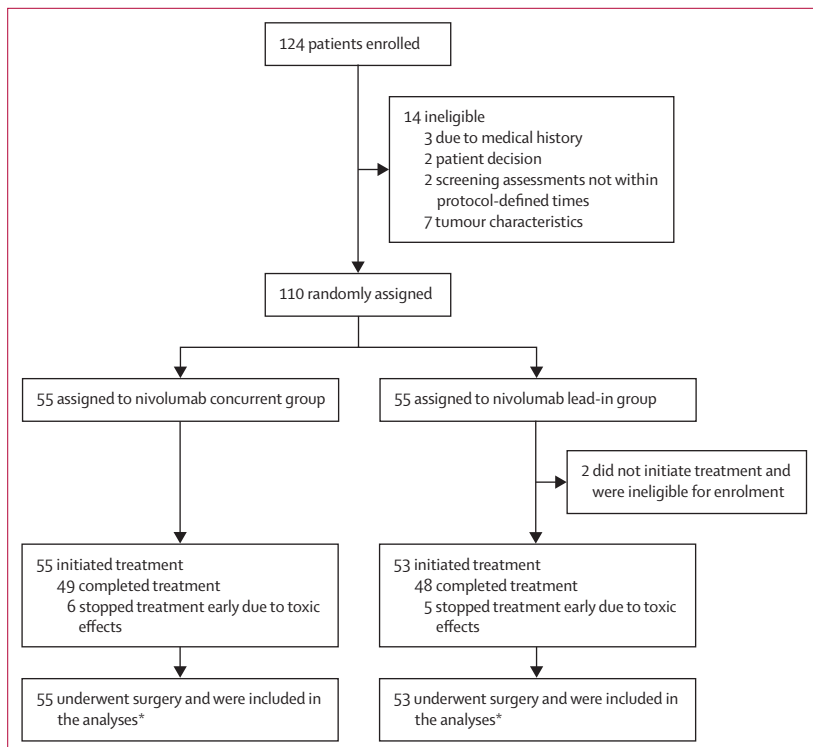


Figure 1: Trial profile

*All patients who initiated therapy were included in modified intention-to treat analysis.

prognosis seen in patients with early triple-negative breast cancer who had 30% or higher stromal tumour-infiltrating lymphocytes, which was associated with higher pathological complete response rates.¹⁴ Investigator attributed immune-related adverse events are still being collected until 3 years after randomisation and are not reported herein.

Statistical analyses

A Simon two-stage non-comparative Bayesian pick-the-winner design²⁷ was used to test the null hypothesis of a pathological complete response rate in breast and lymph nodes of 40% or less versus an alternative hypothesis of 60% or more. A preplanned interim analysis was conducted after the first 24 participants were enrolled in each study group requiring at least ten patients with a pathological complete response for enrolment to continue to a total of 54 participants in each study group. Each study group was assessed separately, requiring at least 28 pathological complete responses in 54 evaluable participants per study group to continue the study (one-sided $\alpha=0.05$ and a power of 0.90). A post-hoc combined analysis was also conducted.

The primary outcome was calculated as the number and proportion of evaluable participants who reached a pathological complete response with 90% CIs. The prespecified secondary endpoint of pathological complete response by subgroup was estimated in those with high tumour-infiltrating lymphocytes ($\geq 30\%$) or PD-L1 positive tumours ($\geq 1\%$), or both. Other secondary endpoints were calculated using the same methods as the primary endpoint. Two-sided 90% CIs of pathological complete response overall and by treatment study group were adjusted for the two-stage design, all other CIs for binary proportions were estimated using the exact binomial.²⁸ Primary and secondary outcomes were analysed in the modified intention-to-treat population (defined as evaluable patients who received at least one dose of all three study treatments). Adverse events are reported for participants who received at least one dose of the study treatment. Participants who were randomly assigned but did not receive any study treatment, or did not have breast surgery, were not evaluable. Formal hypothesis testing was not done and p values were not calculated for comparison of the primary endpoint between groups because this was a phase 2 trial that was not powered for a formal statistical comparison. The difference in Ki-67 from baseline to surgery was summarised as median and IQR. Study drug administration was summarised as the total drug dose administered divided by the planned total drug dose according to treatment group as a whole. Post-hoc analyses of endpoints were conducted according to stage and nodal status. Data were analysed using the SAS Enterprise Guide (version 7.15) and R (version 4.4.0).

