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ORIGINAL ARTICLE

nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial

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Background: Metastatic triple-negative breast cancer (mTNBC) has a poor prognosis and aggressive clinical course. tnAcity evaluated the efficacy and safety of first-line *nab*-paclitaxel plus carboplatin (*nab*-P/C), *nab*-paclitaxel plus gemcitabine (*nab*-P/G), and gemcitabine plus carboplatin (G/C) in patients with mTNBC.

Patients and methods: Patients with pathologically confirmed mTNBC and no prior chemotherapy for metastatic BC received (1 : 1 : 1) *nab*-P 125 mg/m^2 plus C AUC 2, *nab*-P 125 mg/m^2 plus G 1000 mg/m^2, or G 1000 mg/m^2 plus C AUC 2, all on days 1, 8 q3w. Phase II primary end point: investigator-assessed progression-free survival (PFS); secondary end points included overall response rate (ORR), overall survival (OS), percentage of patients initiating cycle 6 with doublet therapy, and safety.

Results: In total, 191 patients were enrolled (*nab*-P/C, $n = 64$; *nab*-P/G, $n = 61$; G/C, $n = 66$). PFS was significantly longer with *nab*-P/C versus *nab*-P/G [median, 8.3 versus 5.5 months; hazard ratio (HR), 0.59 [95% CI, 0.38–0.92]; $P = 0.02$] or G/C (median, 8.3 versus 6.0 months; HR, 0.58 [95% CI, 0.37–0.90]; $P = 0.02$). OS was numerically longer with *nab*-P/C versus *nab*-P/G (median, 16.8 versus 12.1 months; HR, 0.73 [95% CI, 0.47–1.13]; $P = 0.16$) or G/C (median, 16.8 versus 12.6 months; HR, 0.80 [95% CI, 0.52–1.22]; $P = 0.29$). ORR was 73%, 39%, and 44%, respectively. In the *nab*-P/C, *nab*-P/G, and G/C groups, 64%, 56%, and 50% of patients initiated cycle 6 with a doublet. Grade ≥3 adverse events were mainly hematologic.

Conclusions: First-line *nab*-P/C was active in mTNBC and resulted in a significantly longer PFS and improved risk/benefit profile versus *nab*-P/G or G/C.

Key words: chemotherapy, triple-negative breast cancer, *nab*-paclitaxel, gemcitabine

Introduction

Triple-negative breast cancer (TNBC) accounts for ≈12% of all breast cancers and occurs disproportionately in black women, premenopausal women, and those with a *BRCA1* gene mutation [1]. Patients with early-stage TNBC face a relatively poor prognosis and aggressive clinical course, including a shorter median time to relapse and death compared with other breast cancer subtypes [2, 3]. In fact, both the likelihood of distant recurrence and the risk of visceral metastases are increased within 5 years of diagnosis [2, 4, 5]. Likewise, metastatic TNBC (mTNBC) is associated with a shorter median survival time versus metastatic disease from other types of breast tumors, and >40% of patients with mTNBC develop central nervous system metastases [5, 6].

The identification of several diverse genetic subtypes and the lack of common targetable mutations have been formidable obstacles to successful TNBC drug development [2, 7]. Although generally associated with poor breast cancer–specific outcomes, TNBC is a chemosensitive disease [2, 3, 5, 8]. Chemotherapy combinations that include a taxane appear to clinically benefit patients with TNBC [2]. Platinum-containing regimens are also active in these patients, with platinum agent activity demonstrated in preclinical models of *BRCA*-mutated TNBC [9–11]. Systemic chemotherapy remains the only standard treatment option for patients with TNBC [12, 13]. In most circumstances, single agents are currently preferred over chemotherapy combinations for the treatment of recurrent/metastatic breast cancer; however, this recommendation is based on a lack of compelling evidence demonstrating superiority of combination chemotherapy over treatment with sequential single agents in terms of survival [12, 14]. However, features that often accompany TNBC relapses such as short disease-free intervals (DFIs), high tumor burdens, significant visceral disease, and/or symptomatic disease warrant the consideration of combination chemotherapy in these settings. Treatment guidelines specifically addressing patients with mTNBC are limited, and no specific standard of care exists for this patient population [12, 13].

