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ORIGINAL ARTICLE

Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial

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Background: Primary analyses of the phase III BrighTNess trial showed addition of carboplatin with/without veliparib to neoadjuvant chemotherapy significantly improved pathological complete response (pCR) rates with manageable acute toxicity in patients with triple-negative breast cancer (TNBC). Here, we report 4.5-year follow-up data from the trial.

Patients and methods: Women with untreated stage II-III TNBC were randomized (2 : 1 : 1) to paclitaxel (weekly for 12 doses) plus: (i) carboplatin (every 3 weeks for four cycles) plus veliparib (twice daily); (ii) carboplatin plus veliparib placebo; or (iii) carboplatin placebo plus veliparib placebo. All patients then received doxorubicin and cyclophosphamide every 2-3 weeks for four cycles. The primary endpoint was pCR. Secondary endpoints included event-free survival (EFS), overall survival (OS), and safety. Since the co-primary endpoint of increased pCR with carboplatin plus veliparib with paclitaxel versus carboplatin with paclitaxel was not met, secondary analyses are descriptive.

Results: Of 634 patients, 316 were randomized to carboplatin plus veliparib with paclitaxel, 160 to carboplatin with paclitaxel, and 158 to paclitaxel. With median follow-up of 4.5 years, the hazard ratio for EFS for carboplatin plus veliparib with paclitaxel versus paclitaxel was 0.63 [95% confidence interval (CI) 0.43-0.92, $P = 0.02$], but 1.12 (95% CI 0.72-1.72, $P = 0.62$) for carboplatin plus veliparib with paclitaxel versus carboplatin with paclitaxel. In *post hoc* analysis, the hazard ratio for EFS was 0.57 (95% CI 0.36-0.91, $P = 0.02$) for carboplatin with paclitaxel versus paclitaxel. OS did not differ significantly between treatment arms, nor did rates of myelodysplastic syndromes, acute myeloid leukemia, or other secondary malignancies.

Conclusions: Improvement in pCR with the addition of carboplatin was associated with long-term EFS benefit with a manageable safety profile, and without increasing the risk of second malignancies, whereas adding veliparib did not impact EFS. These findings support the addition of carboplatin to weekly paclitaxel followed by doxorubicin and cyclophosphamide neoadjuvant chemotherapy for early-stage TNBC.

Key words: carboplatin, veliparib, neoadjuvant chemotherapy, triple-negative breast cancer, phase III

INTRODUCTION

Triple-negative breast cancer (TNBC) is defined by no or minimal staining for estrogen and progesterone receptors and lack of overexpression of human epidermal growth factor receptor 2 (*HER2*).[1] Whereas there is some heterogeneity among cancers classified as TNBC, overall these cancers are associated with a higher risk of recurrence and

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worse overall prognosis than other breast cancer subtypes.[1,2] Neoadjuvant chemotherapy (NACT) followed by surgery has become a standard treatment of patients with stage II-III TNBC.[3-5] Patients with pathological complete response (pCR) following NACT have substantially improved outcomes compared with patients with residual invasive disease following NACT, but only approximately one-third of patients have pCR at surgery with conventional anthracycline- and taxane-based regimens.[6,7]

The addition of carboplatin to NACT significantly improved pCR rates in patients with stage II-III TNBC in two large, randomized phase II trials.[8,9] In the CALGB/Alliance 40603 trial of 443 patients, the addition of carboplatin to weekly paclitaxel followed by doxorubicin plus cyclophosphamide, with or without bevacizumab, increased the pCR (breast and lymph node) rate from 41% to 54%.[9] In the GeparSixto trial, which included a cohort of 315 patients with stage II-III TNBC, the addition of carboplatin to a backbone regimen of weekly paclitaxel and liposomal doxorubicin with bevacizumab increased the pCR (breast and lymph node) rate from 43% to 53%.[8] Both studies reported increased rates of hematological toxicities in the carboplatin-containing arms, resulting in more frequent treatment delays and dose modifications.[8,9]

Poly(ADP-ribose) polymerase (PARP) 1 plays an important role in the repair of damaged DNA, whether spontaneous or caused by DNA-targeted cytotoxic agents, and is particularly important in cancer cells with impairment of homologous recombination repair, including those with germline pathogenic variants in *BRCA*1 and *BRCA*2.[10,11] For this reason, it was hypothesized that veliparib, a PARP1/PARP2 inhibitor with a relatively low degree of PARP trapping activity, might provide therapeutic benefit when combined with platinum chemotherapy.[12,13] Early phase studies of the combination of veliparib with platinum chemotherapy did not demonstrate a substantial increase in adverse events (AEs), and a phase III trial of the addition of veliparib to paclitaxel and carboplatin in patients with metastatic breast cancer and a pathogenic variant in *BRCA*1 or *BRCA*2 has demonstrated significant improvements in progression-free survival, including in those with TNBC.[14,15] We have previously reported significant improvement in pCR rate, along with an acceptable safety profile, with the addition of carboplatin with (53%) or without (58%) veliparib compared with standard NACT alone (31%) in patients with operable TNBC.[16] Whereas we observed higher rates of hematologic and gastrointestinal toxicities with the addition of carboplatin, with or without veliparib, there was a low incidence of febrile neutropenia (1%-2% with carboplatin versus 0 without) and grade $\geq$3 non-hematologic toxicities.[16] In addition, there was not a substantial compromise in delivery of planned treatment, likely attributable to the treatment guidelines employed in the study (described below).

Despite consistently higher pCR rates with the addition of carboplatin to standard NACT in TNBC, the inclusion of platinum agents in this setting remains controversial, due to the lack of demonstration of improvement in long-term outcomes, coupled with the increased hematologic toxicities associated with this treatment.[3,8,9,17-19] The aim of the analyses reported herein was to assess whether the improvement in pCR observed in the BrighTNess trial (Clinical trial number: NCT02032277) with the addition of carboplatin, with or without veliparib, to paclitaxel is associated with long-term survival benefits and/or an increased risk of second malignancies.[16] Here, we report the long-term efficacy and safety outcomes from the BrighTNess trial with a minimum of 4 years of post-surgery follow-up.

