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Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND

Triple-negative breast cancers have inherent defects in DNA repair, making this cancer a rational target for therapy based on poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition.

METHODS

We conducted an open-label, phase 2 study to compare the efficacy and safety of gemcitabine and carboplatin with or without iniparib, a small molecule with PARP-inhibitory activity, in patients with metastatic triple-negative breast cancer. A total of 123 patients were randomly assigned to receive gemcitabine (1000 mg per square meter of body-surface area) and carboplatin (at a dose equivalent to an area under the concentration–time curve of 2) on days 1 and 8 — with or without iniparib (at a dose of 5.6 mg per kilogram of body weight) on days 1, 4, 8, and 11 — every 21 days. Primary end points were the rate of clinical benefit (i.e., the rate of objective response [complete or partial response] plus the rate of stable disease for ≥6 months) and safety. Additional end points included the rate of objective response, progression-free survival, and overall survival.

RESULTS

The addition of iniparib to gemcitabine and carboplatin improved the rate of clinical benefit from 34% to 56% (P=0.01) and the rate of overall response from 32% to 52% (P=0.02). The addition of iniparib also prolonged the median progression-free survival from 3.6 months to 5.9 months (hazard ratio for progression, 0.59; P=0.01) and the median overall survival from 7.7 months to 12.3 months (hazard ratio for death, 0.57; P=0.01). The most frequent grade 3 or 4 adverse events in either treatment group included neutropenia, thrombocytopenia, anemia, fatigue or asthenia, leukopenia, and increased alanine aminotransferase level. No significant difference was seen between the two groups in the rate of adverse events.

CONCLUSIONS

The addition of iniparib to chemotherapy improved the clinical benefit and survival of patients with metastatic triple-negative breast cancer without significantly increased toxic effects. On the basis of these results, a phase 3 trial adequately powered to evaluate overall survival and progression-free survival is being conducted. (Funded by BiPar Sciences [now owned by Sanofi-Aventis]; ClinicalTrials.gov number, NCT00540358.)

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Metastatic triple-negative breast cancer — which is estrogen-receptor (ER)–negative and progesterone-receptor (PR)–negative and has no overexpression of human epidermal growth factor receptor type 2 (HER2) — is an aggressive subtype of breast cancer marked by higher rates of visceral and central nervous system metastases and poorer disease-specific survival than hormone receptor–positive subtypes.[1-4] Patients with triple-negative breast cancer treated with preoperative chemotherapy have higher rates of pathological complete response than patients with hormone receptor–positive breast cancer.[5,6] However, patients in whom metastatic disease develops have a very poor prognosis, with a median survival of approximately 1 year.[7] No standard-of-care therapy exists for patients with metastatic triple-negative breast cancer, and therefore they have an unmet need.

Accounting for 15 to 20% of all cases of breast cancer,[1,8,9] triple-negative breast cancer shares clinical and pathological features with hereditary *BRCA1*-related breast cancers. In sporadic triple-negative breast cancer, dysregulation of BRCA1, a protein with critical roles in the homologous-recombination–dependent DNA-repair pathway, has been attributed to a number of mechanisms, including BRCA1-promoter methylation and overexpression of the negative regulators ID4 and HMG.[10-13] Other defects in homologous-recombination pathways have also been implicated in the tumorigenesis of triple-negative breast cancer (including aberrations in MRE11–RAD50–NBS1, ATM, p53, and PALB2),[14-17] providing a strong rationale for developing new agents that exploit DNA-repair defects in these cancers.

Poly(adenosine diphosphate–ribose) polymerase 1 (PARP1), an important regulator of the DNA base-excision–repair pathway, has emerged as a therapeutic target for triple-negative breast cancer. Preclinical studies have shown that combining PARP1 inhibitors with platinum chemotherapy agents, which induce DNA damage through adducts and cross-linking, potentiates chemotherapeutic cytotoxicity.[18,19] Iniparib (also known as BSI-201) is an anticancer agent with PARP inhibitory activity in preclinical models. Although the full mechanism of its antitumor activity is still under investigation, iniparib enhances the antiproliferative and cytotoxic effects of carboplatin and gemcitabine in in vitro models of triple-negative breast cancer.[19,20] In clinical studies, the combination of gemcitabine and carboplatin chemotherapy has demonstrated activity in patients with metastatic breast cancer, with rates of response ranging from 26 to 34%.[21-23] This phase 2 study was designed to evaluate whether iniparib could potentiate the antitumor effects of gemcitabine and carboplatin with acceptable toxicity levels.