Combination chemotherapy regimens containing a platinum agent or a taxane have been shown to be efficacious in patients with mTNBC in clinical trials. In a phase III trial of gemcitabine plus carboplatin (G/C) with or without iniparib for third-line or earlier treatment of patients with mTNBC ($N = 519$), first-line G/C resulted in a median progression-free survival (PFS) of 4.6 months and a median overall survival (OS) of 13.9 months [10]. Activity in mTNBC has also been observed for *nab*-paclitaxel (*nab*-P)–based regimens [15–17]. In an exploratory subset analysis of patients with mTNBC ($n = 201$) from the phase III CALGB 40502 trial, first-line *nab*-P in combination with bevacizumab resulted in a median PFS of 7.4 months [15]. The combination of *nab*-P plus carboplatin (*nab*-P/C) with bevacizumab demonstrated a median PFS of 9.2 months and overall response rate (ORR) of 85% in a phase II trial [16]. In another phase II trial ($N = 30$), adding bevacizumab to *nab*-P plus gemcitabine (*nab*-P/G) resulted in a robust ORR of 69% in patients with mTNBC [17]. Taken together, these results warrant further investigation of *nab*-P–based regimens for the first-line treatment of patients with mTNBC. The tnAcity trial evaluated the safety and efficacy of first-line *nab*-P/C, *nab*-P/G, and G/C in patients with mTNBC.

Patients and methods

Patients

The tnAcity trial design and patient population have been described previously [18]. Briefly, women ≥18 years with mTNBC [estrogen receptor negative, progesterone receptor negative, and lacking human epidermal growth factor receptor 2 (HER2) overexpression] and having received no prior cytotoxic chemotherapy for metastatic breast cancer were enrolled in this study. Key eligibility requirements included measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, Eastern Cooperative Oncology Group performance status 0–1, and prior adjuvant or neoadjuvant anthracycline therapy (unless not indicated by physician).

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Informed consent was obtained from all patients before study entry. The trial is registered at ClinicalTrials.gov (NCT01881230).

Study design

This multicenter, open-label, randomized study was conducted in 11 countries. The phase II portion of the study was designed to evaluate the risk/benefit profiles of 2 *nab*-P experimental arms and to identify via a ranking algorithm the *nab*-P combination for use in a phase III portion of the study. In phase II, patients were randomized 1 : 1 : 1 to receive *nab*-P 125 mg/m^2 plus carboplatin area under the curve 2, *nab*-P 125 mg/m^2 plus gemcitabine 1000 mg/m^2, or gemcitabine 1000 mg/m^2 plus carboplatin area under the curve 2; all agents were given on days 1 and 8 every 3 weeks (supplementary Figure S1, available at *Annals of Oncology* online).

On 29 May 2015, the independent data monitoring committee carried out a scheduled, protocol-defined data review of unblinded data from the first 168 patients enrolled into the phase II portion of the study using a data cutoff date of 27 April 2015. The data monitoring committee concluded that the number of patients already enrolled into the phase II portion and the current data collected were sufficient to enable the selection of the *nab*-P regimen according to the predefined algorithm. Treatment and follow-up of patients continued per protocol.

End points and study assessments

The primary end point for the phase II portion of the trial was investigator-assessed PFS per RECIST v1.1. As prespecified in the statistical analysis plan, pair-wise differences in PFS were assessed with nominal *P* values (without adjustment for multiplicity) at a two-sided significance level of 0.2 using a stratified log-rank test with disease free interval (≤1 year; >1 year) as the stratification factor. This was intended to provide an indication of strength of association regarding treatment differences. Secondary end points included investigator-assessed ORR, the percentage of patients who initiated cycle 6 receiving doublet combination therapy, OS, and safety. OS was evaluated in a similar fashion to PFS.