PATIENTS AND METHODS

Study design and patient population

Full details of the study design, patient selection criteria, and endpoints have been reported previously.[16] In summary, BrighTNess was a phase III, randomized, double-blind, placebo-controlled trial conducted across 145 sites in 15 countries. Eligible patients were women aged $\geq$18 years with histologically or cytologically confirmed invasive stage II-III TNBC; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; adequate hematological, renal, and hepatic function; germline *BRCA* (g*BRCA*) mutation status; who were considered candidates for potentially curative surgery.

Patients were randomized (2 : 1 : 1) to receive paclitaxel [80 mg/m^2 intravenously (i.v.) weekly for 12 doses] concurrently with: (i) carboplatin (area under the curve 6 mg/ml/min, i.v. every 3 weeks, for four cycles) plus veliparib (50 mg orally twice daily); (ii) carboplatin plus veliparib placebo; or (iii) carboplatin placebo plus veliparib placebo. To facilitate administration of planned treatment during this first phase of NACT, treatment could be extended up to 16 weeks to allow for receipt of the intended 12 doses of weekly paclitaxel and the investigational agents in patients with hematologic or non-hematologic toxicities requiring dose delays. In the second phase of NACT, all patients were to receive doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 or 3 weeks for four cycles. Randomization was stratified according to g*BRCA* status, nodal stage, and planned schedule of doxorubicin and cyclophosphamide administration. g*BRCA* status was determined by results from testing previously ordered by sites or by central testing (BRACAnalysis CDx, Myriad Genetics Inc, Salt Lake City, UT). According to the standards of the testing laboratory, patients with variants of uncertain clinical significance were considered to not have a g*BRCA* gene mutation, whereas patients with deleterious mutations or suspected deleterious mutations were considered to have a g*BRCA* gene mutation. Surgery was to be carried out 2-8 weeks after the last dose of chemotherapy. Adjuvant radiotherapy was given at the discretion of the investigator; no adjuvant systemic therapy was allowed.

The study was originally designed to follow patients for recurrence and survival events for up to 10 years after surgery. Following the planned statistical analysis of the co-primary endpoints, which demonstrated improvement in

pCR rate with the addition of carboplatin plus veliparib to paclitaxel compared with paclitaxel alone, but no improvement with the addition of carboplatin plus veliparib to paclitaxel compared with carboplatin plus paclitaxel, the protocol was amended to continue follow-up for up to 4 years after surgery to obtain information on long-term efficacy and safety of the addition of carboplatin to paclitaxel as well as long-term safety of the addition of carboplatin plus veliparib to paclitaxel. Post-surgery follow-up information was collected every 3 months until 1 year after surgery, then every 6 months until 2 years after surgery, then yearly until 4 years after surgery, or until an event-free survival (EFS) event. Following a non-death EFS event, patients were followed every 6 months for survival and the development of a second cancer until 4 years post-surgery. Follow-up analyses were conducted using unadjudicated events as reported by sites and confirmed by site monitors.

The study was approved by the institutional review board of all participating sites and conducted in line with the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

Endpoints and assessments

The study's co-primary endpoints were to compare pCR rates between patients randomized to the addition of carboplatin plus veliparib to those randomized to paclitaxel alone, and, if the difference was significant, to compare pCR rates between patients randomized to the addition of carboplatin plus veliparib to those randomized to the addition of only carboplatin (pCR was defined as absence of residual invasive disease in the resected breast specimen and lymph nodes following completion of neoadjuvant systemic therapy). These results have been previously reported, along with a *post hoc* comparison of pCR rates in patients randomized to the addition of only carboplatin with those randomized to paclitaxel alone.[16] Secondary efficacy endpoint analyses reported here include EFS and overall survival (OS) after 4 years of follow-up after surgery. EFS is defined as the time from randomization to documentation of the first of the following events: discontinuation of study therapy due to protocol-defined progression before surgery; local, regional, or distant invasive recurrence of breast cancer following curative surgery; a new breast cancer or secondary malignancy; or death from any cause. Local and regional recurrences or new breast cancer required cytological or histological evidence; bone and visceral recurrences were biopsied to confirm recurrent disease. OS is defined as the time from randomization to death. Rates of second malignancies and myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML) per the Standardized Medical Dictionary for Regulatory Activities (MedDRA) query were also assessed.

Statistical analysis

The primary and secondary endpoints were assessed in all randomized patients (intent-to-treat population). Safety analyses included all patients who received at least one dose of study drug. The primary and secondary endpoints were analyzed using a fixed-sequence testing procedure in the order of (i) carboplatin plus veliparib with paclitaxel versus paclitaxel alone; then (ii) carboplatin plus veliparib with paclitaxel versus carboplatin with paclitaxel. Because the planned statistical analysis of the co-primary endpoint of pCR did not differ between the carboplatin plus veliparib with paclitaxel group and the carboplatin with paclitaxel group, subsequent secondary analyses must be considered as descriptive with nominal *P* values. Stratification factors were used for analyses of the primary and secondary endpoints. Analyses of EFS by stratification factor included *BRCA* status [g*BRCA* mutant (g*BRCA*m), g*BRCA* wildtype, or unknown], clinical lymph node stage (N0 or N1-2), and planned schedule of doxorubicin and cyclophosphamide (every 3 or every 2 weeks). Other subgroups for analysis included age cohort ($\leq$50 years, $>$50 to $\leq$65 years, or $>$65 years), tumor diameter ($\leq$30 or $>$30 mm), and ECOG PS (0 or $\geq$1).