The Neo-N independent data monitoring committee reviewed the activity data, accrual rate, interim analysis,

	Nivolumab lead-in group (n=53)	Nivolumab concurrent group (n=55)
Age at baseline, years	50 (40–59)	49 (45–60)
Germline BRCA status		
BRCA1 mutation	6 (11%)	4 (7%)
BRCA2 mutation	2 (4%)	..
No BRCA1 or BRCA2 mutation	24 (45%)	34 (62%)
Unknown	21 (40%)	17 (31%)
Age at baseline		
<40 years	9 (17%)	9 (16%)
≥ 40 years	46 (87%)	46 (84%)
BMI		
<25	27 (51%)	18 (33%)
25–30	10 (19%)	15 (27%)
≥ 30	16 (30%)	22 (40%)
Menopausal status		
Premenopausal or perimenopausal	28 (53%)	31 (56%)
Postmenopausal	22 (42%)	22 (40%)
Unknown	3 (6%)	2 (4%)
Indigenous status		
Aboriginal or Torres Strait Islander origin (or both)	1 (2%)	..
Neither Aboriginal or Torres Strait Islander origin	44 (83%)	45 (82%)
Not stated or unknown	8 (15%)	10 (18%)
Clinical tumour stage		
T1c	21 (40%)	24 (44%)
T2	32 (60%)	29 (53%)
T3	..	2 (4%)
Clinical nodal stage		
N0	47 (89%)	43 (78%)
N1	6 (11%)	11 (20%)
N3	..	1 (2%)
cTNM stage		
Stage I	18 (34%)	19 (35%)
Stage IIA	31 (58%)	24 (44%)
Stage IIB	4 (8%)	11 (20%)
Stage III	..	1 (2%)
Disease laterality		
Left breast	32 (60%)	31 (56%)
Right breast	21 (40%)	24 (44%)
Centrally assessed tumour-infiltrating lymphocyte status		
High tumour-infiltrating lymphocytes ($\geq 30\%$)	18 (34%)	18 (33%)
Low tumour-infiltrating lymphocytes (<30%)	33 (62%)	37 (67%)
Unknown	2 (4%)	..
Centrally assessed PD-L1 status		
Positive ($\geq 1\%$)	23 (43%)	28 (51%)
Negative (<1%)	24 (45%)	21 (38%)
Unknown	6 (11%)	6 (11%)
Ki-67	70% (5–90; IQR 40–90)	70% (5–90; IQR 40–80)

Data are median (range), median (range; IQR), or n (%). All patients were female and had locally assessed triple-negative breast cancer.

Table 1: Participant baseline characteristics

and safety or toxicity data every 6 months or more frequently (if required) and provided recommendations to the trial steering committee.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 6, 2020, and April 1, 2022, 124 participants were enrolled and 14 were ineligible (figure 1). 110 female participants were randomly assigned, 108 of whom were included in the modified intention-to-treat analysis (53 in the lead-in group and 55 in the concurrent group). Two participants in the nivolumab lead-in group did not receive study treatment because they were subsequently found to have bilateral or multifocal breast cancer and were not eligible. One participant in the nivolumab concurrent group had clinical stage II breast cancer at random assignment, but was found on retrospective review to have stage III breast cancer at diagnosis and was included in the analysis. At data cutoff on Oct 19, 2022, representing the last patient's 100-day safety follow-up, median follow-up was 12 months (IQR 7–18) and no participants were lost to follow-up.

All patients were female with a median age of 49 years (IQR 43–60). 45 (42%) patients had cT1c, 61 (57%) had cT2, and two (2%) had cT3 tumours. 18 (17%) patients had clinically node-positive disease; 37 (34%) had clinical stage I, 70 (65%) had stage II, and one (1%) had stage III disease. 36 (33%) patients had tumours with high stromal tumour-infiltrating lymphocytes, median Ki-67 was 70% (IQR 40–80), and 51 (47%) patients had PD-L1 positive tumours (table 1). All tumours were locally

assessed as triple negative, with central pathological review identifying two (2%) participants with low oestrogen receptor positivity (one with 5% and another with 10% of cells). At the time of analysis, germline *BRCA1* or *BRCA2* mutation status was unknown in 38 (35%) patients.