Phase 1–1b studies of iniparib alone and iniparib in combination with chemotherapy in patients with advanced solid tumors have shown iniparib to have mild toxicity, with no maximal dose reached in terms of side effects.[24,25] In the present study, we investigated the efficacy and safety of iniparib in combination with gemcitabine and carboplatin chemotherapy in patients with metastatic triple-negative breast cancer.

METHODS

PATIENTS

Inclusion criteria for the study were female sex, an age of 18 years or older, and a diagnosis of metastatic breast cancer with measurable disease that was histologically documented as ER-negative, PR-negative, and not having overexpression of HER2. Other inclusion criteria were Eastern Cooperative Oncology Group performance status score (which ranges from 0 to 5) of 0 or 1, with 0 representing a patient who is fully active and able to carry out predisease performance without restrictions, and 1 representing a patient who is restricted with respect to physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework or office work)[26]; and adequate bone marrow, hepatic, and renal function. Central nervous system metastases were permitted if the patient did not require glucocorticoids or brain radiotherapy and if brain metastases were clinically stable. Up to two prior chemotherapy regimens for metastatic disease were permitted, as was prior adjuvant or neoadjuvant chemotherapy, with the exception of treatment with gemcitabine, carboplatin, cisplatin, or a PARP inhibitor.

All patients provided written informed consent before enrollment. All tests (immunohistochemistry for ER, PR, and HER2 and fluorescence in situ hybridization for HER2) were done according to each institution's standards and were performed with the use of archived-tissue specimens, the majority of which were derived from primary breast cancers.

STUDY DESIGN

The study was approved by the central institutional review board of US Oncology (www.usoncology.com) and complied with the provisions of the Good Clinical Practice guidelines. The study was sponsored by BiPar Sciences (now a wholly owned subsidiary of Sanofi-Aventis). The study was designed by the principal academic investigator and lead academic author in collaboration with other academic authors and authors from BiPar Sciences. Data collection and analysis were performed by ICON Clinical Research in collaboration with the sponsor. The academic authors vouch for the completeness and accuracy of the data, the data analyses, and the fidelity of this report to the study protocol (available with the full text of this article at NEJM.org). The article was written by one academic and one industry author, with editorial assistance provided by the sponsor, and was reviewed by all coauthors and the sponsor.

This multicenter, open-label, randomized, phase 2 study was conducted at 20 centers within the US Oncology network. Patients were recruited from September 2007 through March 2009. All eligible patients were randomly assigned, in a 1:1 ratio, to receive gemcitabine plus carboplatin, either alone (the chemotherapy-alone group) or in combination with iniparib (the iniparib group). Assignment to treatment groups was conducted by means of an integrated web randomization system. Randomization was not stratified according to study center.

Primary end points were the rate of clinical benefit (defined as the percentage of patients who had a complete response, a partial response, or stable disease for at least 6 months), as well as safety and tolerability of iniparib. Secondary end points were the overall rate of response and progression-free survival, defined as the time from randomization to confirmation of disease progression or death. Overall survival (defined as the time from randomization until the date of death) was not prespecified as an end point but was analyzed to explore the potential effect of iniparib on survival.

TREATMENT

Patients received chemotherapy as follows: during each 21-day period, on days 1 and 8, intravenous gemcitabine (1000 mg per square meter of body-surface area) over a 30-minute period and carboplatin (at a dose equivalent to an area under the concentration–time curve of 2) over a 60-minute period. This regimen was administered either alone or together with intravenous iniparib (4.0 mg per kilogram) over a 60-minute period, on days 1, 4, 8, and 11.