Ranking algorithm and statistical analysis

Identification of the *nab*-P experimental arm with the best risk/benefit profile to proceed to phase III was based on an algorithm ranking key efficacy and safety end point parameters [18]. The five parameters included hazard ratio (HR) of PFS (*nab*-P/G/*nab*-P/C), ratio of ORR, percentage of patients initiating cycle 6 receiving a doublet, percentage of patients with myelosuppression-related events (including grade 3 or 4 neutropenia, thrombocytopenia, anemia, bleeding, febrile neutropenia, or red blood cell/platelet transfusion), and percentage of patients who discontinued from all study treatment due to adverse events. The PFS and ORR efficacy end points carried twice the weight as the remaining three end

Table 1. Baseline characteristics

Variable	*nab*-P/C ($n = 64$)	*nab*-P/G ($n = 61$)	G/C ($n = 66$)
Age, median (range), years	55 (27–82)	53 (27–80)	59 (30–79)
<65 years, No. (%)	48 (75)	43 (70)	49 (74)
Race, No. (%)			
White	55 (86)	50 (82)	54 (82)
Black or African American	6 (9)	9 (15)	8 (12)
Not collected or reported	3 (5)	2 (3)	4 (6)
Region, No. (%)			
North America	31 (48)	29 (48)	31 (47)
Western Europe	24 (38)	26 (43)	30 (45)
South America	9 (14)	6 (10)	4 (6)
Australia	0	0	1 (2)
ECOG PS, No. (%)			
0	38 (59)	34 (56)	42 (64)
1	26 (41)	25 (41)	22 (33)
2	0	1 (2)	0
Missing	0	1 (2)	2 (3)
Disease-free interval, No. (%)			
≤1 year	16 (25)	17 (28)	20 (30)
>1 year	48 (75)	43 (70)	45 (68)
Missing	0	1 (2)	1 (2)
Triple negative at primary diagnosis, No. (%)	53 (83)	51 (84)	48 (73)
Metastatic triple negative at primary diagnosis, No. (%)	17 (27)	11 (18)	10 (15)
Site of metastasis, No. (%)			
Lymph node(s)	50 (78)	38 (62)	51 (77)
Lung/thoracic	42 (66)	42 (69)	41 (62)
Bone	21 (33)	23 (38)	25 (38)
Liver	16 (25)	17 (28)	23 (35)
Prior neoadjuvant/adjuvant therapy, No. (%)			
Anthracyclines	43 (67)	37 (61)	42 (64)
Taxanes	36 (56)	41 (67)	42 (64)

ECOG PS, Eastern Cooperative Oncology Group performance status; G/C, gemcitabine plus carboplatin; *nab*-P/C, *nab*-paclitaxel plus carboplatin; *nab*-P/G, *nab*-paclitaxel plus gemcitabine.

points. The *nab*-P regimen with the more desirable treatment effect received a higher rank. The *nab*-P regimen with the higher total rank was deemed the selected *nab*-P experimental arm, supported by the totality of the safety and efficacy data. The G/C arm was a reference for the comparisons between the 2 *nab*-P experimental arms and was not ranked. Additional study design details are provided in supplemental materials, available at *Annals of Oncology* online.

Results

Patients

Baseline characteristics of patients with mTNBC treated with *nab*-P/C ($n = 64$), *nab*-P/G ($n = 61$), and G/C ($n = 66$) are summarized in Table 1. Baseline characteristics were comparable across treatment groups, with a few exceptions. Median age was lower in the *nab*-P/C and the *nab*-P/G groups versus the G/C group. The *nab*-P/C group had a lower proportion of patients who were black or African American or were from Western Europe, and had a DFI of ≤1 year compared with the *nab*-P/G and G/C groups. Although all patients had mTNBC at baseline, more patients in the *nab*-P/C and the *nab*-P/G groups had a primary diagnosis of triple-negative disease compared with patients in the G/C group.