Overall, 57 (53% [90% CI 44–61]) of 108 patients had pathological complete response (figure 2). The pathological complete response rate was 27 (51% [39–63]) of 53 patients in the nivolumab lead-in group and 30 (55% [43–66]) of 55 patients in the concurrent group. One participant with clinically node positive disease in the lead-in group had no evidence of residual invasive cancer in breast or lymph nodes (ypT0 ypN0), but was designated as non-pathological complete response because fewer than three lymph nodes were removed at surgery. In a post-hoc combined analysis, the pathological complete response rate was 49% (34–63; 18 of 37 patients) in stage I and 55% (45–65; 39 of 71) in stage II or III (figure 2; appendix p 2). Pathological complete response according to a post-hoc analysis of baseline nodal status is shown in figure 2. Pathological complete response in breast only was reported in 28 (53%) of 53 patients in the lead-in group and 33 (60%) of 55 patients in the concurrent group (appendix p 3).

Residual cancer burden 0 and 1 rates were overall 69% (60–76; 74 of 108), with 64% (52–75; 34 of 53) in the lead-in group and 73% (61–82; 40 of 55) in the concurrent group (appendix p 5 and 6). Overall, of 108 patients, 32 (30%) patients reached complete tumour clinical response rates according to WHO criteria, 55 (51%) reached partial response, 15 (14%) reached stable response, three (3%) reached progressive response, and three (3%) were not evaluable for WHO response.

In the prespecified subgroup biomarker analysis, pathological complete response was 67% ([90% CI 52 to 80]; 24 of 36 patients) for high ($\geq 30\%$) versus 46% ([36 to 56]; 32 of 70) for low ($< 30\%$) stromal tumour-infiltrating lymphocytes and in the PD-L1 subgroup analysis, pathological complete response was 71% ([58 to 81]; 36 of 51) for PD-L1 positive status versus 33% ([22 to 47]; 15 of 45) for PD-L1 negative status ($< 1\%$; figure 2, appendix p 2). Patients with PD-L1 positive or high tumour-infiltrating lymphocyte status (24 [25%] of 96), performed by central pathology assessment, showed the highest pathological complete response rate at 75% ([57 to 89]; 18 of 24). The second highest was PD-L1 positive or low tumour-infiltrating lymphocyte status at 67% ([49 to 81]; 18 of 27), then PD-L1 negative or high tumour-infiltrating lymphocyte status at 50% ([19 to 81]; four of eight), and PD-L1 negative or low tumour-infiltrating lymphocyte status at 30% ([18 to 44]; 11 of 37; appendix p 1). Median difference in Ki-67 (baseline minus surgery) was -60% (IQR -30 to -80%) combined.

Treatment-related grade 3–4 adverse events occurred in 70 (65%) of 108 patients (32 [60%] of 53 in the lead-in group and 38 [69%] of 55 in the concurrent group) and