The protocol was amended in January 2008 to increase the iniparib dose to 5.6 mg per kilogram on the basis of emerging phase 1 safety data. Twenty patients received the lower iniparib dose before the amendment and thereafter had the dose increased to 5.6 mg per kilogram. Patients randomly assigned to the chemotherapy-alone group were allowed to cross over to receive iniparib plus gemcitabine and carboplatin if disease progression occurred.

ASSESSMENT

Tumor response was based on investigator assessment of target and nontarget lesions and was assessed by means of computed tomography or magnetic resonance imaging at baseline and every 6 weeks thereafter, in the absence of clinically evident disease progression. Tumor measurements according to the modified Response Evaluation Criteria in Solid Tumors, version 1.0, were used to evaluate tumor response and to establish disease progression (for details, see the Supplementary Appendix, available at NEJM.org).[27]

Safety was assessed with the use of standard clinical and laboratory tests (hematologic tests, blood chemical tests, and urinalysis) throughout the study period until 30 days after the last dose of a study drug was administered. Adverse event grades were defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Serious adverse events were monitored and reported to MedWatch and the ICON safety group by the primary investigator at each site.

STATISTICAL ANALYSIS

The primary objective of the trial was to estimate the rate of clinical benefit in the iniparib group. We calculated that with a sample size of 60 patients per group, assuming that the observed rate of clinical benefit in the iniparib group was approximately 0.60 (or 60%), the half-width of the exact 90% binomial confidence interval would be approximately equal to 0.11. In particular, for an observed rate of clinical benefit of 0.60, the exact 90% binomial confidence interval was 0.49 to 0.71. In contrast, the anticipated rate of clinical