Efficacy

nab-P/C treatment resulted in a significantly longer PFS versus *nab*-P/G (median, 8.3 versus 5.5 months; HR, 0.59 [95% CI, 0.38–0.92]; $P = 0.02$) and versus G/C (median, 8.3 versus 6.0 months; HR, 0.58 [95% CI, 0.37–0.90]; $P = 0.02$), respectively (Figure 1A). A similar trend in 12-month PFS rate was observed between the groups (30%, 13%, and 11%, respectively). Treatment with *nab*-P/C resulted in a numerically longer OS compared with either *nab*-P/G (median, 16.8 versus 12.1 months; HR, 0.73 [95% CI, 0.47–1.13]; $P = 0.16$) or G/C (median, 16.8 versus 12.6 months; HR, 0.80 [95% CI, 0.52–1.22]; $P = 0.29$) (Figure 1B). A numerically higher ORR was observed in patients receiving *nab*-P/C compared with those receiving *nab*-P/G or G/C (73% versus 39% or 44%) (Figure 2). A waterfall plot of best

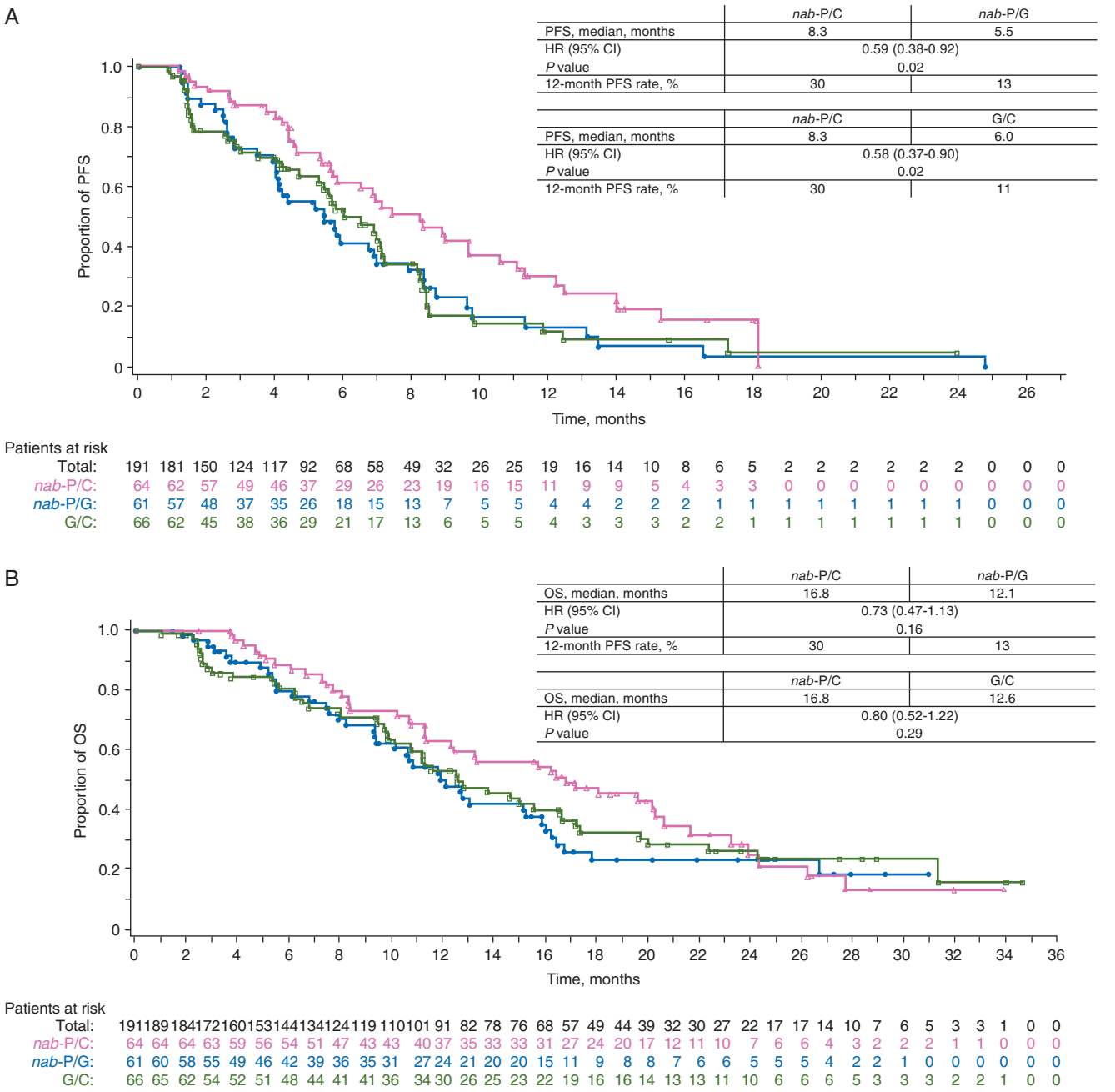

Figure 1. Kaplan–Meier curve of (A) progression-free survival (PFS) and (B) overall survival (OS). G/C, gemcitabine plus carboplatin; HR, hazard ratio; *nab*-P/C, *nab*-paclitaxel plus carboplatin; *nab*-P/G, *nab*-paclitaxel plus gemcitabine.