RESULTS

Between 4 April 2014 and 18 March 2016, 634 patients were enrolled and randomized to carboplatin plus veliparib with paclitaxel ($n = 316$), carboplatin plus veliparib placebo with paclitaxel ($n = 160$), or carboplatin placebo plus veliparib placebo with paclitaxel ($n = 158$; Figure 1). Three of the randomized patients did not receive any study drug. Key demographic and disease characteristics at baseline were balanced across the treatment arms as previously published (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.01.009).[16] The last study visit was in October 2020, and the database cut-off was 23 December 2020. The median follow-up time was 4.5 years and did not differ by arm.

Analyses of EFS stratified by g*BRCA* status, lymph node stage, and schedule of doxorubicin plus cyclophosphamide administration are shown in Figure 2. Significant improvement in EFS was demonstrated among patients assigned to carboplatin plus veliparib with paclitaxel compared with paclitaxel alone [hazard ratio (HR) 0.63; 95% confidence interval (CI) 0.43-0.92; nominal $P = 0.02$] but no difference was demonstrated in EFS between patients assigned to carboplatin plus veliparib with paclitaxel versus carboplatin with paclitaxel (HR 1.12; 95% CI 0.72-1.72; $P = 0.62$). A *post hoc* comparison of patients assigned to carboplatin with paclitaxel versus paclitaxel alone demonstrates improvement in EFS (HR 0.57; 95% CI 0.36-0.91). Unstratified analysis also showed improved EFS with paclitaxel plus carboplatin with or without veliparib versus paclitaxel alone, but no improvement with carboplatin plus veliparib with paclitaxel compared with carboplatin with paclitaxel (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.01.009). The EFS rates at 4 years after surgery are 78% (95% CI 73.5-83.2) with carboplatin plus veliparib with paclitaxel, 79% (95% CI 72.9-86.2) with carboplatin with paclitaxel, and 69% (95% CI 61.3-76.6) with paclitaxel alone. EFS events of any type were experienced

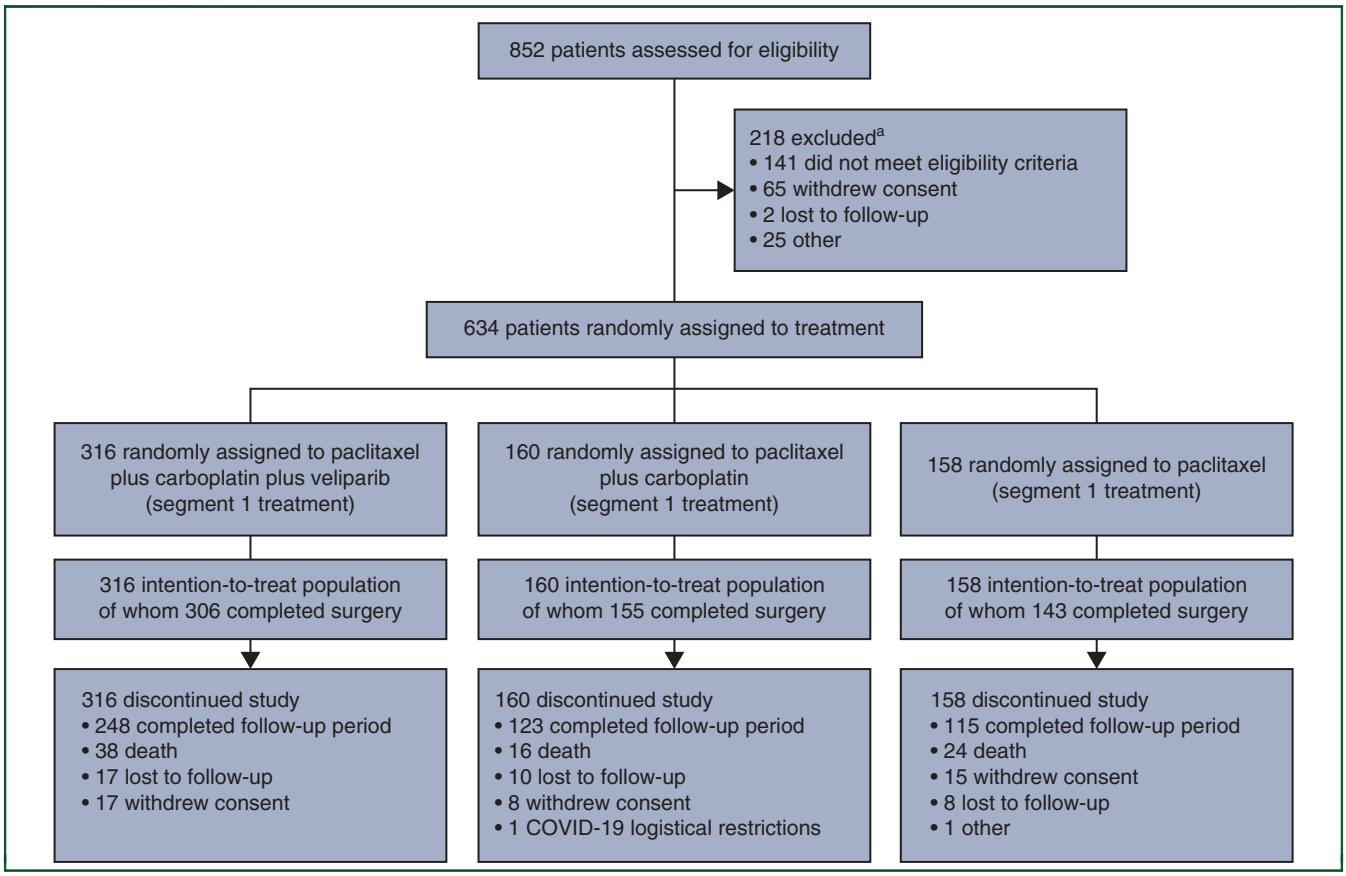

Figure 1. Patient disposition.
[a]Sites were able to enter more than one reason for screen failure.