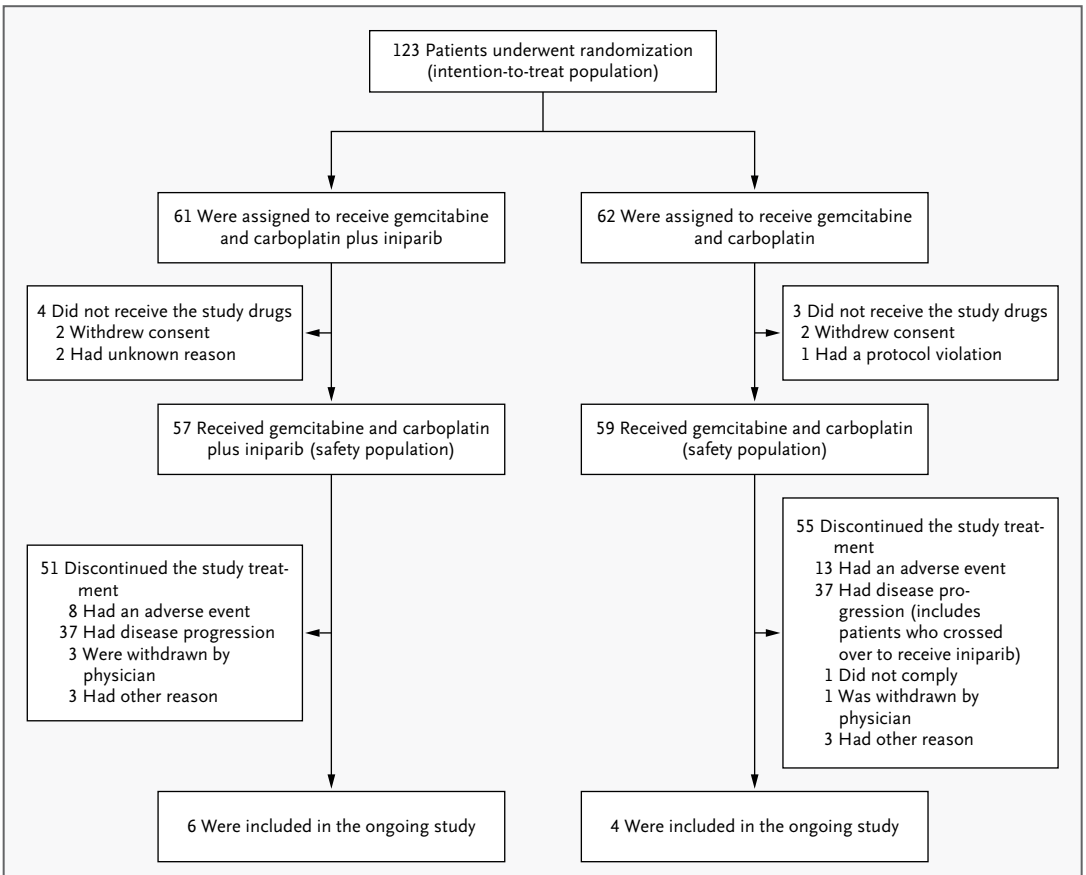

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.

benefit in the chemotherapy-alone group was assumed to be approximately 0.45. If the rate of clinical benefit in the iniparib group was 0.674 or greater, then — on the basis of a one-sided test of equality of proportions at the 5% level of significance — the trial would have a power of at least 80% to detect an increase from the rate of clinical benefit of 0.45 in the chemotherapy-alone group.

In each of the two groups, the primary efficacy end point (i.e., the rate of clinical benefit) and the overall rate of response were estimated, and the exact two-sided 95% confidence interval was calculated. The rates of clinical benefit and the overall rates of response in the two groups were compared with the use of the Pearson chi-square test. Efficacy end points of progression-free and overall survival were estimated, and 95% confidence intervals were calculated by means of the Kaplan–Meier method. The distributions of progression-free and overall survival in the two groups were compared with the use of the log-rank test. P values were not adjusted for multiple interim analyses. All P values and confidence intervals reported are two-sided, and all analyses are of data for the intention-to-treat population unless otherwise noted. Adverse events and serious adverse events were tabulated according to trial group and the *Medical Dictionary for Regulatory Activities* (MedDRA) System Organ Class categorization and preferred terms. For patients in the chemotherapy-alone group who crossed over to the iniparib group, safety data reported after the crossover were analyzed separately.

RESULTS

PATIENTS

Between October 16, 2007, and March 9, 2009, 123 patients were randomly assigned to a treatment group: 62 to the chemotherapy-only group and 61 to the iniparib group. A total of 116 patients (94%) received at least one dose of a study drug (Fig. 1): 57 patients in the iniparib group

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.

Characteristic	Gemcitabine–Carboplatin and Iniparib (N=61)	Gemcitabine–Carboplatin Alone (N=62)
Female sex — no. (%)	61 (100)	62 (100)
Age — yr		
Median	56	53
Range	34–76	26–80
Race — no. (%)*		
White	48 (79)	48 (77)
Black or African ancestry	9 (15)	12 (19)
Asian	1 (2)	0
Unknown	3 (5)	2 (3)
ECOG performance status — no. (%)†		
0	42 (69)	42 (68)
1	18 (30)	20 (32)
Missing data or unknown	1 (2)	0
No. of metastatic organ sites — no. (%)		
1	7 (11)	7 (11)
2	19 (31)	12 (19)
≥3	35 (57)	43 (69)
Metastatic site — no. (%)		
Bone	20 (33)	23 (37)
Brain	2 (3)	6 (10)
Chest wall or skin	18 (30)	12 (19)
Liver	24 (39)	28 (45)
Lung	38 (62)	32 (52)
Lymph nodes	40 (66)	39 (63)
Prior neoadjuvant or adjuvant chemotherapy — no. (%)	47 (77)	43 (69)
No. of prior courses of chemotherapy for metastases — no. (%)		
0	35 (57)	37 (60)
1	21 (34)	13 (21)
2	4 (7)	6 (10)
3	0	1 (2)
Missing data	1 (2)	5 (8)
Bevacizumab-containing regimen — no. (%)	9 (15)	8 (13)
Taxane-containing regimen — no. (%)	51 (84)	44 (71)
Anthracycline-containing regimen — no. (%)	45 (74)	40 (65)

* Race was self-reported.
† The Eastern Cooperative Oncology Group (ECOG) performance status reflects the daily-living abilities of the patient, on a scale of 0 (fully active without symptoms) to 5 (dead).

and 59 patients in the chemotherapy-alone group. These 116 patients were included in the safety analysis. As of the date of data cutoff, November 16, 2009, a total of 6 of the 57 patients (11%) in the iniparib group and 4 of the 59 patients (7%) in the chemotherapy-alone group were still receiving treatment. Thirty of 59 patients (51%) in the chemotherapy-alone group crossed over to receive iniparib in combination with gemcitabine and carboplatin.