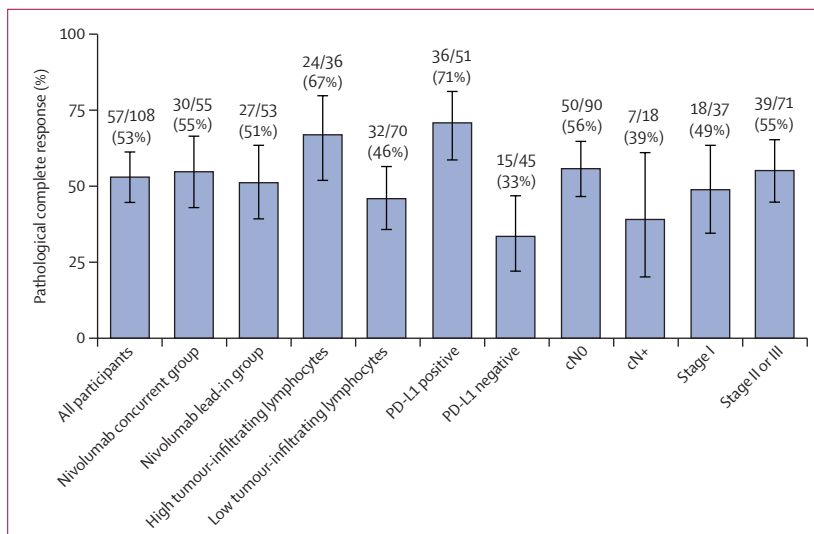


Figure 2: Pathological complete response (breast and axilla) by subgroups

Bars show 90% CIs for all participants and by treatment study group adjusted for the two-stage design.

	Nivolumab lead-in group (n=53)			Nivolumab concurrent group (n=55)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Any treatment-related adverse event	21 (40%)	27 (51%)	5 (9%)	16 (29%)	31 (56%)	7 (13%)
Neutrophil count decreased	5 (9%)	20 (38%)	5 (9%)	3 (5%)	24 (44%)	4 (7%)
Fatigue	35 (66%)	1 (2%)	0	37 (67%)	1 (2%)	0
Alopecia	27 (51%)	0	0	33 (60%)	0	0
Nausea	26 (49%)	0	0	23 (42%)	0	0
Peripheral sensory neuropathy	22 (42%)	1 (2%)	0	23 (42%)	2 (4%)	0
Constipation	20 (38%)	1 (2%)	0	24 (44%)	0	0
Rash maculopapular	16 (30%)	2 (4%)	0	21 (38%)	4 (7%)	0
Anaemia	18 (34%)	6 (11%)	0	15 (27%)	10 (18%)	0
Diarrhoea	16 (30%)	2 (4%)	0	16 (29%)	1 (2%)	0
Infusion-related reaction	11 (21%)	0	0	15 (27%)	2 (4%)	0
Mucositis oral	10 (19%)	0	0	9 (16%)	0	0
Alanine aminotransferase increased	11 (21%)	3 (6%)	0	8 (15%)	3 (5%)	0
Gastroesophageal reflux disease	7 (13%)	0	0	11 (20%)	0	0
Hypothyroidism	7 (13%)	0	0	9 (16%)	0	0
Epistaxis	8 (15%)	0	0	6 (11%)	0	0
Arthralgia	5 (9%)	0	0	8 (15%)	0	0
Dysgeusia	7 (13%)	0	0	6 (11%)	0	0
Platelet count decreased	5 (9%)	1 (2%)	0	8 (15%)	3 (5%)	0
Dyspnoea	3 (6%)	0	0	8 (15%)	0	0
Myalgia	7 (13%)	0	0	4 (7%)	0	0
Hyperthyroidism	6 (11%)	1 (2%)	0	4 (7%)	1 (2%)	0
Hypomagnesaemia	0	0	0	0	0	1 (2%)
Hyponatraemia	0	0	0	0	0	1 (2%)
Hypophysitis	0	0	0	0	0	1 (2%)
Fever	0	0	0	0	1 (2%)	0
Gamma-glutamyl transpeptidase increased	0	0	0	0	1 (2%)	0
Haemorrhoids	0	1 (2%)	0	0	0	0
Alkaline phosphatase increased	0	0	0	0	1 (2%)	0
Hyperglycaemia	0	0	0	0	1 (2%)	0
Hypokalaemia	0	0	0	0	1 (2%)	0
Immune mediated interstitial nephritis	0	0	0	0	1 (2%)	0
Lipase increased	0	0	0	0	1 (2%)	0
Lung infection	0	0	0	0	1 (2%)	0
Myocarditis	0	0	0	0	1 (2%)	0
Pruritus	0	1 (2%)	0	0	0	0
Rash acneiform	0	1 (2%)	0	0	0	0
Wound infection	0	0	0	0	1 (2%)	0
Creatine phosphokinase increased	0	1 (2%)	0	0	0	1 (2%)
Acute kidney injury	0	2 (4%)	0	0	0	0
Adrenal insufficiency	0	0	0	0	2 (4%)	0
Aspartate aminotransferase increased	0	1 (2%)	0	0	1 (2%)	0
Folliculitis	0	0	0	0	2 (4%)	0
Lymphocyte count decreased	0	2 (4%)	0	0	0	0
Thromboembolic event	0	1 (2%)	0	0	1 (2%)	0
White blood cell decreased	0	1 (2%)	0	0	1 (2%)	0
Colitis	0	2 (4%)	0	0	1 (2%)	0
Febrile neutropenia	0	0	0	0	3 (5%)	0

Data are n (%). Data shown are grade 1-2 treatment-related adverse events that occurred in at least 10% of the overall cohort and all grade 3-4 treatment-related adverse events. No grade 5 treatment-related adverse events were reported.