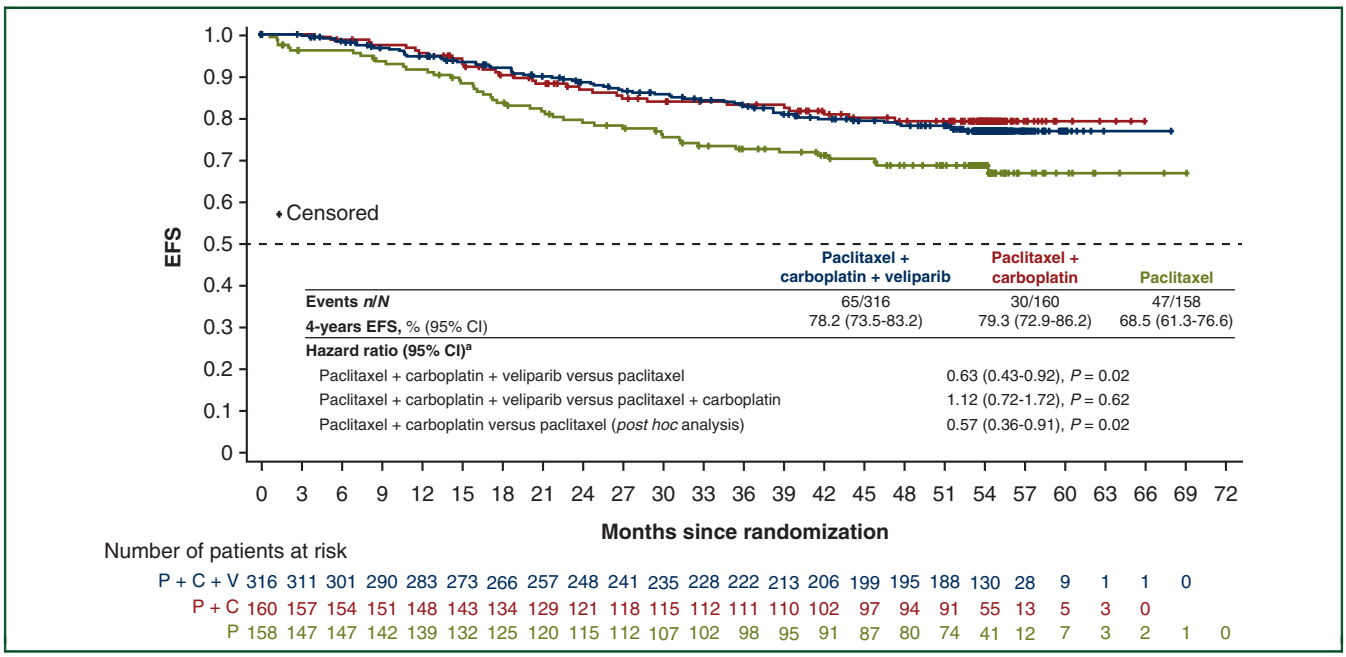

Figure 2. EFS with a median of ≥4.5 years of follow-up.
Final analysis of EFS carried out ≥4 years after surgery.
C, carboplatin; CI, confidence interval; EFS, event-free survival; g*BRCA*, germline *BRCA*; P, paclitaxel; V, veliparib.
[a]Stratified by g*BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.

Table 1. Summary of EFS events

	Paclitaxel + carboplatin + veliparib ($n = 316$)	Paclitaxel + carboplatin ($n = 160$)	Paclitaxel ($n = 158$)
Patients with EFS event[a]	65 (21)	30 (19)[b]	47 (30)
PD before surgery	2 (1)	1 (1)	6 (4)
Any recurrence or new malignancy	50 (16)	26 (16)	35 (22)
Distant	22 (7)	12 (8)	14 (9)
Local	16 (5)	10 (6)	10 (6)
Ipsilateral breast	6 (2)	4 (3)	5 (3)
Regional	4 (1)	3 (2)	11 (7)
Contralateral breast cancer	2 (1)	1 (1)	4 (3)
AML/MDS	4 (1)	2 (1)	2 (1)
New malignancy other than breast cancer or AML/MDS	10 (3)	1 (1)	3 (2)
Death as first event	13 (4)	3 (2)	6 (4)

Data are *n* (%).

AML, acute myeloid leukemia; EFS, event-free survival; MDS, myelodysplastic syndromes; PD, progressive disease.

[a]EFS events were summarized by types of events reported as documented on date of first event(s). Patients may have had multiple types of EFS events reported on the same day. Major EFS categories were: (i) PD before surgery; (ii) any recurrence or new malignancy; and (iii) death as first event. Patients might have had more than one type of EFS event documented at the time of their first event(s).

[b]Post analysis adjudication of second malignancies identified a second malignancy reported in three patients on the paclitaxel plus carboplatin arm (squamous skin cancer, AML, and colon cancer) who had not been reported with a prior EFS event and were not classified as an EFS event.