percent change from baseline in total length of longest diameters of target lesions is provided in supplementary Figure S2, available at *Annals of Oncology* online. Median duration of response was 6.2 months (95% CI, 4.0–10.2) in patients treated with *nab*-P/C, 5.8 months (95% CI, 2.9–10.4) with *nab*-P/G arm, and 5.0 months (95% CI, 4.2–7.7) with G/C. Stable disease of ≥16 weeks was achieved by 20%, 44%, and 32% of patients, respectively. The percentage of patients with progressive disease as best response was 6%, 10%, and 21% in the *nab*-P/C, *nab*-P/G, and G/C groups, respectively.

Response was also analyzed in patients with a DFI of ≤1 year and DFI of >1 year. Overall, 20% of patients had a primary diagnosis of mTNBC and were classified as a DFI of >1 year. In patients with a DFI of ≤1 year, the ORRs were 69% with *nab*-P/C, 41% with *nab*-P/G, and 35% with G/C, and the ORRs in patients with a DFI of >1 were 75%, 37%, and 47%, respectively, suggesting consistent activity in patients who received *nab*-P/C.

Treatment exposure

Overall, 188 patients discontinued treatment, mostly due to progressive disease (53%) and adverse events (18%). Other reasons leading to treatment discontinuation are reported in the CONSORT diagram (supplementary Figure S3, available at