Table 2: Treatment-related adverse events

were consistent with the known toxic effects of the nivolumab chemoimmunotherapy regimen (table 2). The most common grade 3–4 treatment-related adverse events were decreased neutrophil count (25 [47%] of 53 in the lead-in group vs 28 [53%] of 55 in the concurrent group), anaemia (six [11%] vs ten [19%]), and increased alanine aminotransferase (three [6%] vs three [6%]). Of 108 patients, 17 (16%; 11 in the lead-in group and six in the concurrent group) discontinued nivolumab early and 15 (14%; nine in the lead in group and six in the concurrent group) discontinued due to treatment-related adverse events. 11 (10%; five in the lead-in group and six in the concurrent group) patients discontinued all treatment and 25 (23%) discontinued at least one study treatment early due to treatment-related adverse events. Reasons for early discontinuation of all neoadjuvant treatment are listed in the appendix (p 7). On average based on 53 in the lead-in group and 55 in the concurrent group, 93% of the total planned dose of nivolumab was administered to the lead-in group versus 94% in the concurrent group; of the planned paclitaxel, 87% versus 90% was administered; and of planned carboplatin, 96% versus 97% was administered. Investigator reported immune-related adverse events attributed to nivolumab occurred in 66 (61%) patients, with grade 3 or worse events seen in 17 (16%; table 3). Immune-related adverse events responded promptly to supportive protocol-directed treatment strategies. Serious adverse events were reported in 16 (30%) patients in the lead-in group and 26 (47%) in the concurrent group. Treatment-related

serious adverse events occurred in seven (13%) patients in the lead-in group and 20 (36%) in the concurrent group. The most common serious adverse events were febrile neutropenia (five [9%] of 53 in the lead-in group vs three [6%] of 55 in the concurrent group), fever (two (4%) vs six [11%]), and anaemia (two [4%] vs five [9%]; appendix pp 8–19). No treatment-related deaths occurred during the study. Event-free survival and overall survival data are immature and will be reported later, in addition to translational data.

Discussion

Although the Neo-N trial did not support the hypothesis that lead-in nivolumab before chemotherapy was associated with a pathological complete response advantage, the results showed a clinically relevant pathological complete response rate of 53% with a short-course, anthracycline-free neoadjuvant regimen of nivolumab, carboplatin, and paclitaxel for patients with stage I–II triple-negative breast cancer, with similar rates observed independent of scheduling nivolumab initiation. Those with PD-L1 positive tumours (using the SP142 immunohistochemistry assay ≥1%) or at least 30% stromal tumour-infiltrating lymphocytes cutoff had higher pathological complete response rates than those with PD-L1 negative or low tumour-infiltrating lymphocytes, supporting that the anthracycline component might not be needed for patients who already show an existing robust immune response in their tumour using these assays. Long-term data are awaited, but patients with immune enriched tumours who reached residual cancer burden class I–II might possibly also have a good prognosis despite not reaching a pathological complete response.