Overall, the two treatment groups were well-balanced with regard to the baseline characteristics of the patients (Table 1). A total of 60% and 57% of patients in the chemotherapy-alone and iniparib groups, respectively, received study treatment as first-line therapy for metastatic disease. In all, 65% and 74% of patients, respectively, had received prior anthracycline-containing therapy, and 71% and 84% of patients, respectively, had received prior taxane-containing therapy.

EFFICACY

In the intention-to-treat population, the rate of clinical benefit was 56% (34 of 61 patients) in the iniparib group and 34% (21 of 62 patients) in the chemotherapy-alone group (P=0.01). The overall rate of response was 52% (32 of 61 patients) in the iniparib group and 32% (20 of 62 patients) in the chemotherapy-alone group (P=0.02) (Table 2).

For patients who received at least one cycle of therapy and underwent both baseline and post-treatment assessments of tumor size, the rate of clinical benefit was 62% (34 of 55 patients) in the iniparib group and 39% (21 of 54 patients) in the chemotherapy-alone group (P=0.02). The overall rate of response among these patients was 58% (32 of 55 patients) in the iniparib group and 37% (20 of 54 patients) in the chemotherapy-alone group (P=0.03).

The median progression-free survival in the intention-to-treat population was 5.9 months in the iniparib group and 3.6 months in the chemotherapy-alone group (hazard ratio for disease progression with iniparib, 0.59; 95% confidence interval [CI], 0.39 to 0.90; P=0.01) (Fig. 2A and Table 2).

The median overall survival in the intention-to-treat population was 12.3 months in the iniparib group and 7.7 months in the chemotherapy-alone group (hazard ratio for death with iniparib, 0.57; 95% CI, 0.36 to 0.90; P=0.01) (Fig. 2B and Table 2).

A total of 30 of 59 patients (51%) in the chemotherapy-alone group crossed over to receive iniparib in combination with gemcitabine and carboplatin, after disease progression occurred. Patients who crossed over received a median of 1.5 cycles of iniparib; 25 of the 30 patients (83%) discontinued treatment after one or two cycles.

Table 2. Summary of Efficacy Measures in the Intention-to-Treat Population.*

Outcome	Gemcitabine–Carboplatin and Iniparib (N=61)	Gemcitabine–Carboplatin Alone (N=62)	P Value†
Overall survival			
Months — median (95% CI)	12.3 (9.8–21.5)	7.7 (6.5–13.3)	0.01
Hazard ratio (95% CI)	0.57 (0.36–0.90)		
Progression-free survival			
Months — median (95% CI)	5.9 (4.5–7.2)	3.6 (2.6–5.2)	0.01
Hazard ratio (95% CI)	0.59 (0.39–0.90)		
Overall rate of response — no. (%)	32 (52)	20 (32)	0.02
Best overall response — no. (%)			
Complete response	2 (3)	1 (2)	
Partial response	30 (49)	19 (31)	
Stable disease	11 (18)	13 (21)	
Stable disease for ≥6 mo	2 (3)	1 (2)	
Progressive disease	10 (16)	18 (29)	
Not able to be evaluated‡	8 (13)	11 (18)	
Clinical benefit — no. (%)§	34 (56)	21 (34)	0.01

* CI denotes confidence interval.
† P values were not adjusted for multiple interim analyses.
‡ Patients for whom best overall response could be evaluated had completed at least one cycle of treatment and had undergone both baseline and post-treatment assessment of tumor size.
§ The rate of clinical benefit was defined as the percentage of patients who had a complete response, a partial response, or stable disease for at least 6 months.