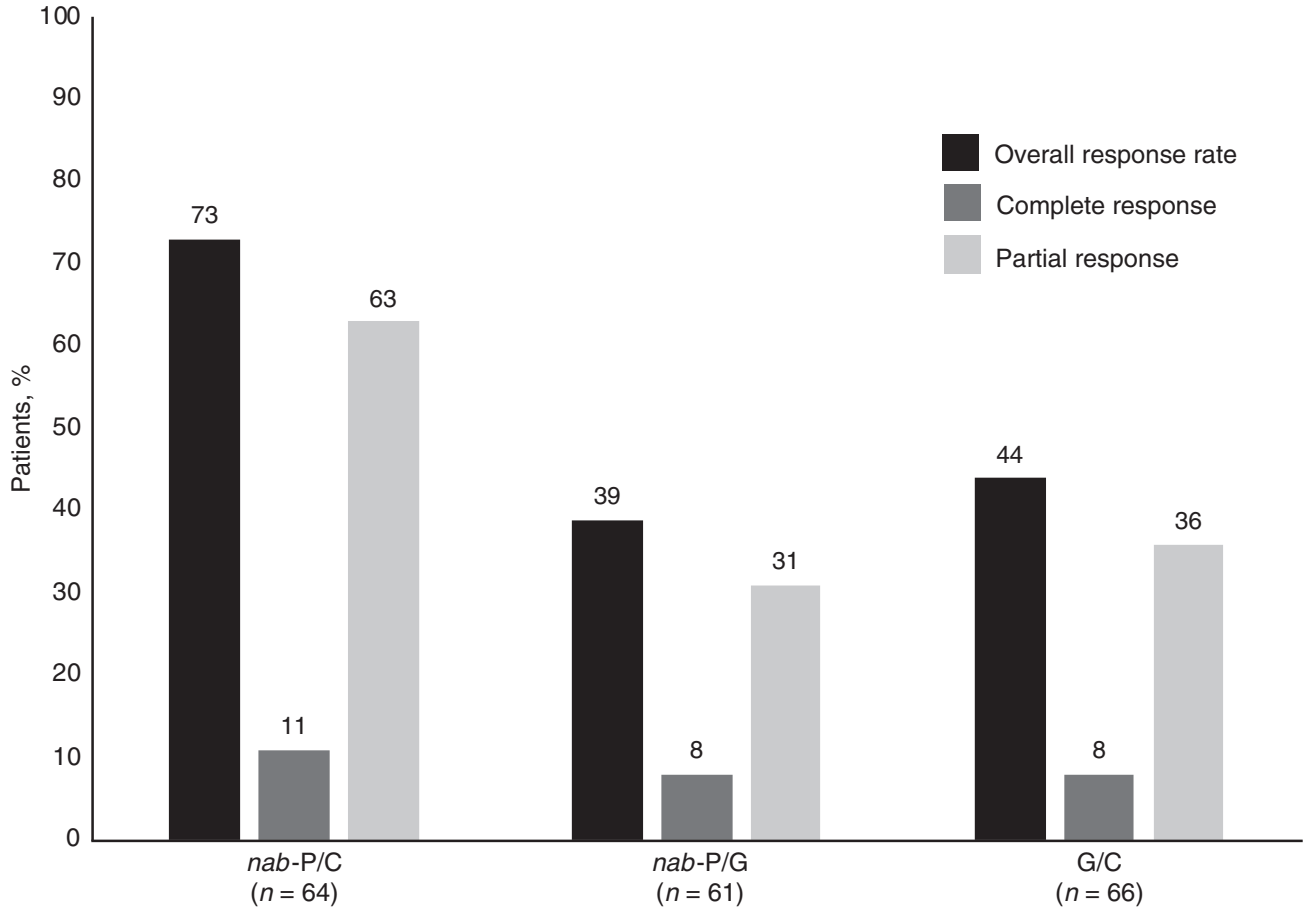

Figure 2. Best response.

Annals of Oncology online). The most common adverse events leading to discontinuation included thrombocytopenia (3%), neutropenia (3%), drug hypersensitivity (3%), and fatigue (3%). Dose reductions were more common in the G/C group versus the other treatment groups (supplementary Table S1, available at *Annals of Oncology* online). Across all treatment arms, neutropenia was the most common adverse event leading to dose reduction. The median treatment duration was 25.0, 18.1, and 20.1 weeks, and the median number of cycles administered was 8, 6, and 6 in the *nab*-P/C, *nab*-P/G, and G/C groups, respectively. In the *nab*-P/C, *nab*-P/G, and G/C treatment groups, 64%, 56%, and 50% of patients, respectively, initiated cycle 6 with a doublet.