Our randomised trial explored different scheduling of nivolumab initiation (previous or concurrent with chemotherapy); however, we did not observe higher pathological complete response rates in the nivolumab lead-in group, as hypothesised from the exploratory analysis of the GeparNuevo study.¹⁶ The GeparNuevo trial, investigating 24-week anthracycline and taxane chemotherapy with lead-in plus concurrent durvalumab, has subsequently shown that the addition of durvalumab (a PD-L1 inhibitor) had improved event-free survival independent of pathological complete response rates, suggesting that small pathological complete response rate changes might be clinically relevant when checkpoint inhibition is used.¹⁷ Further, although initial studies indicated that the pathological complete response benefit was seen only with lead-in rather than concurrent durvalumab, ultimately this result did not correlate with improved event-free survival.¹⁶ Our findings also cast doubt on the hypothesis that the immunosuppression and myelosuppression associated with corticosteroids and the chemotherapy regimen used in this study can substantially impair checkpoint inhibitor efficacy in patients with early breast

	Nivolumab lead-in group (n=53)			Nivolumab concurrent group (n=55)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any immune-related adverse event	27 (51%)	8 (15%)	0	22 (40%)	8 (15%)	1 (2%)
Rash maculopapular	21 (40%)	2 (4%)	0	28 (51%)	4 (8%)	0
Infusion-related reaction	11 (21%)	0	0	15 (27%)	2 (4%)	0
Hypothyroidism	7 (13%)	0	0	10 (18%)	0	0
Fever	4 (8%)	0	0	9 (16%)	3 (5%)	0
Rash (other)	5 (9%)	0	0	7 (13%)	0	0
Pruritus	6 (11%)	1 (2%)	0	4 (7%)	0	0
Hyperthyroidism	6 (11%)	1 (2%)	0	4 (7%)	1 (2%)	0
Hypophysitis	0	0	0	0	0	1 (2%)
Cholelithiasis	0	1 (2%)	0	0	0	0
Deranged liver function test	0	0	0	0	1 (2%)	0
Hyperglycaemia	0	0	0	0	1 (2%)	0
Myocarditis	0	0	0	0	1 (2%)	0
Rash acneiform	0	1 (2%)	0	0	0	0
Acute kidney injury	0	2 (4%)	0	0	0	0
Adrenal insufficiency	0	1 (2%)	0	0	2 (4%)	0
Colitis	0	3 (6%)	0	0	1 (2%)	0

Data are n (%). Data shown are grade 1–2 immune-related adverse events that occurred in at least 10% of the overall cohort and all grade 3–4 immune-related adverse events. No grade 5 immune-related adverse events were reported.

Table 3: Suspected immune-related adverse events

cancer.^{18,23,29,30} The neoMono trial also showed similar pathological complete response rates with or without an atezolizumab monotherapy lead-in window with an anthracycline, taxane, and carboplatin regimen in a prespecified interim analysis in all 359 patients, although higher pathological complete response rates were reported in patients with PD-L1-positive tumours.³¹

The NeoPACT randomised phase 2 trial showed a 58% (95% CI 48–67) pathological complete response rate with 18 weeks of once every 3 weeks carboplatin-docetaxel chemotherapy with concurrent pembrolizumab in 111 patients with stage I to III triple-negative breast cancer.³² Estimated 3-year event-free survival was 86% (95% CI 77–95; 98% in the pathological complete response group vs 68% in the non-pathological complete response group). Immune enrichment (defined using the combined positive score PD-L1 ≥ 10 assay or stromal tumour-infiltrating lymphocyte $\geq 30\%$) in NeoPACT was also associated with higher pathological complete response rates and was in the same range as seen in Neo-N. In a randomised phase 2 trial (NCI10013) investigating 12 weeks of paclitaxel and carboplatin with or without atezolizumab, the pathological complete response rates were similar to Neo-N at 56% (95% CI 40–70; 75% when PD-L1 positive) with atezolizumab and 19% (95% CI 4–46) without atezolizumab.³³ The shorter duration of treatment in the Neo-N trial resulted in a lower pathological complete response rate compared with KEYNOTE-522, but this finding underscores the need to consider biomarker-based patient selection given the ability of these patients to reach pathological complete response with less treatment in the form of fewer drugs, lower dosage or shorter duration. We also observed that although patients with concordant high tumour-infiltrating lymphocyte and positive PD-L1 status had the highest pathological complete response rates, discordant patients still had pathological complete response rates that were clinically meaningful. Patients with both PD-L1 (<1%) and low tumour-infiltrating lymphocyte tumours had the lowest pathological complete response rates. If our results can be further validated in future studies, these biomarkers could be used to select patient subgroups for whom the duration of chemotherapy or immunotherapy regimen could be individualised.