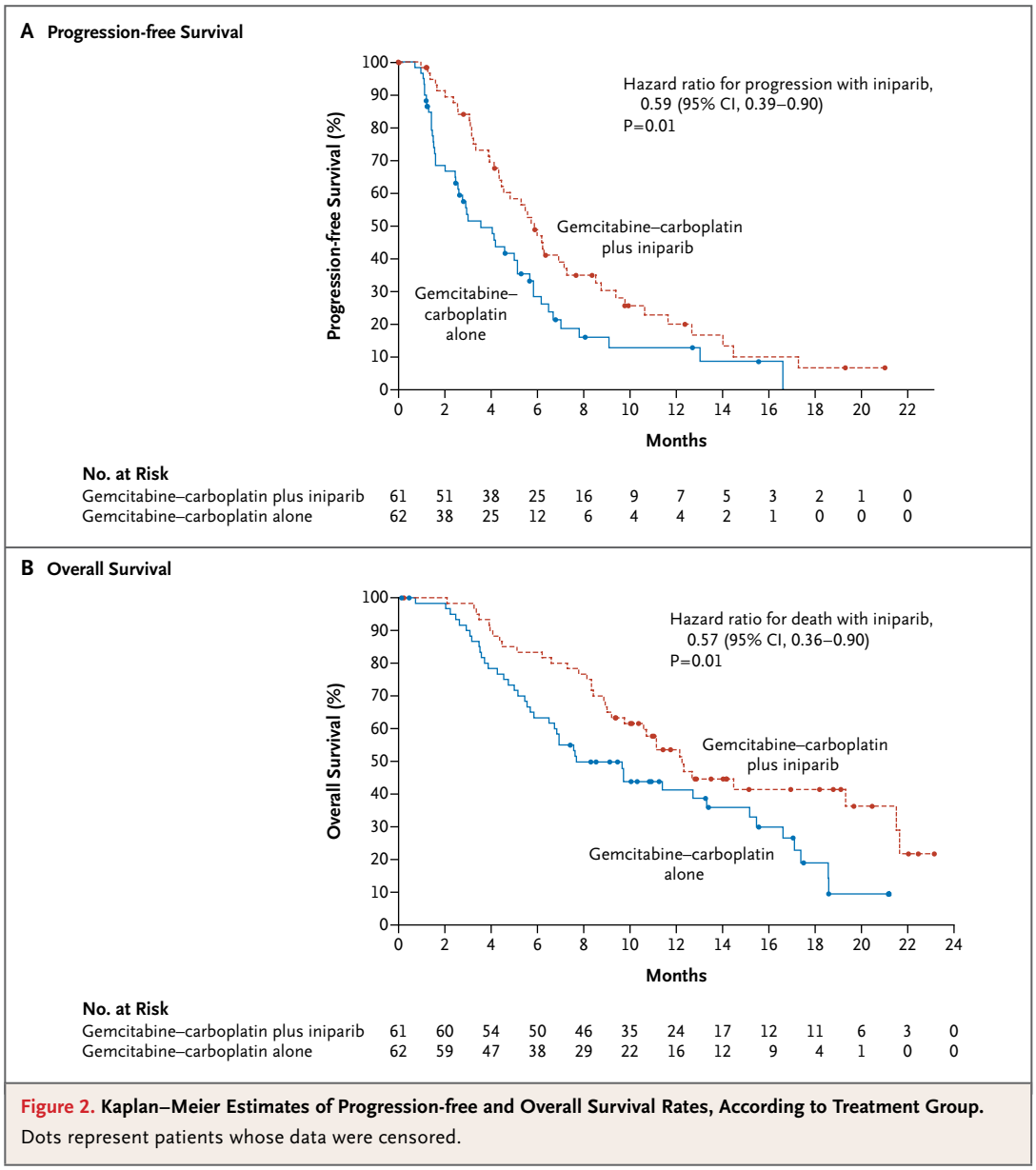

Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival Rates, According to Treatment Group.
Dots represent patients whose data were censored.

In 1 of the 30 patients (3%), there was an unconfirmed partial response, and 4 of the 30 patients (13%) had stable disease.