Safety

At least 1 grade ≥3 adverse event was reported in 80%, 77%, and 84% of patients in the *nab*-P/C, *nab*-P/G, and G/C groups, respectively (Table 2). In all treatment groups, grade ≥3 adverse events were mainly hematologic and included neutropenia, anemia, and thrombocytopenia. Grade ≥3 febrile neutropenia occurred in 5% and 2% of patients in the *nab*-P/C and *nab*-P/G arms; no febrile neutropenia was reported in patients receiving G/C. In the *nab*-P/C arm, the frequency of grade 3/4 neutropenia was highest at cycle 2 and then stabilized, whereas the frequency of grade 3/4 neutropenia peaked in later cycles in the *nab*-P/G and G/C arms (supplementary Figure S4, available at *Annals of Oncology* online). Grade ≥3 peripheral neuropathy occurred in 5%, 7%, and 2% of patients in the *nab*-P/C, *nab*-P/G, and G/C groups, respectively.

Ranking algorithm

Based on an algorithm of the performance of five selected efficacy and safety end point parameters and the totality of the efficacy and safety data, the rank-sum values of the *nab*-P/C and *nab*-P/G arms were 5 and 2, respectively (supplementary Table S2, available at *Annals of Oncology* online). Therefore, the rank sum favored *nab*-P/C.

Discussion

First-line *na*b-P/C demonstrated a significantly longer PFS compared with either *nab*-P/G or G/C in patients with mTNBC in the tnAcity trial. Further, treatment with *nab*-P/C resulted in a numerically longer OS and higher ORR compared with the other treatment arms. Treatment with *nab*-P/C also resulted in a numerically higher ORR in patients with a shorter DFI. A longer treatment duration and greater exposure were also reported with *nab*-P/C than with *nab*-P/G or G/C. Grade ≥3 adverse events were mainly hematologic in all treatment groups.

TNBC is characterized by an aggressive clinical course and high tumor burden, with patients experiencing frequent relapses following a short DFI, as well as visceral involvement [2–5, 19].

Table 2. Summary of treatment-emergent adverse events

Parameter, *n* (%)	*nab*-P/C (*n* = 64)	*nab*-P/G (*n* = 60)	G/C (*n* = 64)
Patients with TEAE	63 (98)	60 (100)	64 (100)
Grade ≥3, total	51 (80)	46 (77)	54 (84)
Grade ≥3, hematologic			
Neutropenia	27 (42)	16 (27)	33 (52)
Anemia	8 (13)	7 (12)	17 (27)
Thrombocytopenia	6 (9)	4 (7)	18 (28)
Leukopenia	4 (6)	2 (3)	7 (11)
Febrile neutropenia	3 (5)	1 (2)	0
Grade ≥3, nonhematologic			
Peripheral neuropathy	3 (5)	4 (7)	1 (2)
Fatigue	2 (3)	9 (15)	2 (3)
Serious	20 (31)	22 (37)	25 (39)
Patients with a TEAE leading to discontinuation of any study drug	29 (45)	16 (27)	15 (23)
Patients with a TEAE leading to dose reduction of any study drug	20 (31)	23 (38)	25 (39)
Patients with a TEAE leading to dose interruption of any study drug	50 (78)	31 (52)	50 (78)
Patients with a TEAE leading to death	1 (2)	2 (3)	2 (3)
Use of growth factors	29 (45)	15 (25)[a]	31 (47)[b]

[a] $n = 61$ patients for use of growth factors.
[b] $n = 66$ for use of growth factors.
TEAE, treatment-emergent adverse event.