Neo-N, NeoPACT, GeparNeuvo, and the NeoTENNIS trials did not continue the PD-1 targeting agent postoperatively compared with the KEYNOTE-522 trial, which used 24-week anthracycline–taxane chemotherapy with concurrent carboplatin plus concurrent and adjuvant postsurgical pembrolizumab.^{6,17,29,32} Despite this strategy, excellent event-free survival outcomes have been reported by some of these trials (NeoPACT and GeparNuevo) with mature data in patients who reached pathological complete response. These results call into question whether continuation of postoperative pembrolizumab—the current standard of care—is beneficial, especially for patients who reached

pathological complete response. At least one ongoing large phase 3 study is examining this specific question (OptimICE-PCR, NCT05812807). Considering the positive prognostic effect of stromal tumour-infiltrating lymphocytes, the ongoing ETNA trial (NCT06078384) is evaluating whether adjuvant therapy can be omitted completely in patients with stage I triple-negative breast cancer who have high tumour-infiltrating lymphocytes.

Although the use of anthracyclines has had clear benefits for patients with breast cancer, the acute and chronic toxicity profile of this class of drugs is important. Nausea, myelosuppression, cardiomyopathy, and second malignancies are all established side-effects that require clinicians to identify patients who do not need anthracycline treatment or those who require alternative and better tolerated or shorter treatments that are at least as efficacious.¹⁰ However, checkpoint inhibitors (including nivolumab) have a range of distinctive toxicities that can also have short-term and long-term effects. Notably, endocrinopathies can occur in some patients, and might require lifelong hormone supplementation. Our safety data are consistent with previous reports of single agent PD-1 in an early-stage setting.^{6,17} This trial regimen was associated with low rates of adverse events, with discontinuation of nivolumab due to treatment-related adverse events in 14% of patients and of any trial drug in around 23% of patients, which is similar to the rates reported in KEYNOTE-522. Many long-term immune effects occur with longer PD-1 treatment; we observed low rates of grade 3–4 immune-related adverse events, which responded promptly to treatment. NeoPACT also reported a low incidence of endocrine dysfunction.³² Data are still being collected in Neo-N with regards to long-term immune-related adverse events occurring after cessation of immunotherapy and if there was resolution. Long-term immune adverse events are an important issue since there are concerns regarding long-term effects on fertility that have not yet been investigated thoroughly.³⁴ Novel biomarkers, such as minimal residual disease detection, might also assist with shortening and optimising neoadjuvant regimens in the future.³⁵ Paclitaxel was the taxane of choice in Neo-N, as used in KEYNOTE-522, with proven efficacy in the early stage and metastatic settings.⁶ Although avoidance of corticosteroid premedication in combination with immunotherapy has theoretical advantages, taxanes are routinely used with carboplatin and these data support immunotherapy activity despite their use.⁶

Our phase 2 trial has limitations. Since data on survival are still immature, the trial was not powered to assess long-term outcomes or compare pathological complete response rates in subgroups. Small subgroup analyses need to be interpreted with caution, and the biomarker analyses were part of secondary prespecified outcomes and therefore, are not definitive. Early imaging correlations to predict pathological response were not

assessed and would be difficult to contextualise given the small number of patients. Longer term follow-up of event-free survival and overall survival in Neo-N will provide additional valuable data, especially for patients with a pathological complete response given that there was no adjuvant nivolumab component in this study.

Although scheduling of nivolumab did not meaningfully affect pathological complete response rates in patients with stage I or II newly diagnosed triple-negative breast cancer, our results support that a 12-week non-anthracycline regimen in combination with PD-1 targeted therapy has merit, particularly in patients with high stromal tumour-infiltrating lymphocytes or PD-L1 positive tumours. Confirmation of our findings in further studies might pave the way towards shorter chemoimmunotherapy for patients with early stage immune-enriched triple-negative breast cancer and future trials are warranted to compare this regimen with the current standards of care.