SAFETY

Table 3 lists the most common adverse events in the safety population. The most frequent adverse events included grade 1 nausea, fatigue or asthenia, and constipation; grade 3 anemia; and grade 3 or 4 neutropenia. The incidence of grade 3 or 4 adverse events was 86% in the iniparib group and 81% in the chemotherapy-alone group; these events included neutropenia, thrombocytopenia, anemia, and leukopenia. The rates of both grade 3 or 4 anemia and thrombocytopenia were more than 5% higher in the iniparib group than in the chemotherapy-alone group, but no significant differences were observed in the frequency of any adverse event between the two treatment groups ($P>0.05$ for any grade of adverse events and for grade 3 or 4 adverse events).

The rate of serious adverse events was similar in the two groups (29% in the chemotherapy-alone group and 28% in the iniparib group). In

Table 3. Common Adverse Events in the Safety Population.*

Event	Gemcitabine–Carboplatin and Iniparib (N=57)			Gemcitabine–Carboplatin Alone (N=59)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
	number of patients (percent)					
Any event	57 (100)	30 (53)	19 (33)	59 (100)	26 (44)	22 (37)
Neutropenia	46 (81)	25 (44)	13 (23)	48 (81)	21 (36)	16 (27)
Anemia	38 (67)	13 (23)	0	40 (68)	9 (15)	0
Thrombocytopenia	36 (63)	10 (18)	11 (19)	30 (51)	6 (10)	10 (17)
Leukopenia	16 (28)	7 (12)	0	13 (22)	6 (10)	0
Fatigue or asthenia	40 (70)	4 (7)	0	43 (73)	10 (17)	1 (2)
Nausea	38 (67)	0	0	39 (66)	1 (2)	0
Constipation	24 (42)	1 (2)	0	32 (54)	1 (2)	0
Vomiting	16 (28)	1 (2)	0	21 (36)	1 (2)	0
Dyspnea	16 (28)	2 (4)	0	19 (32)	2 (3)	0
Headache	14 (25)	0	0	18 (31)	0	0
Pyrexia	14 (25)	0	0	10 (17)	0	0
Diarrhea	11 (19)	1 (2)	0	18 (31)	1 (2)	0
Stomatitis	11 (19)	0	0	9 (15)	0	0
Peripheral edema	11 (19)	0	0	9 (15)	1 (2)	0
Cough	10 (18)	1 (2)	0	10 (17)	0	0
Increased ALT	10 (18)	3 (5)	0	9 (15)	1 (2)	0
Arthralgia	9 (16)	1 (2)	0	10 (17)	0	0
Peripheral neuropathy	9 (16)	0	0	7 (12)	0	0
Alopecia	9 (16)	0	0	7 (12)	0	0
Anorexia	8 (14)	0	0	10 (17)	1 (2)	0
Dizziness	8 (14)	0	0	7 (12)	0	0
Bone pain	8 (14)	1 (2)	0	5 (8)	1 (2)	0
Anxiety	8 (14)	0	0	11 (19)	0	0
Increased AST	7 (12)	1 (2)	0	9 (15)	2 (3)	0
Dyspepsia	6 (11)	0	0	7 (12)	0	0
Insomnia	6 (11)	1 (2)	0	7 (12)	0	0
Dehydration	6 (11)	1 (2)	0	4 (7)	0	0
Depression	6 (11)	0	0	7 (12)	1 (2)	0
Rash	5 (9)	0	0	10 (17)	0	0
Hyperglycemia	5 (9)	1 (2)	0	6 (10)	0	0
Abdominal pain	3 (5)	0	0	8 (14)	2 (3)	0
Decreased weight	1 (2)	0	0	6 (10)	0	0