by 21% of patients in the carboplatin plus veliparib with paclitaxel group, 19% of the carboplatin with paclitaxel group, and 30% of the paclitaxel group (Table 1). Disease recurrence was the most common event, occurring in 16% of patients in the carboplatin plus veliparib with paclitaxel group, 16% of the carboplatin with paclitaxel group, and 22% of the paclitaxel alone group. These differences primarily reflect higher rates of disease progression during neoadjuvant therapy (4%) and regional recurrences (7%) on the paclitaxel alone arm, compared with rates of disease progression during NACT of 1% for both carboplatin regimens and regional recurrences rates of 1% for carboplatin plus veliparib with paclitaxel and 2% for carboplatin with paclitaxel. Rates of distant recurrences as a first event were similar across the three arms (7% for carboplatin plus veliparib with paclitaxel, 8% for carboplatin with paclitaxel, and 9% for paclitaxel alone). There were no imbalances between the three arms regarding radiation therapy fields delivered following surgery, specifically radiation therapy to regional nodes was delivered in 33%, 34%, and 34% of patients undergoing surgery for the three arms, respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.01.009). Rates of death as first event were low and similar across arms (4%, 2%, and 4%, respectively). Analyses of EFS by stratification variables and other subgroups showed consistency of the HR favoring carboplatin plus veliparib with paclitaxel versus paclitaxel alone in all subgroups (Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2022.01.009), but no subgroup demonstrated improvement in EFS with the addition of veliparib to carboplatin with paclitaxel versus carboplatin with paclitaxel (Supplementary Figure S1B, available at https://doi.org/10.1016/j.annonc.2022.01.009).

Following the database lock and Statistical Analysis Plan-specified analysis, adjudication of reported EFS events with second malignancies reported as AEs of special interest (AESIs) identified three patients on the paclitaxel plus carboplatin arm with a second malignancy (squamous skin cancer, AML, and colon cancer, respectively) reported as an AESI but not reported as an EFS event. These events were not included in the analyses of EFS but were included as identified second malignancies in Table 2.

The cohort of patients with a pCR across treatment arms had significant improvement in EFS compared with the cohort without a pCR across treatment arms (HR 0.26; 95% CI 0.18-0.38; $P < 0.0001$; Figure 3A). Subgroup analysis by g*BRCA* status identified significant improvements in EFS for patients with pCR versus non-pCR both in patients with an identified germline pathogenic variant in *BRCA*1 or *BRCA*2 (HR 0.14; 95% CI 0.05-0.41; $P < 0.01$; Figure 3B) and in *BRCA* wildtype patients (HR 0.29; 95% CI 0.19-0.44; $P < 0.0001$; Figure 3C).

Both stratified and unstratified analyses showed that there were no statistically significant differences in OS between carboplatin plus veliparib with paclitaxel versus paclitaxel or versus carboplatin with paclitaxel (Figure 4, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.01.009). The HR for OS by stratified analysis was 0.82 (95% CI 0.48-1.38, $P = 0.45$) for carboplatin plus veliparib with paclitaxel versus paclitaxel alone, 1.25 (95% CI 0.70-2.24, $P = 0.46$) for carboplatin plus veliparib with paclitaxel versus carboplatin with paclitaxel, and 0.63 (95% CI 0.33-1.21, $P = 0.17$) for carboplatin with paclitaxel versus paclitaxel alone. The number of OS events was relatively small, however, with deaths occurring in just 38/316 patients (12%) with carboplatin plus veliparib with paclitaxel, 16/160 (10%) with carboplatin with paclitaxel, and 22/158 (14%) with paclitaxel alone.

Acute toxicities from this study have been previously reported[16]; the present analysis focuses on late AEs, primarily treatment-related second cancers. The rates of treatment-emergent and post-treatment-emergent MDS and second non-breast primary malignancies, as defined by Standardized Medical Dictionary for Regulatory Activities Queries (SMQ), were similar between all treatment groups (Table 2). MDS SMQ, which included pancytopenia and MDS, occurred in 5 (2%) of 313 patients treated with carboplatin plus veliparib with paclitaxel, 3 (2%) of 158 patients treated with carboplatin with paclitaxel, and 1 (1%) of 157 patients treated with paclitaxel alone. Non-breast second malignancies occurred in six (2%) patients, six (4%) patients, and four (3%) patients among the three groups, respectively. AML or acute leukemia were the identified second malignancy in three (2%) patients, three (2%) patients, and one (1%) patient among the three groups, respectively.

DISCUSSION

BrighTNess, a phase III study, was designed to corroborate the findings from the carboplatin plus veliparib arm of the

Table 2. Frequency of TEAEs of MDS, AML, and other secondary malignancy at ≥4-year of follow-up

	Paclitaxel + carboplatin + veliparib (n = 313)	Paclitaxel + carboplatin (n = 158)	Paclitaxel (n = 157)
MDS SMQ	5 (2)	3 (2)	1 (<1)
Pancytopenia	4 (1)	3 (2)	0
MDS	1 (<1)	0	1 (<1)
Second malignancies SMQ	6 (2)	6 (4)	4 (3)
Acute leukemia	1 (<1)	0	0
AML	2 (<1)	3 (2)	1 (<1)
CML	1 (<1)	0	0
Lung neoplasm	1 (<1)	0	0
Malignant melanoma	1 (<1)	0	0
Basal cell carcinoma	0	1 (<1)	0
Colon cancer	0	1 (<1)	0
Pancreatic carcinoma	0	0	2 (1)
Squamous cell carcinoma of skin	0	0	1 (<1)

Data are n (%).

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; EFS, event-free survival; MDS, myelodysplastic syndrome; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Queries; TEAEs, treatment-emergent adverse events.

I-SPY2 trial, which demonstrated an increase in pCR rate from 26% to 51% in patients with TNBC with the addition of veliparib and carboplatin to weekly paclitaxel, followed by doxorubicin and cyclophosphamide.[12] In order to isolate the contribution of veliparib to the increased activity of this regimen, however, BrighTNess included a second control arm in which patients received carboplatin with paclitaxel without veliparib. Primary analysis of the trial demonstrated that the addition of carboplatin plus veliparib to paclitaxel resulted in a significant improvement in pCR in patients with operable TNBC relative to paclitaxel alone, but also demonstrated no benefit from the addition of veliparib to carboplatin with paclitaxel relative to carboplatin with paclitaxel.[16] Although BrighTNess was not designed to formally evaluate the benefit of adding carboplatin to paclitaxel, the aggregate results indicated that the improvement in pCR with the addition of carboplatin and veliparib to paclitaxel reported in I-SPY2 and BrighTNess was likely attributable to the addition of carboplatin alone, with no additional benefit from veliparib.[12] Given the ongoing controversy regarding the role of carboplatin as a component of NACT in TNBC, and the continued need to improve treatment outcomes in these high-risk patients, BrighTNess collected information on EFS events, deaths, and secondary malignancies for at least 4 years after surgery. Whereas this period of patient follow-up is inadequate to fully assess OS, it is sufficient to identify most recurrences that would be expected in the study population.