Contributors

NZ contributed to project administration, study validation, and data visualisation. MJJK-H contributed to the investigation, methodology, and supervision of the study. SMN contributed to data curation, formal analysis, methodology, software programming, study validation, and visualisation. PAF contributed to the investigation and methodology. SB-H, WF, and AMM contributed to the investigation. RA contributed to data curation, formal analysis, funding acquisition, investigation, methodology, and project administration; and was responsible for the resources, software, supervision, study validation, and visualisation. KP contributed to the investigation and supervision. SZ contributed to the data curation, project administration, study validation, and visualisation. MMR contributed to data curation, formal analysis, methodology, software, supervision, study validation, and visualisation. SL contributed to funding acquisition, investigation, methodology, supervision, and visualisation. All authors conceptualised or designed the manuscript; acquired, analysed, or interpreted the data; drafted or critically reviewed the manuscript; and wrote, reviewed, and edited the original draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. SMN and MMR have accessed and verified the data.

Declaration of interests

SL reports research funding from Novartis, Bristol Myers Squibb, Puma Biotechnology, Astra Zeneca–Daiichi Sankyo, Roche-Genentech, and Seattle Genetics; has acted as a consultant and received honoraria from Roche-Genentech, MSD, Gilead Sciences, Astra Zeneca–Daiichi Sankyo, Bristol Myers Squibb, Novartis, Eli Lilly, Amaroq Therapeutics, Mersana Therapeutics, Domain Therapeutics, BioNTech, Bicycle Therapeutics, and Exact Sciences; and has received conference travel support from Bristol Myers Squibb, Eli Lilly, and Novartis. AMM has served on advisory boards for Bristol Myers Squibb, MSD, Novartis, Roche, Pierre-Fabre, and QBiotech. SBH has acted as a consultant to MSD, Gilead Sciences, Astra Zeneca–Daiichi Sankyo, Novartis, Pfizer, GSK, and Eisai. WF received funds as a trial site investigator for the Neo-N trial from Breast Cancer Trials. PF receives honoraria from Lilly. MMR received research funding from ETOP IBCSG Partners Foundation (including Biotheranostics, Merck, Novartis, Pfizer, Roche, and TerSera Therapeutics), Bayer, and Bristol Myers Squibb; consulting fees from Bristol Myer Squibb, TerSera Therapeutics, and Tolmar Pharmaceuticals; honoraria from Canadian Urological Association, St Gallen Oncology Conferences, Bristol Myers Squibb, and McGill University (funded by Merck); and participation in data and safety monitoring boards (Austrian Breast and Colorectal Cancer Study Group) and advisory boards (AstraZeneca, TerSera Therapeutics, and Tolmar Pharmaceuticals). MKH has acted as consultant to AstraZeneca and has contract with Breast Cancer Trials Group to perform the Neo-N study. KP received research funding from MSD, Gilead, and Sanofi. KP received honoraria

for advisory and consultancy roles from AstraZeneca, Eli Lilly, Exact Sciences, Focus Patient, Gilead Sciences, Izidok, Medimix, Medscape, MSD, Mundi Pharma, Need, Novartis, Pfizer, Hoffmann–La Roche, Sanofi, and Seagen; conference travel support from Gilead Sciences and MSD; and honoraria for advisory board functions from AstraZeneca, Eli Lilly, Exact Sciences, Gilead Sciences, MSD, Novartis, Pfizer, Hoffmann–La Roche, Sanofi, and Seagen. KP has leadership roles as a steering committee member in several oncology trials; is a steering committee member of the European Organisation for Research and Treatment of Cancer Breast Group; vice president of Belgian Society of Medical Oncology; has an external advisory role for the national reimbursement committee; advisory role for the Belgian Commission on Personalised Medicine, European Medicines Agency, and European Society of Medical Oncology. NZ received honoraria from Novartis, AstraZeneca, Gilead, Lilly, Roche, Pfizer, and MSD; conference travel support from Novartis, Pfizer, Roche, and Gilead; and institutional research funding from AstraZeneca, MSD, Pfizer, and Roche. All other authors declare no competing interests.

Data sharing

Anonymised individual patient data collected during the trial, the trial protocol, and a data dictionary will be made available on appropriate request for data sharing after publication of the main and final study results with no end date. Data sharing requests can be made via the Australian Research Data Commons <https://researchdata.edu.au/>. Further information can be viewed at <https://doi.breastcancertrials.org.au/103>.

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