* Patients could have more than one adverse event. The safety population included all patients who received at least one dose of a study drug. Other adverse events reported for at least 10% of patients included urinary tract infection, decreased appetite, dysgeusia, exertional dyspnea, oropharyngeal pain, erythema, back pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, and pain in an extremity. No significant differences were observed in the frequency of any adverse event between the two treatment groups ($P>0.05$ for any grade of adverse events and for grade 3 or 4 adverse events.) ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

the safety population, 8 of 57 patients (14%) in the iniparib group and 13 of 59 patients (22%) in the chemotherapy-alone group discontinued treatment because of adverse events. The dose of gemcitabine was reduced in 63% of patients (37 of 59) receiving chemotherapy alone and in 65% of patients (37 of 57) receiving iniparib. The dose of carboplatin was reduced in 78% of patients (46 of 59) receiving chemotherapy alone and in 84% of patients (48 of 57) receiving iniparib. The dose of iniparib was reduced in 26% of patients (15 of 57). The median number of treatment cycles administered was seven in the iniparib group and four in the chemotherapy-alone group. Fatal adverse events occurred in 2 of the 59 patients (3%) in the chemotherapy-alone group and 3 of 57 patients (5%) in the iniparib group, all attributable to disease progression within 30 days after receipt of study treatment.

DISCUSSION

This open-label phase 2 trial showed that the addition of iniparib to gemcitabine and carboplatin significantly improved all measures of efficacy, including the rate of clinical benefit, overall survival, progression-free survival, and the rate of objective (complete or partial) response, in patients with metastatic triple-negative breast cancer.

The rate of clinical benefit, which encompasses both objective responses and stable disease for at least 6 months, was selected as the primary end point for this study, rather than the more commonly used phase 2 efficacy end point of overall rate of response. The rate of clinical benefit was selected on the basis of the hypothesis that iniparib may exert cytostatic effects rather than, or in addition to, cytotoxic effects when used in combination with chemotherapy, resulting in disease stabilization in addition to tumor regression. For this reason, stable disease lasting at least 6 months was regarded as clinically meaningful in assessing the antitumor activity of iniparib.

The gemcitabine–carboplatin combination has been evaluated in several studies of metastatic breast cancer and has demonstrated activity at various doses and schedules. In our study, both chemotherapy agents were given on days 1 and 8, in close proximity to the doses of iniparib, to take advantage of possible synergy among the agents. The overall rate of response in the chemotherapy-alone group (32%) was similar to the rate described in previous studies of gemcitabine–platinum therapy for metastatic breast cancer (range, 26 to 34).[21-23] The addition of iniparib to chemotherapy significantly increased the overall rate of response to 52% ($P=0.02$), suggesting that iniparib may overcome the intrinsic drug resistance of some triple-negative breast cancers. The fact that nearly all patients eventually had disease progression while receiving iniparib plus chemotherapy suggests an acquired resistance to iniparib.

Minimal antitumor activity of iniparib was observed in crossover patients whose disease had progressed on chemotherapy alone. These data are analogous to the decreased benefit of olaparib in patients with BRCA1/2-associated metastatic breast cancer whose disease was platinum-resistant.[28]

Iniparib–gemcitabine–carboplatin therapy showed no significant increase in toxicity as compared with gemcitabine–carboplatin. The similar safety profiles in the two groups may be attributable to specificity in the targeting of tumor cells deficient in homologous-recombination–dependent DNA repair, which spares normal, homologous-recombination–proficient cells.[29,30] Differences in the risk of adverse events between the two groups were minimal, despite the greater exposure to gemcitabine and carboplatin of patients in the iniparib group than patients in the chemotherapy-alone group (seven vs. four cycles of treatment).

Limitations of this open-label, phase 2 study include the small sample size, which limits our assessment of overall survival; potential investigator bias in assessing the rate of clinical benefit and progression-free survival; and the slight imbalance in prognostic factors, favoring the iniparib group over the chemotherapy-alone group — including the number of patients with three or more metastatic sites and the particular sites of metastases (Table 1). Finally, multiple interim analyses were conducted to assess the need for and design of a subsequent phase 3 trial.

In conclusion, despite its limitations, this phase 2 study provides proof of concept that the combination of iniparib with gemcitabine–carboplatin provides significant clinical benefit with a favorable safety profile in patients with metastatic triple-negative breast cancer. On the basis of these results, a phase 3 trial of iniparib plus chemotherapy in patients with metastatic triple-

negative breast cancer, adequately powered to study overall survival and progression-free survival, is being conducted (ClinicalTrials.gov number, NCT00938652).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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