These follow-up data demonstrate that the improved pCR rate with the addition of carboplatin to standard NACT is associated with improvement in EFS in the BrighTNess patient population which had presented with operable stage II-III TNBC. With a median follow-up of 4.5 years, 4-year absolute EFS rates were ∼10% higher in patients who received paclitaxel plus carboplatin, with or without veliparib, compared with those who received paclitaxel alone, consistent with carboplatin being responsible for the improvement in EFS. The differences in EFS were driven by higher rates of progression of disease during neoadjuvant therapy and regional recurrences among patients assigned to the non-carboplatin-containing control arm. While the incidences of distant recurrence as the first EFS event did not differ substantially between treatment arms, the adverse impact of isolated locoregional recurrences on the subsequent prognosis of patients with TNBC is illustrated by results from the CALOR trial.[20]

In addition, analyses consistently favored carboplatin-containing treatment over paclitaxel alone in groups defined by g*BRCA* status, lymph node status, planned schedule of doxorubicin and cyclophosphamide, and other baseline characteristics, while, consistently demonstrating no benefit from the addition of veliparib to this regimen. The addition of carboplatin did not increase the number of treatment-emergent or post-treatment-emergent MDS, AML, or other second malignancies compared with the control regimen of chemotherapy, and the rate of second cancers was low across all arms. In the BrighTNess study, second malignancies were reported as AESIs, but were also to be identified as an EFS event in the absence of disease progression on neoadjuvant therapy or recurrence of breast cancer. Post-analysis adjudication of second malignancies identified three patients in the carboplatin plus paclitaxel arm which were reported as second malignancies but were not classified as an EFS event for the analysis of EFS. These will be included as EFS events in future planned correlative and pooled analyses.

Patients without pCR following NACT did not receive adjuvant systemic therapy on BrighTNess, as data demonstrating benefit of such treatments were unavailable when patients were treated within this study. Subsequently, the CREATE-X trial demonstrated improved outcomes with administration of adjuvant capecitabine in TNBC patients with residual invasive cancer following NACT.[21] More recently, the OlympiA study demonstrated improved outcomes with adjuvant olaparib in TNBC patients with g*BRCA* mutation following NACT.[22] While it is gratifying to have effective adjuvant treatment options for TNBC patients without pCR following NACT, such treatments substantially extend the duration of therapy. Since pCR status remains a powerful predictor for favorable outcomes in TNBC, our results support the addition of carboplatin to weekly paclitaxel followed by anthracycline-containing NACT regimens for patients with stage II-III TNBC to maximize the likelihood for pCR status at surgery and to avoid prolonged adjuvant therapy.

The long-term results of BrighTNess must be assessed in the context of results from two previous phase III trials that were also powered to assess pCR but not long-term outcomes. CALGB/Alliance 40603 demonstrated a significant increase in the pCR rate with the addition of carboplatin to weekly paclitaxel followed by doxorubicin and cyclophosphamide, a regimen identical to that used in our study except that half of the patients on the CALGB/Alliance trial also received bevacizumab.[9] With a median follow-up of