Therefore, agents or regimens that may result in higher response rates to treatment may be incrementally more important for patients with TNBC compared with other breast cancer subtypes. Current treatment strategies include taxanes and platinum analogues, which may be agents of choice for patients with mTNBC [2, 20]. In patients with locally advanced TNBC or mTNBC, outcomes are similar with first-line docetaxel and carboplatin treatment (ORR, 36% and 31%; median PFS, 4.5 and 3.1 months; median OS, 12.3 and 12.4 months, respectively) [21]. Although typically used in the second-line and later settings, gemcitabine has also demonstrated activity in TNBC as part of first-line combination regimens [17, 22]. Furthermore, the two studies including G/C carried out by O'Shaughnessy et al. [9, 10] comprise one of the largest bodies of evidence in this patient population, thus, addition of G/C for comparison in this study was rational. Combination therapies have generally demonstrated higher response rates compared with those observed with single agents, which suggests that multiagent regimens may be optimal for disease management in patients with TNBC [12]. In this regard, the 73% response rate observed with the *nab*-P/C doublet in tnAcity is compelling. Results with this combination are also encouraging in the neoadjuvant setting, with a reported pathological complete response rate of 49% and excellent tolerability in the phase II ADAPT TN trial (NCT01779206; $n = 336$) [23]. In an era of novel therapeutics, including immunotherapies, cytotoxic agents remain an important foundation for the treatment of TNBC due to the immediate need for tumor responses in patients with this aggressive breast cancer subtype [24].

Several first-line combination regimens have been explored in patients with mTNBC, with varying efficacy profiles. A meta-analysis of three randomized phase III trials evaluating first-line combinations with bevacizumab in patients with HER2− metastatic breast cancer ($N = 2447$) evaluated the subset of patients with mTNBC [25]. In this subset of patients treated with bevacizumab plus a chemotherapy regimen ($n = 363$), median PFS was 8.1 months, median OS was 18.9 months, and ORR was 42%. Results from tnAcity provide further support for the role of doublet regimens as first-line treatment of patients with mTNBC.

Several novel strategies are being evaluated in phase III TNBC trials, including immunotherapy, poly(ADP-ribose) polymerase inhibition for TNBC associated with BRCA mutations (NCT02032277, NCT03150576, OlympiAD [completed] [26]), antibody-drug conjugates (NCT02574455), and androgen receptor inhibitors (NCT03055312). Successful enrollment of the phase III portion of the tnAcity study, which was designed before the ongoing trials were initiated, was considered unlikely due to these competing trials and a finite existing pool of patients with TNBC; therefore, the phase III portion of the tnAcity trial was canceled.

nab-P continues to be evaluated as a partner for immunotherapeutic agents in the treatment of TNBC in several ongoing trials in the neoadjuvant and metastatic settings. In the neoadjuvant setting, the phase III NeoTRIPaPDL1 trial is evaluating the efficacy and safety of *nab*-P/C with or without the programmed cell death ligand 1 inhibitor atezolizumab in locally advanced TNBC (NCT02620280). Another programmed cell death ligand 1 inhibitor, durvalumab, is being evaluated in combination with sequential *nab*-P followed by epirubicin plus cyclophosphamide in patients with early TNBC in the phase II GeparNuevo trial (NCT02685059). In the metastatic setting, preliminary data from patients with mTNBC ($N = 32$) in a phase Ib trial (NCT01633970) of atezolizumab in combination with *nab*-P chemotherapy

demonstrated a confirmed ORR of 38%, with complete and partial responses observed in 3% and 34% of patients, respectively, with no new safety signals reported [27]. The phase III IMpassion130 trial is evaluating the safety and efficacy of first-line *nab*-P plus atezolizumab in patients with mTNBC (NCT02425891). Results from these ongoing trials will continue to provide insight on the clinical benefit of *nab*-P as a chemotherapy backbone for the treatment of TNBC.

The results from phase II portion of the tnAcity trial suggest that chemotherapy remains a viable option in patients with mTNBC with manageable toxicity. Furthermore, in this study, treatment with *nab*-P/C resulted in a longer PFS and OS, as well as a higher ORR compared with *nab*-P/G or G/C. Treatment with *nab*-P/C also resulted in a numerically higher ORR in patients with a short DFI. These findings support combination chemotherapy, including *nab*-P/C, as a treatment option in this difficult-to-treat patient population.

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