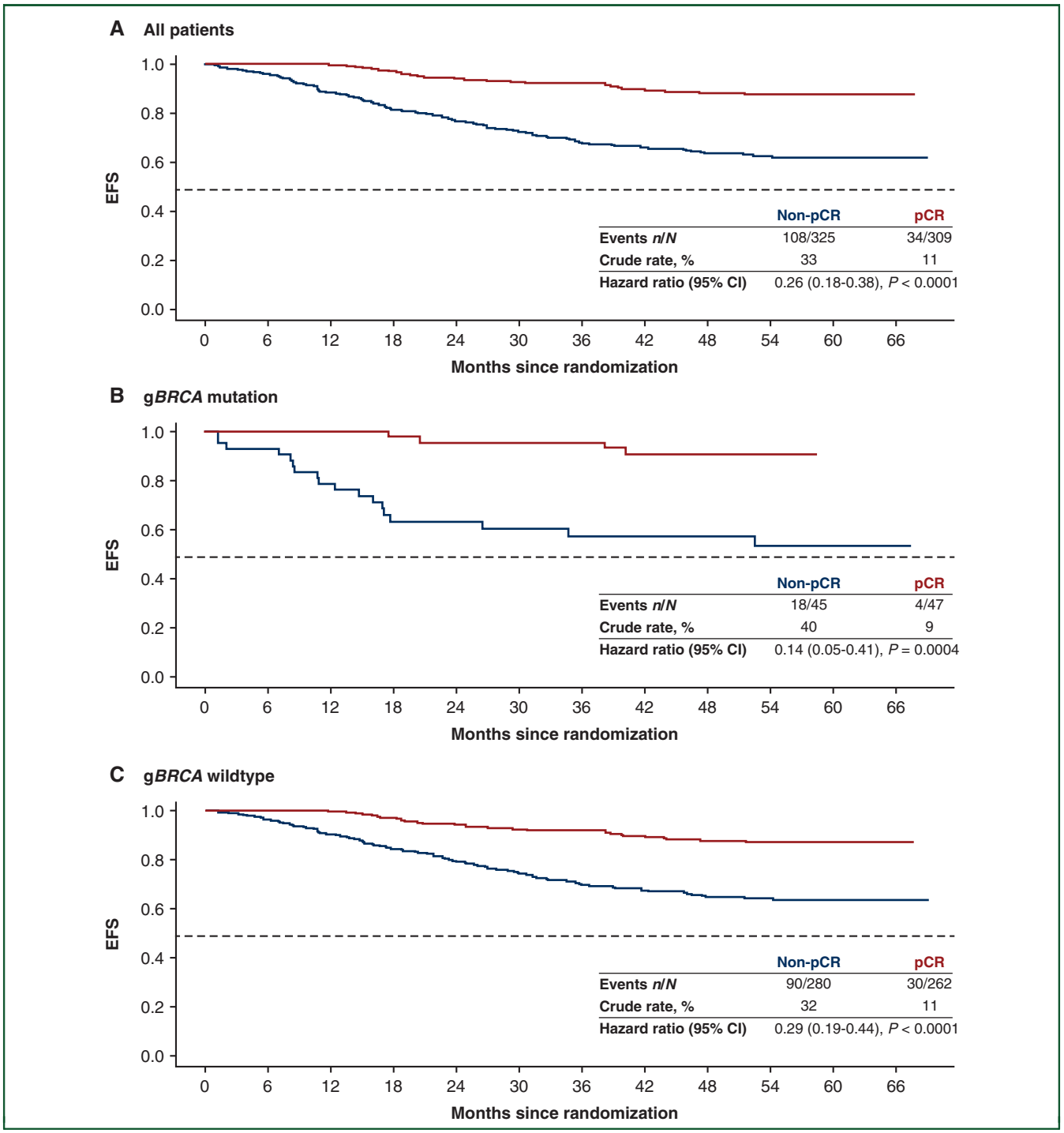

Figure 3. EFS by pCR status in (A) all patients, (B) patients with g*BRCA* mutations, and (C) patients with g*BRCA* wild type.
CI, confidence interval; EFS, event-free survival; g*BRCA*, germline *BRCA*; pCR, pathological complete response.

5.7 years, the cohort of patients with a pCR exhibited significant improvements in EFS (HR 0.28) and OS (HR 0.28).[23] No improvements in EFS (HR 0.99) or OS (HR 1.14) were identified, however, with the addition of carboplatin.[23] The GeparSixto trial also demonstrated improvement in pCR with the addition of carboplatin to a novel anthracycline-taxane regimen (weekly nonpegylated liposomal doxorubicin and paclitaxel with every 3-week bevacizumab).[8] With a median follow-up of 47.3 months, the study reported that the addition of carboplatin was associated with significantly improved disease-free survival (DFS; HR 0.56, $P = 0.02$; 3-year DFS, 86% versus 76%); there was also a numerical improvement in OS, though this did not reach statistical significance (HR 0.55; 95% CI 0.27-1.14, $P = 0.10$).[19] Because none of these three studies were prospectively powered for definitive assessment of DFS/EFS and OS endpoints, a future pooled analysis of the long-term outcomes from BrighTNess, GeparSixto, and CALGB/Alliance

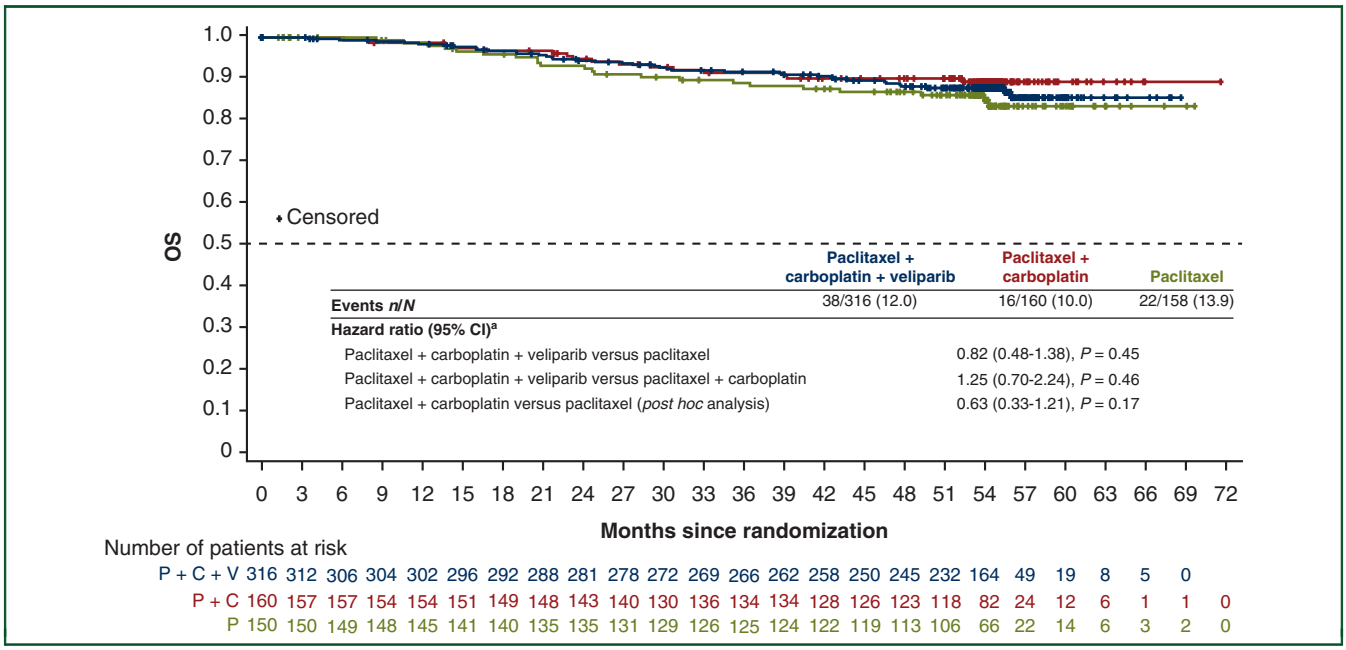

Figure 4. OS with a median of ≥4.5 years of follow-up. Final analysis of OS carried out ≥4 years after surgery.
C, carboplatin; CI, confidence interval; g*BRCA*, germline *BRCA*; OS, overall survival; P, paclitaxel; V, veliparib.
[a]Stratified by g*BRCA* status, lymph node status, and planned doxorubicin cyclophosphamide dose intensity.

40603 is planned to address the power limitations of the three studies. The pooled analysis will also strengthen correlative studies that may help elucidate the role of immune activation in therapeutic responses and potentially identify prognostic features and patient subsets that may or may not benefit from addition of carboplatin.

Despite similarities in randomized designs evaluating carboplatin, BrighTNess had important differences from these prior studies as well. Patients in the control arm of GeparSixto did not receive cyclophosphamide, a deviation from standard NACT regimens but a clear design to answer the carboplatin question.[8] In CALGB/Alliance 40603, the duration of paclitaxel with or without carboplatin phase of treatment was limited to 12 weeks with treatments omitted rather than delayed for hematologic and other toxicities, after which patients were transitioned to doxorubicin and cyclophosphamide.[9] This resulted in substantial reductions in dose delivery of paclitaxel in the trial, particularly on the carboplatin arms. In contrast, BrighTNess extended the allowed treatment duration for paclitaxel with or without carboplatin to 16 weeks, which enhanced delivery of planned treatment.[16] In an exploratory analysis of the CALGB/Alliance 40603 trial, investigators demonstrated that patients who missed multiple doses of weekly paclitaxel had inferior EFS, and that this occurred more frequently in patients assigned to carboplatin (35%) than those who were not (15%).[23] Among patients who received at least 11 doses of weekly paclitaxel, the addition of carboplatin resulted in a higher pCR rate (61%) and numerically higher 5-year EFS (79% with carboplatin versus 72% without; HR 0.72, $P = 0.16$).[23] As discussed in the initial publication of these results, 88% of BrighTNess patients on the paclitaxel plus carboplatin arm received all 12 doses of paclitaxel, compared with only 64% on CALGB/Alliance 40603.[9,16]

In a randomized phase II study, patients who received six cycles of docetaxel and carboplatin had a similar pCR rate (52%) to the weekly paclitaxel and carboplatin followed by the doxorubicin and cyclophosphamide regimen used in our study (55%)[24]; more recently, these investigators reported equivalent EFS and OS at a median follow-up of 38 months.[25] Moreover, in the recently reported phase III PATTERN trial with 647 randomized TNBC patients, those assigned to adjuvant weekly paclitaxel and carboplatin had significantly improved 5-year DFS compared with those assigned to the control regimen of cyclophosphamide, epirubicin, and fluorouracil followed by docetaxel (87% versus 80%, HR 0.65; 95% CI 0.44-0.96, $P = 0.03$).[26] These results, together with our data, support consideration of a prospective, adequately powered trial investigating whether administration of carboplatin with a taxane would allow de-escalation of NACT in TNBC, by permitting elimination of the anthracycline, without compromising outcomes (pCR, EFS, and OS).

NRG-Oncology BR003 (NCT02488967), an ongoing, phase III, adjuvant trial approaching the end of accrual, randomizes patients with TNBC treated with initial surgery to adjuvant doxorubicin and cyclophosphamide followed by paclitaxel with and without carboplatin, with invasive DFS as the primary endpoint.[27] The results from this trial will further address long-term outcomes with the addition of carboplatin to standard chemotherapy in TNBC.

Several studies have suggested that pCR may not accurately predict DFS or relapse-free survival benefit in patients with g*BRCA* pathogenic variants despite higher pCR rates

compared with patients with wildtype *BRCA*.[28] In contrast, subgroup analysis from BrighTNess demonstrates a strong association between pCR and EFS, regardless of *BRCA* status (*BRCA* mutations, HR 0.14; *BRCA* wildtype, HR 0.29). This is consistent with the secondary analysis of the GeparSixto trial which showed a significant correlation of pCR rates with DFS rates irrespective of the *BRCA*1 and *BRCA*2 mutation status.[29]

Our follow-up of the BrighTNess trial also assessed long-term safety beyond the standard period of 30 days following cessation of study treatment. We observed low incidences of MDS, AML, and other second malignancies among all treatment groups, suggesting that the addition of carboplatin to standard chemotherapy does not appreciably increase the risk of developing secondary hematologic malignancies and MDS. Second malignancies were also not increased with veliparib. It should also be noted that while administration of PARP inhibitors has been associated with an increased risk of developing secondary MDS and AML in patients with ovarian cancers, the overall incidence is relatively low (<1.5%).[30,31] Our results show that adding veliparib at the dose and schedule employed in this trial did not increase the risk of developing MDS (<1%), AML (<2%), or second malignancies in patients with TNBC. Given their role in inhibiting DNA damage repair, however, continuing surveillance for second malignancies following treatment with PARP inhibitors is warranted.

In summary, the superior pCR rates with the addition of veliparib plus carboplatin or carboplatin alone to NACT demonstrated in BrighTNess translated into long-term improvements in EFS. In addition, veliparib plus carboplatin or carboplatin alone was not associated with increased risk of developing MDS, AML, or other second cancers. There was no evidence, however, of benefit from the addition of veliparib to the carboplatin plus paclitaxel regimen in any identified patient subgroup. Our results suggest that when carboplatin is added to weekly paclitaxel, treatment guidelines should permit delays when necessary to facilitate administration of treatment as planned. Long-term results of BrighTNess add to the growing body of evidence supporting carboplatin as a component of NACT in stage II-III TNBC.

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DATA SHARING

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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